J. Fernando Arévalo *Editor*

Retinal and Choroidal Manifestations of Selected Systemic Diseases

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Foreword

Few abnormalities are so prevalent and devastating as those seen as ocular manifestations of systemic diseases. These lesions are associated with systemic disorders, which include familial, degenerative, oncological, inflammatory, vascular diseases … and beyond. Yet, very little is known about the pathogenesis and treatment of many of these syndromic conditions. Given the expanding and developmental use of evolving ophthalmic imaging modalities, there has been improvement in early recognition and precise identification of focal and generalized ocular-systemic-related manifestations. In particular, diseases related with permeability, ischemic, proliferative, inflammatory, and infectious abnormalities have become increasingly associated with certain ocular-systemic relationships.

Fortunately, clinical research and imaging developments have made notable advances in identifying these ocular changes and have been incorporated in *Retinal and Choroidal Manifestations of Selected Systemic Diseases* to enhance the educational value of this superb text. The selected ocular-systemic relationships have also provided a better understanding of the primary diseases and the mechanisms for the abnormalities expressed in the eye. These relationships have been spirited by discoveries in molecular biology, genetics, biochemical and vasogenic processes, and degenerative pathways. In particular, new imaging technology has aided in displaying micro-abnormalities related to the pathogenesis of these systemic diseases, expanding our understanding of the specific entities and the nature of the mechanisms responsible for the ocular manifestations. Knowledge of these associations in our diagnostic and therapeutic capabilities has offered physicians and patients a better prognosis and, in some cases, a better form of management in each disease than in the past.

Beginning with improvement in photographic, ultrasonographic, and angiographic technology in the 1960s, several comprehensive textbooks and atlases have been written to compile these newly recognized and defined relationships between ocular manifestations and systemic diseases. For sure, the editor, Dr. Fernando Arévalo, and the contributing authors of this text have provided by far the best documentation of the nature of ocular manifestations in systemic diseases for its readers. Indisputably, the coauthors are all well-known leaders in their respective fields with notable original and lasting contributions to one or more of the principal selected subjects covered in the text. Accordingly, each section discusses the most advanced concepts regarding

the clinical expectations and management considerations of these disorders. Each section also provides the latest information on the natural course, the limitations and potential adverse effects of treatment, and the anticipated benefits. A review of the ophthalmic literature leading to standards of care based on evidence-based medicine, specifically the randomized trial, is also incorporated into these discussions. In essence, all new information on retinal genetics, molecular biology, risk factors, natural course, diagnostic testing, and specialized imaging and, whenever possible, correlating histopathology has been compiled in this text in an authoritative and comprehensive format not found in any similar, previous publication. An attempt to assimilate ocular-clinical information into logical explanations on the mechanisms of the related pathophysiological manifestations and recommendations for converging lines of future clinical and experimental research for practical means of prevention and treatment have been addressed.

Rarely have students, comprehensive physicians, ophthalmologists, and ancillary medical personnel alike had the opportunity to read such a scholarly approach on this subject. There have been several publications which have specific associations, but none has attempted to engage an elite corps of experts to elegantly describe and amply illustrate the gamut of ocular abnormalities that are the result of systemic disorders. In short, Fernando Arévalo has achieved success in fulfilling a challenging goal in this concise, salient, and excellent text. The principal author and editor and his expert contributors are to be congratulated for compiling an educational masterpiece of encyclopedic medical information on ocular manifestations and associated systemic diseases. Essentially, this new text represents a labor of love by an elite corps of expert clinical and scientific contributors. Their monumental efforts will be rewarded by the gratitude of clinicians and patients who will receive immense pleasure, whether a casual or discerning reader.

Lawrence A. Yannuzzi, M.D.

Preface

I was privileged to be the senior author of a course entitled "Retinal and Choroidal Manifestations of Selected Systemic Diseases" at the American Academy of Ophthalmology (AAO) Annual Meeting, New Orleans, LA, November 2007. My faculty included prestigious international experts in the field such as Rubens Belfort Jr., Carol L. Shields, Jerry A. Shields, Careen Lowder, Lihteh Wu, William F. Mieler, Francisco J. Rodríguez, and Alay S. Banker. Our course has been accepted for presentation every year since 2007 with a rotation of the selected systemic diseases discussed each year.

The popularity of our course is based on the necessity to link ophthalmology to other specialties in medicine. We as ophthalmologists need to be aware of recent advances in other fields in medicine. However, at the same time, we need to demonstrate to other physicians the importance of ophthalmic consultation. To be aware of the retinal and choroidal manifestations of a series of systemic diseases may save sight and even life itself in some cases. The best way to reach all of our colleagues in other specialties in medicine is through a book that touches both fields.

Our AAO course has served as the trigger to start the editing of a comprehensive presentation of the current clinical aspects of *Retinal and Choroidal Manifestations of Selected Systemic Diseases*. This book includes contributions from an internationally renowned group of experts from the USA, Brazil, Colombia, Costa Rica, Mexico, Turkey, India, Israel, and Venezuela. The topics discussed in this book do not pretend to be all inclusive but include retinal and choroidal manifestations of AIDS, diffuse unilateral subacute neuroretinitis (DUSN), posterior pole manifestations of cysticercosis, toxocariasis, tuberculosis, toxoplasmosis, viral diseases, fungal diseases, endogenous endophthalmitis, sarcoidosis, Behçet's disease, intraocular lymphoma, choroidal and retinal metastasis, autoimmune retinopathy, paraneoplastic syndromes – MAR and CAR, retinal and choroidal manifestations of diseases of the gastrointestinal tract, phacomatosis, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome, retinal detachment and lens subluxation in Marfan syndrome, diabetic retinopathy, retinal and choroidal changes in systemic hypertension, posterior pole manifestations of hematologic diseases, carotid artery disease, renal diseases, retinal and choroidal changes in pregnancy, and retinal and choroidal toxicity of systemic drugs.

The impetus to edit this book has come from my students and my colleagues in all fields of medicine. The book is intended for retina and vitreous

specialists, uveitis and ocular oncology specialists, retina and vitreous fellows, uveitis and ocular oncology fellows, ophthalmology residents, comprehensive ophthalmologists, and physicians in general.

The principal objective of this text is to present the current information on retinal and choroidal manifestations of systemic diseases from leading experts in the field. We hope their knowledge and experience will assist ophthalmologists, retina specialists, uveitis and ocular oncology specialists, and physicians in general approach a level of knowledge about retinal and choroidal manifestations of systemic diseases to benefit their patients in everyday clinical practice.

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Retinal and Choroidal Manifestations of HIV/AIDS

1

J. Fernando Arévalo, Rafael A. García, Nikolas J.S. London, Emmett T. Cunningham Jr., Rubens Belfort Jr., and William R. Freeman

Abstract

The human immunodeficiency virus (HIV) pandemic has continued despite the advent of new antiviral therapies; this is responsible for an increase in the number of patients with this entity and its survival. The majority of ocular manifestations of HIV infection involve the posterior segment of the eye. Prior to the introduction of highly active antiretroviral therapy (HAART), retinal microvasculopathy and cytomegalovirus (CMV) retinitis accounted for more than 80% of the ocular complications in HIV-positive patients. To date, HIV disease and CMV retinitis have become chronic diseases. Many challenges remain to be addressed. HAART has indeed decreased the incidence of some ophthalmic problems, such as CMV retinitis, and it has brought with it new challenges, such as immune recovery uveitis (IRU). Ocular disorders associated with HIV disease remain important problems in the world, despite HAART, and increasingly are more significant and frequent. The approach to diagnosis and management of different pathological presentations at the posterior pole is very important.

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Introduction

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) pandemic has continued now for more than 25 years [1, 2]. This pandemic and the advent of new antiretrovirals are responsible for an increase in the number of patients with this entity and its survival. It was estimated in 2007 that 33.2 million people were infected with HIV worldwide, accounting for 0.8% of the world's population. This included roughly 7,000 new infections each day, totaling approximately 2.5 million new infections for the entire year—a figure that was slightly higher than the 2.1 million estimated AIDS-related deaths during the same period [3]. HIV is the fourth largest killer in the world after respiratory infections, diarrheal disorders, and tuberculosis, and the leading cause of death in Africa [4]. While cases of HIV/AIDS have been reported from virtually every part of the world, over 90% of people with HIV/AIDS live in developing countries [5].

Due to global efforts, the epidemic appears to be stabilizing [3, 5]. The incidence of new infections is believed to have peaked in the late 1990s and then declined between 2001 and 2007 [3]. While the global prevalence of HIV/AIDS rose from 29.5 million in 2001 to 33 million in 2007, the prevalence rate stayed level at 0.8% [3]. This is attributable to increased preventive education and dramatically increased availability of antiretroviral medications throughout the world, including a 20-fold increase in sub-Saharan Africa since 2003.

Despite these encouraging trends, the pandemic persists in several areas, including the ongoing epidemics in sub-Saharan Africa, the Caribbean, and Southeast Asia [6]. Sub-Saharan Africa, with 22 million people infected, accounts for roughly two-thirds of all HIV infections and 90% of all infected children. In South Africa, an astonishing one in five people are infected, and AIDS remains the leading cause of death in this region. A global epidemic also continues among high-risk populations, including intravenous (IV) drug abusers, prostitutes, and men who have sex with men [7].

Moreover, the chances of this group of patients to develop one of its (HIV/AIDS) ocular manifestations also increase. Ocular disease occurs in 50–75% of HIV-infected patients [8–14]. In Western countries, the most common manifestation is HIV microvasculopathy, followed by cytomegalovirus (CMV) retinitis, ocular toxoplasmosis, non-CMV herpetic retinitis, neuro-ophthalmic complications, herpes zoster ophthalmicus (HZO), and ocular neoplasia [9, 10, 15]. This spectrum appears to be different in developing countries [16–18] where poorer access to highly active antiretroviral therapy (HAART) and medications for opportunistic infections translates into higher mortality rates and fewer patients surviving with profound immunosuppression. Ocular complications have been reported in 29–60% of patients in the developing world [8, 19, 20]. In sub-Saharan Africa, CMV retinitis is less common than in the United States or Europe, while anterior segment and external manifestations such as HZO and conjunctival squamous cell carcinoma (SCC) appear to be more common [12, 21–24].

Similarly, the chances that some of these patients are presented to the consultation of a

general ophthalmologist or any subspecialist increase considerably every day, and we must therefore be prepared to recognize these ocular manifestations and management. Infection with HIV leads to a derangement of cell-mediated immunity, which in turn predisposes to a series of events that affect the retina and choroid. These manifestations can be divided into two broad categories: those associated with noninfectious etiologies and a much larger group of secondary infections with varied clinical presentations. With the advent of effective treatments for these infections that threaten the vision of these patients, an accurate differentiation of these entities may allow the clinician to initiate appropriate treatment in many cases with improved quality of life and survival. The matter is highly complicated, however, because many HIV-infected people, even if they know of their HIV status, may be incompletely treated. Thus, knowledge of the actual immune status, best but not perfectly represented by the CD4 T-cell count, is very important for the ophthalmologist.

Posterior Segment Manifestations of HIV/AIDS

The majority of ocular manifestations of HIV infection involve the posterior segment of the eye. Prior to the introduction of HAART, retinal microvasculopathy and CMV retinitis accounted for more than 80% of the ocular complications in HIV-positive patients. CMV retinitis, in particular, is by far the single most significant cause of loss of vision in this population, affecting up to 40% of patients [25–27] prior to the widespread use of HAART. Since that time, the prevalence of CMV retinitis has fallen dramatically [15].

Noninfectious Retinal Manifestations

The clinical spectrum of HIV retinopathy includes infarct of the nerve fiber layer (often called cotton-wool spots), retinal hemorrhages, telangiectasia, lack of capillary perfusion, and vascular occlusion. This microangiopathy is clinically apparent in 70% of patients with AIDS but is less frequent as the degree of immunosuppression decreases [28].

Hypotheses regarding the pathogenesis of retinal microvasculopathy parallel those suggested for conjunctival vascular changes [29, 30] and include HIV-induced increase in plasma viscosity, HIV-related immune complex deposition [31], direct infection of the conjunctival vascular endothelium by HIV, and increased rigidity of circulating neutrophils [29, 32–35]. HIV-associated retinal microvasculopathy is typically asymptomatic but may play a role in the progressive optic nerve atrophy [36, 37], electroretinographic abnormalities, [38] loss of color vision, contrast sensitivity, and visual field observed in HIV-infected patients [30, 39]. The role of retinal microvasculopathy in the development of CMV retinitis is controversial, with some investigators finding no relationship [40] and others suggesting that retinal vascular damage may provide increased access to circulating CMV-infected lymphocytes.

Cotton-wool spots are the most common finding and earlier of the noninfectious retinopathy HIV and occur in approximately 50–60% of cases in clinical series [32, 40]. The whitish color by ophthalmoscopy represents areas of focal thickening of the nerve fiber layer caused by infarction of the adjacent capillaries. Histologically, these lesions are known as cytoid bodies and are composed by cytoplasmic accumulation of debris due to obstruction of axoplasmic flow in the ganglion cells. Cotton-wool spots typically cluster around the optic disk and are only rarely seen over 30° of the papilla. Its clinical appearance is that of white opacities with margins as a feather, located in the nerve fiber layer of the retina, and its size is usually larger than one-third of disk diameter (Fig. 1.1). They are by nature evanescent, disappearing within a few weeks and being replaced by new ones in different locations of the retina. Cotton-wool spots may be confused with lesions of very early CMV retinitis but are distinguished by their smaller size, superficial location, and lack of progression. Recent studies of these cotton-wool spots using optical coherence tomography (OCT) have shown that after resolution, there is permanent damage to that area of the retina, particularly destruction

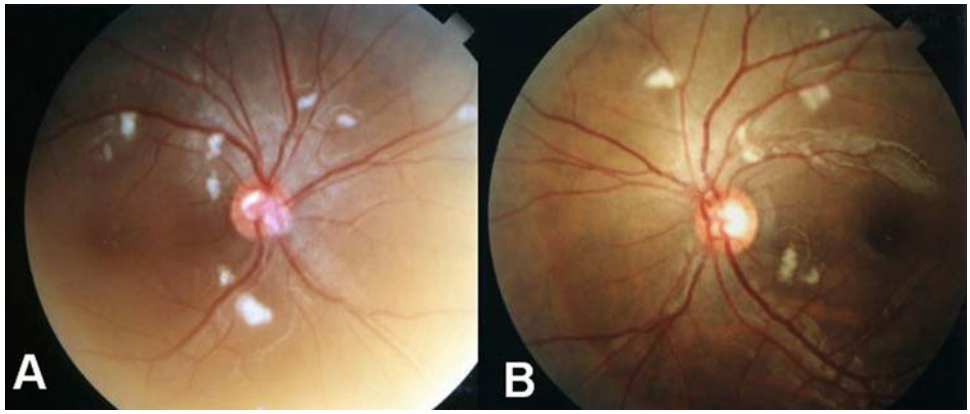

Fig. 1.1 Cotton-wool spots at the posterior pole of a patient with AIDS. Note the peripapillary location. (**a**) Right eye. (**b**) Left eye

of the inner retina. The accumulation of such areas of damage may play a role in the documented visual dysfunction seen in HIV patients, particularly those with a history of immunocompromise [41].

Hemorrhages associated with HIV infection are less common than cotton-wool spots but occur in approximately 20% of patients with AIDS. These hemorrhages may be present in the nerve fiber layer (hemorrhages in flames) and in deeper layers of the retina (spot or pinpoint hemorrhages) (Fig. 1.2). White center hemorrhages (Roth's spots) have also been described.

In AIDS patients, telangiectatic retinal vessels are observed frequently and commonly are associated with microaneurysms [32, 40]. In association with these vascular anomalies, it is usual to find the demonstration of nonperfusion areas in the fluorescein angiogram. Less common vascular findings in these patients include arterial and venous occlusions (Fig. 1.3), perivasculitis, and retinal neovascularization. Importantly, these findings (microangiopathy related to AIDS) are nonspecific, but their presence in a young patient should immediately arouse suspicion of HIV seropositivity.

The majority of studies in the post-HAART era report a substantial decline in HIV-related retinal microvasculopathy, likely a result of fewer patients with sustained, profound immune suppression.

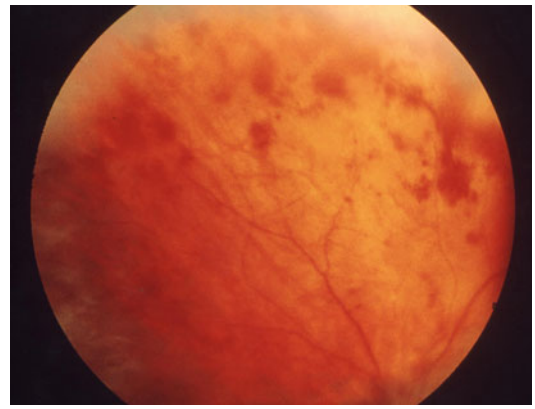

Fig. 1.2 Pinpoint and flame hemorrhages on the periphery of an AIDS patient

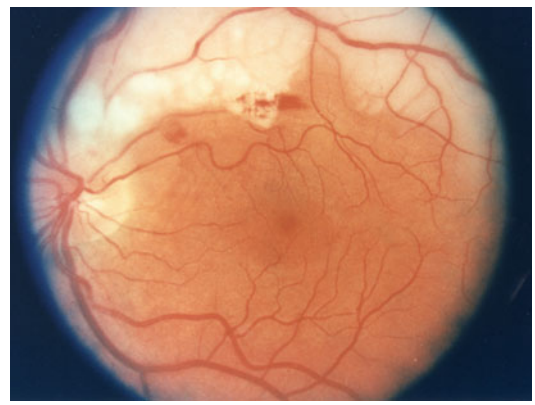

Fig. 1.3 Superotemporal branch retinal artery occlusion simulating a cytomegalovirus retinitis. Note the presence of flame hemorrhages

Infectious Manifestations of the Posterior Segment

Cytomegalovirus Retinitis

In most developed countries, CMV seroprevalence steadily increases after infancy, and 10–20% of children are infected before puberty. In adults, the prevalence of antibodies ranges from 40% to 100%. Although CMV has a worldwide distribution, infection with CMV is more common in the developing countries and in areas of low socioeconomic conditions, which is predominantly related to the closeness of contacts within these populations.

Despite a marked decline in incidence since the advent of HAART, CMV retinitis continues to be the most common AIDS-related opportunistic infection and remains an important cause of visual morbidity. CMV retinitis frequently occurs in AIDS patients with a CD4+ count <50 cells/uL and is the most common ocular opportunistic infection associated with AIDS. Prior to HAART, CMV retinitis affected 30–40% of HIV-infected patients [10, 25, 27, 31, 42], whereas most studies in the era of HAART have shown a decline in the incidence of CMV retinitis by about 75% [43], as well as a 50% reduced risk of retinitis progression, even in patients with persistent immune suppression [44, 45]. The use of HAART changed the natural history of HIV-associated CMV retinitis in two important ways. First, since fewer patients have CD4+ T-lymphocyte counts below 100 cells/μL, fewer patients are at risk for the development of CMV retinitis [16]. Second, patients receiving such therapy who have early or partial reconstitution of CD4+ cell populations may have otherwise uncommon features of CMV infection, including moderate-to-severe anterior chamber or vitreous inflammation and spontaneous healing in the absence of specific anticytomegalovirus therapy. Unfortunately, approximately 90% of the world's AIDS population has no access to HAART and therefore continues to present the classic ocular presentation [1].

Affected patients typically report gradual visual field loss or the onset of floaters. The three main clinical forms of CMV retinitis are a hemorrhagic retinitis with prominent edema, a granular type with satellite lesions, and a less common perivascular retinitis. The most important clinical features of CMV retinitis include a white granular border, intraretinal hemorrhages, slow progression of lesions, peripheral location (where they take on a more granular aspect) or along the retinal vascular arcades, and the lack of a prominent intraocular inflammatory reaction (Fig. 1.4). This last feature is observed in most cases; therefore, the presence of severe vitreous inflammation should lead us to consider a different diagnosis.

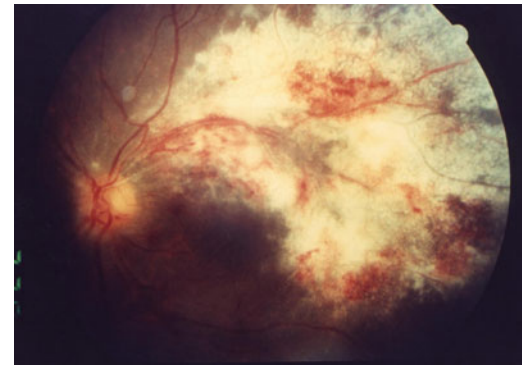

Fig. 1.4 Cytomegalovirus retinitis along the vascular arcades

CMV retinitis is asymptomatic in up to 15% of patients, and all HIV/AIDS patients with a CD4+ cell count under 50 cells/μ(mu)L should have a dilated ophthalmoscopic examination every 3 months [46]. The location and extent of CMV retinitis should be determined by indirect ophthalmoscopy, revision of stereo color photographs, and retinal drawings. The Study of Ocular Complications of AIDS (SOCA) [47] has adopted the following division of the retina into zones: zone 1 is the area of the retina surrounding the optic disk by 1,500 μ and the center of the fovea by 3,000 μ; zone 2 extends anteriorly from the edge of the zone 1 to a circle identified by the vortex veins; and zone 3 extends above the edge of zone 2 to the ora serrata. The total area of retinitis is determined by calculating the area (percentage) of the retina affected by CMV (retinitis healed and active), while the area of the retina with active CMV retinitis is denoted as the

length of active edge (white) measured in disk diameters (DD).

Rhegmatogenous retinal detachment (RD) is a frequent complication in patients with CMV retinitis. Prior to HAART, the incidence of RD in patients with CMV retinitis ranged from 18% to 29%. Jabs and colleagues have reported that there is a cumulative risk of RD up to 50% a year of diagnosis of CMV retinitis [48]. The incidence of bilaterality of RD is also high in this group of patients, and reports in the literature vary from 17% to 67% [48–53]. Risk factors for RD to this group of patients include extension of retinitis and activity [52]. In the era of HAART, the incidence of retinal detachment as a complication of CMV retinitis has declined by more than 60% [54].

Retinal detachments associated with CMV retinitis have characteristics of a rhegmatogenous RD (caused by ruptures of the retina) but are atypical in several ways. These RDs are often associated with multiple breaks or holes, most of which are very difficult to visualize in large areas of gliotic retina (often already healed). Breaks are usually located at the junction between the normal and atrophic retina or in areas of atrophic retina. Since most of these patients are young, the vitreous is well formed, and it may not be fully detached at the time of surgery. This finding explains the relatively flat appearance (nonbullous) for most of these RD (Fig. 1.5) in contrast to the bullous appearance of RD in patients with complete posterior vitreous detachment (PVD) or RD in eyes with greater vitreous pathology (Fig. 1.6) [53]. Vitreoretinal proliferation (PVR) is a rare complication associated with CMV retinitis and is at least seen in 20% of cases.

Several reports have shown good results repairing these detachments with primary vitrectomy, endolaser of retinal breaks, and inferior peripheral retina associated with the use of 5,000-cs silicone oil (Fig. 1.7) [48–53]. This method has the advantage of providing a faster visual recovery than if we use gas (C3F8 or SF6) and have a permanent tamponade of multiple retinal holes in the atrophic retina. This is of particular benefit to patients in whom retinitis progresses

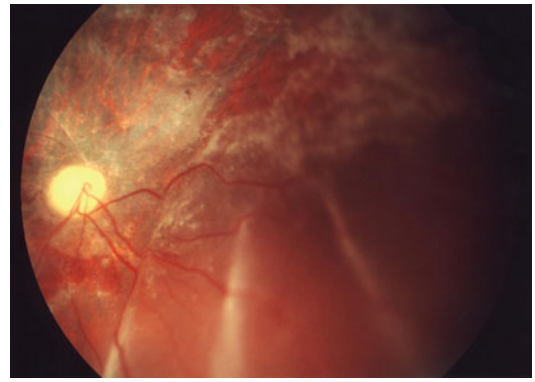

Fig. 1.5 Retinal detachment is flat in a patient with cytomegalovirus retinitis without a posterior vitreous detachment

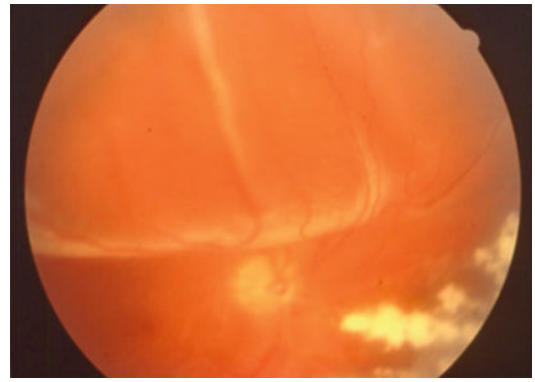

Fig. 1.6 Bullous retinal detachment in a patient with cytomegalovirus retinitis with a posterior vitreous detachment

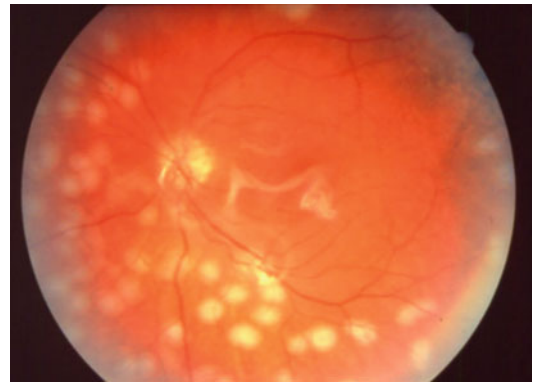

Fig. 1.7 Appearance of the retina after retinal detachment repair with primary vitrectomy, endolaser, and injection of silicone oil of 5,000 centistokes (cs)

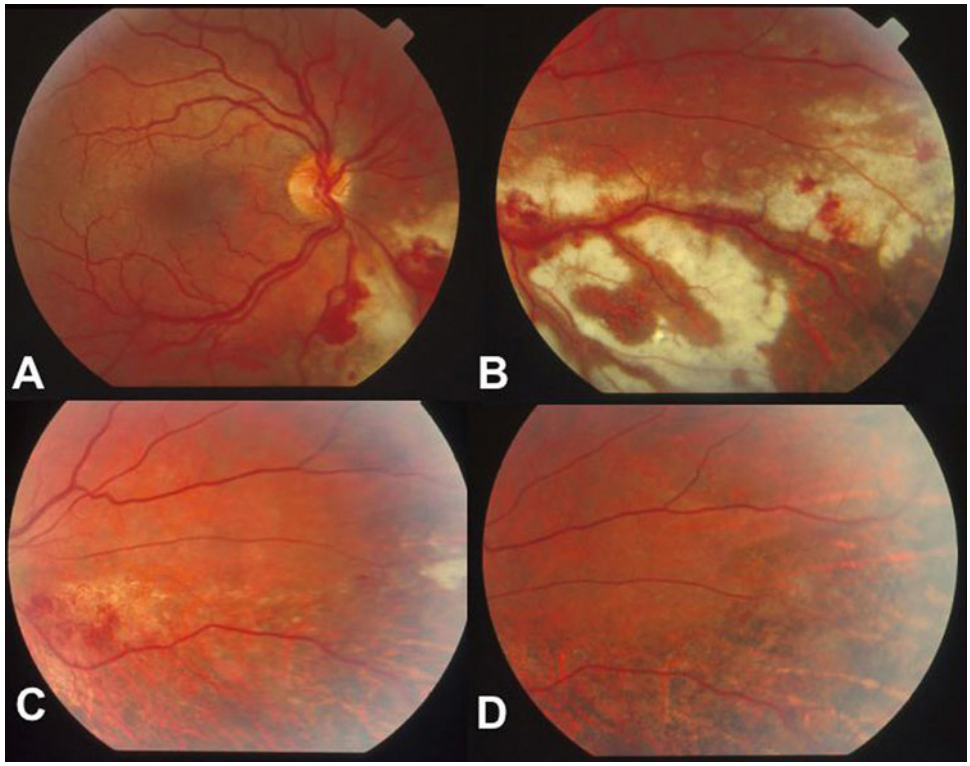

Fig. 1.8 Orally administered valganciclovir appears to be as effective as intravenous ganciclovir for induction treatment and is convenient and effective for the long-term management of cytomegalovirus (CMV) retinitis in patients with AIDS. (**a** and **b**) CMV retinitis before valganciclovir. (**c** and **d**) After 3 weeks on valganciclovir 900 mg twice a day (Reprinted with permission from Arevalo JF, ed. Manifestaciones Oculares del SIDA en el Nuevo Milenio: Texto y Atlas [Ocular manifestations of AIDS in the New Milenium: Text and Atlas]. Panama City, Panama: Highlights of Ophthalmology 2004 [55]

and has a potential risk of forming new holes in other areas of retinal necrosis.

Treatment of CMV retinitis is complicated and needs to be individualized for each patient. Current US Food and Drug Administration (FDA)-approved treatments for active retinitis include intravenous ganciclovir, foscarnet, or cidofovir, and oral valganciclovir. The standard treatment for CMV retinitis is oral valganciclovir induction followed by maintenance. Intravenous ganciclovir is generally reserved for those with malabsorption syndromes. Probably second-line treatment is cidofovir, and last is foscarnet. The implant can be used in cases of resistance; if it is used for primary therapy, oral valganciclovir maintenance is important to prevent systemic disease. Ganciclovir is administered intravenously at doses of 5 mg/kg every 12 h for 2–4 weeks (induction dose) and then 5 mg/kg/day (maintenance dose). Foscarnet is administered intravenously at a dose of 180 mg/kg/day for 2–4 weeks (induction dose) and then decreases to a dose of 120 mg/kg/day (maintenance dose). Valganciclovir is given at 900 mg PO twice daily for 2–4 weeks (until retinitis is healing), then 900 mg PO daily (Fig. 1.8). Cidofovir is administered intravenously once a week for 2 weeks at a dose of 5 mg/kg (induction dose) and then once every 2 weeks at the same dose (maintenance). Cidofovir compares favorably to ganciclovir and foscarnet as to its effectiveness against CMV (cidofovir is ten times more powerful). Patients with high-level ganciclovir toxicity may be resistant to cidofovir.

The significant problems of intravenous therapy are the development of resistance to ganciclovir

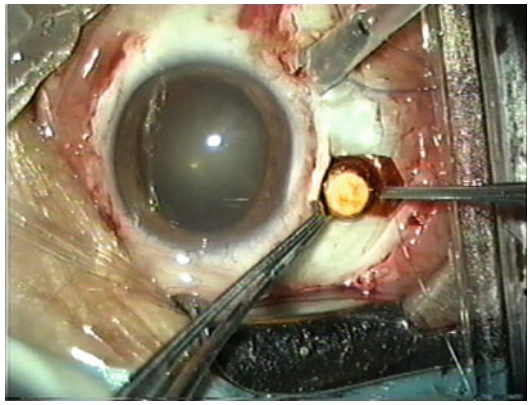

Fig. 1.9 The ganciclovir intraocular implant confers longer retinitis inactivity

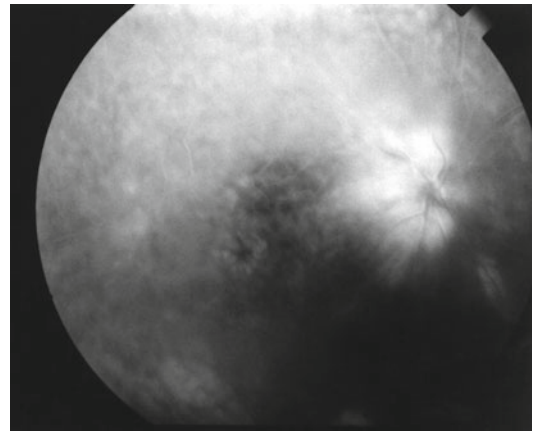

Fig. 1.10 Papillitis and cystoid macular edema associated to immune recovery uveitis (Reprinted with permission from Arevalo JF, Mendoza AJ, Ferretti Y. Immune recovery uveitis in AIDS patients with cytomegalovirus retinitis treated with highly active antiretroviral therapy in Venezuela. Retina 2003;23:495–502)

and foscarnet, systemic toxicity of the antivirals, the risk of sepsis (by prolonged use of a central catheter), and the great inconvenience of daily intravenous infusions [56–58]. The significant problems of intravenous therapy have led to local and oral therapy. Currently, local therapy has two clear lines: (1) intravitreal (IVT) implant of ganciclovir (Fig. 1.9) [56] (that is inserted through the pars plana after a limited vitrectomy and has a duration of approximately 8 months) and (2) IVT injections of ganciclovir at doses of 400–2,000 μg two times a week for 3 weeks and then once weekly, IVT injections of ganciclovir at a dose of 5,000 μg once weekly, IVT injections of foscarnet at a dose of 2,400 μg two times a week for 3 weeks and then once weekly, and finally IVT injections of cidofovir administered at a dose of 15–20 mg every 6 weeks [57, 59].

Choice of an appropriate antiviral and route of delivery needs to be individualized, based on consideration of the location and extent of ocular and systemic disease, understanding of potential drug-related side effects, and knowledge of viral response to past treatments. Today, the trend and standard treatment is to combine systemic treatment, intravenous (ganciclovir or foscarnet) or oral with valganciclovir (900 mg BID as induction and 900 mg/day as maintenance), with local treatment (intravitreal injections versus implant of ganciclovir [Vitrasert, Bausch & Lomb, Madison, NJ, USA]).

Maintenance therapy should be continued for as long as active retinitis is present and/or CD4+ cell counts remain below 150 cells/μL. Only after 3–6 months of inactive disease with CD4+ cell counts above 150 cells/μL and reduced HIV in the blood should consideration be given to discontinuing maintenance therapy [60, 61].

The improvement in immune function in AIDS patients receiving HAART may alter the way the eye responds to CMV. Karavellas and colleagues reported five patients treated with protease inhibitors that had elevated levels of CD4 + T cells and inactivated retinitis by CMV [62]. All showed moderate vitritis and papillitis, some with cystoid macular edema (CME). They attributed these complications to the inflammation induced by increased immunocompetence of these patients. They called this new syndrome "immune recovery vitritis." Several studies have been published since then, and the term immune recovery uveitis (IRU) has been used extensively to describe various inflammatory ocular manifestations in AIDS patients with inactive CMV retinitis. IRU is a chronic intraocular inflammatory disorder that manifests symptomatically with painless decrease of vision and floaters. The clinical spectrum of IRU includes vitritis, papillitis, cystoid macular edema (CME) (Fig. 1.10),

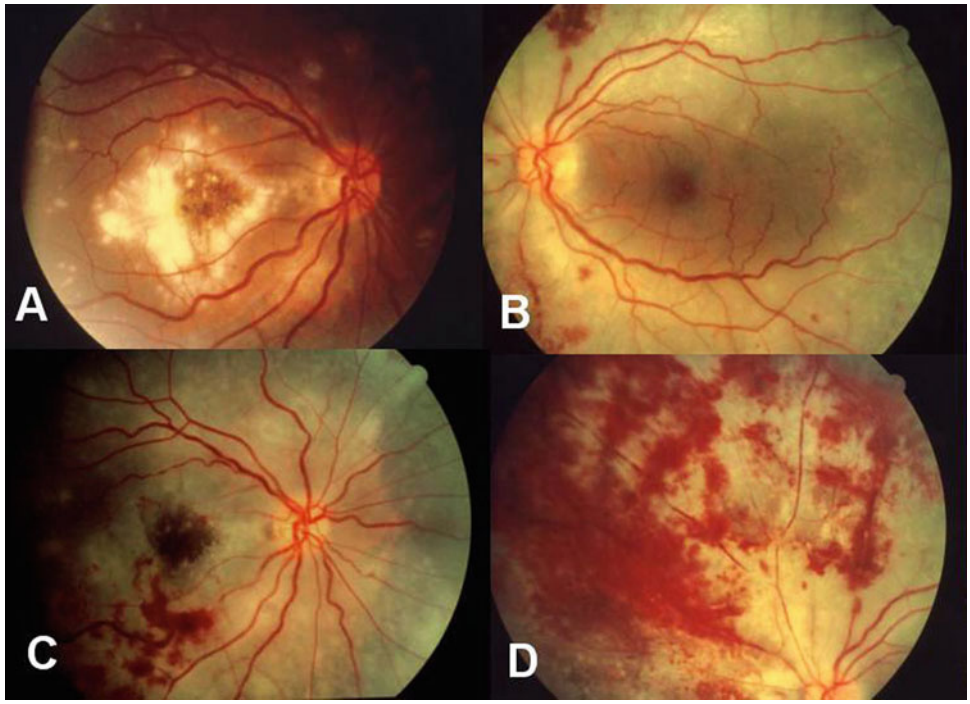

Fig. 1.11 Progressive outer retinal necrosis with retinal vein occlusion of inferotemporal branch in a patient with AIDS. (**a** and **b**) Right eye (RE) and left (LE), with a typical onset in the posterior pole in the RE and atypical uninvolvement of the posterior pole in the LE. (**c** and **d**) The evolution with involvement of the entire retina and vein occlusion

epiretinal membrane (ERM), vitreous hemorrhage, retinal neovascularization, vitreomacular traction syndrome (VMTS), and PVR. Both the extent of past CMV retinitis and prior use of cidofovir appear to be risk factors for the development of IRU [63]. IRU should be treated with topical, periocular, and/or intraocular corticosteroids, as indicated [64].

Recently, there has been a report of a new clinical entity, CMV retinitis occurring in HIV-positive or HIV-negative patients after intravitreal triamcinolone injection. This likely occurs because of the immunosuppressed ocular environment after such injections. One must be aware that viral retinitis, though rare, may also occur after intravitreal triamcinolone [65].

To minimize the opportunity for IRU in patients not on HAART at the time of diagnosis, HAART should be started following the induction phase of anti-CMV treatment, and the CMV retinitis should be treated aggressively through the period of immune recovery [66].

Necrotizing Herpetic Retinitis (by Varicella Zoster)

Clinically, varicella zoster virus (VZV) may cause different diseases. Other than the classic picture of herpes zoster ophthalmicus, it has two other clinical forms: acute retinal necrosis (ARN) syndrome, a necrotizing retinitis that responds well to antiherpetic medication and can occur at any CD4+ T-lymphocyte counts, and progressive outer retinal necrosis syndrome which is associated with low CD4+ T-lymphocyte counts [1].

Retinitis caused by VZV in patients with AIDS is a clinical entity characterized initially by a multifocal outer retinitis that typically affects the posterior pole followed by a progressive outer retinal necrosis (PORN) with or without vitritis or with limited vasculitis (Fig. 1.11) [65–69]. Retinal whitening is occasionally accompanied by retinal hemorrhages. The visual prognosis is extremely poor; most of the cases reported so far have a final visual acuity of hand motions or worse. Although the reported incidence is only

4% of all retinal infections associated with AIDS, VZV retinitis is the second (in frequency) retinal infection in this patient group. The prevalence of PORN has dropped by nearly 90% in recent studies [15]. A concurrent or recent herpes zoster dermatitis provides added circumstantial support for the diagnosis [66–72], and 4–17% of HIV/AIDS patients with herpes zoster ophthalmicus go on to develop necrotizing herpetic retinopathy [73, 74]. The visual effects in the infected eyes are the most severe of all eye infections associated with HIV. In addition, contralateral eye involvement (initially not involved) even under antiviral therapy is over 70%, and the retinal detachments are common (>75% of cases) [65–71]. The risk of RD is greater than that observed with CMV retinitis. Herpes simplex virus is a rare cause of retinitis in HIV-infected patients [75, 76]. Like VZV retinitis, onset of symptoms and disease progression are rapid. Clinical appearance may mimic VZV retinitis.

VZV retinitis in AIDS patients currently consists of the following characteristics: (1) frequent previous episodes of cutaneous zoster in the 18 months preceding retinitis, (2) an account of CD4 + lymphocyte less than 50 cells/μL, (3) multifocal outer retinitis with initial predilection for the posterior pole, (4) relative absence of intraocular inflammation, (5) poor visual prognosis despite aggressive and prolonged intravenous therapy, and (6) increased risk of VZV encephalitis. These features distinguish it from acute retinal necrosis syndrome that typically occurs in immunocompetent patients but may also occur in HIV-positive patients with relatively higher CD4+ cell counts [71]. This may explain the features that differentiate ARN from PORN, including more prominent vitritis, more apparent involvement of the inner retina, retinal vasculitis, and involvement of the anterior segment.

In patients with severe immune compromise, VZV retinitis occurs with less iridocyclitis, vitritis, and vasculitis than typically seen in ARN. Furthermore, there is a trend of initial lesions to appear at the posterior pole rather than at the periphery and to be multifocal rather than confluent. The progression is fulminant with dramatic changes taking place in a week even under therapy. Another interesting feature is that perivascular involvement occurs early and then progresses into the area between the vessels. This pattern leaves a perivascular area of retinal atrophy that appears to be relatively respected or unaffected, when in reality it is a completely atrophic area. It is not uncommon the progression to total retinal atrophy and retinal detachment in a few weeks despite antiviral treatment.

There are HIV-positive cases (with a lower degree of immunosuppression) with clinical characteristics identical to those of ARN in immunocompetent patients [71]. Is likely to be of the same illness (necrotizing herpetic retinitis) and with a progressive immunosuppression, depending on the degree of this, the clinical features of infection may change from ARN to PORN with fulminant course and extremely poor visual prognosis in most cases.

Treatment involves the use of intravenous, oral, and intravitreal antivirals. PORN has been suggested to be less responsive than ARN to therapy with intravenous (IV) acyclovir, or intravitreal ganciclovir or foscarnet [66, 77]. Despite the availability of at least three effective antivirals (acyclovir, ganciclovir, and foscarnet) with high activity in vitro against herpes virus family, the results are still unsatisfactory, and proper management of these patients is still unclear. Because most patients have been in contact with acyclovir in a chronic form (for the treatment of skin lesions), many have drug resistance. Therefore, a combined therapy of intravenous ganciclovir and foscarnet should be instituted immediately, and this should be continued indefinitely. In addition, one must consider the possibility of injecting foscarnet (2,400 μg) or high-dose ganciclovir (5,000 μg) into the vitreous cavity immediately to minimize the time that antiviral therapy will take to reach the affected tissue in an attempt to improve the prognosis of this devastating eye infection.

Toxoplasmic Retinochoroiditis

While ocular toxoplasmosis affects less than 1% of HIV-infected patients in the United States [78–84], there are areas with a higher seroprevalence of *Toxoplasma gondii*. The prevalence of toxoplasmosis varies according to dietary habits

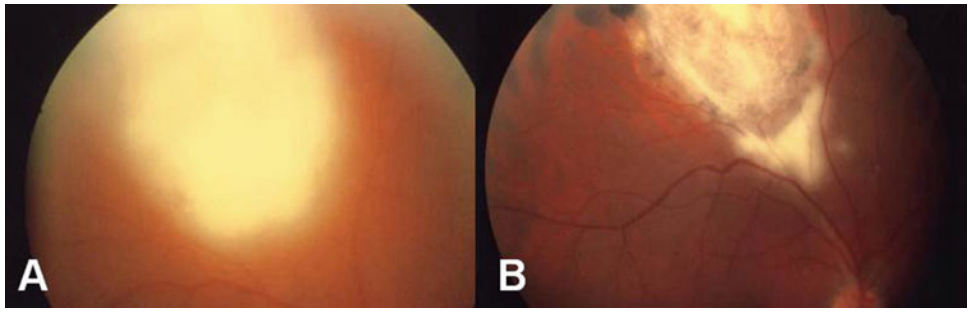

Fig. 1.12 Peripheral retinal lesion of acquired toxoplasmosis in an AIDS patient. (**a**) Before treatment. (**b**) Following standard treatment. Note the little hyperplasia of the retinal pigment epithelium in immunocompromised patients

and, therefore, from country to country. In Latin America, the rate is as high as 65% in some populations. As an example, in a native Yucpa community in Venezuela, the overall prevalence of infection was 63%. Fifty-nine subjects had total antibodies and 14 had IgM antibodies [85]. In addition, ocular toxoplasmosis affects up to 8.5% of patients with AIDS in Brazil [1].

Unlike ocular toxoplasmosis in immunocompetent individuals, the retinal lesions in toxoplasmic retinitis in patients with AIDS include multifocal or diffuse yellow-white areas of necrotizing retinitis with edematous aspect, blurred edges, and a relative lack of retinal hemorrhage (Fig. 1.12). The lesions are more edematous in appearance than those associated with CMV. Occasionally, vascular sheathing (usually periarterial) may be seen in these cases [78, 81]. Also, there may be a moderate-to-severe anterior chamber and vitreous inflammation (but in a much lesser degree than that observed in immunocompetent individuals) in one or both eyes which can cause visual impairment if left untreated. In contrast to infection in immunocompetent patients, the disease does not appear to originate from previous scars and probably results from a recently acquired infection or the spread of organisms from extraocular foci of disease.

Between 30% and 50% of patients with ocular toxoplasmosis will have involvement of the central nervous system, and all patients with HIV/AIDS thought to have toxoplasmic retinochoroiditis should undergo magnetic resonance imaging (MRI) scanning of the brain [80, 81]. The infection can be generalized, involving the brain, eyes, lungs, heart, gastrointestinal tract, lymph nodes, liver, spleen, and bone marrow. Cerebral toxoplasmosis is the most common cerebral infection in AIDS and requires urgent treatment because it can be rapidly fatal [71].

Testing should include serological assays for IgG and IgM antibodies against toxoplasmosis, although the results may be negative in profoundly immunosuppressed patients [16]. The analysis of polymerase chain reaction (PCR) from samples of aqueous and vitreous humor has been reported, and this test is becoming more widespread and available.

Treatment consists of sulfadiazine (2 g initial dose and then 1 g orally every 6 h) and pyrimethamine (two doses of 50 mg every 12 h and then 25 mg orally every 12 h) or clindamycin (300 mg by mouth every 6 h for 4 to 6 weeks), either alone or in combination. Trimethoprim/sulfamethoxazole (800/160) is given as one tablet by mouth twice daily. Atovaquone has been used successfully [1, 81] but is expensive and has yet to be shown superior to standard therapy [1]. Atovaquone is given as 750 mg by mouth four times daily for 3 months. Steroids are uncommonly used in HIV-positive patients with ocular toxoplasmosis unless there is a very severe vitreous reaction. Chronic or repeated therapy is often necessary, because reactivation and progression of retinochoroiditis occur frequently, particularly in patients with persistent severe immune deficiency. Silveira et al. have reported some evidence that long-term intermittent treatment with trimethoprim/sulfamethoxazole can reduce the rate of recurrent toxoplasmosis retinochoroiditis [86].

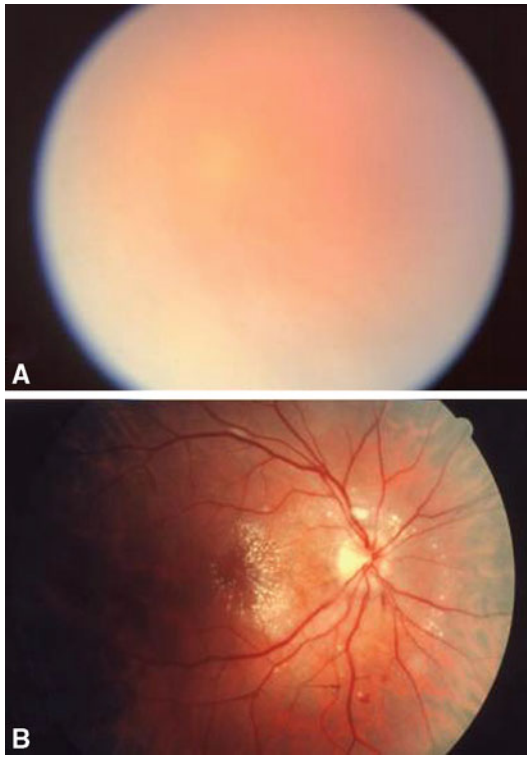

Fig. 1.13 (**a**) Luetic vitritis in a patient with AIDS. (**b**) Neurosyphilitic retinitis in a patient with AIDS

Syphilitic Uveitis, Papillitis, and Retinitis

Ocular syphilis is the most common intraocular bacterial infection in HIV-positive patients, historically affecting up to 2% of patients. The prevalence may be on the rise, with current estimates on the order of 6–9% [87], presumably due to resurgence in syphilis infections. The ocular manifestations of syphilis in patients with HIV are varied (syphilis is the "great imitator") and include chorioretinitis, iridocyclitis, papillitis, vitritis (Fig. 1.13), intraretinal hemorrhages, and perivasculitis [88]. Intraocular inflammation may result in epiretinal membrane formation and tractional retinal detachment. The clinical appearance can vary; however, over 80% of HIV-positive patients with ocular syphilis have clinical or serological evidence of infection of the central nervous system (CNS) by *Treponema pallidum*. Therefore, we recommend conducting serological testing for confirmation of clinical diagnosis (FTA-ABS, VDRL, RPR); the tests are useful in most cases (but may be negative in some cases of HIV-positive patients with evidence of secondary or tertiary syphilis).

The high correlation between neurosyphilis and ocular manifestations supports the current recommendation to perform a lumbar puncture and analysis of cerebrospinal fluid (CSF) in all HIV-positive patients with ocular syphilis. The treatment of ocular syphilis in this population should be the same as that used in cases of neurosyphilis: high doses of aqueous penicillin G at doses of 12–24 million units daily intravenously for 10–14 days. Most recommend IV therapy, but a second-line therapy includes 2.4 million units of intramuscular procaine penicillin daily plus 500 mg of oral probenecid four times daily for 10–14 days [89]. Recurrences may occur even after adequate treatment, and it is important to monitor serum and CSF reagin titers monthly for 3 months following the cessation of treatment, and every 6 months thereafter until the CSF-VDRL becomes nonreactive and the CSF white cell count normalizes.

Candida Vitritis and Retinitis

Immunosuppression is a risk factor for the development of systemic candidemia with endogenous ocular affection, especially in patients who have been or remain with a central line catheter for a long time. AIDS patients fall naturally within this category, and *Candida* ocular involvement occurs frequently in HIV-positive patients.

Candida typical lesions have the appearance of white spots, not well-defined edges, often bilateral and located on the inner surface of the retina with frequent extension into the vitreous (Fig. 1.14). The vitreous usually shows inflammatory activity (vitreous abscesses have been reported in immunocompetent patients). If left untreated, these focuses of Candida will increase in size, resulting in extensive involvement with diffuse vitritis and potential severe vision loss (endogenous endophthalmitis).

Amphotericin B remains the drug of choice. This drug can be administered intravenously but has potentially severe side effects; therefore, each case must be individualized. The resolution of retinitis has been reported with a single intravitreal injection of amphotericin B (dose of

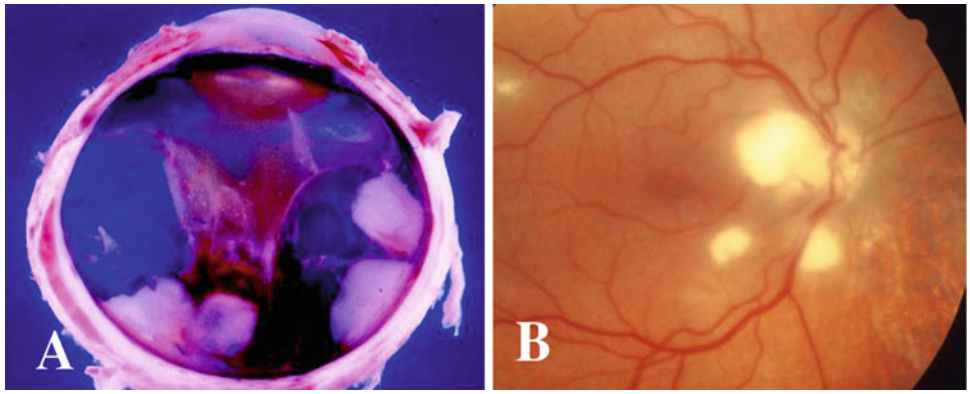

Fig. 1.14 Candida vitritis (**a**) and retinitis (**b**). (**a**) Gross examination shows multifocal candidal retina abscess with "cotton ball" vitreous opacities (Courtesy of Dario Savino-Zari, MD). (**b**) Candida retinitis (Reprinted with permission from Arevalo JF, ed. Manifestaciones Oculares del SIDA en el Nuevo Milenio: Texto y Atlas [Ocular manifestations of AIDS in the New Milenium: Text and Atlas]. Panama City, Panama: Highlights of Ophthalmology 2004 [55]

5–10 μg). Other agents, such as fluconazole, ketoconazole, and miconazole, have been used successfully to treat *Candida* chorioretinitis. Recently, there is experience using intravitreal voriconazole (50–100 μg/0.1 mL) combined successfully with oral voriconazole, but the experience is still limited. In addition, intravitreal voriconazole has been found effective in cases resistant to amphotericin B and fluconazole. A vitrectomy is of great help in these cases followed by intravitreal antifungal therapy. Vitreous biopsy and blood cultures may be useful in the diagnosis of systemic candidemia.

Drug addicts (intravenous drug abusers) who develop AIDS are likely to present an increased risk of ocular infection by *Candida*.

Pneumocystis carinii Choroiditis

Pneumocystis carinii pneumonia (PCP) has been the most common systemic opportunistic infection associated with AIDS. It affected more than 60% of patients with AIDS in the 1980s, but with the advent of effective prophylaxis using trimethoprim/sulfamethoxazole in HIV-positive patients with a count of CD4 + <200 cells/uL, the incidence of systemic disease by *Pneumocystis* has decreased significantly. *Pneumocystis carinii* choroiditis (PCC) was described in 1989 [90, 91]. Lesions respond to systemic treatment (intravenous or oral) with pentamidine (4 mg/kg/day) or a combination of trimethoprim (15–20 mg/kg/day) and sulfamethoxazole (75–100 mg/kg/day) for 3–4 weeks. PCC has become very rare, and this is likely because it is almost exclusively seen as a disseminated form of *Pneumocystis* that has been controlled with local inhalational pentamidine. That therapy is rarely used since the disease does disseminate. Systemic treatment of *Pneumocystis* likely prevents the appearance of choroiditis and other disseminated infections in most patients.

The clinical appearance of the PCC is very characteristic. The lesions are yellow-white, round, circumscribed, flat, or slightly elevated, located at the posterior pole with a diameter ranging between 500 μ and 3,000 μ (Fig. 1.15). They are usually multifocal and bilateral but may be unifocal and unilateral. Rarely lesions are visually significant, although foveal and optic nerve lesions can sometimes cause visual impairment. The lesions occur with little or no vitritis [90–93].

Cryptococcus neoformans Chorioretinitis

Cryptococcus neoformans is a yeast that rarely is associated with disease in humans but can cause opportunistic infection in the immunocompromised patient. CNS involvement with *Cryptococcus* infection is relatively common in AIDS patients and often results in meningitis and secondary ocular findings (in 75% of cases) [94]. Choroiditis and chorioretinitis by *Cryptococcus* has been reported in patients with AIDS and appears to be associated with central nervous sys-

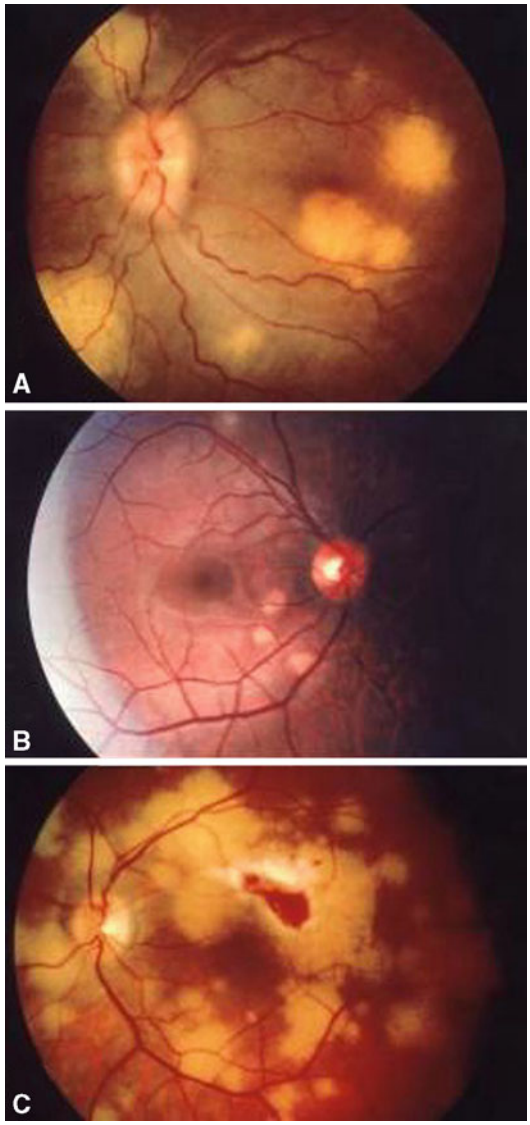

Fig. 1.15 Deep lesions in the posterior pole corresponding to the diagnosis of *Pneumocystis carinii* choroiditis. (**a**) Accompanied by papilledema by *Cryptococcus neoformans*. (**b**) Very subtle. (**c**) Large, confluent, and accompanied by a "patch" caused by cytomegalovirus retinitis

tem involvement (Fig. 1.16a). The typical lesions of this entity are located in the choroid and retina; the appearance is of multiple yellowish spots, circumscribed, with a variable diameter of 500–3,000 μ (Fig. 1.16b–d). They may be accompanied by perivascular sheathing (vasculitis), vitritis, and anterior uveitis with keratic precipitates mutton fat (granulomatous). Papilledema may be present owing to increased intracranial pressure caused by meningitis. Visual loss may occur as a result of cryptococcal involvement of the optic nerve, chiasm, and optics tracts [94].

Treatment in patients with AIDS and cryptococcal ocular involvement has included amphotericin B and 5-fluorocytosine; the combination of these two drugs has been effective in the treatment of cryptococcal chorioretinitis. Ketoconazole also appears to be effective and appears to be synergistic with 5-fluorocytosine.

Mycobacterium Choroiditis

The mycobacterial ocular infections in AIDS patients are infrequent and are caused primarily by *Mycobacterium* tuberculosis or *Mycobacterium avium* intracellulare (MAI) [95–97]. In either case, the eye infection is a manifestation of disseminated systemic disease. MAI ocular infections have only been described in autopsy series; however, clinically apparent cases of ocular infection by *Mycobacterium* tuberculosis have been described. Ocular findings in *Mycobacterium* tuberculosis infection in AIDS patients (similar to those of immunocompetent patients) include a prominent granulomatous reaction of the anterior chamber with posterior synechiae, a moderate vitritis and yellowish-white choroidal elevated lesions (granulomas) with retinal spearing (Figs. 1.17 and 1.18).

Treatment is focused on control of systemic disease, although topical corticosteroids can be used to help control the anterior chamber reaction. The lesions caused by MAI described in autopsies are choroidal granulomas that are slightly elevated. The organisms were observed in choriocapillaris and choroidal vessels. The lesions do not appear to be of clinical significance unless accompanied by vitritis.

Tuberculosis remains common throughout Latin America. The impact of HIV and multidrug resistance on tuberculosis control has been enormous. HIV-positive patients may be at ten times greater risk of multidrug-resistant tuberculosis than HIV-negative patients. Hopefully, improved diagnostic techniques will allow more rapid diagnosis of tuberculosis. However, in alarming reports, only 58% of patients were

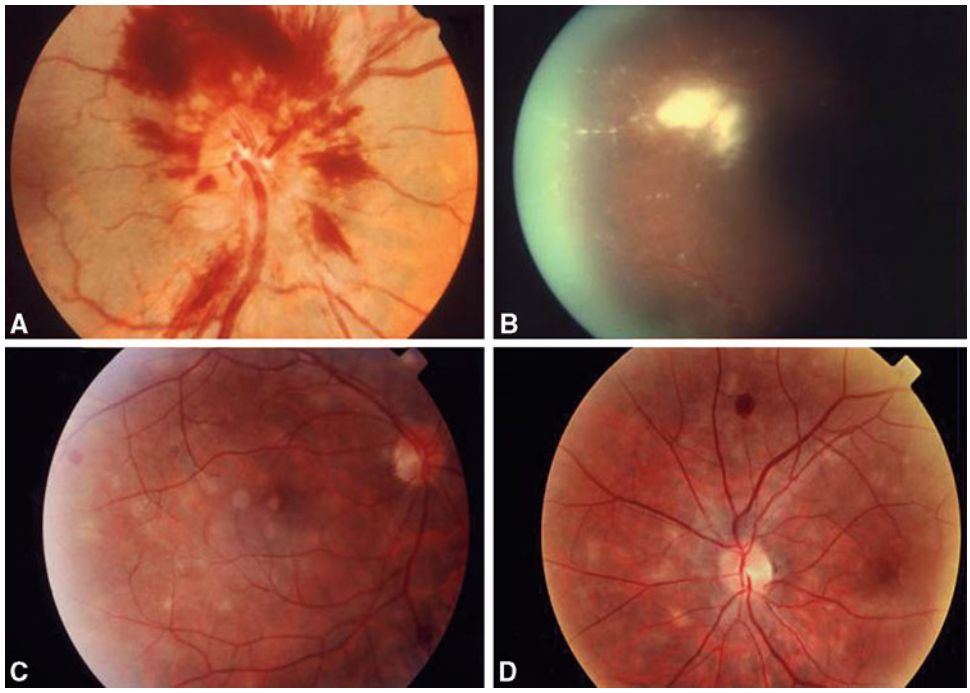

Fig. 1.16 (**a**) Hemorrhagic papilledema by *Cryptococcus neoformans*. (**b**) Peripheral retinal lesion by *Cryptococcus neoformans*. Note the associated vasculitis. (**c** and **d**) Left and right eye of patient with multifocal lesions by *Cryptococcus neoformans* and blot hemorrhages

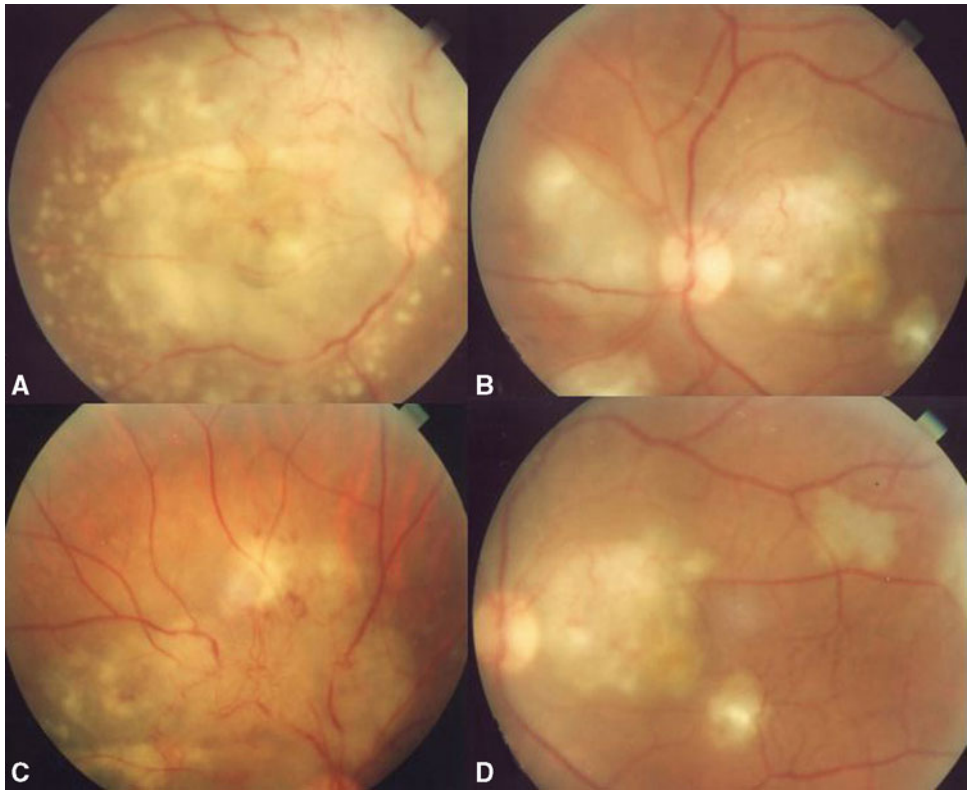

Fig. 1.17 Multiple bilateral choroidal TB granulomas. Color photos. (**a** and **c**) Right eye. (**b** and **d**) Left eye

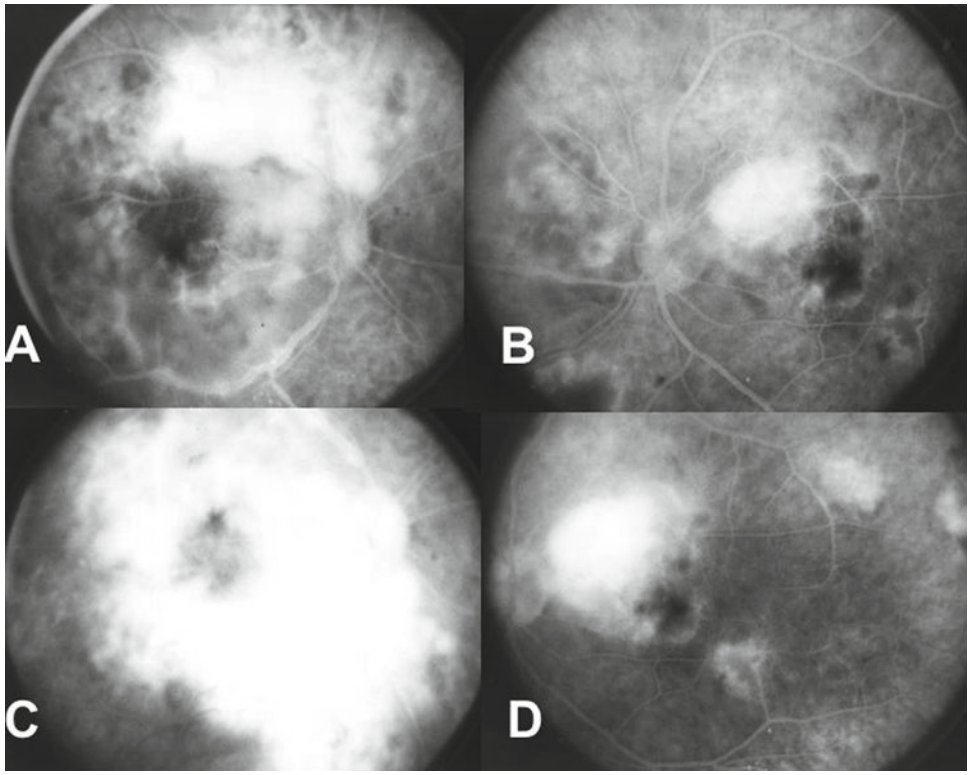

Fig. 1.18 Multiple bilateral choroidal TB granulomas. Fluorescein angiography showing hyperfluorescence in early frames. (**a** and **c**) Right eye. (**b** and **d**) Left eye

treated with the recommended treatment regimen in a Brazilian study, and dropout from treatment in parts of Bolivia was common. Many failings could be combated by rigorous education of patients and physicians. In an encouraging advance, multidrug-resistant tuberculosis was successfully treated in a community-based program, saving an estimated 90% of the cost of hospital-based treatment. An opportunity to identify treatment failure earlier is demonstrated by the finding that 2 months after the initiation of therapy, positive smears were found in only 3% of those whose treatment was successful, but 74% of those whose treatment failed [98].

B-Cell Lymphoma

While obviously this entity is not an infectious manifestation associated with AIDS, we wanted to include it in this review as it is one of the most frequent pathologies of the posterior pole in these patients that may mimic atypical infectious retinitis and therefore we keep it on our list of differential diagnoses.

HIV-infected patients are at increased risk for developing non-Hodgkin's lymphoma [99], which tends to occur at a younger age than in their immunocompetent counterparts [100–102]. B-cell non-Hodgkin's lymphoma is a cancer more frequently associated with AIDS. Lymphoma can be visceral or affect the CNS [103]. Ocular B-cell lymphoma in AIDS patients (similar to those of immunocompetent patients) consists of a mild-to-moderate vitritis, lesions of the uvea and retina. Ocular manifestations in this disease occur more frequently when there is a CNS involvement than when there is a systemic involvement. While intraocular lymphoma typically develops late in the course of HIV/AIDS, it can occur as an AIDS-defining illness [104, 105]. The incidence of HIV-associated primary intraocular and CNS

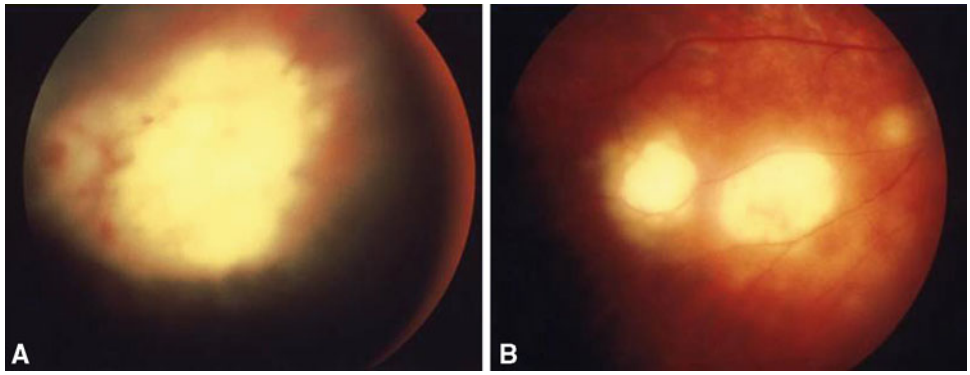

Fig. 1.19 (**a** and **b**) Well-defined retinal lesions in a patient with AIDS and ocular lymphoma with central nervous system involvement

lymphoma has declined by greater than 50% in the HAART era [106, 107]. However, the overall prevalence of intraocular lymphoma may be on the rise. In one large retrospective study, the proportion of intraocular lymphoma as an AIDS-defining illness rose from 4.4% to 6.3% following the advent of HAART [108].

In non-Hodgkin's lymphoma with CNS involvement, symptoms include floaters and vision loss; non-Hodgkin's lymphoma usually shows lesions in the retina, in the subretinal pigment epithelial space, and optic nerve, whereas the ocular manifestations of systemic lymphoma typically affect the uveal tract due to invasion through the choroidal circulation. Vitritis is common in both categories. Deep retinal lesions typically associated with CNS lymphoma in AIDS patients are of a creamy white appearance, may have associated retinal hemorrhages, and can be large with well-defined edges (lesions can be confused with atypical CMV) (Fig. 1.19). Uveal manifestations of lymphoma in these patients include serous retinal detachments and alterations of retinal pigment epithelium.

Brain MRI and analysis of cerebrospinal fluid for cytology are mandatory in all patients suspected of having intraocular or CNS disease [109]. Treatment at this time includes chemotherapy and radiation that are based on the stage and extent of disease, but the long-term prognosis is poor.

Controversies and Perspectives

- The next era will be one that improves our understanding of disease processes, refines treatments, and returns to the study of HIV-related eye disease.
- Retinal and optic nerve damage that occurs in the absence of clinically apparent infections needs additional study. Of particular importance is whether damage progresses despite HAART and immune recovery.
- Better long-term strategies for the management of CMV retinitis and its complications are required. Issues include not only treatment but also prevention and visual rehabilitation. Strategies appropriate for the developing world must be considered.
- A still better understanding of CMV retinitis is needed, especially with regard to risk factors for its development and recurrence. Studies of human genes that regulate the immune response to specific infections hold promise in this area. Additional studies of CMV immunity may lead to tests that are useful for predicting those at highest risk.
- The basis for alterations in vision that have been documented in the absence of clinical lesions (abnormal color vision, reduced contrast sensitivity, and visual field changes) should be explored further.
- Study of the retinal vasculature also may provide insights into other nonocular disorders

associated with HIV disease. Renal disease and cardiovascular disease have become important in the HAART era and may share disease mechanisms with the microvasculopathy of HIV disease.

Focal Points

- AIDS is a condition characterized by severely compromised cell-mediated immunity, predisposing patients to opportunistic infections and neoplasms.
- Approximately about 0.8% of the world's population is infected with HIV. Of these patients, more than 90% are unaware that they are infected and up to 70% have ocular complications related to HIV/AIDS.
- Proper diagnosis of ocular complications by HIV is critical because failure to diagnosis can lead to severe and permanent vision loss, because specific therapy is available for many of the more common disorders, and because ocular disease may be the initial manifestation of an underlying disseminated infection.
- HIV retinopathy is the most common retinal manifestation. It is characterized by the formation of cotton-wool spots, hemorrhages, and microaneurysms, and it is typically asymptomatic.
- Important ocular infections seen in patients with HIV/AIDS include CMV retinitis, the most common, VZV herpetic retinitis, toxoplasmic retinochoroiditis, syphilis, *Pneumocystis carinii* choroiditis (PCC), *Mycobacterium* tuberculosis, and cryptococcal choroiditis.
- Noninfectious causes of uveitis observed in patients with HIV/AIDS include neoplastic disease, drug-induced uveitis, and immune recovery uveitis (IRU).
- HAART has had a substantial impact on HIV in wealthy countries, including immune reconstitution for many patients with resultant improved survival and declines in opportunistic infections. However, HIV/AIDS remains a leading cause of death in developing countries, particularly sub-Saharan Africa.

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Diffuse Unilateral Subacute Neuroretinitis (DUSN)

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Abstract

Diffuse unilateral subacute neuroretinitis (DUSN) is a usually unilateral inflammatory disease characterized by an insidious, usually severe, loss of peripheral and central vision. Clinical characteristics are manifested in early and late stages. Parasites of different sizes and several species of nematodes have been reported as the etiology of DUSN without conclusive evidence about the specific agent. Because serologic testing has been variable, the definitive diagnosis is made when the clinical characteristics of DUSN are found in conjunction with an intraocular worm. Laser photocoagulation, pars plana vitrectomy, thiabendazole, and albendazole have been used to treat DUSN with variable success.

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Keywords
Ancylostoma caninum • *Baylisascaris procyonis* • *Toxocara canis* • Diffuse unilateral subacute neuroretinitis (DUSN)

Introduction

Diffuse unilateral subacute neuroretinitis (DUSN) was described by Gass in 1977 [1], who called it "unilateral wipe-out syndrome." The term diffuse unilateral subacute neuroretinitis was first used by Gass in 1978 [2]. He described 29 patients seen with consistent features that included insidious, usually severe, loss of peripheral and central vision with associated findings of vitreous inflammation, diffuse and focal epithelial derangement with relative sparing of the macula, narrowing of the retinal vessels, optic atrophy, increased retinal circulation time, and subnormal electroretinographic findings (Fig. 2.1). However, the cause of the inflammation in DUSN was still unknown. In May 1978, Gass et al. reiterated his definition because the progressive unilateral visual loss was believed to be secondary to inflammation of the retina, retinal vessels, retinal pigment epithelium (RPE), and optic nerve head [3]. Later in 1983, Gass and Braunstein observed a nematode in two patients with DUSN [4]. On further searching of the literature, Gass was able to identify previously reported cases of similar nematodes that produced the same clinical picture appearing as early as 1952 [5]. Hence, a syndrome of initially unknown cause that was classified only by clinical description was later found to be related to a nematode in the subretinal space [6]. Although evidence suggests that most patients with DUSN will not develop it in the fellow eye, bilateral cases have been reported; therefore, a more appropriate term for this ocular condition might be *diffuse subacute neuroretinitis* [7]. Cortez et al. described the clinical features and management in the largest reported series to date of patients with DUSN [8]. The charts of all patients coded as having DUSN in a vitreoretinal clinic in Caracas, Venezuela, between July 1979 and August 2000 were retrospectively reviewed. They identified 82 eyes of 78 patients with DUSN. The mean age at diagnosis was 16.7 years. Thirty-three (42.3%) of the patients were female. The presenting visual acuity was 20/400 or worse in 69 eyes (84.1%). The subretinal nematode was identified in 33 eyes (40.2%), and all nematodes were small, approximately 400 μ(mu)m in length [8].

Etiologic Agent

Parasites of different sizes and several species of nematodes have been reported as the etiologic agent of DUSN, including *Toxocara canis, Baylisascaris procyonis,* and *Ancylostoma caninum*, and most of these reports do not present conclusive evidence about the specific agent. In the southeastern United States, the Caribbean islands, and South America, the nematode varies in length from approximately 400–700 μm. In the other endemic area, the north Midwestern United States, it measures approximately 1,500–2,000 μm in length [9]. However, Cialdini et al. reported the first South American case of DUSN caused by the larger nematode [10]. In earlier reports, serologic testing was negative in most of the patients with viable intraretinal nematodes, which led Gass and Braunstein to suggest that *Toxocara* was not the causative nematode in most patients with DUSN [4]. They suggested that the nematode less than 1,000 μm in length was the dog hookworm, *Ancylostoma caninum,* and Kazacos et al. suggested that the larger nematode was the raccoon ascarid, *Baylisascaris procyonis* [11].

Retinal biopsy for DUSN via transcleral approach has been performed by Blumankranz and Culbertson [12]. However, precise identification of the nematode was not made [13]. Gass transclerally extracted one nematode from beneath the retina after killing it with cryotherapy; histologic details were poor, and he was

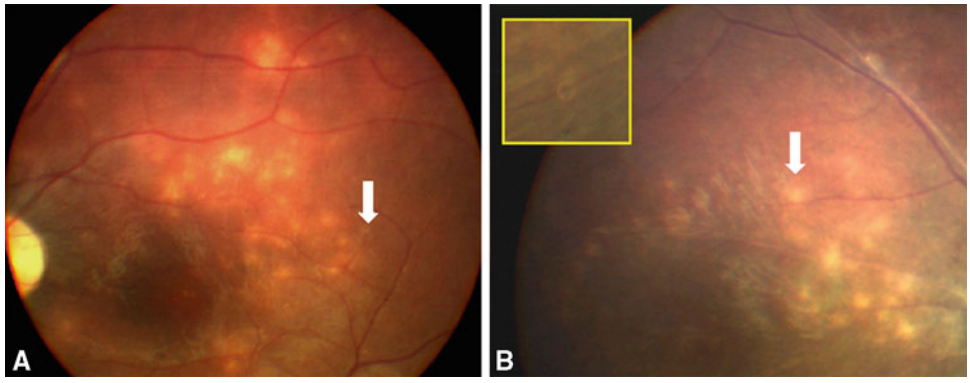

Fig. 2.1 (**a** and **b**) Patients during early stages usually present mild to moderate vitreitis, mild optic disk edema, and recurrent crops of evanescent, multifocal, gray-white lesions at the level of the outer retina (*arrows*). These lesions typically are clustered in only one segment of the fundus. The intraocular worm is seen as a motile, white, often glistening nematode that is gently tapered at both ends and varies in length from 400 to 2,000 μm (*inset* in b)

unable to identify the nematode [14]. Via transvitreal approach, de Souza et al. recovered the nematode intact and motile [13]. Several parasitologists in São Paulo, Brazil, examined the nematode; the measurement of body size and the morphologic features were more consistent with a third-stage *Toxocara* larva, but because of poor fixation, definitive identification of the worm was not possible. However, Bowman recently reviewed the pictures of the worm removed by de Souza and concluded that it is most likely *Ancylostoma caninum* [9]. Because none of the nematodes described from patients with DUSN have been recovered intact, identification must, therefore, be based on a combination of careful measurement of the parasite, serologic testing, and epidemiological studies, all of which have their limitations [15].

Toxocara canis

Gass et al. initially concluded that *Toxocara* was a cause of DUSN [3] but, however, discarded this possibility based on negative serology in many of the reported patients [4]. In addition, Gass and Olsen later suggested that *T. canis* was not the cause based on the following: (1) there is a lack of serologic evidence, (2) the small size of the infective second-stage larval form of T. canis makes it difficult to be visualize biomicroscopically, (3) the clinical picture is unlike that associated with ocular toxocariasis, and (4) the worldwide prevalence of *T. canis* is not in keeping with the endemic distribution of DUSN [16]. However, Goldberg et al. reported that low or nondiagnostic serum titers are well described in cases of *Toxocara* ocular larva migrans and suggested a similarity with the overall reduced sensitivity of serodiagnostic tests for DUSN [15, 17, 18]. Oppenheim et al. reported a case of *Toxocara* DUSN in which the patient's positive ELISA titer decreased fourfold over a 2-year period [19]. Therefore, the lack of serologic confirmation of toxocaral infection in some patients may be a reflection of the timing of the serology in relation to the onset of the disease or the immune status of the patient.

Ancylostoma caninum

The association of cutaneous larva migrans months, several years, or immediately preceding the onset of DUSN in some patients suggests that *Ancylostoma caninum* may be the small nematode that causes the syndrome [9, 16]. *A. caninum* is a frequent cause of cutaneous larva

migrans in the southeastern United States. In addition, the infective third-stage larva of *A. caninum* is approximately 650 μm in length and is capable of surviving in host tissue, including that of humans, many months and probably years without changing size or shape [16].

Baylisascaris procyonis

In 1984, it was suggested by Kazacos that the larger worm in patients with DUSN living in more northern climates was *Baylisascaris procyonis*, a nematode found in raccoons [20]. He proposed that *B. procyonis* larvae produce ocular larva migrans with a clinical picture that is similar to that of early DUSN in subhuman primates and other experimental animals after oral infection [11]. Additionally, the *B. procyonis* larvae may grow while they are within the eye and would account for the range of lengths of larvae seen, such as those that are 400–2,000 μm. The large nematode variant of DUSN matches the size range of *Baylisascaris*. Nevertheless, some controversy exists because most patients with DUSN have no history of exposure to raccoons [7]; however, most patients with large nematode DUSN were from areas of the United States where raccoons are not only common, but commonly infected with *B. procyonis* [21]. Significant morphometric, serologic, and epidemiologic support for *Baylisascaris* as the causative agent of DUSN was published by Goldberg [15]. A large worm of 1,500 μm length presenting in a German patient was thought to be consistent with *Baylisascaris* species [22]. In humans, the organism is capable of causing visceral larva migrans, eosinophilic meningoencephalitis, and ocular larva migrans. In addition, Mets et al. have reported two patients with eye manifestations of DUSN, both with severe neurologic degeneration and indirect immunofluorescence assays on serum and cerebrospinal fluid positive for *B. procyonis* in one and serially positive and increasing in the second [23]. In addition, Goldberg et al. suggest that ocular larva migrans and DUSN can occur without evidence of visceral larva migrans or central nervous system dysfunction [15].

Trematodes

McDonald et al. encountered two cases of human intraocular infection with mesocercariae of *Alaria* (Trematoda) in the eyes of two unrelated Asian men with signs of DUSN in which the probable source of infection was ingestion of undercooked frogs' legs containing the trematode [24]. The worm in their case 1 was analyzed from projected fundus photographs and diagnosed as an *Alaria* mesocercaria on the basis of its shape, size (500 × 150 μm), and movement. The worm in their case 2 was removed surgically from the vitreous and identified as *Alaria* mesocercariae, 555 × 190 μm in size, most likely *A. americana*. They concluded that *Alaria* mesocercariae could be a cause of DUSN.

Mode of Transmission

Baylisascaris procyonis, a parasitic infection of raccoons in the United States, causes severe neurologic and ocular disease in humans when infectious eggs from raccoon feces are ingested. However, *Ancylostoma caninum*, a parasitic infection of dogs (or sometimes a fox infection) in South America, causes cutaneous larva migrans in humans when infectious eggs from dog feces are ingested or from larvae entering through the skin (usually the foot) migrate through the bloodstream to the lungs and trachea, and are coughed up and swallowed. They attach themselves to the intestinal wall and thus complete the life cycle.

Diagnosis and Pathogenesis

Because serologic testing has been variable, the diagnosis is made when the clinical characteristics of DUSN are found in conjunction with an intraocular worm (Table 2.1). Clinical characteristics are manifested in early and late stages. DUSN most frequently is seen in healthy children or young adults with no significant past ocular history.

Table 2.1 Diffuse unilateral subacute neuroretinitis (DUSN) diagnosis

DUSN diagnosis	
Test	Findings
Ocular fundus signs	*Early stage*: mild to moderate vitreitis, mild optic disk edema, and recurrent crops of evanescent, multifocal, gray-white lesions at the level of the outer retina typically clustered in only one segment of the fundus. Others: iridocyclitis, perivenous exudation, subretinal hemorrhages, serous exudation, and subretinal neovascularization
	Late stage: progressive optic atrophy, mild or moderate vitreitis, multifocal choroiditis episodes, increase in the internal limiting membrane reflex (Oréfice's sign), presence of small white spots suggestive of calcifications, tunnels in the subretinal space (Garcia's sign), narrowing of the retinal arteries, and marked focal and diffuse degenerative changes in the RPE and retina
	Early or late disease: in 25–40%, the worm is visualized
Serologic test	Unless a peripheral eosinophilia is present, no further evaluation seems warranted to make the diagnosis
FA	*Early stage*: hypofluorescence of the focal gray-white lesions followed by staining. Leakage from the capillaries on the optic disk. Perivenous leakage of dye
	Advanced stages: irregular increase in the background choroidal fluorescence
ICG-A	Dark spots present in the initial ICG-A phase that seem to either disappear or persist in the late phase of the examination
ERG	b-wave of maximum combined response is flat, with below-normal response and a decrease in relation to b/a
EOG	One-half of patients can have a normal electrooculogram
Multifocal-ERG	Variable changes as decreased foveal response density and increased parafoveal and perifoveal waveform amplitudes
Visual field test	Different lesion patterns that cannot be explained with the findings of the ocular fundus changes
SLO	High-contrast image facilitating visualization of the nematode
OCT	Decreased RNFL thickness
GDx®	*Early disease*: increase in thickness due to transitory edema
	Chronic phase: decrease in RNFL thickness

FA fluorescein angiography, *ICG-A* indocyanine green angiography, *ERG* electroretinogram, *EOG* electrooculogram, *Multifocal-ERG* multifocal electroretinogram, *SLO* scanning laser ophthalmoscopy, *OCT* optical coherence tomography, *GDx®* nerve fiber analyzer, *RPE* retinal pigment epithelium, *RNFL* retinal nerve fiber layer

Early Stage

Central or paracentral scotoma is the principal complaint of symptomatic patients in the early stage [2]. Visual loss is rarely reversible and usually less than 20/200 in about one-half of patients [4]. Patients with acute visual loss during early stages of the disease usually present mild to moderate vitreitis, mild optic disk edema, and recurrent crops of evanescent, multifocal, gray-white lesions at the level of the outer retina. These lesions typically are clustered in only one segment of the fundus (Fig. 2.1a) [16]. Less frequently, symptoms and signs include ocular discomfort, congestion, iridocyclitis, perivenous exudation, subretinal hemorrhages, serous exudation, and evidence of subretinal neovascularization [16]. In approximately 25–40% of cases, a worm is visualized during eye examination [8, 25]. The intraocular worm is seen as a motile, white often glistening nematode that is gently tapered at both ends and varies in length from 400 to 2,000 μm (Fig. 2.1b). It can be seen during any stage of the disease, and if active gray-white lesions are present, the nematode usually will be found in their vicinity. The examining light may cause the worm to move by a series of slow coiling and uncoiling movements and less often by slithering snakelike movements in the subretinal space [9]. Gass and Braunstein reported that there is a greater likelihood of the longer worm leaving a tract of coarse clumping of RPE in the wake of its travels [4].

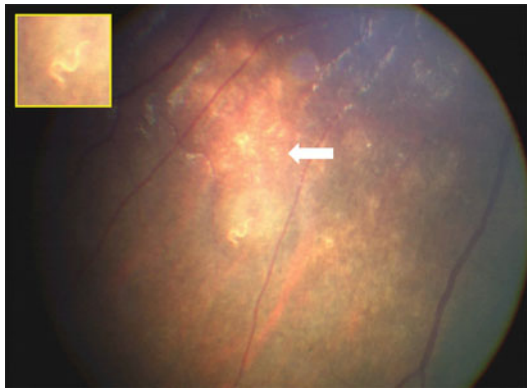

Fig. 2.2 There is a greater likelihood of the longer worm leaving a tract of coarse clumping of RPE in the wake of its travels. The shorter worm (*inset*) tends to leave focal, chorioretinal atrophic scars (*arrow*)

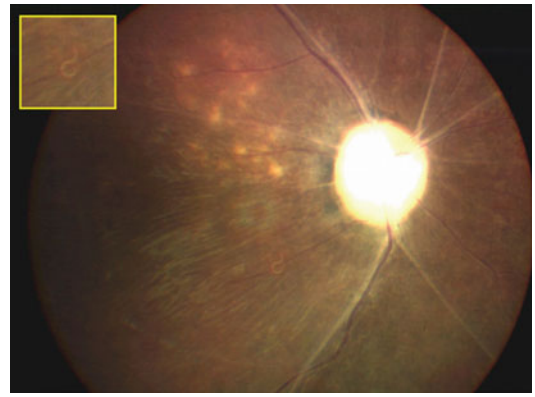

Fig. 2.3 The clinical picture of late-stage disease usually shows progressive optic atrophy, narrowing of the retinal arteries, marked focal as well as diffuse degenerative changes in the pigment epithelium and retina, and severe permanent loss of vision. The intraocular worm is shown in the *inset*

The shorter worm tends to leave focal, chorioretinal atrophic scars (Fig. 2.2). The focal pigment epithelial changes seen are easily explained by the location or the travel pattern of the worm. It is speculated that focal chorioretinal white spots are an immune response to a secretion or excretion from the worm [3]. The diffuse pigment epithelial changes are somewhat more difficult to explain except as a toxic reaction [26]. The active gray-white evanescent lesions, which probably are caused by substances left by the nematode in its wake, disappear in 1–2 weeks as the nematode moves elsewhere in the eye [16].

Late Stage

The clinical picture of late-stage disease usually demonstrates progressive optic atrophy with the subsequent afferent pupillary defect, mild or moderate vitreitis, multifocal choroiditis episodes, increase in the internal limiting membrane reflex (Oréfice's sign), presence of small white spots suggestive of calcifications, evidence of tunnels in the subretinal space (Garcia's sign), retinal narrowing of the retinal arteries, marked focal as well as diffuse degenerative changes in the RPE and retina, and severe permanent loss of vision (Fig. 2.3) [16, 27]. Visual acuity in late stages is profoundly decreased, with 80% or more showing vision 20/200 or worse [26]. Over a period of weeks or months, diffuse as well as focal depigmentation of the RPE occurs, usually most prominent in the peripapillary and peripheral retina, and less prominent in the central macular area [9]. Optic atrophy and severe retinal arteriole narrowing seem to define the late stage best. Retinal arteriole narrowing may vary by quadrant and, in conjunction with optic atrophy, usually are accompanying the progressive changes in the RPE. Choroidal neovascularization can occur usually in the periphery [26]. Although information about the pathogenesis of the disease is speculative, toxic products released by the larva in the subretinal space would locally affect the external portion of the retina and a diffuse tissue reaction would lead to external and internal retinal damage. Over the years, vascular narrowing and progressive ganglionar cell loss would occur until optic atrophy resulted [28].

Ancillary Tests

Serologic Test

Serologic testing, stool examinations, and peripheral blood smears are of little value in making the diagnosis of DUSN [3], and no serologic test currently is available for *Ancylostoma* [16]. When a

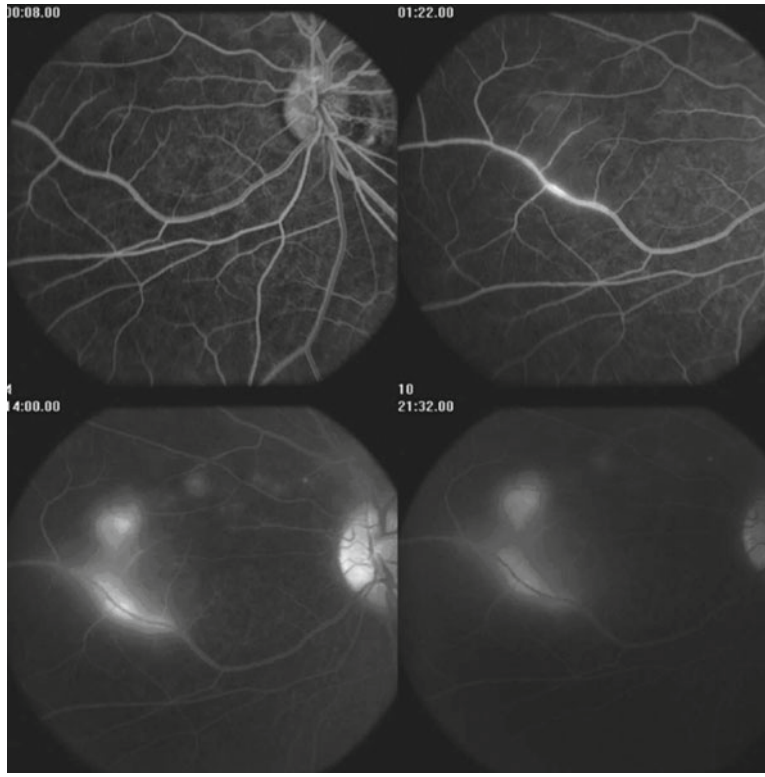

Fig. 2.4 Serial fluorescein angiogram performed on a patient with early-stage DUSN showing areas of both vascular and retinochoroidal leakage and staining

worm is identified within the eye of an otherwise healthy person, unless a peripheral eosinophilia is present, no further evaluation seems warranted to make the diagnosis.

Fluorescein Angiography

In the early stage, there is hypofluorescence of the focal gray-white lesions of active retinitis followed by staining. Leakage of dye is seen from the capillaries on the optic disk. Occasionally, there is evidence of prominent perivenous leakage of dye (Fig. 2.4). In more advanced stages of the disease, angiography shows greater evidence of loss of pigment from the RPE manifested angiographically as an irregular increase in the background choroidal fluorescence (Fig. 2.5) [16].

Indocyanine Green Angiography (ICG-A)

Indocyanine green angiography (ICG-A) features suggest that the choroid is also involved in early-stage DUSN. Choroidal infiltration, which prevented normal choroidal indocyanine green impregnation, most probably is the physiopathogenic explanation for the hypofluorescent dark spots seen in the affected eye. The dark spots present in the initial ICG-A phase seem to either disappear or persist in the late phase of the examination. Hypofluorescent dots persisting in the late phase are interpreted as full-thickness lesions allowing no ICG diffusion, whereas dots becoming isofluorescent in the late phase are interpreted as partial-thickness lesions progressively surrounded by ICG fluorescence (Figs. 2.6 and 2.7) [29].

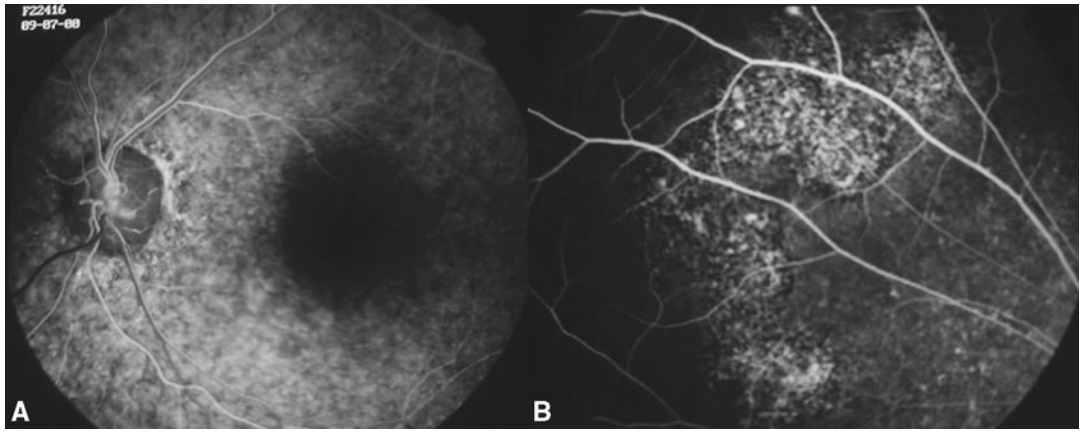

Fig. 2.5 (**a**) In the early stage, there is hypofluorescence of the focal gray-white lesions of active retinitis followed by staining. (**b**) In more advanced stages of the disease, angiography shows greater evidence of loss of pigment from the RPE manifested angiographically as an irregular increase in the background choroidal fluorescence (Courtesy of Dario Fuenmayor-Rivera, M.D.)

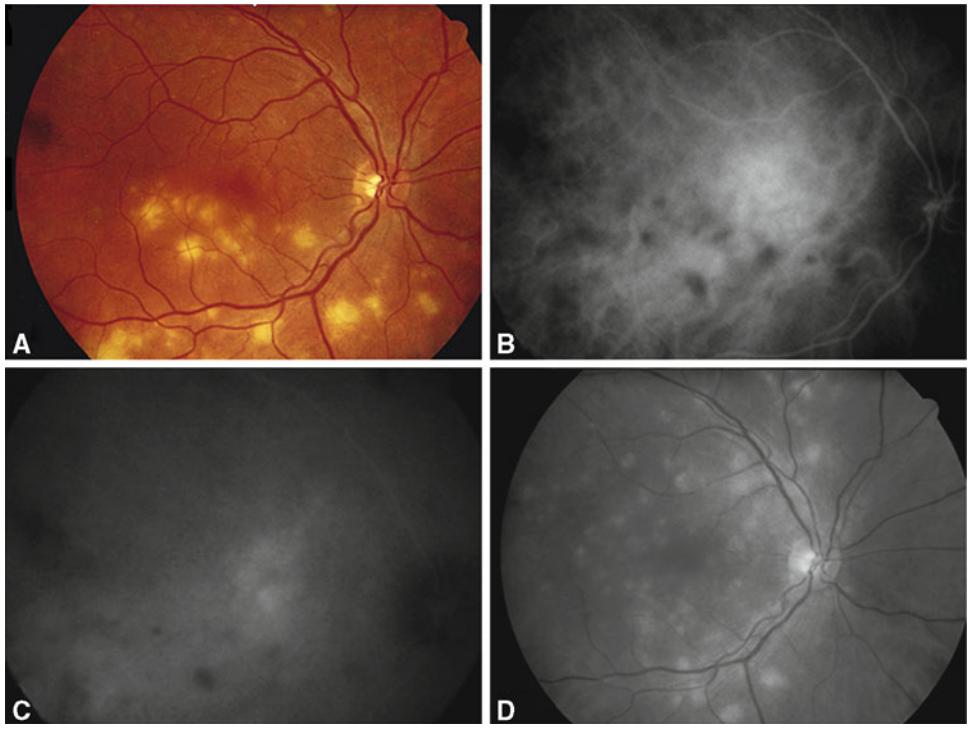

Fig. 2.6 Early-stage DUSN. (**a**) The affected eye revealed multiple yellow-white subretinal lesions at the posterior pole. (**b**) Early-phase ICG-A shows hypofluorescence of the lesions. (**c**) Late-phase ICG-A reveals few hypofluorescent dots and a fuzzy hyperfluorescence in the macular region. (**d**) After 1 month, the superior subretinal lesions increased in number and became more evident (Reprinted with permission from Vianna RN, Onofre G, Ecard V, Muralha L, Muralha A, de A Garcia CA. Indocyanine green angiography in diffuse unilateral subacute neuroretinitis. Eye. 2006;20:1113–1116)

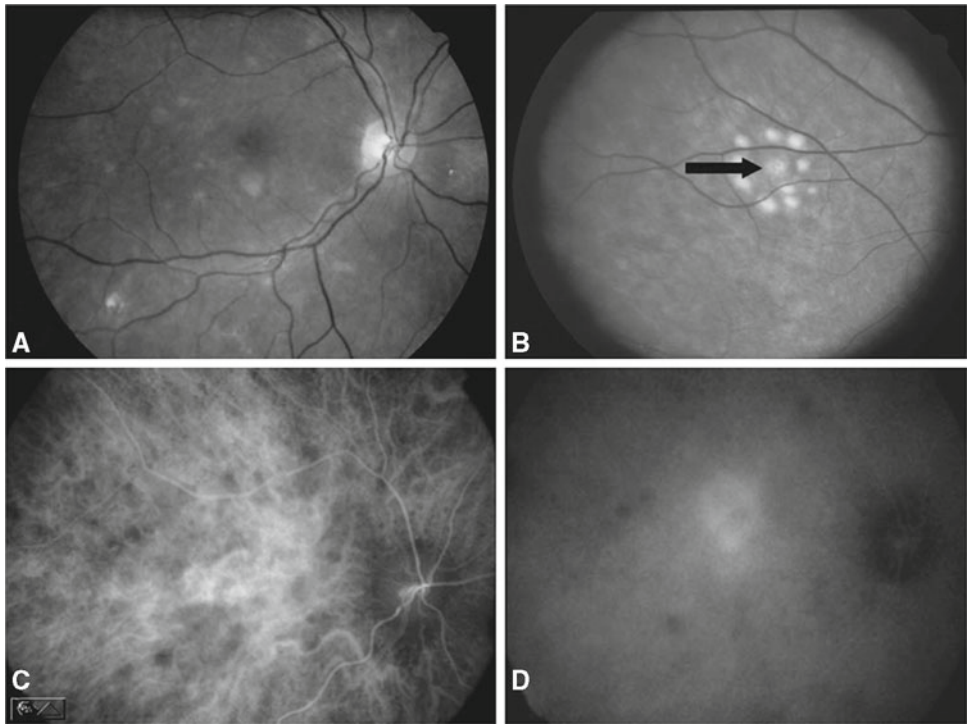

Fig. 2.7 Late-stage DUSN. (**a**) Observe many round hypopigmented lesions throughout the posterior pole as well as mild optic disk atrophy, discrete narrowing of the retinal vessels, and diffuse RPE degeneration. (**b**) The located worm surrounded by laser spots. (**c** and **d**) Early- (**c**) and late-phase ICG-V (**d**) revealed hypofluorescent spots and an area of hyperfluorescence in the macular region (Reprinted with permission from Vianna RN, Onofre G, Ecard V, Muralha L, Muralha A, de A Garcia CA. Indocyanine green angiography in diffuse unilateral subacute neuroretinitis. Eye. 2006;20:1113–1116)

Electroretinogram (ERG), Electrooculogram (EOG), and Multifocal Electroretinogram

Electroretinographic changes include a mild to moderate decrease in rod and cone function, with the b-wave being more affected than the a-wave. DUSN presents a very characteristic and reproducible electroretinographic picture also found in ischemic retinal cases: negative electroretinogram (b-wave of maximum combined response is flat, with below-normal response and a decrease in relation to b/a). The mechanism of this interesting phenomenon is explained by Oréfice et al. as being a consequence of a possible autoimmune, inflammatory, and/or toxic aggression toward retinal bipolar cells [27, 28]. The ERG in the affected eye is usually abnormal even if tested early in the course of the disease [8]. The more common one-half of patients can have a normal electrooculogram (EOG), and the finding of normal EOG and abnormal ERG suggests a neuroepithelium disease [25]. It is important that the ERG is rarely extinguished completely, which differentiates it from some tapetoretinal degeneration [30]. According to Martidis et al., multifocal electroretinography findings before laser treatment showed decreased foveal response density and increased parafoveal and perifoveal waveform amplitudes. Two months after laser photocoagulation of a subretinal nematode, multifocal electroretinography showed full recovery of normal findings and visual acuity remained 20/20 [31].

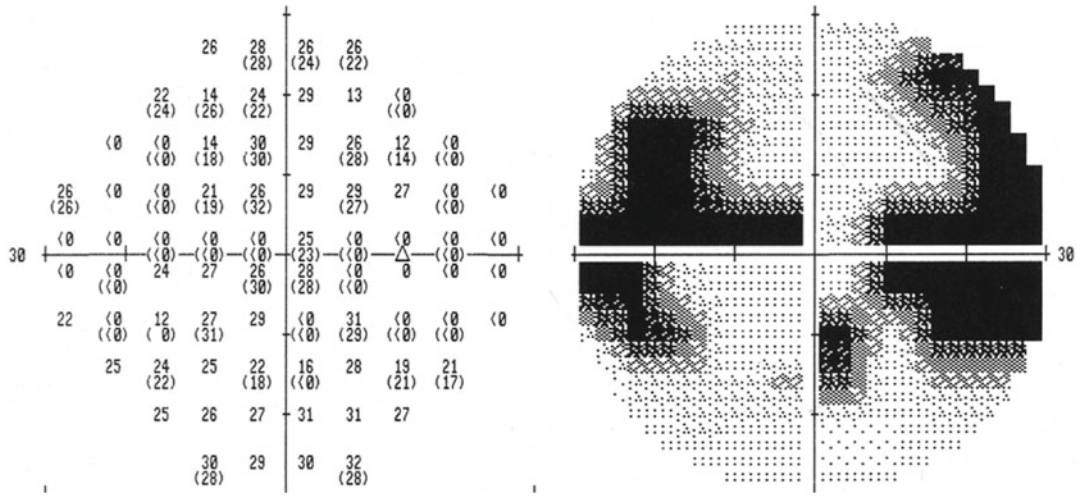

Fig. 2.8 Visual field demonstrates different lesion patterns that cannot be explained with the findings of the ocular fundus changes. Goldman perimetry is useful to evaluate remaining visual field before and after treatment of the disease

Visual Field Studies

Visual fields show different lesion patterns that cannot be explained with the findings of the ocular fundus changes [16]. Goldman perimetry is useful to evaluate remaining visual field before and after treatment of the disease (Fig. 2.8) [30].

Scanning Laser Ophthalmoscopy (SLO)

Examination with scanning laser ophthalmoscopy (SLO) provides a high-contrast image that may facilitate visualization of the nematode. Live video imaging with the SLO may also help document motility [10].

Optic Coherence Tomography (OCT)

Statistical analysis with the Stratus OCT showed that there was no significant difference between the retinal nerve fiber layers (RNFL) thickness in patients with or without live worm. However, there was statistical significance between decreased RNFL thickness and worse visual acuity [32].

GDx® Nerve Fiber Analyzer

The GDx® nerve fiber analyzer (Carl Zeiss Meditec, Inc., Jena, Germany) is a scanning confocal laser polarimeter, which uses a polarized light source to analyze the retinal nerve fiber layer around the optic nerve. According to Garcia et al. it is possible to have two types of RNFL alterations: (1) increase in thickness, due to transitory edema or (2) decrease in thickness secondary to nerve fiber loss that occurs with the progression of the disease. They concluded that GDx was able to demonstrate a decrease in RNFL thickness during the chronic phase. This is especially important for patients whose larva was not found and who underwent only clinical treatment so that the progression of the disease may be monitored [27].

Differential Diagnosis

Early signs of DUSN often are mistaken for sarcoid, and other entities that cause focal chorioretinitis, including toxoplasmosis and histoplasmosis, multifocal choroiditis, serpiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent

white dot syndrome, nonspecific optic neuritis, and papillitis. The late stage of DUSN is often mistaken for posttraumatic chorioretinopathy, occlusive vascular disease, or sarcoid or toxic retinopathy [16].

Management

Laser Treatment

At present, treatment of a visible worm with photocoagulation seems to offer the best chance for halting worm motility and resolution of the active gray-white lesions without causing significant intraocular inflammation or toxic damage to the eye. Some improvement in vision and visual field may occur after laser treatment of the worm [33]; however, in late stages of the disease, laser treatment does not improve the visual acuity of affected patients [34]. Previous studies have demonstrated the photosensitivity of different species of ocular infecting parasites, and this may be utilized in luring the target organism away from the macula. In some patients with the worm very close to the center of the fovea in which heavy photocoagulation may damage the remaining central vision, it may be possible to use low level of illumination or very light applications of the laser to chase the worm into the midperiphery, where it may be destroyed with less retinal damage [35].

Oral Treatment

Usually thiabendazole and corticosteroids have not been successful for the treatment of DUSN, except in patients with vitreous inflammation. Gass et al. reported that thiabendazole could be effective in some patients when the worm cannot be found and when DUSN is accompanied by moderate degrees of vitreous inflammation that is associated with a breakdown in the blood-retinal barrier [16]. Similarly, in this group of patients without visible worm and the typical migration of the evanescent lesions, Gass proposed the use of moderately intense scatter photocoagulation in the vicinity of the white lesions to break down the blood-retinal barrier before the administration of thiabendazole. Observation of new white retinal lesions 4–7 days after medical treatment may indicate death of the nematode. Souza et al. reported 12 Brazilian patients who improved visual acuity, visual field, and active ocular inflammatory signs after treatment exclusively with high-dose oral albendazole (400 mg/day) for 30 days [36]. In addition, during the first weeks of treatment, they observed worm inactivation in four patients in which the worms were visible. No adverse drug side effects were observed in any of their cases during follow-up.

Pars Plana Vitrectomy (PPV)

Pars plana vitrectomy is not the standard of treatment for DUSN when the nematode is found because it can be eradicated in cooperative patients with laser. However, as previously stated, de Souza et al. recovered the nematode intact with a PPV approach and in an uncooperative young patient to standard laser treatment [13]. In addition, Meyer-Riemann et al. demonstrated that when a nematode larva is near the posterior pole, surgical extraction of the worm using vitrectomy techniques may be favorable compared to photocoagulation [37].

Controversies and Perspectives

Diffuse unilateral subacute neuroretinitis is a usually unilateral inflammatory disease characterized by an insidious, usually severe, loss of peripheral and central vision with associated findings of vitreous inflammation, diffuse and focal epithelial derangement with relative sparing of the macula, narrowing of the retinal vessels, optic atrophy, increased retinal circulation time, and subnormal electroretinographic findings. Parasites of different sizes and several species of nematodes have been reported as the etiologic agent of DUSN, including *Toxocara canis, Baylisascaris procyonis,* and *Ancylostoma caninum*, and most of these reports do not present conclusive evidence about the specific agent.

Clinical characteristics are manifested in early and late stages, but pathogenesis of the disease is speculative including autoimmune, inflammatory, and/or toxic mechanism of aggression as a possible cause of retinal damage. Laser photocoagulation offers the best chance for clinical resolution of the disease; however, in only 25–40% of cases, the worm is visualized during eye examination. In those patients who cannot receive laser, other treatments including pars plana vitrectomy, thiabendazole, and albendazole have been used with variable success. Probably, nowadays, the best protocol option for oral treatment is albendazole; however, the optimal dosing and duration of treatment for DUSN has still not been determined, and the suggestion to use 400 mg for 30 consecutive days is on the basis of the good results observed applying this protocol to patients with neurocysticercosis [36].

Focal Points

1. In order to avoid diagnostic mistakes, it is important to notice that patients may not manifest evidence of systemic disease and stool shedding. Eosinophilia is infrequently detected, and by the time the worm reaches the subretinal space, systemic markers may not be informative as there is likely to be a time lapse between systemic infestation and intraocular involvement, so the definitive diagnosis is made when the clinical characteristics of DUSN are found in conjunction with an intraocular worm.
2. Whenever the nematode is detected, immediate laser photocoagulation of the worm is necessary as the migratory worm may be difficult to indentify later on. The aim of laser therapy is to achieve death of the worm without inflicting collateral damage to the macula. The leading end of the nematode in forward movement will be the head, and this can be identified by using a low level of illumination to shepherd the nematode away from the macula, with a posterior vertical slit beam, before laser application to the head with a single laser shot. However, it may not be easy to distinguish the head from the tail—especially for small worms [38]. Parameters for laser treatment include spot size ranged from 200 to 300 μm. Power settings range from 150 to 200 mW with an exposure time of 0.2 s. However, Schatz et al. reported a case in which the area of the worm was treated with 200-mW, 200-μm argon green laser spot for 0.2 s with unsuccessful results. They required 0.5 s with 300 mW and a 200-μm spot to kill the worm in the inner retina [39].
3. In patients in whom the worm is visualized and treated with laser, pretreatment immunosuppression with corticosteroids has reduced retinal inflammation (sometimes increased after laser treatment). In the majority of patients in whom laser treatment cannot be done, corticosteroids have uncovered the small worm and made it easy to identify. Different and variable doses have been tested, and one of the schemes includes oral prednisone 40 mg/day for 1 week with or without previous intravenous methylprednisolone at a dose of 1 g for three consecutive days.

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Posterior Pole Manifestations of Cysticercosis

3

Valentina Franco-Cardenas, Naresh Mandava, and Hugo Quiroz-Mercado

Abstract

Cysticercosis is an infestation that results from the ingestion of eggs of *Taenia solium*. Eggs are found in fecally contaminated water or food. Autoinfection as a result of the entry of eggs into stomach due to retroperistalsis or accidental ingestion of eggs is possible. The larval stage *of T. solium* (cysticercus) locates in tissues with high blood requirement, such as the central nervous system (CNS), muscle, or eye. Ocular cysticerci may be located in any part of the eye. For diagnostic purposes, B-ultrasonography should be selected first. Cysticerci induce severe inflammation due to toxins contained inside the cyst. Surgical removal is the treatment of choice.

Keywords

Ocular cysticercosis • Cysticerci • Vitrectomy • Tape worm infestation • *Taenia solium* • Taeniasis • Autoinfection

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Introduction

Taeniasis is caused by infestation with the adult worm of *Taenia solium* in the human gastrointestinal tract. Taeniasis is found worldwide but is endemic in some parts of the world. While taeniasis is rarely seen in those who do not eat pork, cysticercosis occurs in all ethnic groups regardless of dietary habits.

Cysticercosis refers to an infestation by the larva form of *Taenia solium.* The pig is the usual intermediate host, but dogs, cats, and sheep can harbor the larvae as well. When embryonated *T. solium* eggs enter the human intestinal tract by ingestion of contaminated water or food, the hatched larvae are able to

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enter the bloodstream and form cysts in target organs. Poor hygiene and poverty are risk factors for cysticercosis; therefore, the disease is mainly seen among low socioeconomic classes in China, Eastern Europe, India, Indonesia, Latin America, and Pakistan [1].

Although subcutaneous cysticercosis is probably the most common form of the disease, clinical symptoms are usually manifested only in patients with cerebral or ocular involvement [2]. Ocular structures are affected in 13–40% of infected patients, at times leading to impaired vision or blindness [3].

In 1830, Soemmering described the first case of ocular cysticercosis, which was localized to the anterior chamber. In 1854, von Graefe reported a case of cysticercosis in the vitreous cavity, which was surgically removed. Since then, there have been many reports of ocular cysticercosis published in the literature

Epidemiology

Taenia solium has a worldwide distribution, with higher incidence in Mexico, Africa, Southeast Asia, Eastern Europe, and South America. The parasite has also been found in pigs in Colorado and New Mexico, and native acquisition of the disease has been proven in the United States. The incidence of cysticercosis in developed countries has increased in the past 10 years, probably due to an increasing number of immigrants from endemic countries [4]. Even in orthodox Jewish communities with strict dietary habits and in vegetarians, neurocysticercosis has been reported [5, 6]. This is due to the fact that the development of the disease depends strictly on the ingestion of fertilized eggs, which are found in fecal contaminants and not from the ingestion of the larvae that are found in muscle tissues.

Ocular manifestations usually appear in the first four decades of life, without sex predilection and with higher incidence in the first two decades of life, compared with neurocysticercosis [7, 8]. The left eye seems to be more often involved than the right eye.

Etiology and Pathogenesis

The adult form of *T. solium* is 3 mm in length and usually lodges in the proximal portion of the jejunum, where it can live for decades. The globulous scolex or head of the worm has a peak or face with two crowns of hooks. The gravid proglottid measures 6–12 mm approximately, and the uterus has from 8 to 12 lateral branches. The eggs are infectious for both the pig and humans, with a fecal-oral transmission route. Humans can become autoinfected if the gravid portions containing fertilized eggs reach the stomach again through inverse peristalsis, as occurs during regurgitations.

In the intermediate host, the hexacanth embryo is released from the egg, traverses the intestinal wall, and is transported to distant places by the venous of lymphatic system, where it turns into a mature larva or cysticercus cellulosae in a period of 60–70 days [3, 9], with a mean survival of 5 years [4] (Fig. 3.1).

Ocular cysticerci can be localized in any part of the eye, such as the anterior chamber [10, 11], subconjunctival space [12] (Fig. 3.2), optic disc [13], subretinal space [14] (Figs. 3.3 and 3.4), vitreous cavity [15–17], and lacrimal gland or eyelids [18]. Some authors have reported parasites located in the lens [2] that migrate to the sclera [19]. It is hypothesized that the parasite reaches the posterior pole through the posterior ciliary arteries, because it is usually found in the macular subretinal space [20], where it can perforate the retina, spread to the vitreous cavity, and cause a retinal detachment [21] or an inflammatory response with the formation of a macular hole or chorioretinal, scar depending on the exit site [22] (Fig. 3.5). The central retinal artery is the most likely route through which the parasite reaches the optic disc. The ocular adnexa are involved via the anterior ciliary arteries [23]. Some authors suggest that the damage to the ocular structures by ocular cysticercosis is produced by a great amount of toxins released when the parasite dies [2]. Nevertheless, signs of inflammation have been noted even in patients with living parasites.

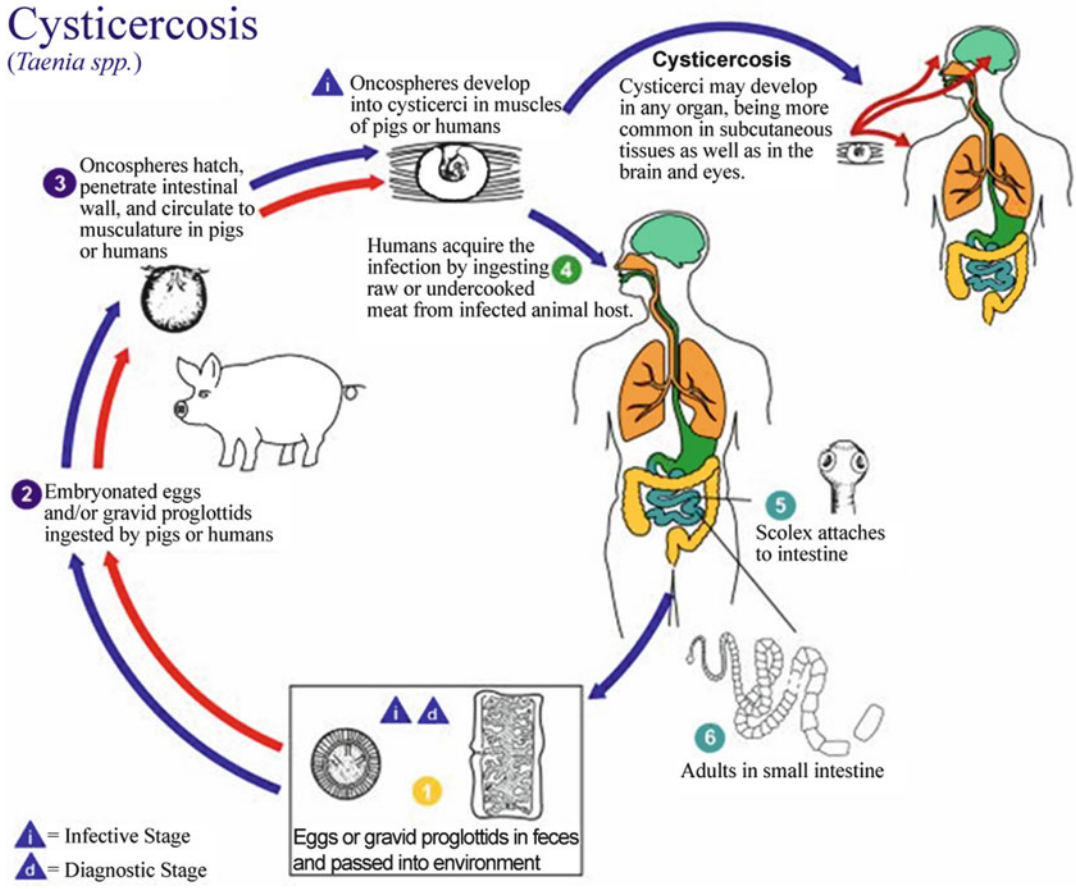

Fig. 3.1 *Taenia solium* life cycle

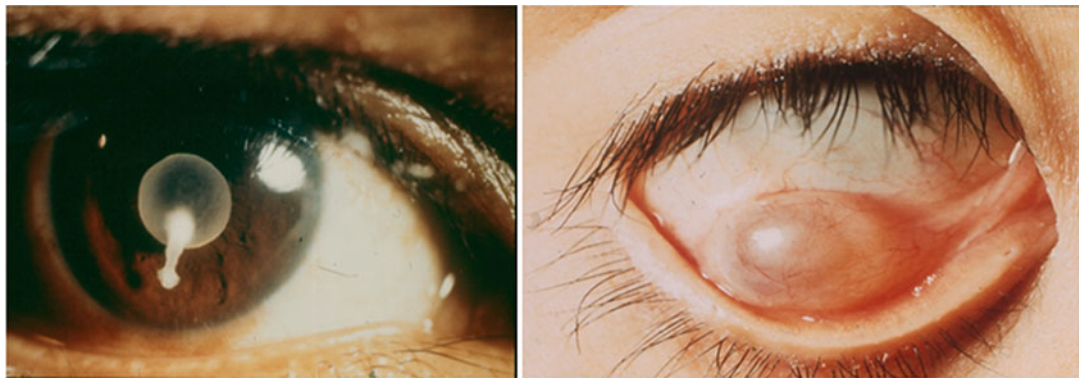

Fig. 3.2 Cysticercus in the anterior chamber showing scolex protruding from the cyst

It has been reported that the inflammatory response associated with ocular cysticercosis is produced by the host immunologic reaction rather than by the cysticercus itself, with a greater response if the parasite is located in the vitreous cavity than if it is found in the subretinal space [24, 25]. In some cases, the inflammatory response can be so intense that it can simulate the

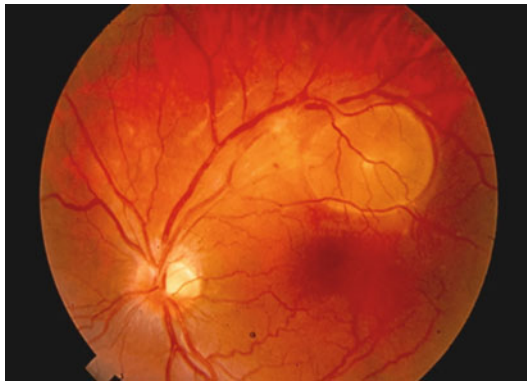

Fig. 3.3 Subretinal cysticercus out of the foveal area

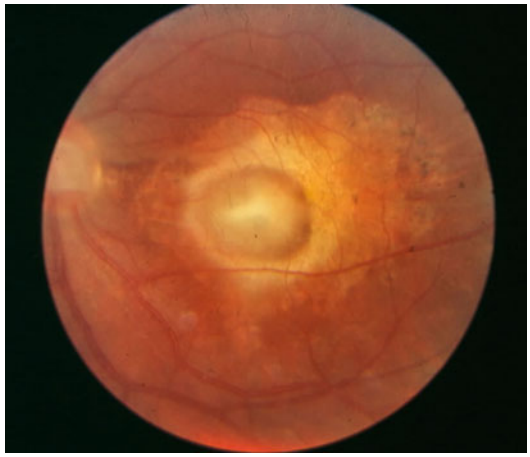

Fig. 3.4 Subretinal cysticercus at the level of the fovea

clinical appearance of endophthalmitis or so indolent that it might cause neovascular glaucoma [26].

In the last 20 years, ocular cysticercosis has shown the following distribution: subconjunctival, 62.7%; intraocular, 26.3%; orbital, 7%; and lid, 4%. A significant decrease has been noted in subconjunctival cases (85% vs. 28%) with a significant rise in intraocular cysticercosis (6% vs. 60%) [27].

Systemic Manifestations

Systemic manifestations of cysticercosis include subcutaneous cysts and inflammatory nodules, seen as calcium deposits in soft tissues on radiographic films or computed tomography (CT) scan. When the central nervous system is involved, the patient may present with seizures, recurrent headaches, and increased intracranial pressure or as a psychiatric disorder. Signs of meningoencephalitis may be observed in cases with multiple cysts [4].

Clinical Intraocular Manifestations

Early in the disease (when the cysticercus is small), intraocular symptoms may be absent. As the parasite grows, it can cause progressive and painless loss of vision [28], described by the patient as a dark, round, and mobile spot in the visual field. If the parasite is located in the macular subretinal space or at the optic disc, there is often an acute decrease in visual acuity, along with defects in the visual field.

Diagnosis

The diagnosis of ocular cysticercosis is to be suspected in those patients living in endemic areas who suffer from uveitis, leucocoria, and neurologic symptoms, as well in those with eyelid nodules and subconjunctival cysts [29].

Indirect ophthalmoscopy and biomicroscopy are of great help in diagnosing the disease. The parasite in the vitreous cavity has a cystic translucent appearance. If it is alive, undulation, contraction, and expansion movements can be seen as a light beam illuminates the cyst [30]. In early stages, when a cyst is located in the macular subretinal space, it may manifest as an acute retinitis with edema and subretinal exudates [31], showing a pearl-like cyst containing the mobile parasite. Retinal holes made by the cysticercus can be observed in the area. If the parasite is located in the subretinal space, the macular area is more commonly involved (80%), likely because of the regional vascular features [20] and thickness.

The diagnosis is more difficult if the parasite is located in the retinal periphery or if there is significant vitreous inflammatory response that precludes adequate visualization [32]. In the latter situation, as well as when a retinal detachment is

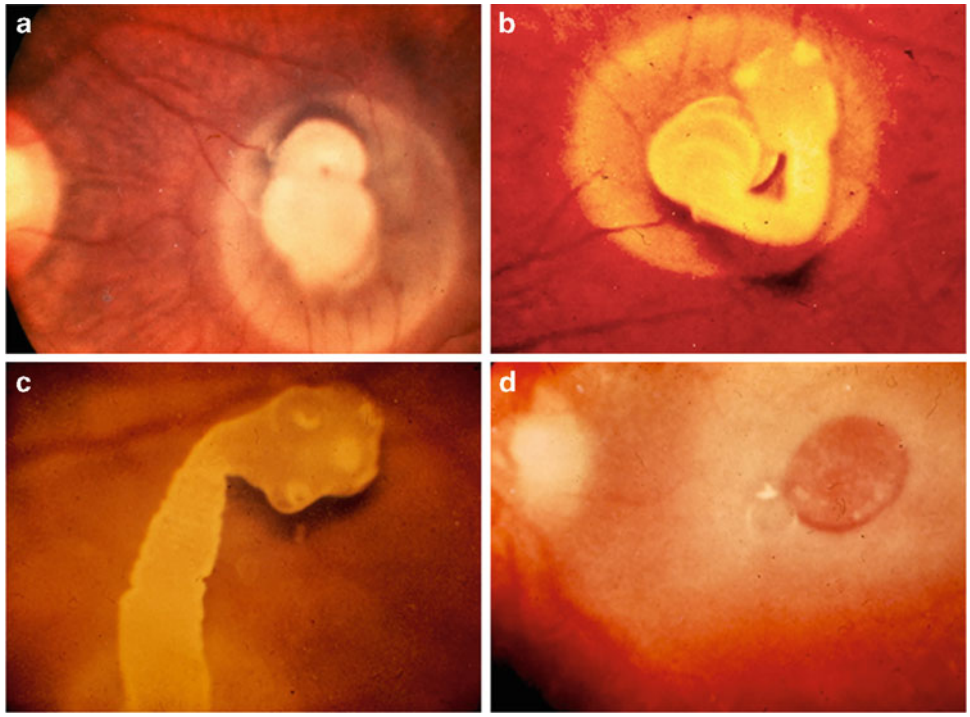

Fig. 3.5 Sequence of a subretinal posterior pole cysticercus migrating to the vitreous cavity. (**a**) Subretinal living cysticercus. (**b**) The macula seems to be the most usual location and the favorite exit site (80%), likely because of regional vascular features and thickness. (**c**) Intravitreal live cysticercus. (**d**) Residual macular hole created by the cysticercus

suspected, imaging techniques become an invaluable diagnostic tool to detect the parasite. The appearance of ocular cysticercosis depends on the site and living status of cysticercus. For diagnosis, B-ultrasonography should be selected first for diagnostic purposes. As a second line, magnetic resonance imaging (MRI) can be used to visualize living cysticerci and CT for nonliving calcified cysticerci [33].

Because ultrasonography is the gold standard, it is important to mention that in the A-mode, two high-reflective spikes showing the anterior and posterior walls of the cyst are seen with an additional 100% reflectivity spike seen inside the cyst, representing the scolex, which usually has an eccentric position. In the B-mode, a cystic mass with high-reflectivity eccentric structure showing undulatory movements can be observed [34] (Figs. 3.6 and 3.7).

Laboratory tests have limited value in the diagnosis of the disease. Immunoelectrotransference testing reaches 100% specificity and 95% sensitivity. ELISA serum testing achieves 63% specificity and 65% sensitivity. ELISA cerebrospinal fluid (CSF) immunotransference testing has 86% specificity and 62% sensitivity [35].

Late-stage histopathology findings as reported by Gomez-Leal [36] include the presence of a central eosinophilic mass with some parasitic elements, surrounded by a polymorphonuclear infiltrate and a layer of granulomatous-type inflammatory responses. These findings are contained in a fibrous capsule infiltrated by chronic inflammatory cells (Fig. 3.8). Other intraocular changes include choroidal infiltration with lymphocytes and plasma cells, retinal detachment with gliosis and atrophy in some areas, lens opacification adherent to the inflammatory process in the vitreous cavity through a cyclitic membrane, iris atrophy with anterior synechiae closing the anterior chamber angle, and partial atrophy of the ciliary body (Fig. 3.9).

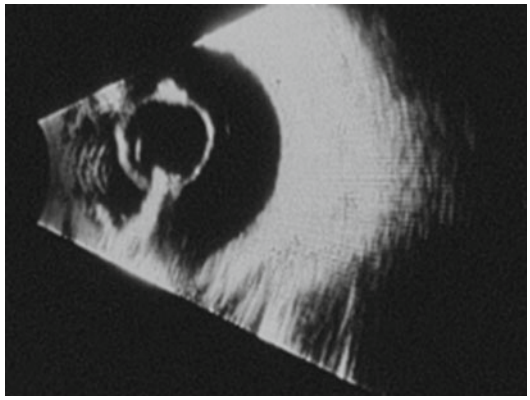

Fig. 3.6 Mode B ultrasonography showing an intravitreal cysticercus. Note the hyperreflective walls, hyporeflective interior, and the hyperreflective eccentric structure that corresponds to the scolex (Courtesy of Dr. Eduardo Moragrega Adame)

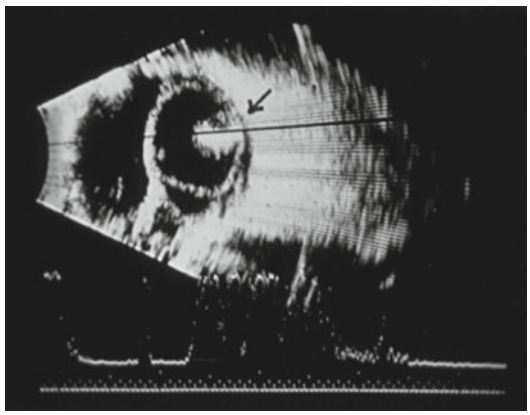

Fig. 3.7 Subretinal cysticercus. Mode A ultrasonography shows three high-reflective spikes that correspond to the retina, anterior and posterior wall of the cyst. An additional 100% reflectivity spike is seen inside the cyst, representing the scolex (Courtesy of Dr. Eduardo Moragrega Adame)

Treatment

Medical treatment with albendazole and praziquantel generally is used for central nervous system cysticercosis [37]. They lack efficacy, however, in the treatment of the ocular form of the disease, as reported by Santos et al. in 1984 [38]. Other authors suggest that oral treatment besides being ineffective hastens progression of the disease by exacerbating the inflammatory response [39].

Diathermy, cryotherapy [40], and photocoagulation [41, 42] are useful methods of destroying the cysticercus. They are rarely used because of the risk of eliciting severe inflammation resulting from the release of toxins from the necrotic cysticercus [22]. Currently, the treatment of choice is the surgical removal of the cysticercus.

Surgical Technique

Removal of the parasite, clearing the vitreous cavity, and removing vitreous membranes are the purposes of the surgery. Once the parasite is dead (cystic lesions without movement seen), the extraction of the cysticercus is not recommended because inflammatory responses associated with parasite death produce multiple adherences, complicating its removal [24]. The best approach to remove a free-floating cysticercus in the vitreous cavity is a pars plana vitrectomy. The vitrectomy is performed around the parasite until it is fully liberated. Then, one sclerotomy is widened according to its size, and the cyst is removed with a passive suction silicon tip probe, avoiding rupture and subsequent toxin release [24].

If the cyst is located in the subretinal space, a complete vitrectomy with a complete posterior vitreous detachment should be achieved. A retinotomy next to the location of the cyst in the temporal side of the macula is performed. The cyst is then removed, with the use of an extrusion soft-tip cannula, from the subretinal space and out of the eye through one of the sclerotomies. The retinotomy is not sealed with laser, in our experience, unless it is large or located in the periphery. Some authors, such as Pavan [43], do prefer sealing the retinotomy with laser.

The procedure is followed by an air-fluid exchange, and the patient is positioned facedown [24, 44].

Controversies and Perspectives

After the ocular cysticercus is removed, a complete work-up for *T. solium* infestation and neurocysticercosis should be addressed. Controversy

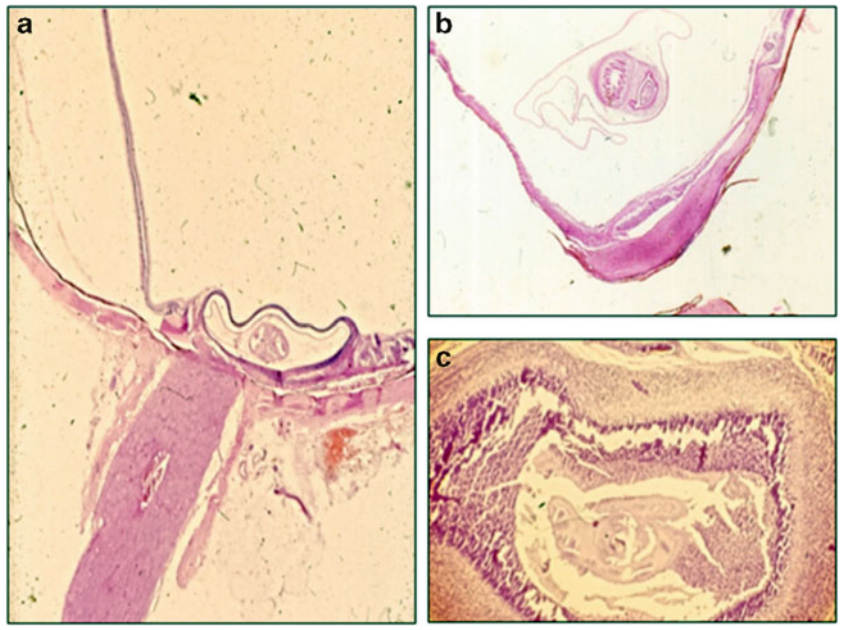

Fig. 3.8 (**a**) Image of an intraocular cysticercus located at the optic nerve producing a retinal detachment. (**b**) Enlarged view of cysticercus scolex. (**c**) Fibrous capsule encircling an eosinophilic mass with some parasitic elements, surrounded by a polimorphonuclear infiltrate and a layer of granulomatous-type inflammatory response (Courtesy of Abelardo A. Rodríguez-Reyes, M.D. and Alfredo Gómez Leal, M.D.)

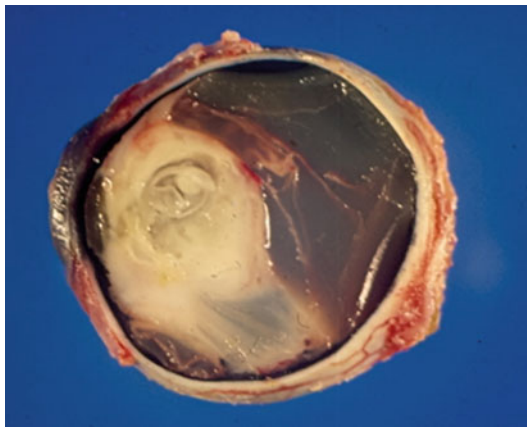

Fig. 3.9 Gross specimen shows a retinal detachment, lens opacification, inflammatory process in the vitreous cavity, cyclitic membrane, iris atrophy with anterior synechiae closing the anterior chamber angle, and partial atrophy of the ciliary body (Courtesy of Abelardo A. Rodríguez-Reyes, M.D. and Alfredo Gómez Leal, M.D.)

over the use of antiparasitic drugs (albendazole or praziquantel) still exists. Even though antihelminthic drugs do reach the CNS and effectively attack the living cysticercus, damage due to the location of the cyst and local inflammation may be irreversible. For calcified cysts with no living parasite, antihelminthic drugs may be ineffective. In patients with viable lesions, evidence from trials suggests albendazole may reduce the number of lesions. In trials of nonviable lesions, seizure recurrence was substantially lower with albendazole treatment. Steroids may reduce headaches during treatment and probably toxin-related inflammation, but further research is needed to test this [45].

Focal Points

It is important to consider the following guidelines during surgery [46]:

- A vitrectomy or vitrectomy lensectomy is advisable whenever the vitreous or the lens is opaque.
- A vitrectomy is indicated to liberate retinal traction or macular folds.
- A scleral buckle is performed in the presence of rhegmatogenous retinal detachment.
- A vitrectomy and scleral buckle are indicated in the presence of considerable traction.

- An inflammatory response to toxins may be present if destruction of the cyst occurs inside the eye.
- A posterior vitreous cortex removal is indicated to prevent contraction in the future.
- Topical, periocular, and even oral steroids, as well as mydriatic agents, are needed to control the inflammatory response after the surgery.

Every case of intraocular cysticercosis represents a poor visual prognosis. If the parasite is located in the vitreous cavity or the subretinal space and it is not removed, a loss of visual function ensues after a period of 3–5 years [47]. In the absence of treatment, the cysticercus may increase in size, release toxins, and provoke an intense inflammatory reaction that eventually destroys other ocular structures.

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Posterior Pole Manifestations of Toxocariasis

4

J. Fernando Arévalo and Juan V. Espinoza

Abstract

Ocular toxocariasis is an uncommon worldwide parasitic infection that affects mostly children and is found in both rural and metropolitan areas. In many parts of the world, parasitic infections of the eye are a major cause of blindness. The diagnosis of toxocariasis is essentially clinical, based on the lesion morphology and supportive laboratory data such as serum ELISA titers and ELISA *Toxocara* titers on aqueous humor; other diagnostic methods are imaging studies including optical coherence tomography (OCT), fluorescein angiography (FA), computed tomography (CT) scan, and ocular ultrasound. Treatment is directed at complications arising from intraocular inflammation and vitreous membrane traction. Early vitrectomy may be of value both diagnostically and therapeutically.

Keywords

Infectious uveitis • Nematode intraocular infections • Ocular toxocariasis • Retinochoroidal granuloma • *Toxocara canis* • *Toxocara cati* • Toxocariasis epidemiology

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Introduction

In many parts of the world, parasitic infections of the eye are a major cause of blindness [1]. Human toxocariasis is probably one of the widest spread zoonotic nematode infections, and it is considered one of the most prevalent helminthiasis in industrialized countries [2, 3]. The nematodes *Toxocara canis* and *Toxocara cati* are parasitic roundworms that infect dogs (toxocariasis), other

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canidae, and cats. Ocular toxocariasis (OT) is an uncommon worldwide infection caused by the nematode larvae of *T. canis*, commonly found in dogs [1].

Nematodes were first recognized as pathogens in the posterior segment of the eye by Wilder in 1950. In 1952, Beaver and associates described the association of *Toxocara* species with human disease [1, 4]. The main source of human infection is considered to be environmental contamination by *Toxocara* spp. eggs, especially in public areas of large urban centers, such as parks and gardens frequented by dogs and cats as well as humans [2, 5]. The epidemiology of toxocariasis in different regions has been studied; an association between the higher frequency of seroreactivity to *T. canis* antibodies in humans and socioeconomic variables, such as educational level, family income, water treatment, and contact with soil, has been observed [2]. It usually affects young children, and it may cause a wide spectrum of ocular disease from an asymptomatic posterior granuloma to total retinal detachment [1, 6]. However, ocular infection appears to be much less common than systemic infection [7].

The objective of this chapter is to describe the posterior pole manifestations of ocular toxocariasis as well as its pathogenesis, epidemiology, diagnosis, and current management.

Pathogenesis and Life Cycle

The first complete description of the *T. canis* life cycle (Fig. 4.1) was provided by Sprent in 1958. This canine roundworm shares certain characteristics with the feline roundworm *T. cati* and with the human roundworm *Ascaris lumbricoides* [1]. Dogs may acquire the intestinal infection in five different ways: (1) by ingestion of infective embryonated eggs with stage 1 larvae encapsulated inside, (2) by ingestion of infective second-stage larvae infesting the meat of a rodent, (3) by ingestion of advance-stage larva from the feces or vomit of prenatally infected pups, (4) by transmammary passage of larvae in milk from a lactating bitch to nursing puppies, and (5) by transplacental migration. In cats, transplacental migration has not been proved [8]. Ingested *Toxocara* eggs, with first- and second-stage larvae emerge in the duodenum, and liberate the third-stage larvae, which perforate the intestinal wall [1, 8]. Once located in the intestinal wall, the larvae pass through the portal circulation and migrate via the liver and heart to alveolar capillaries. In puppies, which are more frequently infected, the larvae are able to complete a migratory and developmental cycle. The worms hatch and migrate through the portal system and undergo transtracheal migration. The third-stage larvae are coughed up and aspirated, and they mature into sexually differentiated forms in the small bowel. If the host is an older puppy or an adult dog, particularly with some immunity acquired from past infection, the larvae do not complete the lung migration. Most puppies acquire the infection prenatally. However, they generally expel the worms before reaching adulthood [8].

In common with other non-canine or non-feline hosts, humans can be paratenic hosts for *T. canis* or *T. cati* and can become infected after the ingestion of infective ova or, less frequently, larvae. Ova hatch in the intestine, releasing the second-stage larvae, which migrate throughout the soft tissues of the body, including the brain, for prolonged periods of time [4]. They are often associated with migratory tracks characterized by hemorrhage, necrosis, and inflammation, with eosinophils predominating. Larvae may become encapsulated within granulomas where they are either destroyed or persist in a viable state for many years. In the eye, where the migration of a single larva can be observed, the inflammatory response can lead to partial or total retinal detachment with visual loss [3]. It appears from histological evidence that it is more likely that larvae travel in blood vessel rather than by burrowing (Fig. 4.2a, b, c). It is probably by transport within blood vessels that the larvae reach the eye [7]. The host immune responses to migrating larvae appear to be directed against the larval excretory-secretory antigens (TES-Ag) [3]. These antigens are

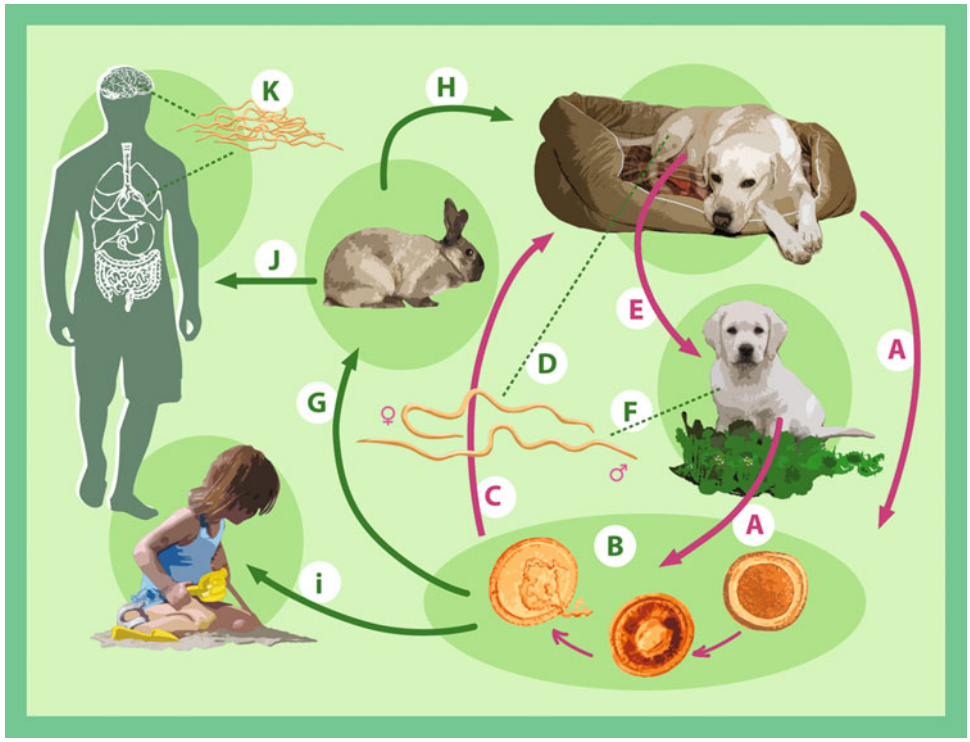

Fig. 4.1 Toxocara life cycle. (*A*) *Toxocara canis* accomplishes its life cycle in dogs, with humans acquiring the infection as accidental hosts. (*B*) Unembryonated eggs are shed in the feces of the definitive host. Eggs embryonate and become infective in the environment. (*C* and *D*) Following ingestion by dogs, the infective eggs hatch and larvae penetrate the gut wall. In younger dogs, the larvae migrate through the lungs, bronchial tree, and esophagus; adult worms develop and oviposit in the small intestine. (*E and F*) In older dogs, patent infections can also occur, but larval encystment in tissues is more common. Encysted stages are reactivated in female dogs during late pregnancy and infect by the transplacental and transmammary routes the puppies, in whose small intestine adult worms become established. Puppies are a major source of environmental egg contamination. (*G*) *Toxocara canis* can also be transmitted through ingestion of paratenic hosts: eggs ingested by small mammals (e.g., rabbits) hatch and larvae penetrate the gut wall and migrate into various tissues where they encyst. (*H*) The life cycle is completed when dogs eat these hosts and the larvae develop into egg-laying adult worms in the small intestine. (*I* and *J*) Humans are accidental hosts who become infected by ingesting infective eggs in contaminated soil or infected paratenic hosts. (*K*) After ingestion, the eggs hatch and larvae penetrate the intestinal wall and are carried by the circulation to a wide variety of tissues (liver, heart, lungs, brain, muscle, eyes). While the larvae do not undergo any further development in these sites, they can cause severe local reactions that are the basis of toxocariasis. The two main clinical presentations of toxocariasis are visceral larva migrans and ocular larva migrans. Diagnosis is usually made by serology or the finding of larvae in biopsy or autopsy specimens

released by larvae from their epicuticle, which is readily sloughed off when bound by specific antibodies [3, 9].

Toxocara larvae secrete and excrete products that are highly immunogenic, which promotes a Th2-type cellular immune response, leading to the production of interleukins 4 and 5 and causing IgE antibody production and eosinophilia [10]. The relative importance of *T. canis* and *T. cati* in causing eye disease has been a matter of debate, and the mechanism by which larvae in tissues are killed and eliminated is not known until now, but there are many hypotheses about it.

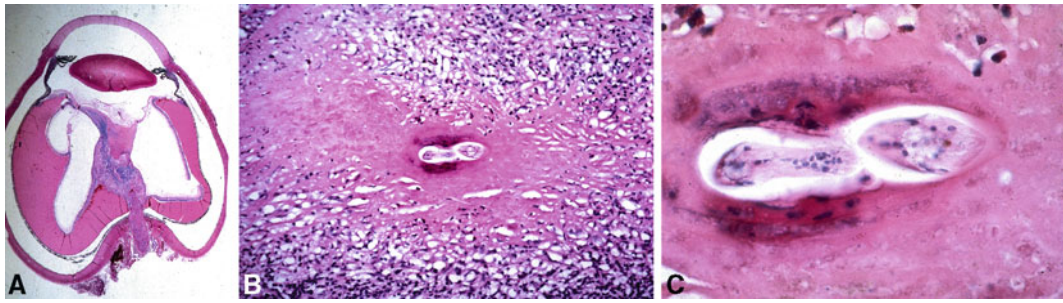

Fig. 4.2 (**a**) Retrolental intravitreal fibroinflammatory mass with retinal detachment. (**b**) Intravitreal mass composed of fibroinflammatory cells with plasma cells, eosinophils, and fibrous tissue surrounding a nematode of *Toxocara canis*. (**c**) Partially well-preserved nematode of *Toxocara canis* (Courtesy of Dario Savino-Zari, M.D.)

Clinical Manifestations

The clinical manifestations of toxocariasis are determined by the size of the *Toxocara* inoculum, frequency of reinfection, organ localization of the larvae, and host response [10, 11]. The spectrum of clinical manifestations varies widely, ranging from predominantly asymptomatic cases to those with severe organ injury [10].

There exist three essential clinical types of human toxocariasis:

1. Visceral larva migrans syndrome (VLM) is due to severe systemic infestation leading to fever, hepatosplenomegaly, pneumonitis, and convulsions. Serum IgE may be elevated, and the blood exhibits substantial eosinophilia and leukocytosis, and affects primarily 1- to 5-year-old children [10, 12].
2. Ocular larva migrans syndrome (OLM) is most commonly seen in otherwise healthy patients, manifesting itself into three clinical types that were classified by Wilkinson and Welch: peripheral inflammatory mass type (Fig. 4.3), posterior pole granuloma type (Figs. 4.4a, b and 4.5a, b), and diffuse nematode endophthalmitis [12–15]. Ocular larva migrans syndrome occurs in children generally older than 8 years of age [10]. These patients have a normal white blood count, normal serum IgE, and show no eosinophilia [12].
3. Covert toxocariasis has been diagnosed in patients who do not fall into the VLM or OLM categories but instead reveal vague symptomatology. Raised levels of *Toxocara* antibodies have been implicated in signs and symptoms, such as hepatomegaly, cough, sleep disturbances, abdominal pain, headaches, and behavioral changes [12].

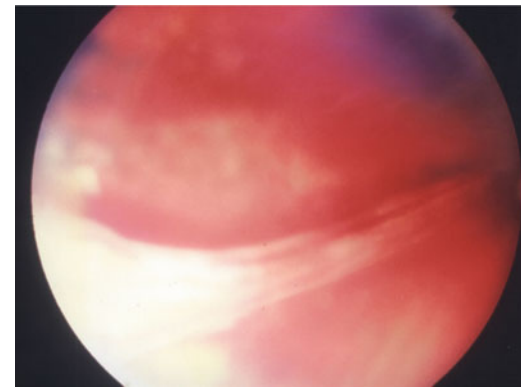

Fig. 4.3 Peripheral inflammatory mass type in a patient with *Toxocara canis*

There are two forms of ocular *Toxocara*, visceral and ocular, that cause an infection with potentially serious consequences for vision [13]. Covert toxocariasis has not been recognized to show ocular manifestations in previous reports.

Probably, the most common presentation of OT is the granuloma found in the posterior pole or at the periphery [13]. There is a high proportion of unilateral ocular infection with mild ocular inflammation in more of 50% of cases, but it may also be a bilateral disease particularly in the

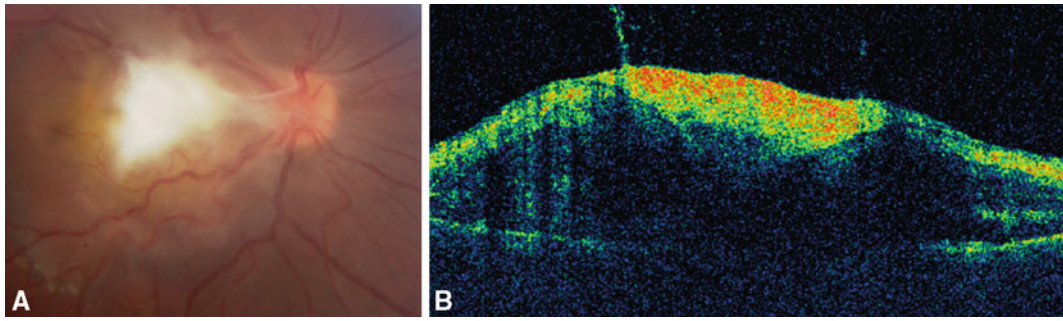

Fig. 4.4 (**a**) Posterior pole granuloma with secondary fibrocellular membranes extending into the optic nerve, vitreous, and surrounding retina in an 8-year-old boy with *Toxocara canis*. (**b**) Optical coherence tomography reveals a characteristic hyper-reflectivity of the internal layers of the retina with tractional macular detachment and posterior shadowing of the choroid

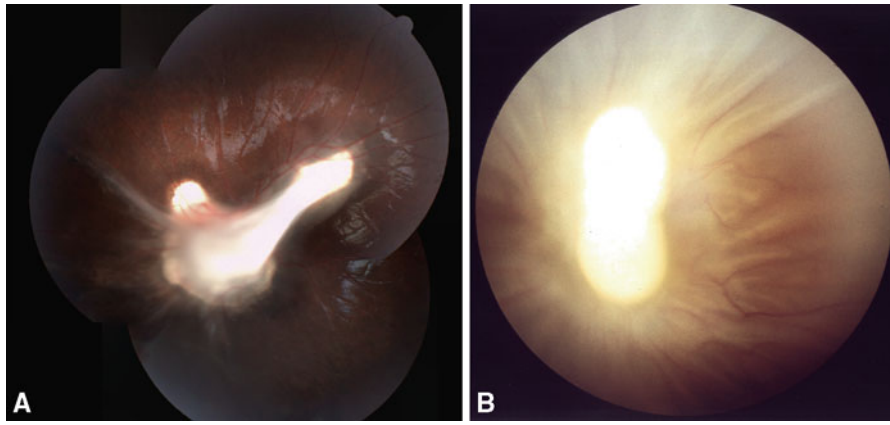

Fig. 4.5 (**a** and **b**) Two patients with posterior pole granuloma and tractional retinal detachment due to *Toxocara canis* (Fig. 4.5a, courtesy of Endalup Reyes, M.D., and Martin A. Serrano, M.D.)

chronic form [14, 16]. In addition, there is recurrence in more of 30% of patients [17]. Some reports have identified that *Toxocara* granuloma was located in the peripheral retina between 50% and 64%, posterior pole granuloma between 25% and 36% of cases [14, 17], and endophthalmitis presentation was identified in less than 25% of cases [17].

Most cases of OT have less than 20/40 of visual acuity (VA) at presentation, with a median VA in eyes with endophthalmitis between 20/200 and 20/400, in eyes with peripheral granuloma a median of 20/70, and in eyes with a posterior pole granuloma a median of 20/50 [17]. The peripheral retina and vitreous sites are the most common; however, those may occur separately or together [1].

A hazy, not well-defined white lesion may be seen in the posterior pole or in the periphery, and different degrees of vitritis may be present. As the inflammation resolves, a peripheral elevated white mass usually is seen, typically associated with retinal folds extending toward the macula [1, 18]. Sometimes, the granuloma presents posteriorly as an intraretinal or subretinal mass (Fig. 4.6a, b). Endophthalmitis usually presents with a quiet external eye with little pain but a severe vitreous inflammation, a mild anterior chamber reaction, and often a secondary cataract [1]. The intraocular inflammation may lead to macular detachment through either direct vitreomacular traction or epiretinal membrane, creating a macular pucker (see Fig. 4.4a). Traction

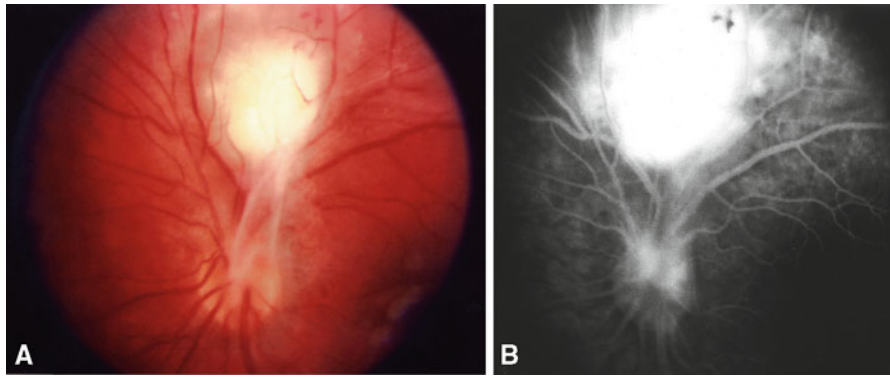

Fig. 4.6 Posterior pole granuloma superior to the optic disk with secondary fibrocellular membranes extending into the optic nerve, vitreous, and surrounding retina in a 10-year-old boy with *Toxocara canis*. (**a**) Color photograph. (**b**) Fluorescein angiogram

also may lead to retinal breaks in atrophic retina, creating a combined tractional-rhegmatogenous detachment [19]. An optic papillitis also can occur, usually because of an invasion of the nerve by the nematode or as an inflammatory response to the organism in another site of the eye [1].

Epidemiology

Uveitis is a common cause of vision loss, accounting for 5–20% of all cases of blindness worldwide [17]. Toxoplasmosis is the most common etiology of infectious posterior uveitis and having OT as one of the less frequent cause [20]. However, the study of the epidemiology of human toxocariasis remains problematic for a number of reasons. First, much of the epidemiology of human toxocariasis is based on serodiagnosis, which has inherent problems, and our understanding of the relationship between exposure and disease remains poor. Second, the lack of standardization of both clinical signs and symptoms and serological testing can introduce variation between studies and make comparisons difficult. Third, randomly selected data at the population level is scarce, and therefore, it is difficult to assess the public health significance of disease in different countries [4].

The prevalence of infection of dogs with adult *Toxocara* worms was reported to be about 25% in Western countries [3, 21], while the rate in cats in France was 30–60% [3]. The prevalence of infection tends to decrease with increasing age of the animal and is lower in well-cared-for pet dogs than in stray or pound dogs. This high prevalence, together with the high fecundity of *Toxocara* and the increasing number of pet animals in Western countries, explains the high level of soil contamination with *Toxocara* eggs in parks, playgrounds, and other public places [3].

Recent studies have demonstrated that soil samples taken from gardens of homes where a clinical case of toxocariasis is found are likely to be contaminated. *Toxocara* eggs have been recovered from salads and other raw vegetables taken from such gardens [3]. Geophagia or soil eating is a specific type of *pica* that increases the risk of toxocariasis, especially in children living in homes with puppies that have not been dewormed. Poor personal hygiene as well as consumption of raw vegetables grown in contaminated kitchen gardens may result in chronic low-dose infections [3].

Toxocara seroprevalences range from 4% to 46% in adults and can be as high as 77.6% in school children [22], and the disease affects females and males with approximately equal frequency [17]. In the United States, the overall prevalence was found to vary between 4.6% and 7.3%, but ranged as high as 10% in the American South and over 30% for socioeconomically disadvantaged African American children. Higher

seroprevalence was also linked to markers of low socioeconomic status, including poverty and crowding and lower educational level for head of household [23, 24]. In 2008, the Centers for Disease Control and Prevention (CDC) in the United States reported on *Toxocara* seroprevalence from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional survey conducted between 1988 and 1994. The survey sampled at higher rates specific minority groups (e.g., non-Hispanic Blacks and Mexican Americans) and age groups (young children and the elderly). Based on a representative sample of just over 20,000 in individuals over the age of 6, the overall seroprevalence was 13.9% [23, 25], suggesting that ten million Americans are infected with *Toxocara.* However, the seroprevalence was found to be considerably higher among non-Hispanic Blacks and people living in poverty.

Based on the number of African Americans living in poverty in the United States, it has been calculated that as many as 2.8 million have toxocariasis, making this disease one of the most common infections among any underrepresented minority groups [23]. In a separate study conducted in the 1990s, high rates of toxocariasis were also found among inner-city Hispanic populations in Bridgeport and New Haven, Connecticut, especially among Puerto Rican immigrants [23, 26]. On the other hand, unlike previous reports in other countries, most patients reported with ocular toxocariasis in Japan are adult, and this prevalence may be due to the changing dietary habit in that country [14].

Diagnosis

The diagnosis of OT is difficult and, in the majority of cases, remains only presumptive. Standard diagnostic methods for ocular *Toxocara* are fundoscopy, imaging, and serologic testing [13].

Most patients with visceral larva migrans will manifest a leukocytosis and hypereosinophilia. On the other hand, eosinophilia is usually absent in OT. Tissue biopsy can show the presence of larvae, but because the larvae rarely are able to finish their life cycle in human beings, stool analysis will not detect *Toxocara* [1]. In the absence of parasitological evidence of infection, diagnosis of toxocariasis has relied mainly on immunological methods [10, 27]. Thus, the *Toxocara* excreted-secreted antigens (TES) have been applied to different immunological assays. The TES-based enzyme-linked immunosorbent assay (ELISA) for detection of IgG-specific antibodies, in particular, is widely preferred for diagnostic purposes and also for seroepidemiologic surveys [10].

Toxocara is a parasite with the ability to evade the immune system, which could explain the chronicity and persistence of the infection [10]. The ELISA has made immunodiagnosis the main serologic method for detecting visceral larva migrans and for confirming the clinical suspicion of OT [1]. Moreover, measurement of avidity (functional affinity) of specific IgG antibodies seems to be useful to discriminate between chronic and early phases of the infection, as in the case for other infectious diseases. In other words, high avidity IgG antibodies are associated with the chronic phase low avidity (functional affinity) of specific IgG antibodies that are associated with the chronic phase and low avidity IgG with freshly acquired toxocariasis. There are few follow-up studies of toxocariasis patients after chemotherapy, but it has been reported that specific IgG antibody levels remain elevated for many years [10]. In toxocariasis, specific IgM antibodies were reported to occur in both acute and chronic phases, differing from most unrelated infections in which they are transient [10]. Lately, IgA and IgE have been found to be useful for diagnosis and follow-up of toxocariasis.

For VLM and some forms of covert toxocariasis, the sensitivity and specificity of the *Toxocara* ELISA are estimated at 78% and 92%, respectively, at a titer of 1:32 [23]. The sensitivity of the ELISA for OLM, however, is considerably less. The larvae may remain alive within the host for months, and host antibody levels may remain strongly positive for 2 or 3 years or more [23, 25]. Therefore, in the CDC, the presence of antibody titers greater than 1:32 may be considered reflective of active infection [23].

The presence of any level of antibodies in the serum is therefore likely to support the diagnosis of *Toxocara* uveitis if the clinical picture raises this possibility. However, most ophthalmologists consider a serum titer of ≥1:8 to be positive for OT if the patient has clinical features consistent with the diagnosis [7, 28]. On the other hand, the absence of serum antibodies does not rule out the diagnosis [17].

The possibility that *T. cati* might play a part in causing ocular lesions has been raised by Petithory et al., who reported positive ELISA test for *T. cati* in the vitreous of six out of nine patients with OLM, all nine of whom also had positive vitreous *T. canis* ELISA tests [29]. Therefore, testing intraocular fluid for antibodies has also been shown to be helpful in diagnosing toxocariasis. These samples often contain higher levels of antibody than the serum [17, 30]. Taking into account that establishing the diagnosis of OT based on clinical features and serologic results is unreliable, we suggest the addition of *T. canis* and *T. cati* Goldmann-Witmer coefficient (GWC) determination to the diagnostic repertoire in patients with unexplained focal chorioretinitis or vitritis [22]. Cytology of the aqueous or vitreous may play a role in the differentiation between retinoblastoma and *Toxocara* posterior pole granuloma in children. The presence of eosinophils in aqueous or vitreous biopsy specimens also suggests the diagnosis to toxocariasis [31].

Imaging studies, particularly ultrasound examination and computed tomography (CT), are useful. Three ecographic patterns in 11 patients with OT were reported [31, 32]: (1) a solid, highly reflective peripheral mass (located in the temporal periphery in 91%) of patients, (2) a vitreous membrane extending between the posterior pole and the mass, and (3) traction retinal detachment or fold from the posterior pole of the mass (Fig. 4.7). Also described was pseudocystic transformation of the peripheral vitreous on ultrasound biomicroscopy. Intraocular calcification is not uniformly present, but may be seen in eyes with ocular toxocariasis with significant ocular disruption or phthisis [31].

Recently, it was demonstrated that optical coherence tomography (OCT) is useful for the differential diagnosis between *Toxocara* granuloma that have subretinal extension and idiopathic choroidal neovascularization in the active stage. In general, OCT examination demonstrates a *Toxocara* granuloma as a highly reflective mass, protruding above the retinal pigment epithelium, and sometimes surrounded by subretinal fluid (see Fig. 4.4b) [13, 33, 34].

Differential Diagnosis

Patients with OT will often seek treatment because of leukocoria. The differential diagnosis of OT varies with the clinical presentation of the disease. It includes retinoblastoma (RB), retinopathy of prematurity (ROP), congenital cataracts, persistent fetal vasculature, infectious endophthalmitis, various forms of trauma, and the general groups of severe exudative and hemorrhagic retinopathies, which may present a similar clinical picture [1].

As RB is the most common malignant intraocular neoplasm of childhood, it is critically important to distinguish it, particularly the sporadic, unilateral variant, from OT. Factors that may be helpful in making this distinction include the following: (1) mean age at presentation for OT, 7.5–8.9 years, versus for RB, 22–23 months; (2) paucity of inflammatory stigmata in RB; and (3) continuous growth of RB lesions. Furthermore, normal levels of aqueous humor lactate dehydrogenase and phosphoglucose isomerase, the demonstration of eosinophils in vitreous or aqueous aspirates, and absence of malignant cells favor a diagnosis of OT [31].

Infectious endophthalmitis is distinguished by the history of recent trauma or ocular surgery. Acute signs of external inflammation typical for bacterial endophthalmitis are uncharacteristic in toxocariasis. However, a delayed onset with less virulent bacterial or fungal organisms needs to be differentiated. Vitreous or aqueous sampling for microscopic examination and microbiologic studies should provide a definitive diagnosis in these cases. Endogenous endophthalmitis usually occurs in the setting of immunodeficiency and positive blood cultures [8].

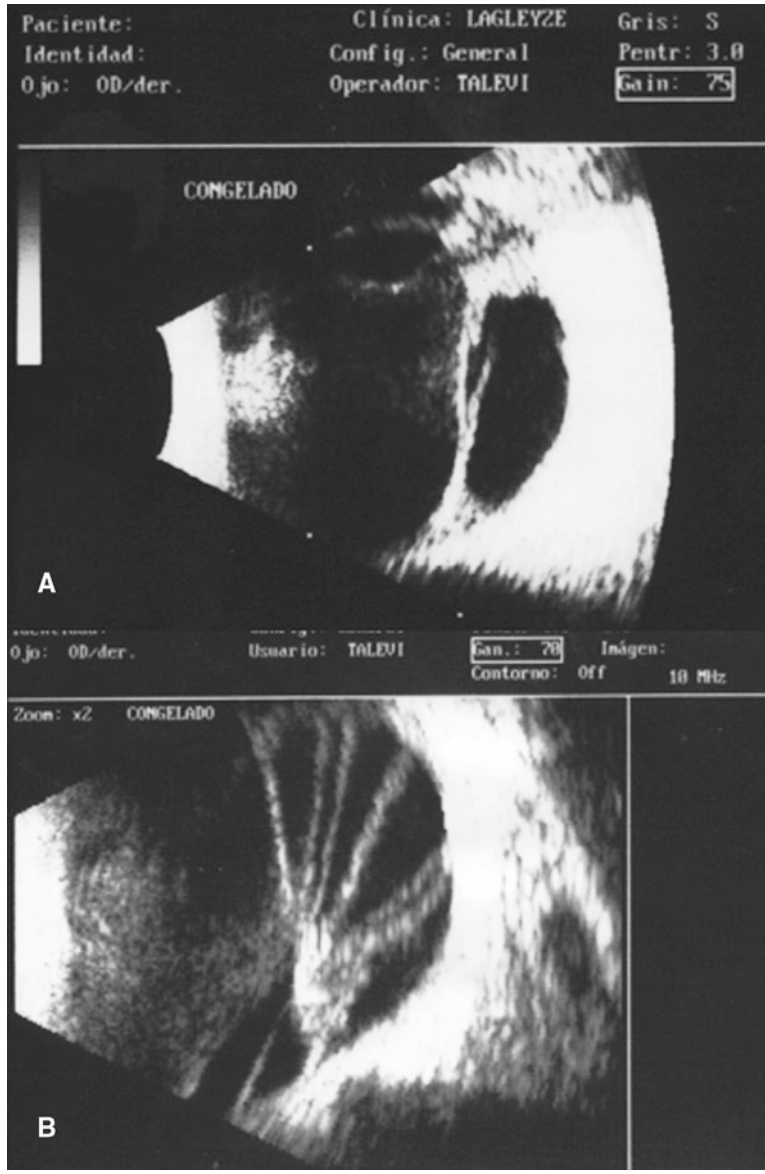

Fig. 4.7 Two different cases demonstrating the ultrasound characteristics of advanced ocular toxocariasis. (**a**) A solid, highly reflective peripheral mass and a vitreous membrane extending between the posterior pole and the mass. (**b**) A tractional retinal detachment at the posterior pole from the mass (Courtesy of Guillermo Talevi, M.D., and Carina Tallano, M.D.)

Differentiation between active toxoplasmic retinochoroiditis and toxocariasis may be difficult, particularly when severe vitritis is present. Serologic studies for toxoplasmosis should provide the diagnosis information [8].

Other pediatric conditions such as ROP, familial exudative vitreoretinopathy (FEVR), persistent fetal vasculature, and Coats' disease usually present neonatally or in early infancy and lack the signs of inflammation of the posterior segment. Retinopathy of prematurity is bilateral, encountered in infants with a history of prematurity and low birth weight, and characterized by proliferative changes and membrane formation.

Persistent fetal vasculature is congenital, unilateral, and associated with micro-ophthalmia. The characteristic morphology includes that of a fibrovascular stalk from the disk to the posterior lens surface, forming a retrolental fibrovascular mass causing ciliary body traction. Coats' disease is a unilateral condition occurring almost exclusively in young males. This is characterized by a white, fibrotic subretinal mass in the posterior pole due to chronic subretinal lipid deposition. There are typical peripheral vascular telangiectasia and lipid exudation with an absence of epiretinal membrane formation [8].

Management

Specific treatment varies greatly depending on the severity of the disease process. The management of the systemic form of toxocariasis includes the use of anthelmintic agents, antibiotics, or steroids [1, 28]. In patients with OT, the visual potential of the eye, the amount of active inflammation, and the macular damage must be considered. Therapy is directed at the inflammatory response to prevent inflammation-induced tissue injury and secondary membrane formation. The inflammation is treated with corticosteroids, either topically or periocularly. Systemic prednisone administered at a rate of 0.5–1 mg/kg/day may be added.

Anthelmintics have been used to destroy viable nematodes and eliminate further migration of the larvae, but the parasites may persist despite treatment [1]. Though numerous anthelmintics have been tested in animal models, controlled randomized studies have rarely been conducted in humans [3]. Magnaval and Glickman have recommended that all cases of VLM should be treated with anthelmintics; they showed similar efficacies of mebendazole (57%), diethylcarbamazine (57%), albendazole (53%), and thiabendazole (47–50%), but moderate efficacy of ivermectin for the treatment of human toxocariasis [3, 12]. Thiabendazole shows negligible larvicidal effects in mice and has a problem in safety, since adverse effects and liver dysfunction occur with a high incidence. In a controlled study, Stürchler et al. reported that albendazole showed a better efficacy for the treatment of OLM when compared to thiabendazole, with milder side effects [35]. In addition, albendazole crosses the blood-brain barrier and has a proven potential for destroying larval stages of *Toxocara spp*. located in the tissues of the paratenic and final host [12]. Diethylcarbamazine, if available, is probably more effective than albendazole; however, its association with gastrointestinal upset and leukopenia (especially in immunocompromised persons) must be borne in mind [4].

Treatment with anthelmintics can lead to severe hypersensitivity reactions caused by dying larvae [36]. Significant allergic or inflammatory reactions can be suppressed with systemic or local corticosteroids. There is no risk of enhancing the infection, as the larvae cannot multiply [12]. Thiabendazole is recommended to be given orally every day in doses of 25–50 mg/kg/day for 7 days, mebendazole's best therapeutic schedule is 20–25 mg/kg/day for 3 weeks, and albendazole is recommended at 10 mg/kg/day for 5 days [3]. Selection of specific drugs depends on several factors, including the physician's previous experience in treating toxocariasis and whether they are locally licensed and available for use. Clearly, there is a need to standardize treatment, where possible, and to adopt a scoring system to quantify clinical severity so that treatment efficacy can be assessed [4].

Peripheral granulomas may be treated with other modalities that include laser photocoagulation; however, any laser procedure may incite an extensive inflammatory response in a uveitic eye [3, 19], and for this reason, combination with steroid therapy to reduce the inflammatory response should be considered. Ocular granulomas can be treated with cryotherapy as well [3, 37]; in children, this procedure is performed under general anesthesia associated to peribulbar anesthesia for intraoperative and postoperative pain control. Cryotherapy is applied directly to the areas of exudation at the pars plana using a double freeze-thaw technique, and periocular steroids should be

administered after the procedure. In cases of residual activity, cryotherapy may be repeated in 3–4 months [19].

Visual loss may result not only from submacular granuloma itself. Intraocular inflammation may lead to macular detachment through either direct vitreomacular traction or epiretinal membrane (ERM), creating a macular pucker that can be demonstrated by OCT (see Fig. 4.4) [19, 38]. Traction also may lead to retinal breaks in atrophic retina, creating a combined tractional-rhegmatogenous detachment as previously stated. A pars plana vitrectomy (PPV) may be beneficial for patients who have not had a satisfactory response to medical treatment or for those who have marked vitreous fibrosis and tractional complications [19, 39]. The fibrous membranes located between the peripheral granuloma and the optic disk usually have extensions into the underlying retina and need to be carefully lifted off from the retinal surface before they can be severed. These membranes usually remain tightly adherent to the optic disk and the peripheral granuloma. They often need to be circumcised rather than delaminated or peeled. Granulomas seem to be an intimal part of the retina; therefore, attempts to extirpate the retinal granuloma usually are unsuccessful and may cause undesirable complications. Therefore, the granulomas are left in place [19, 40].

The results of modern vitreoretinal surgery, in which epiretinal as well as subretinal components of the granuloma are removed by PPV and retinotomy techniques, are reported to provide achievement of macular or complete retinal reattachment in rates up to 100% and 83%, respectively [41]. Additionally, visual improvement after PPV is obtained in 50–66% of cases in some reports [6, 41–43]. Preoperative VA and the presence of tractional retinal folds through the macula affect visual outcome [41, 42]. Even in eyes with chronic tractional retinal detachment, intense anti-inflammatory and orthoptic treatment following surgery can provide ambulatory vision. Pars plana vitrectomy in some cases can also provide diagnostic clues [41].

Controversies and Perspectives

It is difficult to establish the diagnosis of OT based on clinical manifestations solely because ocular symptoms may be diverse and inflammatory signs such as redness and pain are not always present. The diagnosis of OT is often made coincidentally in eyes without inflammation, for instance, during an evaluation for strabismus, in cases of decreased vision, or while undergoing a routine examination [22]. Biopsies are rarely performed, and infection is undetectable in clinically asymptomatic cases. Thus, the sensitivity and specificity of serological tests must be improved.

Although *T. canis* is a parasite of dogs, it can be difficult to distinguish from *T. cati*, a similar parasite of cats; therefore, exposure to both dogs and cats is considered relevant to the condition, and the children are often described to be geophagic [17]. Because *T. canis* is much more prevalent in puppies than in adult dogs, the standardized uveitis questionnaire completed by all patients must ask about exposure to puppies (or kittens) instead of adult animals [17]. The possibility that *T. cati* might play a part in causing ocular lesions has been raised by Petithory et al. who reported positive ELISA tests for *T. cati* in the vitreous of six out of nine patients with OLM, all nine of whom also had positive vitreous *T. canis* ELISA tests [7, 29]. However, it has been reported that standard ELISA tests use the antigen prepared from *T. canis* and show a high cross-reactivity between *T. canis* and *T. cati* [44].

The detection of specific anti-*Toxocara* IgG by ELISA does not appear to be useful for monitoring therapy. When ELISA antibody titers were compared between treated and untreated children, the kinetics of specific anti-*Toxocara* IgG was not affected by anthelmintic treatment. Conversely, the specific anti-*Toxocara* IgE serum concentration does seem to decrease significantly posttreatment if it is markedly elevated prior to therapy, especially in atopic patients [3]. *Toxocara* antibody titers can remain positive in the absence of disease, and eosinophilia can take more than 2 years to decline to normal values.

ELISA has offered the best compromise until now with native proteins, but sensitivity and specificity are dictated by the manufacturer's choice of target antigens and the quality control and quality assurance in place [4]. On the other hand, the absence of serum antibodies does not rule out the diagnosis [17]. Therefore, it has been suggested that sera should be tested at dilutions as low as 1:2 and not 1:8 as much of physician use [22]. Additionally, Magnaval et al. noted that eosinophil counts were useful markers in a post-treatment follow-up study (except for ocular patients) [3].

Testing intraocular fluids for antibodies has also been shown to be helpful in diagnosing toxocariasis. These samples often contain higher levels of antibody than the serum [17]. Also, these intraocular fluids might play a role in the differentiation between RB and *Toxocara* posterior pole granuloma in children. However, the decision to perform paracentesis should be made reluctantly, attributable to the risk of spreading malignant cells in case of RB [22].

For the surgical treatment, Werner et al. have recommended that the removal of all components of a *Toxocara* granuloma can be successful in treating OT and is possible with PPV and subretinal surgical techniques [39]. However, another report suggests that the posterior subretinal granuloma should not always be removed in eyes with OT [38].

The role of *Toxocara* infection in asthma is unclear. A notable association between asthma and recurrent bronchitis and *Toxocara* seropositivity was found in children aged between 4 and 12 years in the Netherlands; and in a mouse model, *Toxocara* was found to provoke airway inflammation. However, other human studies in the United States failed to corroborate the association between asthma and *Toxocara* seropositivity [4, 26].

While the NHANES studies indicate that toxocariasis continues to persist and is underrecognized as a health problem, a full appreciation of the US and global burden of disease caused by toxocariasis demands improved serodiagnostic tools. In the United States, the enzyme immunoassay testing is not widely available because of the limited capacity for parasitic disease diagnosis and the limited availability of antigen made from *T. canis* larvae. In addition, the existing assays have a low sensitivity for detecting ocular larva migrans; therefore, some true cases remain undiagnosed and the approximations of national seroprevalence are underestimated [23]. A role for IgE antibody detection, particularly for posttreatment follow-up, has already been identified, and the role of other bodily fluids, such as ocular fluids, for serology requires further investigation.

Further studies to improve diagnostic testing, treatment strategies, patient management, and expand epidemiologic surveillance should be conducted in parallel with control and prevention efforts. These include periodic deworming of dogs and hand washing to prevent fecal oral contact, and case detection and treatment with anthelmintic (preferably albendazole). Better communication between clinicians and diagnostic laboratories is required so that time-course serostudies can be performed and investigations into antibody and antigen kinetics before, during, and after treatment can be undertaken and evaluated. Given the high prevalence of toxocariasis in areas of poor urban and rural hygiene, improved sanitation and access to clean water may also have important roles.

Currently, the best serodiagnostic options are using the IgG TES-ELISA as a screening test (with confirmation by IgE TES-ELISA) and TES-WB. Increased specificity can be achieved by using an IgG4 TES-ELISA, and IgG4 TES-WB could also be useful because it might provide further discrimination after IgG TES-ELISA screening. Better insight into the significance of minor antibody isotypes can be provided by increasing TES coating concentration, although its usefulness could be outweighed in regions where polyparasitism is endemic [4].

The differential diagnosis of OT is largely based on clinical characteristics, a history of prodromal visual and systemic symptoms, signs of inflammation, size and location of lesions, and including the course of the disease process. Optical coherence tomography has become a valuable ancillary diagnostic tool and can

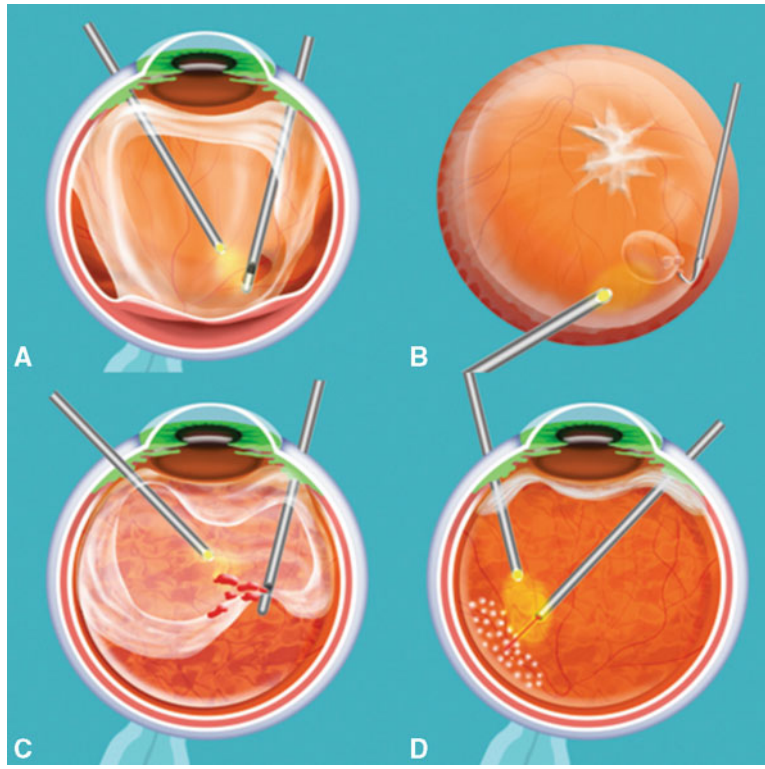

Fig. 4.8 Artist's representation of surgical technique. (**a**) After a core central vitrectomy, a hole is then made in the midperipheral posterior hyaloid. (**b**) Perfluorocarbon liquid (PCL) is injected to mechanically and slowly separate the posterior hyaloid from the retina. A viscodissector attached to a 5-mL syringe filled with PCL to separate membranes from the underlying retina. (**c**) Once all the epiretinal tissues have been separated from the retina, vitrectomy is completed. (**d**) Endolaser is applied under PCL (shown). An air-fluid and an air-silicone oil exchange are performed to finish the case (not shown)

provide useful information on the morphological features associated to the disease. Cross-sectional OCT images may increase understanding of the pathophysiology of presumed subretinal *Toxocara* granulomas and help in the clinical management of the retinal complications related to this disease [13]. The *Toxocara* larva commonly migrates across the retina, and with the actual use of the OCT, Suzuki et al. [45] have reported that the *Toxocara* larva most likely migrate in the nerve fiber layer in a case of posterior pole *Toxocara* granuloma, and Higashide et al. [33] demonstrated by OCT that the granuloma was located in the subretinal space and resembled choroidal neovascularization. Perhaps the pathology of a lesion migrating in the retinal surface is quite different from that of a subretinal lesion.

Pars plana vitrectomy is the choice of treatment to manage the inflammatory complications of OT and also has been considered as a tool of diagnosis, including in cases with chronic disease [41]. Recently, Arévalo and Garcia-Amaris [19] have described a new surgical dissection technique called "En bloc perfluorodissection" that facilitates removal of ERMs and the posterior hyaloid. It is performed by injecting perfluorocarbon liquid (PCL) between the retina and the posterior hyaloid to separate both the posterior hyaloid and epiretinal tissues from the subjacent retina. This technique has demonstrated to be useful during vitrectomy in eyes with tractional retinal detachment and severe OT (Figs. 4.8 and 4.9). Other advantages include retinal stability at the time of vitreous removal, better visualization of vitreous and intraocular structures, rapid retinal reattachment,

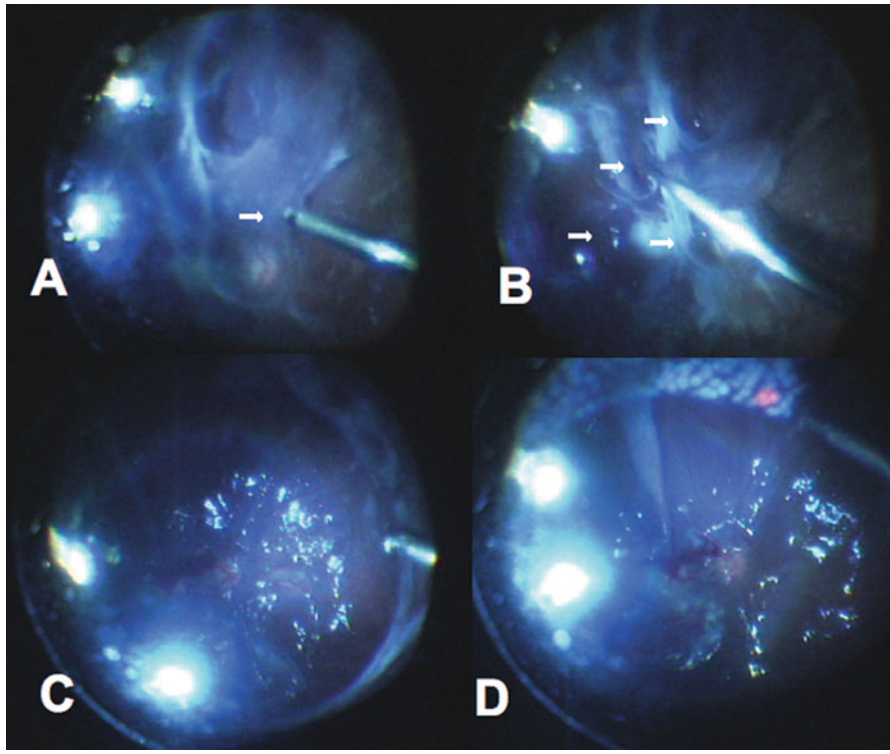

Fig. 4.9 En bloc perfluorodissection performed in a case of tractional retinal detachment in ocular toxocariasis. (**a**) After a core central vitrectomy, a hole is then made in the midperipheral posterior hyaloid (*arrow*). (**b**) Perfluorocarbon liquid (PCL) is injected to mechanically and slowly separate the posterior hyaloid from the retina (*arrows*). A viscodisector attached to a 5 mL syringe filled with PCL is used to separate all the epiretinal tissues from the retina. (**c**) Once all the epiretinal tissues have been separated from the retina, vitrectomy is completed. (**d**) Endolaser is applied under PCL (shown). An air-fluid and an air-silicone exchange are performed to finish the case (not shown)

less blood in the vitreous cavity, subretinal fluid resolution, blood confinement, and easier dissection of ERMs.

Focal Points

Ocular toxocariasis is an uncommon worldwide ocular infection that affects mostly children. It is found in both rural and metropolitan areas. The most common route of infection is the ingestion of soil contaminated with *Toxocara* larva. In most cases, the course of the disease is mild, but the spectrum of clinical manifestations and severity is broad, and the potential for uniocular blindness due to this entity is well recognized. Consequently, to improve the prognosis, visual acuity screening in day-care centers and in schools may be critical to detect this disease in its early stages.

The diagnosis of toxocariasis is essentially clinical, based on the lesion morphology and supportive laboratory data and imaging studies. Differentiation of OT from RB is critical. To avoid unnecessary enucleation of eyes with OT, it is imperative to establish an adequate correlation between the clinical findings and diagnostic methods including serum ELISA titers, radiologic evaluation by ultrasound, and CT scan, and also OCT could be a useful tool. It is of particular importance to perform ELISA *Toxocara* titers on aqueous and/or vitreous humor when the clinical diagnosis is not clear or when the serum ELISA is inconclusive.

Treatment is directed at complications arising from intraocular inflammation and vitreous membrane traction. Early vitrectomy may be of value both diagnostically and therapeutically. Early therapeutic vitrectomy is recommended based on the beneficial results obtained in several series of patients. If an early vitrectomy is performed, then analysis of ELISA titers and cytology of the vitreous humor should be performed for diagnostic purposes.

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Retinal and Choroidal Manifestations of Tuberculosis

5

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Abstract

Ocular tuberculosis has been recognized from the nineteenth century onward due to the work of Gueneau de Mussy, Jaeger, Fraenkel, and Bouchut. Ocular tuberculosis had a high prevalence worldwide in the twentieth century, but this prevalence has reduced significantly in the western hemisphere, a decline that has paralleled the decline of tuberculosis as a common systemic infection. In recent times, the prevalence varies from 18% (Spain) to 1.39% (India). The advent of the human immunodeficiency virus (HIV) epidemic has led to an increase in the prevalence of ocular tuberculosis to up to 23.5%. Manifestations vary depending upon the ocular tissue involved. The manifestations can either be due to direct tissue infection or be hypersensitivity reactions. Rare manifestations include the eyelids (lupus vulgaris), the conjunctiva (conjunctivitis), cornea (ulcers and phlyctenulosis), and the sclera (scleritis). The most common manifestations include uveal involvement in the form of tubercles, tuberculomas, and serpiginous-like choroiditis. Other manifestations include orbital apex syndrome and lesions associated with neurotuberculosis (disc edema and sixth nerve palsies). The diagnostic workup of patients with suspected ocular tuberculosis has both systemic and ocular components. The systemic investigations include (1) radiography: (a) chest X-rays and computed tomography of the chest and (b) abdominal CT

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scan or ultrasonography; (2) Mantoux testing; and (3) interferon-γ(gamma) release assays (IGRA). Ocular investigations of ocular fluids or tissue biopsies include (1) microscopy, (2) culture, and (3) PCR (polymerase chain reaction) techniques. The treatment includes the use of topical, periocular, or systemic corticosteroids with a four-drug regimen of antitubercular therapy.

Keywords
Mycobacterium • Tuberculosis • Ocular • Tubercles • Vasculitis • Choroiditis • Antitubercular therapy

Introduction

Tuberculosis or human infection with mycobacterium species has been reported since prehistoric times, but it needed the development of modern ocular diagnostic tools to identify ocular tuberculosis. Uveal tuberculosis in the form of tubercles was recognized in 1830 by Gueneau de Mussy and by Jaeger, who in 1855 described similar findings. Fraenkel (1867) described the clinical appearance of tubercles, and this work was carried on by Bouchut, Fraenkel, and Weiss. In the early twentieth century, Hoeve (1925), Bollack (1927), and Baldenweck (1938) laid the groundwork for the continued use of fundus examination in the diagnosis of miliary tuberculosis.

Treatment for tuberculosis in the pre-antibiotic era consisted of admission in sanatoriums, fresh air, exercise, and various pneumothorax surgeries, and these institutions reported large numbers of patients of ocular tuberculosis. Of the 10,524 patients that Donoghue examined in the period 1940–1966, he reported that 1.4% of them needed treatment for ocular tuberculosis [1]. Similarly, Illingworth, in an early meta-analysis of publications from 1913 to 1947, noted 206 cases of choroidal tubercles in 737 patients (28%) [2].

Simultaneously, tuberculosis was also the single most common etiological diagnosis in ophthalmology outpatient departments. In 1960, Woods suggested that at least 21.8% of patients presenting with posterior uveitis had ocular tuberculosis.

Current Epidemiology

The advent of improved public health measures and antitubercular therapy has led to a marked reduction in the rates of tuberculosis over the world, and this parallels the reported decline in the incidence of ocular tuberculosis. These declines are more marked in the developed world as compared to the developing world.

Data from several studies in recent times have documented the prevalence of ocular lesions in patients with systemic, largely pulmonary, tuberculosis. In a study from Spain, Bouza et al. examined 100 patients with culture-positive tuberculosis and found tubercular choroiditis (commonly), papillitis, retinitis, vitritis, and vasculitis in 18 patients, suggesting a prevalence of as much as 18%, but 11 of these patients had additional human immunodeficiency virus (HIV) infection [3]. In India, lower prevalence rates were seen in a study of 1,005 patients, of whom 1.39% had ocular lesions [4]. Systemic dissemination has been reported to significantly increase the likelihood of ocular lesions to as much as up to 60% [5].

Tuberculosis is also less prevalent as an etiologic agent in patients with intraocular inflammation in developed countries. This may result from a reduced prevalence of tuberculosis but is also due in part to awareness of other etiologies and better diagnostic techniques. Tuberculosis was found to be responsible for 0.2% of cases of posterior uveitis and in no cases of anterior uveitis in Southern California [6].

Schlaegel and O'Connor reported that tuberculosis was responsible for 0.28% of uveitis cases in the 1970s, which had fallen from an incidence of 8.6% in the 1950s. In developing countries with a still high prevalence of tuberculosis, it remains a relatively common etiologic agent. Studies from North India have estimated that it is the etiological agent in 7.9% of cases of anterior uveitis, 4% of cases of intermediate uveitis, 8.95% of cases of posterior uveitis, and 26% of cases of panuveitis. Overall, 125 patients of 1,233 (10.1%) cases had a tuberculous etiology [7]. Interestingly, a study from Italy revealed tuberculosis as the etiological agent in 3.6% of cases of anterior uveitis, 2.5% of cases of posterior uveitis, and 0.7% of cases of panuveitis [8], suggesting that a diagnosis of ocular tuberculosis is becoming increasingly common in developed countries.

The advent of the HIV epidemic has led to an increase in the prevalence of ocular tuberculosis in patients with systemic HIV-TB (HIV-tuberculosis) coinfection, but large studies are few. In a study of 307 patients in Malawi, choroidal granulomas were seen in 2.8% of patients with mycobacteremia and acquired immunodeficiency syndrome (AIDS) [9]. However, another study showed no lesions suggestive of ocular tuberculosis in 154 patients of AIDS in Burundi [10]. In a prospective study from Mumbai, India, 23.5% of AIDS patients with systemic tuberculosis had ocular lesions [11], but a much lower prevalence was seen in a neighboring city, where although as many as 66% of 1,268 patients had systemic tuberculosis, only 1% of patients had ocular tuberculosis [12].

Etiopathogenesis of Ocular Tuberculosis

Several members of the *Mycobacterium tuberculosis* complex, namely, *M. tuberculosis, M. bovis,* and *M. africanum,* are responsible for the majority of systemic and ocular tuberculous disease. The most important agent is *M. tuberculosis,* which spreads as airborne droplets that are released into the air by patients with pulmonary (usually cavitatory) tuberculosis. Inhalation of these droplets leads to an initial infection where the bacilli multiply and are spread hematogenously to several areas that usually include the lung apices, skeletal system, and the choroid. In most individuals, immune responses prevent the establishment of clinical disease, but a small number develop clinical (primary) disease at this stage. The bacillus in the remaining patients remains in a latent state, but a number of triggers, commonly HIV infection, cancer, or any other immune deficiency state, can produce active clinical disease in 5–10% of patients at some point in their lives. This is termed as reactivation or secondary tuberculosis.

Ocular tuberculosis may occur at both the primary and secondary stages of clinical disease; thus, patients may range in age from childhood to late adulthood. Earlier classifications have described ocular tuberculosis as primary (from direct inoculation of bacilli) or secondary (as a result of hematogenous spread). Current thought holds that virtually all ocular and orbital diseases are a result of hematogenous spread, and thus, this classification is obsolete.

Specific Ocular Manifestations

Ocular tuberculosis can have myriad manifestations and can affect virtually all ocular tissue. These are summarized in Table 5.1.

Eyelid Tuberculosis

This is commonly seen in childhood and is thought to be lupus vulgaris (cutaneous tuberculosis). The clinical appearance includes reddish-brown nodules that exhibit an apple-jelly color on pressure or as erosive skin lesions. Eyelid tuberculosis also commonly mimics chalazia, and unusual or atypical chalazia should be carefully investigated, preferably with a histopathological study. Globe or orbital extensions have been reported [13, 14]. Several authors have described abscesses and cellulitis of the eyelids resulting from tuberculous infection. Raina et al. reported seven children who presented with

Table 5.1 Ocular manifestations of tuberculosis

Ocular tissues	Manifestation	Etiopathogenesis
Eyelids	Lupus vulgaris, lid abscess	Direct infection
Conjunctiva	Conjunctivitis	Direct infection
Cornea	Phlyctenulosis, ulcers, interstitial keratitis	Direct infection/hypersensitivity
Sclera	Scleritis	Direct infection
Uvea	Chronic granulomatous anterior uveitis, tubercles, disseminated choroiditis, panuveitis	Direct infection
Retina	Vasculitis, retinitis	Direct infection/hypersensitivity
Orbit	Proptosis, orbital apex syndrome	Direct infection
Meninges/brain	Optic atrophy, disc edema, cranial nerve palsies	Direct infection

preseptal cellulitis and had evidence of systemic tuberculosis. Spontaneous fistulization was common [15]. Increasingly, atypical mycobacteria have been implicated in periocular infections. Chang et al. described six patients with *Mycobacterium chelonae* or *Mycobacterium fortuitum*. Immunosuppression, nasolacrimal duct obstruction, the presence of a foreign body, and a history of recent surgery were identified as risk factors [16].

Conjunctival Tuberculosis

Conjunctival tuberculosis was initially described by Arlt. An early meta-analysis (Eyre 1912) discussed 177 cases in published literature and 29 of his own who had histology or animal inoculation proven disease. The disease patterns identified included a propensity to affect young adults (<20 years), unilateral disease, and a predilection for involvement of the upper palpebral conjunctiva. Variants identified included ulcerative, hypertrophic, miliary tubercle, lupus, and pedunculated tumor. Only seven of these 160 patients had evidence of systemic tuberculosis.

Recent reviews have described primary tuberculous conjunctivitis presenting as a mucopurulent conjunctivitis with lid edema accompanied by lymphadenopathy that tends to caseate or undergo fistula formation. Conjunctival smears show the presence of acid-fast bacilli on the appropriate stain. Lamba et al. have reported the case of a 30-year-old female patient with miliary tuberculosis who presented with two reddish yellow, soft, nontender conjunctival nodules that revealed acid-fast bacilli on Ziehl-Neelsen stain with subsequent positive cultures [17].

Scleral Tuberculosis

Verhoeff (1907) identified tuberculosis as the etiological agent in patients with scleritis based on histopathological findings. Only 3 of these 13 patients had systemic disease, but the authors concluded that its presence was necessary. Tuberculosis may present as a dark red focal area of necrotizing scleritis that shows chronic granulomatous inflammation with caseating necrosis on histopathology. In rare cases, scleral necrosis can occur. This diagnosis, though rare, is a differential diagnosis in patients unresponsive to traditional methods of treatment. Well-documented scleral tuberculosis was reported by Bloomfield et al. in an 82-year-old female patient whose tissue sections showed acid-fast bacilli, and *M. tuberculosis* was grown on culture. Oral isoniazid and rifampicin, along with topical and subconjunctival streptomycin, led to a complete cure [18]. In a solitary case, Gupta et al. have presented the findings of a 45-year-old female patient of posterior scleritis with a clinical presentation of optic disc edema and choroidal folds. Sclerochoroidal thickening with fluid in the sub-Tenon's space was seen on ultrasonography. Systemic investigations revealed a positive Mantoux test and right upper lobe infiltrates. The patient responded to systemic corticosteroids and antitubercular therapy [19].

Phlyctenulosis

The presence of an allergen within corneal or conjunctival tissue may occasionally produce a nonspecific immune reaction termed as phlyctenular keratoconjunctivitis. The association between tuberculosis and phlyctenulosis was hypothesized in the early twentieth century by several researchers, but the first large series was collected by Gibson (1918), who examined and investigated 92 such patients with phlyctenular keratoconjunctivitis. The overwhelming majority (90%) had positive Mantoux tests, but detectable systemic disease was found in only 26%. In distinction, other large cohorts of 1,073 patients and 105 contacts and another of 600 patients, phlyctenulosis was found in only two patients in either series. However, epidemiological data suggest a strong link between phlyctenulosis and tuberculoprotein hypersensitivity, particularly in areas where tuberculosis is endemic. The common presentation is in malnourished children who display single or multiple grayish limbal nodules of 1–3 mm in size. The overlying epithelium occasionally becomes necrotic and may ulcerate. These ulcers may migrate toward the cornea usually dragging a small leash of superficial blood vessels along with it producing photophobia and watering. Topical steroids are recommended for the ocular inflammation and systemic antitubercular therapy if any systemic disease is detected. The disease tends to be recurrent throughout the patients childhood.

Corneal Tuberculosis

Tubercular infection tends to produce both immune reactions as well as direct infection. The most common immune reaction is interstitial keratitis that is usually a unilateral infiltrate in the peripheral stroma with its accompanying vascularization. The deposition of mycobacterial antigens within corneal tissues is thought to induce a hypersensitivity reaction. Topical steroids are required to resolve these infiltrates as is systemic antitubercular therapy for any associated systemic disease. Other findings include infiltrations and ulcerations. In the recent decades, the growing popularity and numbers of refractive surgery procedures have led to increasing numbers of corneal infections. Patients undergoing laser-assisted intrastromal keratomileusis (LASIK) may be infected with atypical mycobacteria, mainly *M. chelonae*, and these infections usually present as haziness at the flap-corneal interface or even as corneal abscesses in severe cases. Treatment consists of frequent use of fourth-generation fluoroquinolones or, in severe cases, flap excision.

Uveal Tuberculosis

The hallmark manifestation of ocular tuberculosis is infection or inflammation of the uveal layer of the eye.

Anterior Uveitis

Tubercular anterior uveitis produces the prototype granulomatous inflammation along with syphilis and leprosy. This term describes the classically described large and greasy keratic precipitates that appear like "mutton-fat" globules but may be fine and white in some instances. The anterior uveitis may present in an acute fashion but is commonly chronic. Frequently, it may be recurrent in nature. The intensity may range from mild to severe with broad-based dense posterior synechiae. Translucent nodules may occur at the pupillary margins (Koeppe nodules, that are thought to mark the sites of future posterior synechiae) or grayish nodules may form on the iris surface or in the superficial stroma (Busacca nodules). These iris nodules probably represent a form of iris tubercle. Treatment is with topical or periocular steroids and systemic antitubercular drugs (if a focus of systemic tuberculosis is present).

Intermediate Uveitis

Tuberculous infection can also present as a smoldering low-grade chronic intermediate uveitis. There is generally an associated vitritis, snowball opacities (Fig. 5.1), pars plana exudates, and peripheral vascular sheathing. Treatment is with topical or periocular steroids and systemic

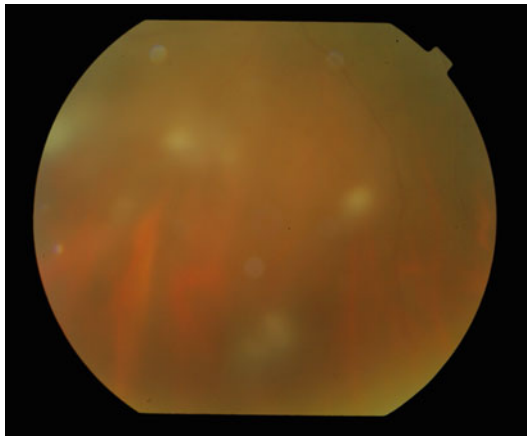

Fig. 5.1 The right eye of a 40-year-old female patient showing multiple *white* fluffy opacities in the vitreous (*snowballs*). The patient had associated mediastinal tuberculosis

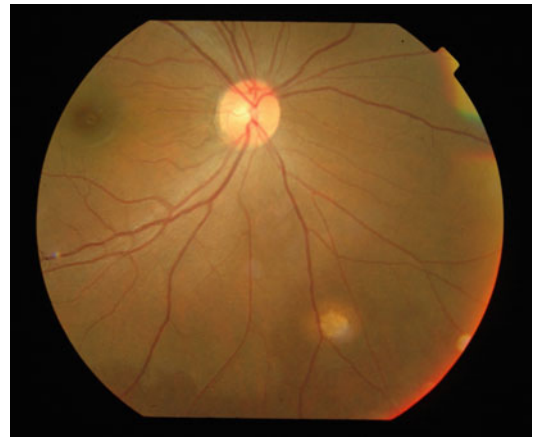

Fig. 5.2 The right eye of a 32-year-old female patient showing a *yellow-white* tubercle in the inferior retina. The patient had associated pulmonary and central nervous system tuberculosis

antitubercular drugs (if a focus of systemic tuberculosis is present).

Posterior Uveitis (Choroidal Tuberculosis)

Choroidal tubercles and tuberculomas (larger-sized lesions) are the most common manifestations of ocular tuberculosis (Figs. 5.2 and 5.3). The prevalence varies from 1.4% in patients with isolated pulmonary tuberculosis to 60% in the disseminated forms of tuberculosis. Tubercles are yellow-white in color and usually have an overlying and surrounding serous retinal detachment in the acute phases. They range from ¼ disc diameter (DD) to several DDs in size and are commonly found in the posterior pole. The number of tubercles varies from 1 to 50 with five being the average. Histopathology of uveal tissue specimens reveals classical caseating granulomas that are characterized by stromal destruction with swelling of the adjacent choroid and infiltration with round cells, epithelioid cells, and giant cells. Appropriate staining techniques have revealed the presence of mycobacteria within the tubercle, suggesting a direct tissue infection. Fundus fluorescein angiography of these tubercles has a distinctive appearance with an early hypofluorescence or minimal hyperfluorescence within the tubercle that increases in the later

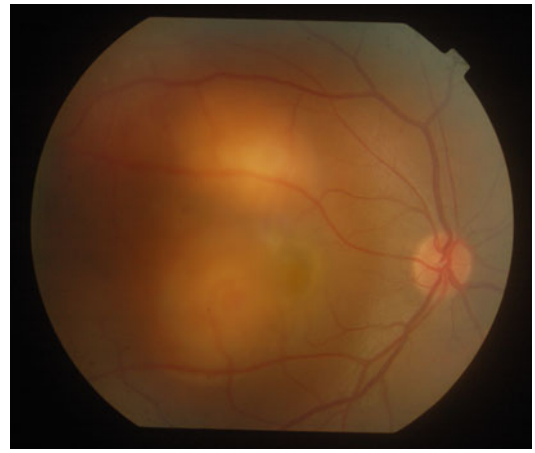

Fig. 5.3 The right eye of a 28-year-old female patient showing multiple large tuberculomas with a surrounding exudative detachment in the posterior pole. The patient had associated miliary tuberculosis

phases. Significant peritubercular fluorescence is seen in all the phases of the angiogram giving a "ring of fire" picture [20], suggesting that the inflammatory activity may extend beyond the boundaries of the visible tubercle. Optical coherence tomography studies reveal attachments between the retinal pigment epithelial-choriocapillaris layer and the overlying neurosensory retina. There is an associated surrounding subretinal

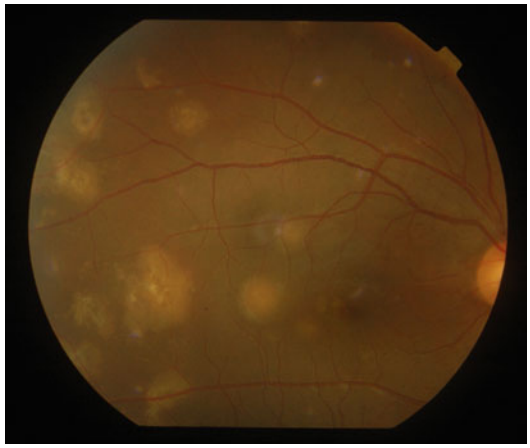

Fig. 5.4 The right eye of a 44-year-old female patient showing multiple confluent areas of choroiditis in a serpiginous pattern

fluid and inflammatory infiltrates in the deeper retinal layers [21]. The differential diagnosis includes sarcoid granulomas, syphilitic gummas, and metastases from malignancies.

A serpiginous-like choroiditis has now been described in patients with systemic tuberculosis (Fig. 5.4). A series of seven such patients was examined and described by Gupta et al. Three patterns of disease were identified: multifocal progressive choroiditis showing a wavelike progression to confluent diffuse choroiditis or diffuse plaque-like choroiditis in an amoeboid pattern. Mycobacterial DNA was identified from the aqueous and vitreous humor via polymerase chain reaction (PCR) studies. A combination of systemic/topical steroids and antitubercular therapy was prescribed for these patients [22].

Orbital Tuberculosis

Tuberculosis of the orbit may either spread from contiguous structures or may spread hematogenously. Orbital lesions are common in young adults (<20 years old), are chronic, slowly progressive, and unilateral, and patients may complain of varying degrees of pain and discomfort. Common signs include proptosis, lid swelling, orbital pain and discomfort, decreased visual acuity, or visual field abnormalities. Evidence of currently active or healed pulmonary tuberculosis is common on radiological studies. Computed tomography (CT) studies are the investigation of choice and may reveal bony erosions. Orbital fine needle aspiration cytology (FNAC) or biopsies and subsequent histopathological examination frequently reveal the diagnosis. Cultures of orbital tissue may be of help in certain cases. Treatment consists of standard antitubercular therapy along with appropriate surgery. Other reported presentation includes patients who have developed a fistula in an orbital abscess, fungating masses [23] or lesions surrounding the optic nerve [24, 25]. The hallmark "cold abscess"—i.e., an infective mass lesion but without the pain, redness, or warmth of an acute bacterial abscess—may be seen in some patients.

Retinal Tuberculosis

Tuberculosis may involve all the components of the retina including the neural tissue (retinitis) and the retinal vasculature (vasculitis).

Retinal Vascular Disease

Two distinct patterns exist. These include (1) Eales' disease and (2) tuberculous retinal vasculitis.

Eales' disease was reported by Henry Eales (1880), who described recurrent retinal and vitreal hemorrhages associated with constipation and epistaxis in a cohort of young men. It is an immune-mediated peripheral retinal periphlebitis that leads to a peripheral retinal ischemia and neovascularization. Eales' disease largely affects young men between the ages of 20–40. Evidence of previous tuberculous infection in the form of positive Mantoux tests is common, but active pulmonary tuberculosis is uncommon. In a series of 32 patients reported by Renie et al., only two had active pulmonary tuberculosis, whereas positive Mantoux tests were the only significant finding in eight of the remaining [26]. However, mycobacterial DNA has been isolated from the vitreous and surgically excised

epiretinal tissue [27]. Classically, there are four described stages:

I. Mild periphlebitis
II. Widespread periphlebitis involving larger vessels and adjacent arterioles
III. Neovascularization with retinal and vitreal hemorrhages
IV. Fibrovascular proliferations with recurrent vitreous hemorrhages

The usual presentation is of unilateral vitreous hemorrhage-induced visual loss. Examination of the fellow eye reveals the characteristic peripheral retinal periphlebitis. Resolution of the vitreous hemorrhage shows hemorrhages and exudates along the peripheral vessels. The visual loss may be reversible as a result of vitreous hemorrhages or may be permanent due to anatomical changes in macular architecture or tractional retinal detachments. A fundus fluorescein angiographic examination helps to assess the severity of vasculitis and study the extent of ischemia and neovascularization. Laser photocoagulation may be needed in patients with extensive peripheral ischemia or neovascularization. Non-clearing vitreous hemorrhages may need a core vitrectomy, laser photocoagulation with additional management as needed for fibrous proliferations or tractional detachments. The medical management includes the use of systemic or periocular corticosteroids for the control of the vasculitis. There is no consensus on the need to use antitubercular therapy in these patients.

In contrast, tubercular retinal vasculitis is associated with active systemic tuberculosis. This form of vasculitis is usually a direct result of infection with *M. tuberculosis* or may be a combination of direct infection with an associated hypersensitivity. Rosen et al. described a series of 12 patients of ocular tuberculosis of whom 9 patients had retinal vasculitis. The common clinical picture was of an acute retinal periphlebitis with a moderate grade of vitreous infiltrate tending to develop a peripheral ischemia and neovascularization. Clinical systemic disease was seen in three patients, but all had strongly positive Mantoux tests [28]. PCR techniques are increasingly being used to identify tubercular retinal vasculitis. In one series, Gupta et al. used this technique to arrive at a diagnosis in 13 patients of retinal vasculitis, and the consistent presence of areas of active or healed choroiditis in these patients led the authors to suggest that presence of these areas may tend to suggest a tubercular etiology [29]. A fundus fluorescein angiographic examination reveals the presence and extent of ischemia and possible neovascularization. Appropriate laser photocoagulation may be necessary for areas of extensive peripheral ischemia or in cases with established retinal neovascularization. The vasculitis may require systemic/periocular corticosteroids, and antitubercular therapy is necessary.

Tubercular retinitis is rare and may result by a process of contiguous spread from the choroid or via hematogenous dissemination and is seen as a focal or diffuse retinitis often accompanied by vitreous opacification.

Tuberculous Panophthalmitis

Rarely, a granulomatous inflammation may affect all the coats of the eye, producing a panophthalmitis. Most case reports describe a painless and progressive disease process with defective vision, ophthalmoplegia, corneal haze and hypotony. Tubercular panophthalmitis is thought to be more common in children, malnourished adults, or in patients with systemic tubercular disease. The histopathological features have been described recently by Chawla et al. in the case of a 12-year-old girl. She presented with a painless and progressive reduction in vision and had corneal vascularization, iris nodules, and scleral necrosis. The eye was enucleated, and examination showed a necrotizing granulomatous inflammation consisting of epithelioid cell granulomas along with areas of caseous necrosis. In the opinion of the authors, the absence of pain, eyeball nodules, and a tendency to perforation may point to a tubercular infection [30]. Antitubercular therapy may be helpful in earlier-stage disease but may be of limited value

in end-stage disease, when enucleation may be necessary to establish the diagnosis.

Neuro-ophthalmological Aspects

Neurotuberculosis is a common presentation of systemic tubercular disease, and as a result, neuro-ophthalmological findings are common and varied. In perspective, 67 (67%) of 100 Indian patients with tubercular meningoencephalitis had neuro-ophthalmic findings, commonly optic neuritis (32% with about half progressing to optic atrophy), gaze palsy (20%), third and sixth nerve palsy, conjugate deviation, primary optic atrophy, and complete ophthalmoplegia [31].

The findings depend in part on the specific clinical pattern of neurotuberculosis in the individual patient. Tuberculous meningitis is the most common pattern and is characterized by the formation of thick exudates at the base of the brain often extending to the basal cisterns and the sylvian fissure. An accompanying vasculitis of the adjacent small- and medium-sized vessels is the norm as is an inflammation of any underlying brain parenchyma. This vasculitis is responsible for the observed cranial nerve involvement including the optic and oculomotor nerves.

Involvement of the optic nerve in tubercular meningitis is common and is responsible for the majority of the ocular morbidity associated with this condition. A primary optic atrophy often ensues in varying degrees. In patients presenting in the acute stages of the disease, an early diagnosis is often possible, moreover, if patients complain of visual loss, but often diagnosis is late as patients who have been critically ill or comatose are unable to articulate visual symptoms. Simultaneous use of systemic corticosteroids along with the antitubercular therapy may reduce this complication. In one clinical trial, 27 patients with tuberculous meningitis were treated with ethambutol, isonicotinic acid hydrazide, streptomycin, and dexamethasone versus a control group of 28 who were treated with triple antituberculous drugs only. Ocular complications were seen in two of the combined dexamethasone and antitubercular therapy group as compared to seven of the group not receiving dexamethasone [32]. However, larger and more controlled double-blind studies are required. Girgis et al. have hypothesized that suggested that the concurrent use of dexamethasone in tuberculous meningitis may reduce the ocular morbidity but may not reverse established damage.

A diagnostic rule has been formulated that tracks five variables (optic atrophy, focal neurological deficit, symptoms lasting longer than 6 days, abnormal movements, and neutrophils constituting less than 50% of CSF neutrophils), and it has a diagnostic sensitivity of 98% and a specificity of 44% when one feature was present and a diagnostic sensitivity of 55% and specificity of 98% when three or more features are present [33].

Involvement of the oculomotor nerves is also well known with the VI being the most commonly involved followed by the III and the IV [34]. In a review of tuberculous meningitis, up to 30–40% of patients had a VI nerve palsy as compared to 5–15% with a III nerve palsy [35]. Oculomotor nerve palsies may either recover fully or may be a part of permanent neurological sequel.

Other patterns of neurotuberculosis include the avascular spherical granulomatous lesions termed as tuberculomas. Tuberculomas may directly compress any part of the visual pathway (commonly the optic nerve) or any of the oculomotor nerves producing either visual loss or oculomotor palsies.

Intracranial tuberculosis in any pattern can cause a raised intracranial pressure that is visible clinically as papilledema or unilateral or bilateral VI nerve palsy. This raised pressure is due to the exudates associated with tubercular meningitis that tend to block the normal outflow channels of the cerebrospinal fluid at the foramen of Luschka and Magendie or is due to the space-occupying lesion effects of large tuberculomas. A secondary optic atrophy often supervenes if untreated.

Intraocular findings are also frequent including chorioretinitis and tubercles, and retinal vasculitis. As part of the hematogenous dissemination that is

the cause of the neurotuberculosis, choroidal tubercles may occur. The prevalence of such tubercles depends on the extent and pattern of the neurotuberculosis and systemic tuberculosis that is present. In a series of 52 patients with tubercular meningitis, Kennedy et al. detected choroidal tubercles in 2% (1 of 52) of patients [36]. Tubercles are virtually pathognomonic of and more prevalent in patients with miliary tuberculosis, and their presence has been suggested as a diagnostic guideline. Up to 10% of patients with miliary tuberculosis–induced neurotuberculosis may show choroidal tubercles [37]. In recent studies, Mehta et al. have shown that a finding of choroidal tubercles in patients of neurotuberculosis indicates the presence of a concurrent systemic focus of tuberculous infection (usually pulmonary) [38].

Ocular Tuberculosis in HIV-Positive Patients

The epidemic of HIV infection has led to a marked resurgence of systemic tuberculosis. In hyperendemic areas, mycobacterial infections are a common superinfection and may occur due to a reactivation of preexisting latent tuberculosis or due to fresh infections. The prevalence of systemic tuberculosis has increased 20-fold to 8% from the 0.4% normally seen in immunocompetent individuals [39]. This has been termed "the cursed duet". The occurrence of systemic tuberculosis is considered as an AIDS-defining disease and occurs at CD4 counts <500 cells/mm [3]. The manifestations are protean and often difficult to diagnose due to atypical clinical presentations or difficulties in the interpretation of routine investigations such as the Mantoux tests/X-rays/tomography.

Several studies have documented ocular lesions in patients with HIV/AIDS. In one study, 46 AIDS patients were prospectively examined, 17 had systemic tuberculosis, and four of these patients (23.5%) had ocular disease including choroidal tubercles (three patients) (Fig. 5.5) and chorioretinitis (one patient). The mean CD4 count was 250 cells/mm^3 and disseminated tuberculosis was seen in all these patients [11]. Within a large cohort of 766 patients, ocular tuberculosis was seen in 19 eyes of 15 patients (1.95%). Observable lesions included choroidal granulomas (10 eyes), subretinal abscess/panophthalmitis (seven eyes), and conjunctival abscess/panophthalmitis (one eye each). The mean CD4 count was 160.85 cells/mm^3 and pulmonary tuberculosis was seen in all these patients [40]. The detected ocular tuberculosis largely affects the posterior uvea in the form of tubercles and is part of a disseminated tubercular disease with low CD4 counts (<250 cells/mm [3]). Other reported presentations include conjunctival lesions such as masses, eyelid lesions that mimic chalazia, corneal stromal infiltrates with or without scleritis, ulcers, granular masses or pedunculated polypoid tumors [41].

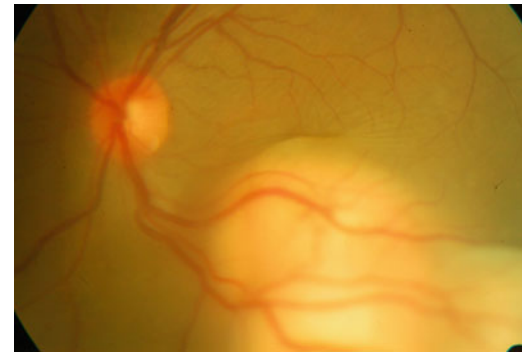

Fig. 5.5 The left eye of a 32-year-old male patient showing a large *yellow-white* tuberculoma and an associated exudative detachment. The patient had acquired immune deficiency syndrome and pulmonary tuberculosis

The techniques of diagnosis are similar to immunocompetent patients, but the interpretation of common tests is difficult. The preexisting immunosuppression can return false-negative Mantoux tests, and chest and abdominal radiography often have atypical findings. The diagnosis often needs a high index of suspicion and cultures or PCR studies of aqueous/vitreous/ocular tissue may be needed to confirm a diagnosis. Due care needs to be given to rifampicin-protease inhibitor interactions to avoid therapeutic failures, and

some authorities have suggested rifabutin in place of rifampicin.

Ocular tuberculosis is also a common infection in patients following renal and other solid organ transplants or those on long-term immunosuppressive agents. The majority of reports describe *Mycobacterium tuberculosis* as the causative agent.

Ocular Tuberculosis Associated with *Mycobacterium bovis*

M. bovis has been identified as the causative agent in isolated cases. Kurup et al. reported a 33-year-old female with nodular scleritis and a choroidal mass. She had undergone partial treatment for abdominal tuberculosis 6 years earlier. Investigations revealed *M. bovis* and intake of bacilli-contaminated unpasteurized milk was thought to be the initiating agent [12].

Rare Presentations

A review of the literature reveals several uncommon presentations.

Isolated Macular Edema

In a case described by Torres, a 61-year-old woman who presented with unilateral defective vision underwent a complete ophthalmologic evaluation. The only significant ocular finding was cystoid macular edema which was confirmed on fluorescein angiography. Systemic evaluation revealed a positive Mantoux test, and tubercle bacilli were detected in her sputum. There was a positive response in terms of reduction of the edema and visual recovery on completion of antitubercular therapy [42].

Isolated Ocular Tuberculosis

Systemic tuberculosis is normally present in most cases of ocular tuberculosis that have been described in worldwide literature. Only a handful of patients have been described with isolated ocular tuberculosis without evidence of systemic disease. Of these five patients, four had choroidal tuberculomas and one had a vitritis/retinitis. In the absence of chest pathology as determined by normal radiography, a conclusive diagnosis was based on Mantoux testing, PCR of the aqueous fluid, or histopathology of the enucleated globe [43].

Intraocular Infection with Pigmented Hypopyon

A 38-year-old female patient undergoing immunosuppressive treatment (cyclophosphamide) for membranous glomerulonephropathy noticed severe visual loss. Examination revealed acute uveitis with a pigmented hypopyon. An aspiration and subsequent pathological examination revealed acid-fast bacilli on culture and staining. Multiple scleral abscesses developed despite a course of antitubercular therapy, and the eye had to be enucleated [44].

Ocular Tuberculosis After Corticosteroid Therapy

Rosen et al. have described the clinical course of a 35-year-old male patient who presented with unilateral anterior uveitis along with bilateral vitritis and periphlebitis. He was prescribed systemic corticosteroid therapy—following which he improved. After a period of 8 months, he presented again with miliary tuberculosis and choroidal tubercles. According to the authors, the earlier inflammation may have been a purely hypersensitivity phenomenon that was steroid sensitive. The steroid therapy may have led to a reactivation of the tuberculosis following which he developed miliary tuberculosis and choroidal tubercles [28].

Investigations and Diagnosis of Ocular Tuberculosis

The diagnostic workup of patients with suspected ocular tuberculosis has both systemic and ocular components.

Systemic Investigations

As the majority of cases of ocular tuberculosis are associated with systemic disease, these investigations are of importance in all patients of ocular inflammatory disease. Evidence of systemic tuberculosis in the presence of ocular inflammation suggests ocular tuberculosis but does not confirm it.

1. *Radiography*—Chest X-rays may reveal active pulmonary tuberculosis in the form of infiltrates and cavitation in apical or posterior segments of the upper lobe or occasionally lower lobe infiltrates. At times, pleural effusions may be seen. Hilar lymphadenopathy as the only feature of pulmonary tuberculosis is common in patients of South Asian origin, and computed tomography may be a better chest imaging modality in these patients [45]. Hilar lymphadenopathy is also a common feature of patients with coexistent HIV. Abdominal CT scan or ultrasonography may reveal mesenteric, periportal, or retroperitoneal lymphadenopathy suggestive of isolated abdominal tuberculosis or as a component of disseminated tuberculosis.
2. *Mantoux Testing*—The Mantoux test assesses the patient's response to a stimulus of PPD (purified protein derivative). Three strengths available are 1, 5, or 250 tuberculin units, and 0.1 cc is injected intradermally into the volar forearm to produce a wheal of 6–10 mm diameter. After 48–72 h, the induration is measured in millimeters at the point of injection and interpreted according to current guidelines. The Mantoux test is a delayed-type hypersensitivity reaction and merely suggests tuberculous infection but not active clinical disease. Common false-negatives include poor test techniques, miliary tuberculosis, sarcoidosis, HIV infection, or active malignancies.
3. *Interferon-γ*(gamma) *Release Assays (IGRA)*—The IGRA tests are the in vitro assays that measure interferon-γ(gamma). This is secreted by previously sensitized T cells after they are stimulated by *Mycobacterium tuberculosis* antigens. The antigens include early secreted antigen target (ESAT) 6 and culture filtrate protein (CFP)-10 that are specific for *M. tuberculosis* and make false-positive readings with BCG vaccine strains unlikely. The commonly used kits are T-SPOT.TB test (Oxford Immunotec Ltd.) and the QuantiFERON-TB Gold (Cellestis Ltd., Australia). Positive IGRA tests suggest latent tuberculosis.

Ocular Investigations

Following a detailed clinical examination, the isolation of *M. tuberculosis* from ocular tissues is often necessary to establish a diagnosis of confirmed ocular tuberculosis. Samples may be obtained from the aqueous humor, vitreous humor, subretinal fluid, specific tissue biopsies (eyelid tissue, conjunctiva, cornea, sclera, retina, or uvea) or the enucleated globe. However, these are often of small volume and pose a risk of ocular morbidity, especially the risks of endophthalmitis and retinal detachment. These samples once obtained may undergo the following:

1. *Microscopy*—This is the easiest test but needs densities of 5,000–10,000 bacilli per ml for a positive result. The success rate may be increased by centrifugation of samples. Tissue sections may be stained after formalin fixation. Stains in use include conventional acid-fast stains (e.g., Ziehl-Neelsen) or fluorescent acid-fast stains.
2. *Culture*—Culturing is more sensitive and is reported to be capable of detecting densities of 10–100 bacilli per ml. Drawbacks include prolonged incubation of up to 8 weeks. Commonly used culture media includes Lowenstein-Jensen.
3. *PCR (Polymerase Chain Reaction) Techniques*—These are becoming the technique of choice in the diagnosis of ocular tuberculosis. They are capable of detecting mycobacterial DNA from all samples and are ideally suited for ocular diagnostic work because they require small volumes and are extremely specific. In one case series of 53 patients, the specificity was 100% and the sensitivity was 37% [46].

Guidelines and Suggested Treatment of Ocular Tuberculosis

The purpose of the investigations (clinical, radiological, and laboratory) is to permit understanding of the specific manifestation in each patient and allow the appropriate therapy. Specific points that need to be elucidated are as follows:

1. *Specific Ocular Etiopathogenesis*—Whether the ocular lesions are a hypersensitivity reaction or a direct infection or both.
2. *Specific Systemic Findings*—A positive Mantoux test or IGRA test indicates previous mycobacterial infection and, in the absence of evidence of systemic infection, suggests latent tuberculosis. In contrast, active systemic tuberculosis is diagnosed by radiological or laboratory evidence of tubercular infection elsewhere in the body.

Some authors have suggested that cases of ocular tuberculosis be classified as (1) presumed when there is only indirect evidence that *M. tuberculosis* is the causative organism (e.g., suggestive ocular disease and evidence of systemic tuberculosis) or (2) confirmed when *M. tuberculosis* bacilli are isolated from ocular tissue or fluids.

Regardless of classification, patients with a diagnosis of presumed or proven tubercular infection in the eye and concomitant systemic or latent tuberculosis (positive Mantoux and/or IGRA tests) need antitubercular therapy with or without corticosteroid therapy. Patients with hypersensitivity reaction alone (e.g., phlyctenulosis), negative Mantoux/IGRA tests, and negative systemic imaging may be treated with corticosteroid therapy alone.

Corticosteroid Therapy

Manifestations that are due to a purely hypersensitivity phenomena such as phlyctenulosis need only corticosteroid therapy. Most direct infections such as anterior or posterior uveitis, retinal vasculitis, or panophthalmitis also need adjunct corticosteroid therapy due to the inflammation they induce. Depending on the site of involvement and severity of the inflammation, topical, periocular, or systemic corticosteroids may be used.

Antitubercular Therapy

Systemic antitubercular therapy must be prescribed in cases of ocular direct infections as well as in cases where a systemic focus is present. At present, there is no commercially available topical antitubercular therapy. Following systemic treatment, all ocular tissues, especially the commonly affected posterior uvea, receive adequate drug concentrations. Schlaegel first suggested a therapeutic trial of isoniazid in suspect cases of ocular tuberculosis, but this has historical value and may actually promote drug resistance. As no randomized controlled trials have been done specifically for ocular tuberculosis, current recommendations rely on the guidelines for pulmonary and extrapulmonary tuberculosis.

All recent consensus statements and institutional guidelines—the American Thoracic Society (ATS), the Centers for Disease Control (CDC), and the Infectious Diseases Society of America (IDSA)—suggest an initial four-drug regime (isoniazid [INH], pyrazinamide [PZA], ethambutol [ETB], and rifampicin [RIF]) for an initial 8 weeks followed by INH and RIF either 7 days a week (Regimen 1a) or twice weekly (Regimen 1b) for a minimum duration of 18 weeks. These guidelines also apply to extrapulmonary forms of the disease or HIV-infected patients, with some data suggesting that similar regimens of four drugs for 6–9 months are equally effective [47].

The World Health Organization (WHO) suggests the use of four drugs (INH/RIF/PZA/ETB) for an initial 2 months followed by INH/RIF for 4 months for category I patients (new sputum positive patients, new sputum negative patients with extensive lung parenchymal disease, and those with severe extrapulmonary disease) and category III patients (new smear negative patients

with lesser lung parenchymal involvement and patients with less severe extrapulmonary disease) [48].

Therapeutic failures may occur and may be due to primary resistance (infection or reactivation of bacilli that are resistant to one or more drugs at the onset of disease itself) or secondary resistance where bacilli develop resistance due to faulty compliance or poor drug selection. Reports of drug-resistant ocular tuberculosis are rare but may be a problem in the future, as the multidrug tuberculosis epidemic expands.

Ocular Toxicity in Antitubercular Therapy

Antitubercular therapy–induced ocular toxicity is rare, and ethambutol is usually the offending drug. The observed toxicity is an optic neuropathy that may be seen in up to 2% of patients on the current recommended dose of 15 mg/kg. Patients present with bilateral visual loss and a normal-appearing fundus. Rarely, hyperemic or edematous discs have been seen. A primary optic atrophy may supervene after 4–6 weeks. Visual field studies may show central, paracentral, or peripheral scotomas. Defective color vision is common, especially in the red-green axis. Patients with acute or chronic renal failure may be at an added risk and need close monitoring or reduced dosages of ethambutol. The neuropathy is usually reversible, but complete recovery may take several months.

Controversies and Perspectives

1. *Use of Antitubercular Drugs*—While the use of antitubercular drugs is mandatory, until recently no large series studied its exact role. Bansal et al. [49] studied 360 patients with at least a 1-year follow-up after starting antitubercular therapy. They studied patients who received four-drug antitubercular therapy and corticosteroids and those that received corticosteroids alone and observed inflammatory recurrences in each group. Significantly fewer recurrences were seen in the first group as compared to the second. The authors estimate that the use of antitubercular therapy reduces the chance of recurrence by up to two-thirds.
2. *Use of 18 FDG-PET (Fluorodeoxyglucose–Positron Emission Tomography) Scans in the Management of Ocular Tuberculosis*—These utilize a radioactive tracer (18 FDG) that accumulates in tissues that rapidly utilize glucose, such as malignancies as well as inflammatory foci. Potentially, use of these scans may help to detect foci of systemic tubercular inflammation. Mehta et al. [50] recently have described the utility of 18 FDG-PET scan in a 35-year-old female patient with recurrent posterior uveitis in whom chest imaging studies of the chest were normal. Increased tracer activity was seen in the right paratracheal, precarinal, and bilateral hilar nodes and in the left choroid. The authors suggest that a FDG-PET/CT scan may be a better choice in detecting coexisting pulmonary tuberculosis as compared to conventional imaging techniques.
3. *Use of an Animal Model*—Histopathological and immunological studies into ocular tuberculosis have been limited by the relative lack of intraocular tissue and fluids. Recent developments of an animal model may change this. Rao et al. [51] have recently used Hartley strain guinea pigs that were infected via an aerosol route. Some animals were infected with low doses of bacteria and were merely observed. Another group received a high-dose infection and was treated with the standard antitubercular regimen. Animal tissues were studied via histopathology and PCR techniques. Uveal granulomatous lesions were found to have acid-fast bacteria and *M. tuberculosis* DNA. The presence of treatment was found to have a protective effect to the development of tubercular uveitis.

Focal Points

The prevalence of ocular tuberculosis has reduced in the twentieth century worldwide, but it is still a common etiological agent in the developing world.

- Ocular TB (largely choroidal or retinal) may be seen in 1.4–60% of patients with systemic TB.
- Tuberculosis is the etiological agent in 0.2–7.9% of patients with all types of intraocular inflammation.
- The HIV epidemic has led to an increase in ocular TB with between 2.8% and 23.5% of HIV/TB coinfections demonstrating ocular lesions.
- The diagnosis of ocular TB is frequently difficult as its manifestations are protean, specimen quantities are limited and often difficult to obtain.
- Ocular evaluation includes clinical examination and collection of specimens from aqueous humor, vitreous humor, uveal or retinal tissue, or subretinal fluid. Processing includes microscopy, culture, or PCR techniques for definitive proof.
- Systemic evaluation includes chest radiography (CT preferred), abdominal radiography, Mantoux testing, and collection/processing of sputum, lymph nodes, and bone marrow as necessary.

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Retinal and Choroidal Manifestations of Toxoplasmosis

6

J. Fernando Arévalo, Rubens Belfort Jr., Juan V. Espinoza, Cristina Muccioli, and Emmett T. Cunningham Jr.

Abstract

Ocular toxoplasmosis is the most prevalent form of infectious posterior uveitis worldwide. Although congenital infections have long been considered to account for most ocular disease, there is now clear evidence that the majority of ocular toxoplasmosis infections are acquired after birth. Following either congenitally or postnatally acquired infection, *Toxoplasma gondii* may induce a latent disease wherein *T. gondii* tissue cysts establish residence in various organs, including the eye. These cysts may subsequently rupture, resulting in clinical recurrence. Active ocular toxoplasmosis may occur at any age but is most common during the second through fourth decades of life.

Keywords

Acquired toxoplasmosis • Congenital toxoplasmosis • Infectious uveitis • Ocular toxoplasmosis • *Toxoplasma gondii* • Toxoplasmic epidemiology • Toxoplasmic retinochoroiditis • Toxoplasmic therapy

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Introduction

Toxoplasmosis is endemic throughout most of the world and affects a large proportion of the adult population [1, 2]. However, the seroprevalence of anti–*Toxoplasma gondii* differs from country to country [3]. It is estimated, for example, that at least 10% of adults in northern temperate countries and more than half of adults in Mediterranean and tropical regions have been infected [4]. *Toxoplasma gondii* is a ubiquitous, obligate intracellular protozoan and is considered to be the most common cause of infective retinitis in immunocompetent humans. A number of factors related to regional climate, hygiene, and dietary habits have been identified [5–7].

Toxoplasma gondii was discovered independently by two investigators in 1908. Alfonso Splendore in Brazil identified the organism in laboratory rabbits, while Charles Nicolle and Louis Manceaux in Tunis observed the organism in the North African rodent *Ctenodactylus gondii.* Nicolle and Manceaux named the parasite *Toxoplasma gondii – Toxoplasma* from the Greek word toxon, meaning arc, describing the small crescent shape of the parasites, and *gondii* from the animal in which it was found (Fig. 6.1) [8]. The first description of congenital toxoplasmosis (CT) with ocular involvement is attributed to Jankû (Prague 1923), who reported an 11-month-old infant with hydrocephalus, microphthalmia, and a retinal "coloboma" in the macular region; [8, 9] and the first photographic documentation of ocular toxoplasmosis was made in Brazil by Belfort Mattos in 1933 [8].

The course of systemic disease in immunocompetent adults is usually asymptomatic and self-limiting. As soon as infection has occurred, the parasite forms latent cysts in many organs, including the retina, that can reactivate years after the initial infection, giving rise to acute retinochoroiditis and, subsequently, the formation

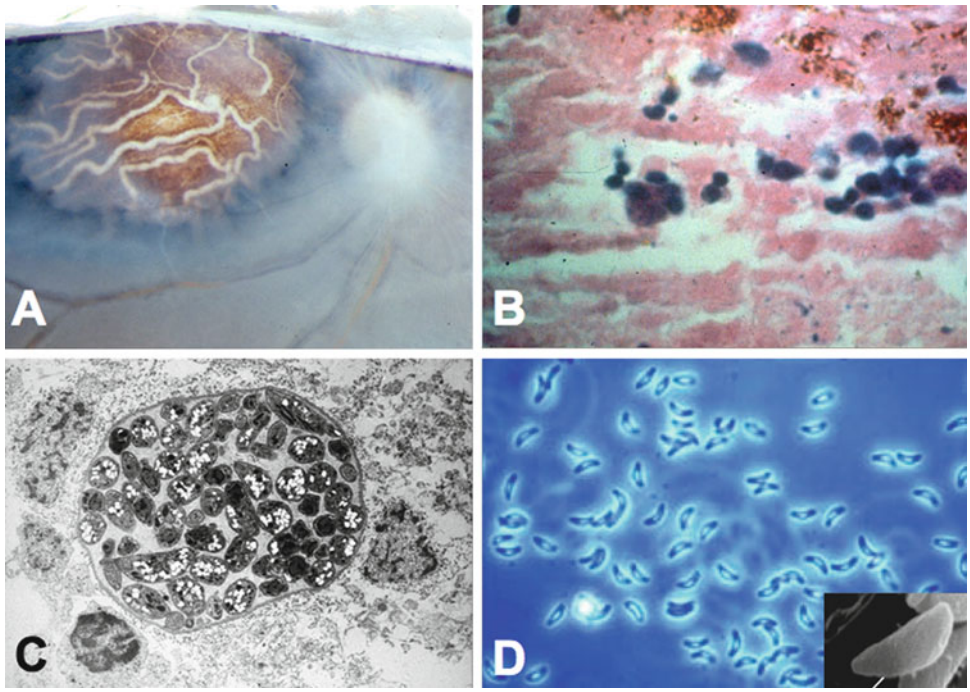

Fig. 6.1 (**a**) Gross appearance of a retinal scar in an enucleated eye bank eye with toxoplasmic retinochoroiditis (TRC). (**b**) Histologic section shows toxoplasmic cysts seen in the neural retina. Note the eccentrically located tiny nuclei in the cysts. (**c**) Retina cyst in TRC visualized with electron microscopy (EM). (**d**) Tachyzoites in lower and higher magnification (with EM; insert)

of new retinochoroidal lesions [4]. Usually, ocular toxoplasmosis (OT) is clinically diagnosed through recognition of a focal retinitis or retinochoroiditis in the setting of an adjacent or nearby retinochoroidal scar. Serum anti–*T. gondii* immunoglobulin G (IgG) antibodies support the diagnosis but are not always necessary. In immunocompromised individuals, however, OT lesions may be extensive or multifocal, complicating the diagnosis [10].

The laboratory diagnosis of toxoplasmosis is based on detection of circulating antibodies directed against *T. gondii* and/or the identification of the specific organism or its antigens using polymerase chain reaction (PCR). Toxoplasmosis therapy includes specific antiparasitic medication and corticosteroids. There are several regimens, with different drug combinations. Medications include pyrimethamine, sulfadiazine, clindamycin, trimethoprim–sulfamethoxazole, spiramycin, azithromycin, atovaquone, tetracycline, and minocycline. The prognosis of OT is usually good in immunocompetent individuals, as long as the macula, the optic nerve, and the papillomacular bundle are not directly involved [11].

The objective of this chapter is to describe the posterior pole manifestations of ocular toxoplasmosis as well as its pathogenesis, epidemiology, clinical findings, diagnosis, and current management.

Pathogenesis

Toxoplasma gondii is a ubiquitous protozoan parasite that infects up to 50% of the population [7]. While systemic infections are typically asymptomatic in immunocompetent patients, life-threatening disease may occur in newborns and in immunocompromised patients [12]. The parasite can be found in the host's tissues and body fluids, such as saliva, milk, semen, urine, and peritoneal fluid. The morphology of the *T. gondii* varies depending on the stage of the life cycle and habitat. It can present in three forms, the tachyzoite, bradyzoite, and sporozoite, or oocyst [8], and these forms can be identified and studied histologically (see Fig. 6.1).

The tachyzoite, also called trophozoite, is the infectious form responsible for the acute phase of the disease. It is approximately 3–7 μ(mu)m in length, 2–4 μm in diameter, and crescent-shaped. The tachyzoite encysts at the first sign of environmental stress, such as the host immune response or the presence of antibiotics. The encysted form, known as the bradyzoite, begins to appear as soon as 1 week following infection. Bradyzoites divide slowly inside a cellular vacuole, which eventually becomes part of the cyst's capsule. The cysts are very resistant and can remain dormant in the host for years without reactivation or tissue damage. For reasons unknown, the cyst may rupture, causing reactivation of the disease and intense inflammation [8].

Oocysts of *T. gondii* are 10–12 μm and oval-shaped. They are found uniquely in the intestinal mucosa of cats. Once they are released, they can be spread to human beings or other animals through a variety of vectors. Although invariably thought to be ingested, the organism may also enter the host through other mucosal surfaces. Humans can also be infected secondarily by meat (pork and lamb particularly, as well as chicken in endemic areas, but probably not unprocessed beef) contaminated with *Toxoplasma* cysts (Fig. 6.2). The two forms of the organism that can be found in humans are bradyzoites, or tissue cysts, and tachyzoites (see Fig. 6.1c, d). Tissue cysts are up to 200 μm in diameter, contain hundreds to thousands of organisms, and have a propensity for cardiac tissue, muscle, and neural tissue, including the retina (see Fig. 6.1a) [13].

Humans can be infected by the infectious forms of either subcycle, that is, by eating undercooked meat containing tissue cysts, or through accidental ingestion of oocysts contaminating garden vegetables, water, or cat litter boxes. Rarely, *T. gondii* can be transmitted by blood transfusion, solid organ transplants, or in contaminated water or air. The life cycle of *T. gondii* is unusual in that the organism is capable of indefinite replication using either sexual or asexual subcycles [14]. After transmission, actively dividing tachyzoites disseminate via the blood stream and lymphatics (see Fig. 6.2) [15]. Up to 10% of infected individuals present with

retinal lesions [15, 16], and these infections account for half to one-third of all cases of posterior uveitis [15]. Most of the ocular cases occur months to years after initial infection, which is often asymptomatic.

The asexual cycle can occur in virtually any warm-blooded animal, ranging from chickens to sea otters to humans. Transmission occurs when an animal ingests bradyzoite-infected tissue through carnivorism or scavenging. Transmission can also occur accidentally through feed that is contaminated with animal parts. Theoretically, this asexual portion of the organism's life cycle could continue indefinitely via the food chain. *Toxoplasma gondii*'s sexual cycle occurs only in cats, where it includes full gametogenesis and mating within the intestinal epithelium and culminates in the generation of oocysts that are shed in the cat's feces. These oocysts are highly infectious and extremely stable in the environment. Likewise, the asexual cycle can readily flow into the sexual side when a cat eats a mouse or bird infected with tissue cysts (see Fig. 6.2) [17].

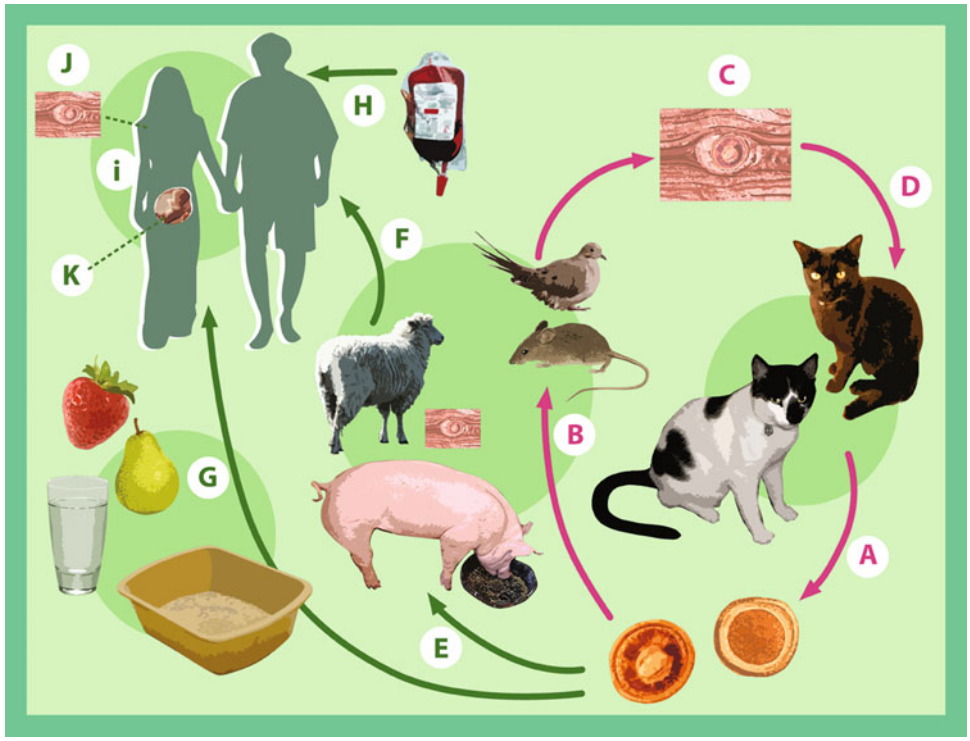

Fig. 6.2 (*A*) The only known definitive hosts for *Toxoplasma gondii* are members of family Felidae (domestic cats and their relatives). Unsporulated oocysts are shed in the cat's feces. (*B*) Although oocysts are usually only shed for 1–2 weeks, large numbers may be shed. (*C*) Oocysts take 1–5 days to sporulate in the environment and become infective. Intermediate hosts in nature (including birds and rodents) become infected after ingesting soil, water, or plant material contaminated with oocysts. Oocysts transform into tachyzoites shortly after ingestion. These tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites. (*D*) Cats become infected after consuming intermediate hosts harboring tissue cysts. (*E*) Cats may also become infected directly by ingestion of sporulated oocysts. Animals bred for human consumption and wild game may also become infected with tissue cysts after ingestion of sporulated oocysts in the environment. (*F*) Humans can become infected by any of several routes: eating undercooked meat of animals harboring tissue cysts; (*G*) consuming food or water contaminated with cat feces or by contaminated environmental samples (such as fecal-contaminated soil or changing the litter box of a pet cat); (*H*) blood transfusion or organ transplantation; and (*I*) transplacentally from mother to fetus. (*J*) In the human host, the parasites form tissue cysts, most commonly in skeletal muscle, myocardium, brain, and eyes; these cysts may remain throughout the life of the host. Diagnosis is usually achieved by serology, although tissue cysts may be observed in stained biopsy specimens. (*K*) Diagnosis of congenital infections can be achieved by detecting *T. gondii* DNA in amniotic fluid using molecular methods such as PCR

Since the 1950s, postnatally acquired infections have been attributed correctly either to ingestion of tissue cysts in raw or undercooked meat or to oocysts on unwashed vegetables that were contaminated with soil containing cat feces. Recent observations have suggested that these are not the only routes of infection, however. Contaminated drinking water, for example, may be an important source of infection in some situations [17].

Although *T. gondii* infects any nucleated cell in culture, human infections often involve the central nervous system (CNS) [15]. *Toxoplasma gondii* disseminates rapidly from the initial site of infection to secondary lymphoid tissues and then on to other organs. Dendritic cells are likely candidates as the "Trojan Horse" that *T. gondii* uses to travel to the spleen and draining lymph nodes. This hypothesis is supported by both in vitro studies and intraperitoneal infection models used to examine dendritic cell migration [18].

Montoya and Remington offer two explanations for preferential involvement of the CNS in toxoplasmosis: (1) ready passage of parasites across the blood-brain barrier or (2) poor clearance of parasites from immune-privileged site. It has been postulated that *T. gondii* is neurotropic because neurological deficits, including blindness, tend to make animal hosts easy prey, facilitating transmission of the parasite [15].

Tachyzoites may reach the retina by (1) migration from the brain via the optic nerve, (2) passage from the retinal circulation in infected monocytes or dendritic cells, or (3) direct infection of the retinal vascular endothelium by circulating tachyzoites. Different and/or multiple routes may account for retinal infection in different patients [15]. Host cell invasion begins with attachment of the parasite to the cell membrane and is complete when the parasite has actively penetrated the membrane, which typically takes less than 40 seconds [15, 19]. Invasion of host cells by *T. gondii* tachyzoites is believed to involve multiple receptor–ligand interactions, and differential expression of host receptors may be one mechanism underlying the variable infectivity observed between cell populations. Proteoglycans are important host cell receptors, and the tachyzoite surface antigens known as SAGs are key ligands [15]. The ability of tachyzoites to infect a number of different cell lines has been correlated with the surface expression of sialic acid residues [15, 20].

Genetic analysis suggests that the majority of *T. gondii* strains identified in Europe and North America fall into one of three distinct genotypes (types I, II, and III, respectively) [14, 21–23]. Type I strains are very virulent (LD_{100} of one parasite). In contrast, types II and III strains are less virulent (LD_{50}~10^3 and ~10^5, respectively). In humans, all three lineages cause disease, but they appear to differ in the tissues they affect and when they infect people. For example, type I strains are more often associated with postnatally acquired ocular infections, whereas type II strains are more associated with congenital infections and toxoplasmic encephalitis [18]. Some recent studies show more atypical (types IV and V) as well as mixed infections in many parts of the world, including Brazil, where they seem to be the rule. The high prevalence of this more virulent strain could also explain the phenomenon of reinfection and recent papers confirming that women may transmit toxoplasmosis to the fetus even when they are known to have had circulating anti–*T. gondii* IgG antibodies for many years. Difference in strain prevalence has also been suggested to explain varying rates of ocular involvement despite similar overall, population-based seroprevalence rates [18].

It is well known that host immune function plays an important role in toxoplasmosis. Immunosuppressed patients, including those with acquired immunodeficiency syndrome (AIDS), are susceptible to severe life-threatening and vision-threatening *T. gondii* infections. It is likely that more subtle changes in immune function also affect disease presentation [24].

Clinical Manifestations

Ocular toxoplasmosis manifests predominantly from the second to the fourth decade of life (probably because most of the cases arise up to 10–20 years after the infection), with either primary

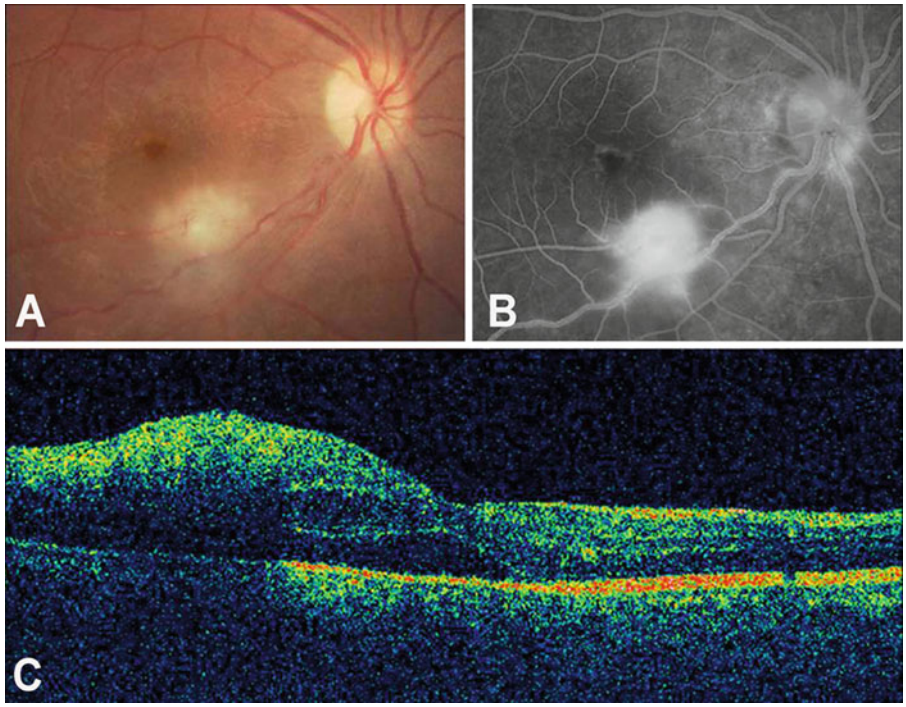

Fig. 6.3 Toxoplasmic retinochoroiditis (TRC). Visual acuity (VA) was 20/70. (**a**) Color fundus photograph of the right eye demonstrating an isolated active lesion along the inferotemporal vascular arcade. (**b**) Fluorescein angiography before intravitreal clindamycin and dexamethasone therapy reveals marked hyperfluorescence resulting from leakage of dye from TRC lesion threatening the fovea. (**c**) A horizontal optical coherence tomography scans obtained through the fovea revealed loss of the normal foveal contour, diffuse macular thickening with subfoveal serous retinal detachment. The retina map analysis indicates a central macular thickness of 421 μm

OT (isolated retinal lesions not arising from scars) (Fig. 6.3), or recurrent OT (active retinal lesions associated with old inactive scars) (Fig. 6.4). Necrotizing retinitis associated to vitreous and anterior chamber inflammation is the hallmark of OT. Recent reports have confirmed that acquired infection can present with vitreitis or anterior uveitis in the absence of retinochoroiditis [25].

Manifestations include retinochoroidal infiltrates, vitreous humor cells and haze, and anterior chamber (AC) cells and flare. The severity of the inflammatory reactions varies substantially between patients, for reasons that are unknown [26].

There can be considerable variation in the clinical features of disease. A review of the literature describing "atypical" cases suggests that they do not represent fundamentally different forms of the disease, however. Knowledge of the various presentations of OT is important for the clinician—diagnosis can be difficult in some cases, and attention to the characteristics of OT may give some insights into disease mechanisms [27].

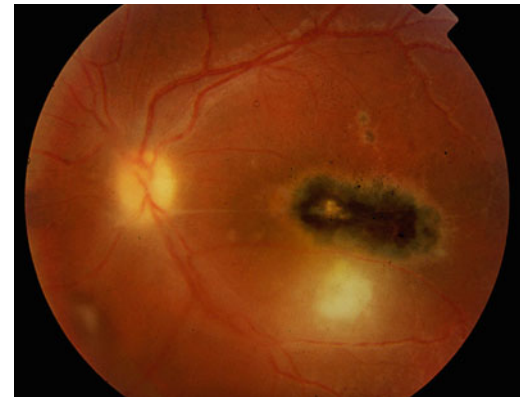

Fig. 6.4 Recurrent ocular toxoplasmosis. Note active retinal lesion associated with old inactive scar

Friedmann and Knox described three specific "forms" of disease that can be related to the specific

strain causing the infection: large destructive lesions, punctate inner lesions, and punctate deep lesions [28]. Small, partial-thickness lesions involving the inner or outer layers of the retina have also been described in patients with AIDS; these small lesions are presumably the earliest manifestations of infection, as most reported patients with AIDS and OT have had extensive areas of full-thickness retinal necrosis (Figs. 6.5, 6.6a, b, and 6.7) [27, 29].

Immunocompetent patients can develop clusters of small, partial-thickness retinal lesions, a condition termed "punctate outer retinal toxoplasmosis" by some investigators. Lesions are typically <1,000 μm in diameter and found in the posterior pole. Although sometimes considered a distinct form of disease, punctate outer retinal toxoplasmosis shares many features with more "typical" lesions. Despite the occurrence of lesions in clusters in patients with punctate outer retinal toxoplasmosis, there is usually only one focus of active disease at any given time [27].

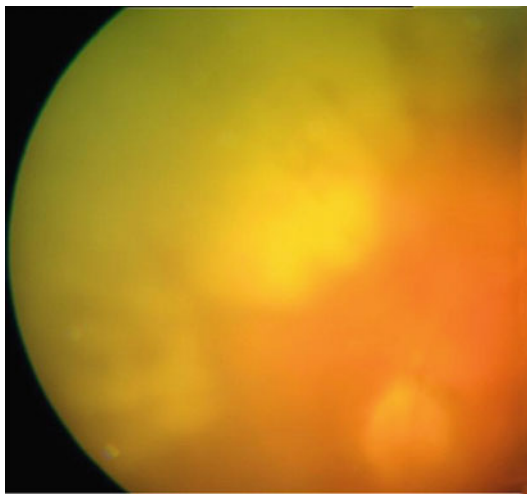

Fig. 6.5 Patients with the acquired immune deficiency syndrome (AIDS) and ocular toxoplasmosis may have extensive areas of full-thickness retinal necrosis that simulate acute retinal necrosis syndrome

Generally active inflammatory disease resolves without treatment, leaving hyperpigmented scars, and recurrences develop as "satellite" lesions (see Fig. 6.4) [27]. On the other hand, there are many publications that also refer to "typical" scars of healed toxoplasmic retinochoroiditis (TRC) lesions, but there is a spectrum to the appearance of scars as well, with variable amounts of pigmentation and loss of choroidal tissue. The area of a scar that is seen clinically can be smaller than the area of inflamed retina during the active stage of the disease. The degree of pigmentation within and around scars may reflect the extent to which the retinal pigment epithelium is damaged during the active stage of disease. In some elderly patients, lesions seem to heal with less severe scarring than would be expected from the extent of infection [27]. Lesions with little associated inflammation may heal with minimal scarring (Fig. 6.8) [27, 30]. Silveira et al. have shown that the spectrum of lesions associated with typical TRC includes similar tiny, nonspecific foci of

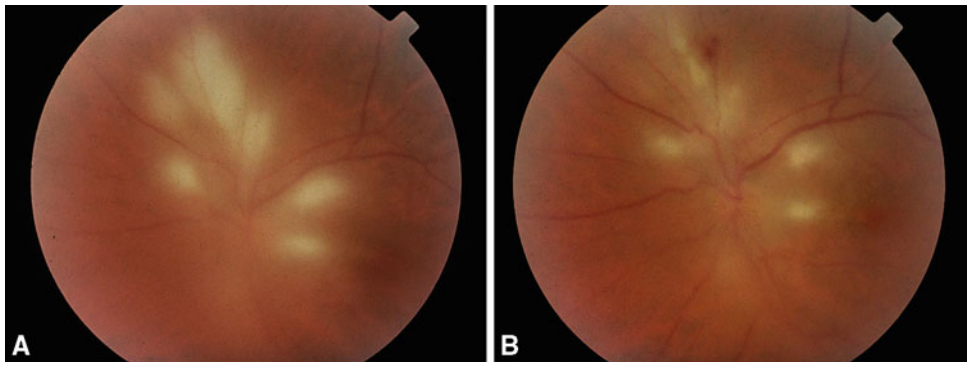

Fig. 6.6 (**a**, **b**) Patients with the acquired immune deficiency syndrome (AIDS) and ocular toxoplasmosis may have atypical presentations. This patient improved 1 week after highly active antiretroviral therapy, pyrimethamine and sulfadiazine (Reprinted with permission from Smith JR, Cunningham ET Jr. Atypical presentations of ocular toxoplasmosis. Curr Opin Ophthalmol. 2002;13:387–92)

pigment, and "classic" lesions can also be found amid clusters of small retinochoroidal scars in any part of the retina [27, 31].

Ocular toxoplasmosis can also be categorized into the congenital (Fig. 6.9a, b) or acquired (Fig. 6.10) forms. Congenital and acquired presentations can be divided into neonatal or late forms. Every newborn whose mother contracted toxoplasmosis during the pregnancy must receive treatment during the first year of life, independent of the presence of ocular involvement in the time of the birth. Congenital toxoplasmosis is most commonly acquired during the last trimester of pregnancy, and the infants are usually asymptomatic. Acquired toxoplasmosis (AT) can be concomitant when it occurs during systemic disease and delayed when there is a variable period of time (usually 5–10 years) between systemic and ocular disease [11].

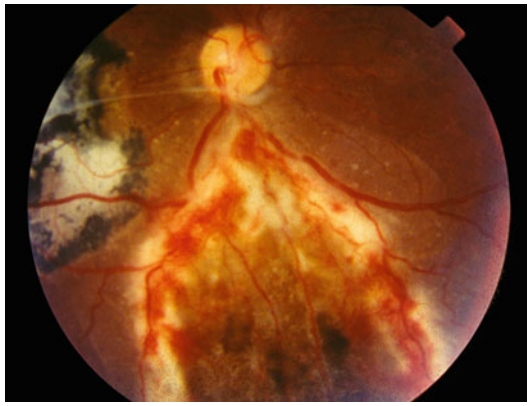

Fig. 6.7 Patients with the acquired immune deficiency syndrome and ocular toxoplasmosis may have concomitant extensive areas of full-thickness retinal necrosis of cytomegalovirus retinitis

Toxoplasmic retinochoroiditis is unilateral in 72–86% of cases [11]. The lesions can be solitary, multiple, or satellite (adjacent to a cicatricial lesion). *T. gondii* has a clear preference for the posterior pole, this location occurring in more than 50% of the cases. Typical congenital retinochoroiditis presents as a macular cicatricial lesion, consisting in radial deposition of pigment

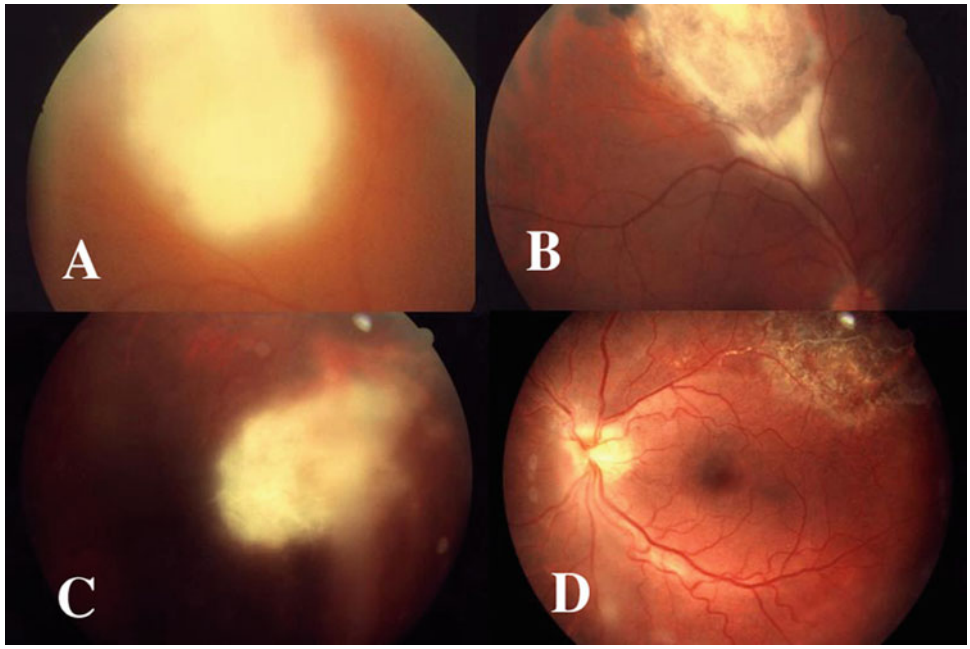

Fig. 6.8 The retinal lesions in toxoplasmic retinitis in patients with acquired immune deficiency syndrome (AIDS) may be focal or diffuse, active in one or both eyes, and can cause visual impairment if left untreated. (**a** and **c**) Toxoplasmic retinitis before therapy. (**b** and **d**) Toxoplasmic retinitis healed after therapy. Note that in patients with the acquired immune deficiency syndrome (AIDS), lesions with little associated inflammation may heal with minimal scarring (Courtesy of William R. Freeman, M.D.)

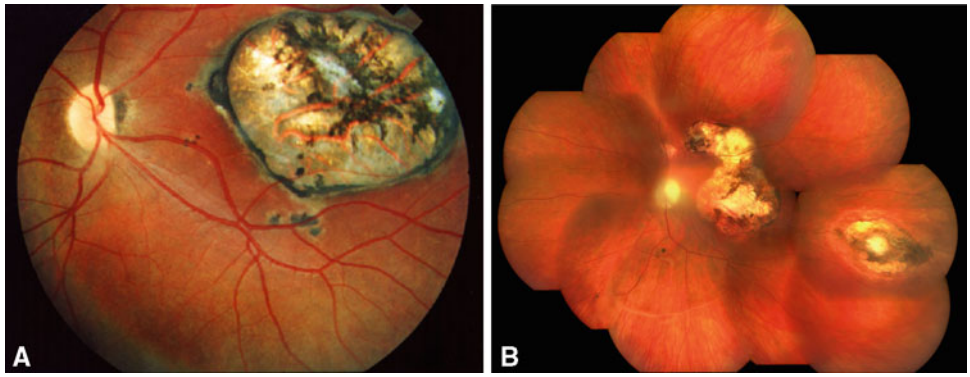

Fig. 6.9 (**a**, **b**) Congenital ocular toxoplasmosis

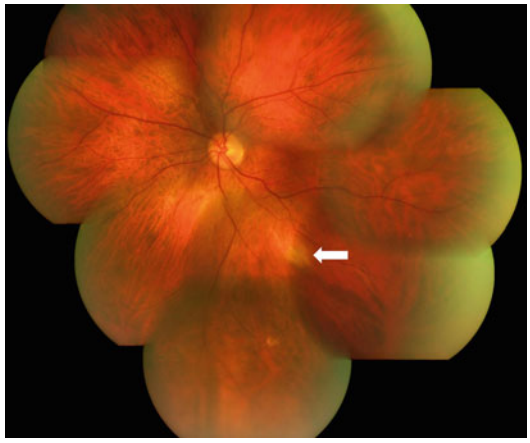

Fig. 6.10 Acquired ocular toxoplasmosis (*arrow*)

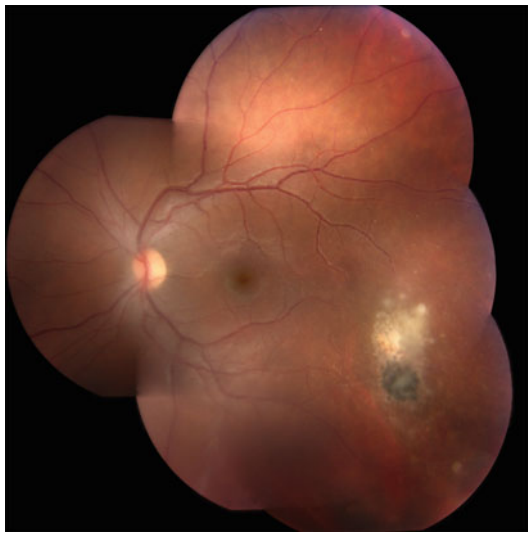

Fig. 6.11 Recurrent satellite lesions of toxoplasmosis. Note active retinal lesion associated with old inactive scar

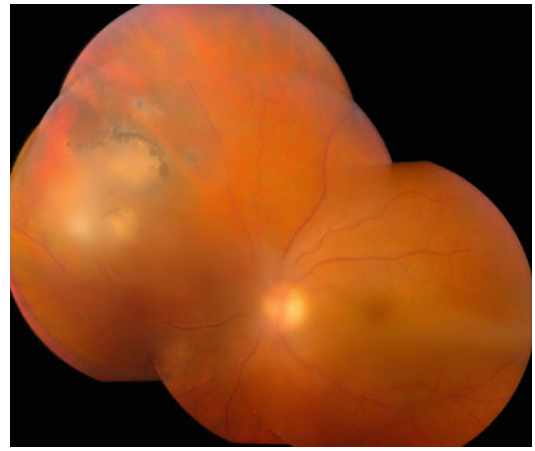

Fig. 6.12 Recurrent satellite lesions of toxoplasmosis and vitritis. Note active retinal lesion associated with old inactive scar

around a central necrotic zone. Anterior uveitis is almost always a complication of retinochoroiditis. In fact, the presence of the parasite in the anterior segment without retinal involvement has only been demonstrated in immunocompromised patients [11].

Recurrences of retinal disease occur with both congenital and postnatally acquired infections. Typically, these recurrences manifest as "satellite lesions" at the border of a preexisting retinochoroidal scar (Figs. 6.4, 6.11, and 6.12), although in some patients, new "primary retinal lesions" (defined as those not arising from retinochoroidal scars) can develop far away from the preexisting scars, in areas of retina that had appeared clinically to be normal (see Fig. 6.10). Recurrences

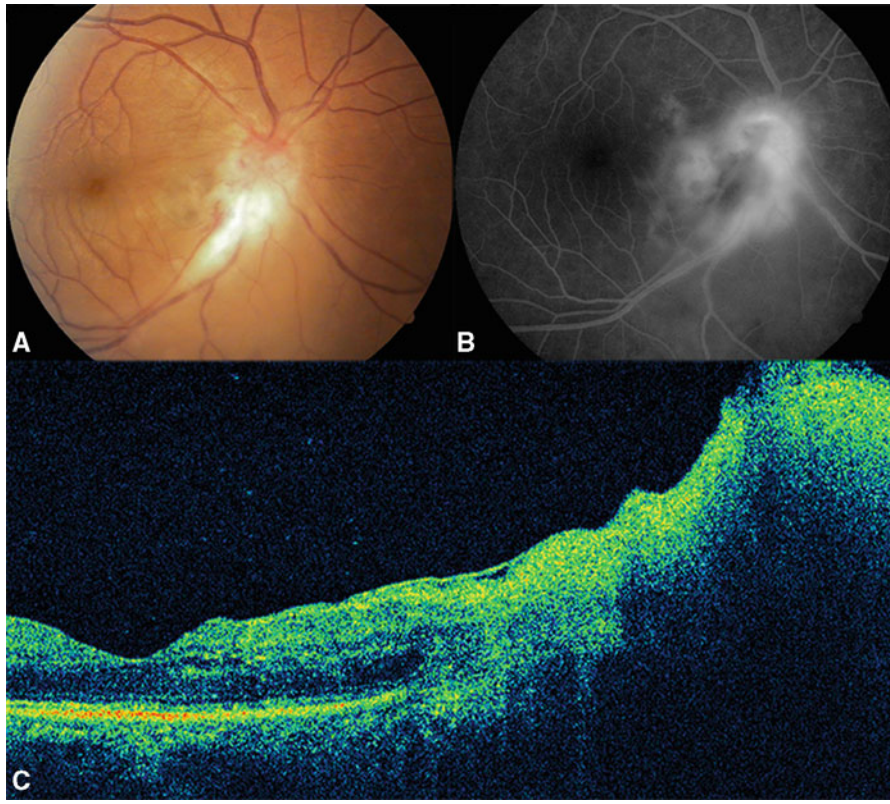

Fig. 6.13 (**a**) Color fundus photograph of the right eye demonstrating an active papillary lesion secondary to toxoplasmic retinochoroiditis (TRC) along the inferotemporal vascular arcade. (**b**) Fluorescein angiography before intravitreal clindamycin and dexamethasone shows remarkable hyperfluorescence resulting from leakage of dye from TRC. (**c**) A horizontal optical coherence tomography scan obtained through the papillomacular bundle demonstrated mild macular thickening with swelling of the optic disc. The retina map analysis indicates a central macular thickness of 256 μm. His visual acuity was 20/125

are generally assumed to be caused by the release of parasites from tissue cysts in the retina [17].

Symptoms of OT vary according to the age of the subject. Signs at birth may include fever, maculopapular rash, hepatosplenomegaly, microcephaly, seizures, jaundice, thrombocytopenia, and lymphadenopathy. The classic triad of CT is retinochoroiditis, hydrocephalus, and cranial calcifications [11]. Children usually present with reduced visual acuity, strabismus, nystagmus, and leukocoria. Teenagers and adults complain of decreased vision and floaters. If anterior uveitis is present, photophobia, pain, and hyperemia may be present [11].

However, toxoplasmosis can also affect the optic nerve in many ways. Atypical presentations of ocular toxoplasmosis have been described: punctate outer retinitis, neuroretinitis, papillitis (Fig. 6.13), pseudo-multiple retinochoroiditis, intraocular inflammation without retinochoroiditis, unilateral pigmentary retinopathy, Fuchs-like anterior uveitis, scleritis, and multifocal or diffuse necrotizing retinitis.

A variety of complications of TRC have been described, including rhegmatogenous retinal detachments, glaucoma, vitreous opacification (Figs. 6.12 and 6.14) or hemorrhage, retinal hemorrhage (Fig. 6.15), optic atrophy, exudative retinal detachments, retinal vessel occlusions, subretinal and choroidal revascularization (CNV), epiretinal membrane formation (Fig. 6.16a, b), and macular edema [11, 17, 32, 33]. In general, they

occur only in patients with severe ocular disease. Rhegmatogenous retinal detachments, for example, have been related to the severity of inflammation. Macular edema is believed to be uncommon [33],

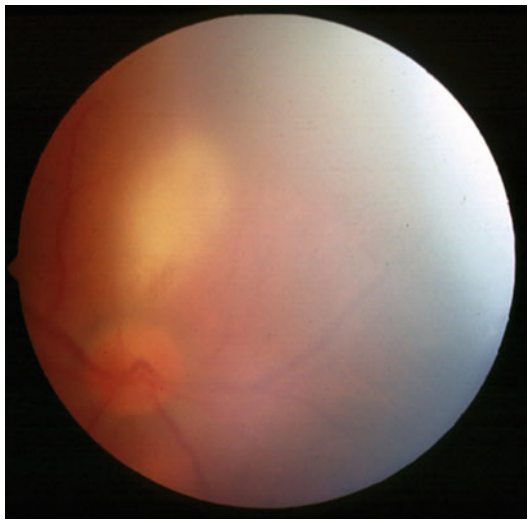

Fig. 6.14 Acquired ocular toxoplasmosis with vitreitis

for unknown reasons (Fig. 6.17a, b). Prolonged infections, intense inflammation, and complications can occasionally lead to phthisis or enucleation [17, 34].

In OT visual acuity may range from 20/20 to 20/400, depending on the extent of macular or optic nerve involvement [34, 35]. Therefore, predicting future vision in a preverbal child should be done with caution. Of the patients followed from the newborn period and treated, 29% had bilateral visual impairment with the vision in the better eye being less than 20/40. Causes for this visual impairment in eyes with quiescent lesions included macular scars, dragging of the macula secondary to a peripheral lesion, retinal detachment, optic atrophy, cataract, amblyopia, phthisis, and other complications that can be prevented in some cases [34]. Tan et al. [35] have concluded that although visual impairment was associated with the presence of posterior pole lesions, just more than half of eyes affected by a posterior pole lesion had normal vision (6/12 or better), compared to 84% of those with peripheral lesions alone.

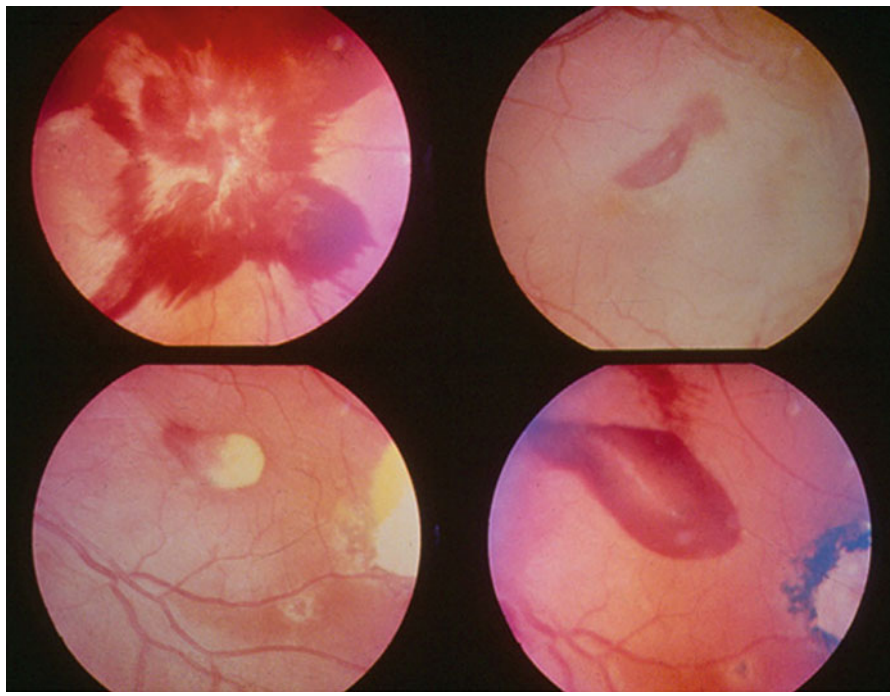

Fig. 6.15 Preretinal hemorrhages in four cases with ocular toxoplasmosis

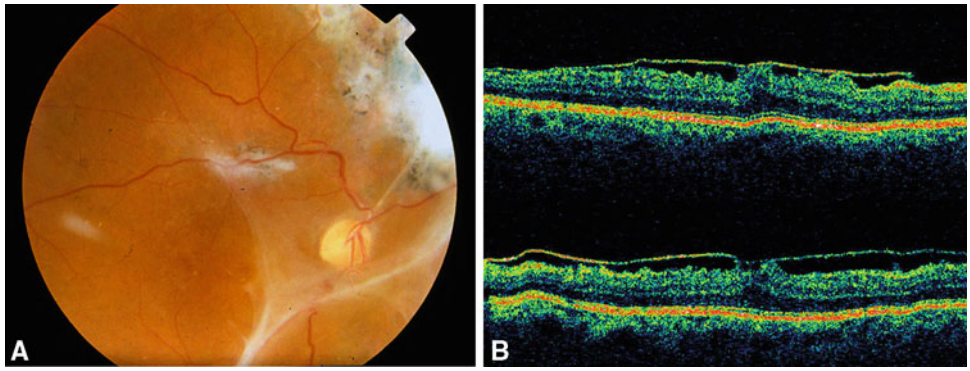

Fig. 6.16 Epiretinal membrane in a case of ocular toxoplasmosis. (**a**) Color photograph of epiretinal membrane in a case of ocular toxoplasmosis. (**b**) Optical coherence tomography horizontal scans demonstrating epiretinal membrane in a case of ocular toxoplasmosis

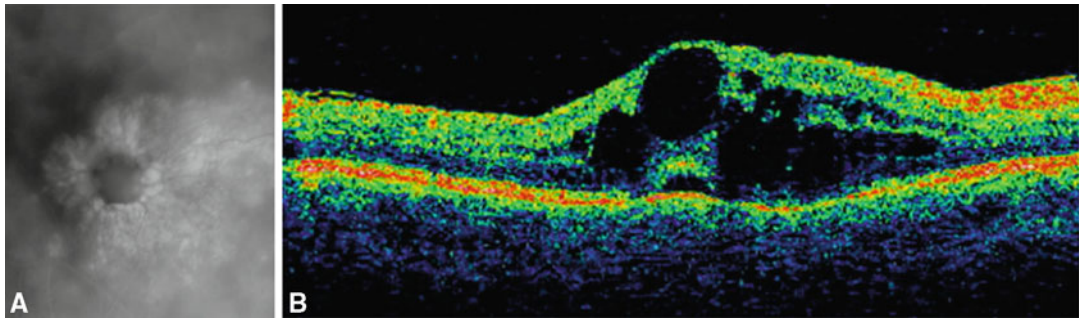

Fig. 6.17 Cystoid macular edema in ocular toxoplasmosis is uncommon. (**a**) Fluorescein angiogram demonstrating the classic petalloid pattern. (**b**) Optical coherence tomography horizontal scan demonstrating cystoid macular edema and a pocket of subretinal fluid

Epidemiology

The factors that affect the epidemiology of OT are related to the parasite as well as the host and the environment, and include endogenous factors such as age, sex, medical history, and immunogenetic background, as well as exogenous factors such as climate, public health, dietary habits, and causative strands. The exogenous factors in particular may change over time, and periodic implementation of epidemiological surveys of OT is important.

Toxoplasmosis is the most frequent cause of infectious uveitis in many countries including Brazil, where it occurs in approximately 30% of patients [25, 36, 37]. Population-based studies of adolescent and adults, most of whom have postnatally acquired infection, report the risk of retinochoroiditis to vary from 2% in North Eastern Brazil to 25% in Southern Brazil [31, 38, 39]. High *T. gondii* seroprevalence has been found in countries (such as France) where undercooked meat is commonly eaten and in tropical areas of Latin America or sub-Saharan Africa where cats are abundant and the climate favors both survival of and exposure to oocysts; [40] with antibodies detectable in as many as 65% of the population age >60 years [41]. Table 6.1 depicts seroprevalence of different populations from around the world, specifically from the developing world [3, 40, 42].

Cats often spread oocysts away from their home, and feral cats may also be responsible for much of the environmental contamination with oocysts.

Table 6.1 Toxoplasmic seroprevalence in different parts of the world

Location	Group of study	Percentage (%) of seroprevalence
France	Pregnant woman	71
Panama	6 years old	13
	60 years old	90
Ibadan in Nigeria	Pregnant woman	78
Somalia	Persons living in the drier regions	44
South Delta in Nigeria	NA	83
United States (NHANES 1988–1994)	Different regions of the country	22.5
Armenia in Colombia	Between 18 and 45 years old	61
Brazil	Adult population	50–80
Mexico	NA	19.5–32
United States (NHANES 1999–2004)	6–49 years old	10.8
Caracas in Venezuela (1964–1965)	NA	47
Maracaibo in Venezuela (2001)	8 months–76 years old	36.6
Panama	NA	0–42.5
Amerindians from Western Venezuela	1–69 years old	49.7
Cuba	Pregnant woman	71
East Africa	NA	29.6–41.7
North Africa	NA	52.2
West Africa	NA	20.6
Ethiopia	NA	80

NA not available, *NHANES* National Health and Nutrition Examination Survey

Owning a cat has been associated with *T. gondii* seropositivity, and was more common among persons in the lower and middle socioeconomic groups [43]. The reports of outbreaks of *T. gondii* infection in Canada [1], Brazil [3], and India [12], after exposure to contaminated water, made this form of transmission evident. Drinking tap water has been associated with an increase risk of *T. gondii* seropositivity [43]. In 2001, there was a large toxoplasmosis outbreak in a city in the state of Parana, in Brazil, and 294 patients were reported to the health authorities with fever, headaches, and myalgias and positive results for both IgM and IgG anti–*T. gondii* antibodies. The outbreak has been linked to the spread of the oocysts through the water [17]. From the affected patients 4.4% showed typical necrotizing retinochoroiditis, and 95% presented without chorioretinitis but had atypical lesions such as retinal whitening, retinal vasculitis, anterior uveitis, and vitreous opacities [43].

Studies linking endemic *T. gondii* infection to contaminated water have been performed in both the developed and developing world. Water from municipal suppliers in urban areas is generally treated with flocculation/sedimentation and is filtered through materials such as anthracite coal and silica sand; the combined process will remove 99% of particles as small as 4 μm in diameter, including *T. gondii* oocysts, which are 12 μm in diameter. Thus, water treatment is not expected to be a routine source of infection in these areas, but periodic filtration failures at water treatment plants could theoretically result in epidemic of *T. gondii* infection, as has occurred with other parasitic diseases, such as cryptosporidiosis [17].

Based on seroprevalence studies in the United States, the proportion of *T. gondii*-infected individuals who have ocular involvement has been estimated to be approximately 2%. In contrast, 17.7% of all individuals in southern Brazil have retinal findings consistent with *T. gondii* infection (21.3% of individuals 13 years of age or older). There may be regions in Africa that also have high rate of OT, although the disease has been studied in less detail on that continent. In one study, 40 (43%) of 93 patients with uveitis in

Sierra Leone were diagnosed with ocular toxoplasmosis [17]. Several studies have estimated the risk of retinochoroiditis in toxoplasma-infected individuals. The lowest estimate is given by Burnett et al. [5], who calculated that between 2,894 and 7,718 individuals acquired the infection during the outbreak in greater Victoria, of whom 20 developed *T. gondii* retinitis and presented to the ophthalmologist: a risk of 0.3–0.7% in the year after the outbreak. On the other hand, a population-based study in southern Brazil [8] showed that approximately 25% of infected adults had retinochoroidal lesions, and 10% developed lesions within 7 years of infection [44]. In London, the prevalence of symptomatic TRC is higher in black individuals born in West Africa than in the general population [39]. Patients from West Africa also have a higher prevalence of OT than black individuals living in London who were born in East Africa, the West Indies, or in Britain, suggesting that conditions in their geographic regions of origin, rather than race per se, influenced the risk of disease. In a northern California study, active TRC was more common among Hispanic patients (8.64 cases/100,000 population) than among non-Hispanics patients (2.56 cases/100,000 population) [27]. The higher prevalence of *T. gondii* infection seen in some areas and in some racial/ethnic group may be due to cultural factors that cause different exposures in terms of parasitic stage, amount of inoculums, or age at infection and reinfections.

Studies have shown that the majority of *T. gondii* infections among immunocompromised patients in North America and Europe are attributable to type II parasites, although types I and III can also be identified in a substantial number of cases. Type II parasites also predominate among congenital infections in North America and France. In contrast, a study of chickens in Brazil showed that most infected birds had type I parasites; some had type III parasites, but none had type II parasites [45].

In vitro studies suggest that strain virulence can affect varying degrees of immune activation, tissue penetration, and the ability of the organisms to encyst. As treatment is effective only during the tachyzoites phase, prior to encystment, this raises the possibility that responses to anti-toxoplasma treatment may differ between strains. As compared to children in Europe, children with CT in Brazil tend to develop retinochoroiditis earlier and are found more often to have either multiple lesions or larger lesions that are more likely to affect the posterior pole and hence to threaten vision. This higher frequency and severity of ocular disease in Brazil compared with Europe has been suggested to be due to exposure to more virulent strains of *T. gondii* [39]. Possible clinical and policy implications of these finding could be the development of targeted treatment and preventive strategies depending on the prevailing parasite genotype.

Lower levels of education have been associated with an increased risk for toxoplasmosis in the overall and race-/ethnicity-specific logistic regression models. Since lower levels of education are associated with lower socioeconomic status, such increased risk may be related to employment in jobs with greater soil exposures. Other food-related factors that could influence trends in *T. gondii* exposure include growth in the frozen preprepared meal and frozen meat markets (because *T. gondii* cysts are usually inactivated by deep freezing) and use of enhancement solutions in commercially prepared pork meat [46].

Clearly, anti–*T. gondii* antibody seroprevalence is higher in Latin America than in Europe or the USA. The varying seroprevalence between African countries might be explained by differences in socioeconomic status, food habits, and even the screening method. To our knowledge, France and Austria are the only countries where testing for toxoplasmosis is required by law in woman of childbearing age. France has the most stringent program, but its epidemiologic impact on OT has not been assessed recently. Toxoplasmosis may be equally important in many other developing and developed countries, where cultural habits and the lack of adequate sanitary conditions expose populations to a variety of diseases. Adequate health education of communities, in general, about the parasites and their prevention, as well as the adoption of measures to improve conditions of hygiene and basic

sanitation for the people of the world are important factors in controlling it and other communicable diseases of public health significance.

Diagnosis

Delaying diagnosis may worsen outcome in patients with OT. This is more important in children, in whom vision is often lost due to retinal complications. Patients come to the ophthalmologist at different stages of the disease and will therefore be tested at different stages of antibody response. In almost all cases the diagnosis is based primarily on dilated fundus examination and confirmed by the presence of circulating specific antibodies against *T. gondii* [47].

Immunocompromised patients are at increased risk for developing acute toxoplasmosis, which has a poor prognosis and may be rapidly fatal if left untreated. Ocular toxoplasmosis may follow a severe course in patients with AIDS, having atypical features (see Figs. 6.5, 6.6, 6.7, and 6.8), such as bilateral active lesions, large areas of active retinal necrosis, lesions arising perivascularly and not from old scars, bilateral inflammation, and inflammation extending into the orbit and causing cellulitis and panophthalmitis [48]. For this reason, an early diagnosis is crucial in these cases with different tests that will be discussed as follows.

Multiple laboratory tests, at different time points, may be required for a more complete assessment. The addition of an anti–*T. gondii* IgA assay to the detection of IgM and IgG increases the sensitivity of identification of cases with recently acquired toxoplasmosis since this class of antibodies disappear quicker than IgM [47]. The detection of anti–*T. gondii* IgM antibodies is not completely reliable for the diagnosis of recent OT infection, because IgM antibody titers can be naturally occurring or can occasionally even persist for more than 2 years after the onset of disease in some cases. For the detection of acute congenital disease in fetuses and newborns, IgA antibodies are often used, because the IgM production is still weak and IgG antibodies can be of maternal origin. Serum IgA antibodies were only found during 6–7 months after primary infection. In contrast to IgM antibodies, natural IgA antibodies have not been reported to date, and anti–*T. gondii* IgA antibodies are not found in chronic toxoplasmosis [47]. Most reports of postnatally acquired ocular toxoplasmosis describe ocular involvement during the acute phase of infection, in which laboratory testing demonstrates a distinct serologic profile including the presence of high levels of IgG [49].

There are several serological tests for toxoplasmosis diagnosis. Sabin–Feldman dye test is the gold standard above all other methods. It is a neutralization assay in which live organisms are lysed in the presence of complement and IgG *T. gondii*–specific antibody. It is only used in research centers and reference laboratories [11].

Indirect fluorescent antibody test (IFAT) is available for IgG and IgM detection. False-positives can occur in the presence of antinuclear antibodies (ANA) for IgG detection and ANA or rheumatic factor (RF) for IgM detection [11].

Demonstration of intraocular antibody production determines the diagnosis of active ocular toxoplasmosis. Antibody titers are measured in aqueous humor and serum, and Goldmann–Witmer coefficient is calculated. Analysis of IgG, IgM and IgA increases the sensitivity of aqueous humor study [11].

Polymerase chain reaction (PCR) is a diagnostic test with the ability to determine the presence of DNA from an infectious agent and not the response to the infection assessed by antibody response. Therefore, its performance is not altered by the immune response of the patient. Polymerase chain reaction is highly sensitive and specific but should be done under standardized conditions. One study showed that the PCR sensitivities for *T. gondii* in aqueous and vitreous were 75% and 50%, respectively, whereas the specificities from these same sources were 100% and 93.7% [17]. The analysis of intraocular fluids such as aqueous and vitreous as well as chorioretinal biopsies is generally reserved for special cases, such as in AIDS patients, where the differential diagnosis with other infections such as necrotizing herpetic retinitis (CMV, VZV, HSV) may be a problem.

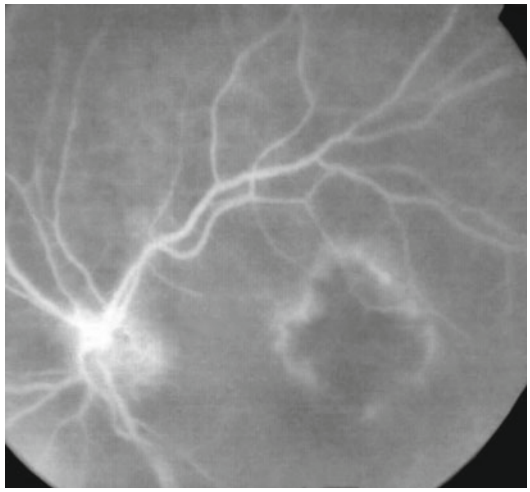

Fig. 6.18 Fluorescein angiography confirmed the presence of a focal lesion of retinochoroiditis. This lesion masked fluorescence early during the study and was surrounded by a hyperfluorescent rim. There was no significant leakage in the late stages of the angiogram. The retinal component of the fluorescein angiogram was normal

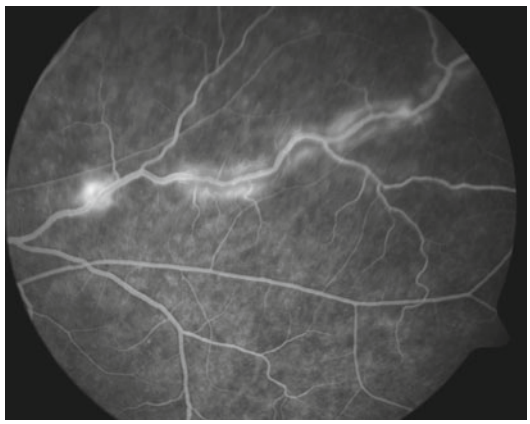

Fig. 6.19 Retinal vasculitis in ocular toxoplasmosis

Fluorescein angiography (FA) does not usually contribute significantly to the diagnosis of OT in typical cases (Fig. 6.18); however, it is helpful in demonstrating associated features such as vasculitis (Fig. 6.19), vascular occlusion, arteriovenous shunt within the retina, retinochoroidal shunts, macular edema (see Fig. 6.17a), and CNV, as well as optic nerve and neuroretinal involvement (see Fig. 6.13a, b) [18]. Indocyanine green (ICG) angiography is useful for the early diagnosis of recurrent OT because it can identify an area of reactivation not yet detectable by ophthalmoscopic examination or FA [8]. Furthermore, future ICG angiography studies might bring new information that could result in improved management of TRC and may give new insights into the pathophysiology of the disease (Fig. 6.20).

Optical coherence tomography (OCT) is a diagnostic tool that enables identification of subtle morphological features not detectable on clinical examination (see Figs. 6.3c, 6.13c, 6.16b, and 6.17b) [50]. Some OCT findings described in acute stages of OT include changes with deposits on the vitreoretinal interface with a focal area of increased intraretinal backscatter and thinning of the retina in this area. Furthermore, the lesions may have significant backscatter anterior to the retina indicative of the migration of inflammatory cells into the vitreous in association with a secondary partially detached posterior hyaloid face. In contrast, OCT may demonstrate an inactive toxoplasmic lesion with a region of enhanced reflectivity within the neurosensory retina corresponding to previous inflammation where there are focal areas of fragmentation within this reflective band corresponding to retinal pigment epithelium proliferation and hyperpigmentation; also, there may be the presence of increased backscatter from the choroid consistent with pigmentary atrophy. The superficial layers of the retina appear to be preferentially involved and thinned, which is consistent with the predilection of toxoplasmosis for neural tissue [51]. Optical coherence tomography also helps to identify vitreoretinal traction in patients with macular edema.

Ocular ultrasound may be helpful in identifying associated retinal pathologies in cases where visualization is impaired by media opacification.

Differential Diagnosis

Congenital toxoplasmosis of the newborn must be differentiated from the other infectious diseases of the TORCH group (rubella, cytomegalovirus, and herpes simplex virus, as well other congenital infectious diseases that may simulate toxoplasmosis, such as syphilis and tuberculosis).

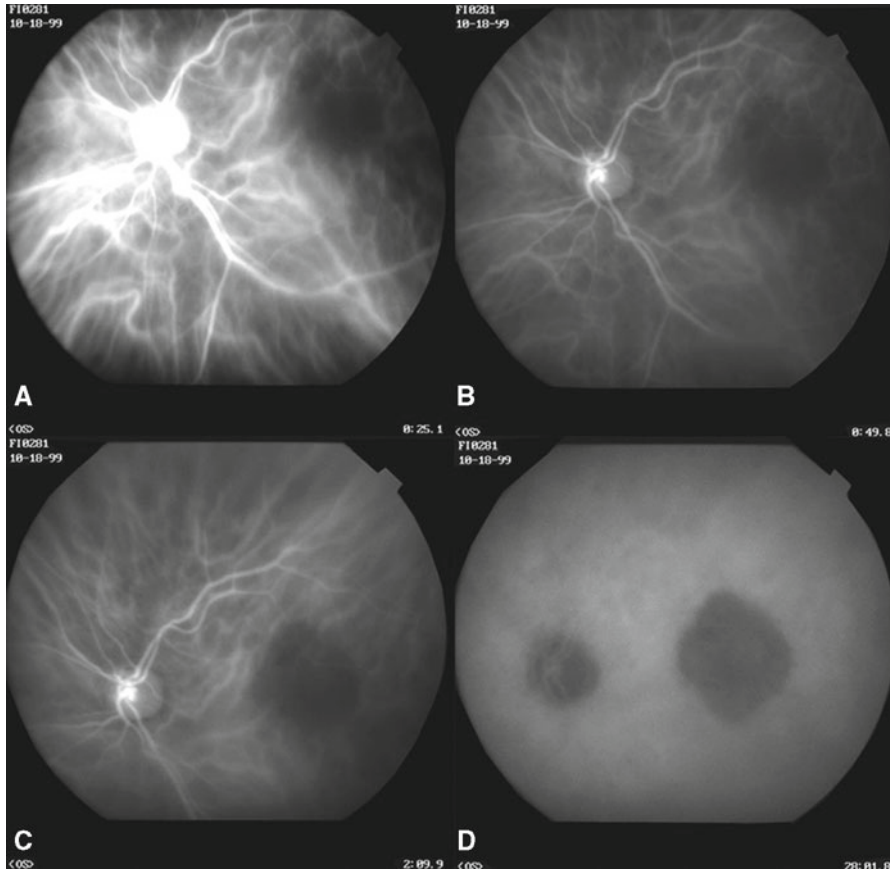

Fig. 6.20 An indocyanine green angiography confirmed the presence of a lesion of Fig. 6.18 that masked fluorescence throughout the study (**a**–**d**) and remained hypofluorescent in the late frames (**d**)

Important noninfective ocular entities that may be confused with CT include coloboma, persistent hyperplasic primary vitreous, and retinoblastoma [8].

Recurrent *Toxoplasma* lesions adjacent to retinochoroidal scars may resemble serpiginous choroiditis. Other conditions that are important in the differential diagnosis of ocular toxoplasmosis are necrotizing retinitis caused by herpes viruses (CMV, herpes simplex, herpes zoster), fungal retinitis (candidiasis, blastomycosis), septic retinitis, ocular toxocariasis, sarcoidosis, syphilis, and tuberculosis [8].

The atypical forms of OT, that were described above, deserve distinct differential diagnosis awareness. In cases of *Toxoplasma* neuroretinitis, other causes of neuroretinitis, such as cat scratch disease and viral syndromes, must be excluded. *Toxoplasma* neuroretinitis should be differentiated from the optic neuritis associated with sarcoidosis and CMV [8].

Management

Antimicrobial therapy is absolutely required for systemic toxoplasmosis in newborns, pregnant woman, and immunosupressed patients and in acute symptomatic disease specially when threatening vision due to the anatomic location and/or severe inflammation. Patients with chronic toxoplasmosis do not require treatment when the disease is inactive, except in special cases where it is used to decrease the chance of recurrence as no treatment is effective at eliminating the tissue cyst.

In general, TCR resolves spontaneously within 6–8 weeks in most patients, although symptoms arising from the accompanying intraocular inflammation (e.g., floaters from the presence of vitreous cells) often take longer. Permanent visual impairment occurs when lesions affect the posterior pole (within the macular arcade or adjacent to the optic disc) or because of complications of inflammation (e.g., vitreous opacity, epiretinal membranes, retinal detachment) develop [4].

The lack of effective and early therapy for OT is responsible for the loss of eyesight in this parasitic disease. The experience in the treatment of OT in patients with AIDS has shown that antitoxoplasmic therapy is efficient. The problem is that recurrences are generally unavoidable, and in non-immunosupressed patients, the immune system also plays an important role causing destructive inflammation. Treatment has to be started before the process causes necrosis and destruction of the retina, and often the loss of vision is caused by recurrent bouts of the disease.

The type and duration of OT treatment should be individualized. It is determined by several factors such as, the immune status of the patient, severity of the inflammatory response, and if the site of the lesion is close to the macular area or optic nerve head. The current drugs are directed against active lesions but are unable to eradicate tissue cyts. Generally, initial antibiotic treatment includes oral pyrimethamine, sulfadiazine, and folinic acid. Folinic acid is usually added to decrease the risk of leukopenia and thrombocytopenia associated with pyrimethamine therapy [52]. However, a very well-tolerated therapy that has been used very effectively against OT is the combination of oral trimethoprim–sulfamethoxazole and clindamycin [53]. More recently, other antimicrobials, such as azithromycin and atovaquone, have been used successfully [54–56]. There is no controlled evidence showing that one treatment is better than the other or that the association of other drugs to sulfadiazine and pyrimethamine improves results. All of these regimens are associated with the potential for significant side effects; some of which may be treatment limiting [54, 55]. The purpose of treatment is to limit retinal damage by inhibiting multiplication of the parasites during the active stage of infection. Systemic corticosteroids can be added to avoid further damage of the retina by the inflammation. Classically, the use of intraocular injection of corticosteroids is contraindicated in OT, but injection of short half-life agents, such as dexamethasone, may have a role in selected patients when used together with antitoxoplasmic agents.

We will briefly describe the characteristics of each of the more commonly used systemic antibiotics.

Pyrimethamine

This antibiotic interrupts the metabolic cycle of the parasite by inhibiting the dihydrofolate-reductase enzyme, thereby preventing the conversion of folic acid to folinic acid, which is essential in both DNA and RNA synthesis. Adverse effects of pyrimethamine include dose-related bone marrow suppression (10%) with leukopenia, thrombocytopenia, and megaloblastic anemia, simulating folinic acid deficiency; these effects are reversible by interruption of treatment or administration of folinic acid. *Dosage*: Adults: 100 mg loading dose, followed by 25 mg/day for 30–60 days. Children: 4 mg/kg loading dose followed by 1 mg/kg/day divided in two doses. Newborns should be treated daily for the first 6 months and then three times/week for their first year of life [8].

Sulfonamides

Sulfonamides prevent normal utilization of paraminobenzoic acid (PABA) for the synthesis of folic acid by the parasites. Sulfonamides and pyrimethamine are synergistic, and the concentration of sulfonamides in the eye reaches 50–80% of the simultaneous serum concentration. Precipitation of sulfonamides in the urine may cause crystalluria, hematuria, and renal damage. Adequate hydration with

oral fluids to maintain a urine output of at least 1,500 ml/day should avoid the problem; hypersensivity reactions are quite variable and range from photosensitivity to a severe Stevens–Johnson type of reaction involving skin and mucous membranes. *Dosage*: Adults: 2 g loading dose followed by 1 g every 6 h for 30–60 days. Children: 100 mg/kg/day divided every 6 h. Newborns should be treated daily for their first year of life, with dosage of 100 mg/kg/day divided into two doses [8].

Folinic Acid

Folinic acid is used as an adjuvant in therapy with antifolate agents such as pyrimethamine. Folinic acid can be utilized by human cells but not by *T. gondii* and prevents bone marrow suppression caused by pyrimethamine and other folinic acid antagonists. *Dosage*: 5–20 mg/day during pyrimethamine therapy depending on neutrophil count [8].

Clindamycin

Clindamycin inhibits ribosomal protein synthesis and has good ocular penetration. A skin rash occurs in 10% of the patients treated with clindamycin and diarrhea in 2–20%. Pseudomembranous colitis can develop 0.01–10% of patients treated with clindamycin, requiring immediate interruption of therapy and administration of vancomycin or metronidazole. *Dosage*: 300 mg every 6 h for 30–40 days. Children: 16–20 mg/kg/day divided every 6 h [8].

Azithromycin

Azithromycin inhibits ribosomal protein synthesis [8]. Azithromycin is a nontoxic antibiotic that penetrates into phagocytic cells and reaches high intracellular and tissue concentrations. In vivo and in vitro efficacy against *T. gondii* has been reported, with an effect on the cystic form if administered for longer than 4 weeks. Furthermore, it penetrates readily into brain tissue. The concentrations of azithromycin in the ocular tissues are not yet known. Azithromycin has been considered for the treatment of OT because of its availability and limited toxicity and because it crosses the blood-brain barrier and appears to be widely distributed to brain tissue. However, resistant cases and recurrences have been reported [54]. *Dosage*: Adult: 1 g in the first day followed by 500 mg once daily for 3 weeks. Children ≥6 months: 10 mg/kg on first day (maximum: 500 mg/day) followed by 5 mg/kg/day once daily (maximum: 250 mg/day) [11].

Trimethoprim and Sulfamethoxazole

The combination of trimethoprim and sulfamethoxazole has been evaluated as a potentially less-toxic alternative for treatment of toxoplasmosis. Grossman et al. were able to demonstrate that the combination of trimethoprim and sulfamethoxazole was synergistic and effective against otherwise lethal *T. gondii* infections in mice. Nguyen and Stadtsbaeder found a synergistic effect of trimethoprim and sulfamethoxazole against intracellular *T. gondii* replication in cell cultures. The most common side effects are mild gastrointestinal problems (nausea, vomiting, cramps, and occasionally diarrhea) and mild skin lesions (usually mild, diffuse maculopapular rashes) attributable to hypersensitivity to sulfamethoxazole. More serious skin hypersensitivity reactions, such as Stevens–Johnson syndrome, can occur but are rare [57]. *Dosage*: 160/800 mg every 12 h for 30–40 days [8].

Spiramycin

Spiramycin is less effective but also less toxic than the combination of pyrimethamine with sulfadiazine, so it is the drug of choice during pregnancy. *Dosage*: Pregnancy: 500 mg every 6 h for 3 weeks; regimen may be repeated after 21 days [8].

Atovaquone

Atovaquone is a hydroxynaphthoquinone that has shown promise for the treatment of *Pneumocystis carinii* pneumonia in patients with acquired immune deficiency syndrome. Atovaquone, which acts by selective inhibition of mitochondria electron transport chain in protozoa, also has been shown to have significant in vitro and in vivo activity against *T. gondii.* In animal models, atovaquone has activity against the tissue cysts (bradyzoites). Atovaquone is associated with very few side effects in healthy patients and appears to be well tolerated in immunocompromised individuals [55]. *Dosage*: 750 mg every 6 h for 4–6 weeks [11].

Other alternative agents are the tetracyclines, but they are contraindicated during pregnancy and in childhood because of the resultant brown discoloration of the teeth and depression of bone growth [8].

Oral corticosteroids must be initiated at least 48 h after antiparasitic drugs. The usual initial dose in adults is 40 mg per day followed by tapering depending on clinical response. Generally, corticosteroids are suspended at least 10 days before the specific anti-toxoplasma drugs [11].

Topical therapy includes corticosteroids and mydriatic drugs. Corticosteroid frequency is indicated depending on the amount of inflammation on the anterior segment. In severe to moderated anterior uveitis, they are initiated every 1 or 2 h, with a gradual decline in dosage over time. Cycloplegic/mydriatic agents are used to prevent or reverse the formation of posterior synechiae and to relieve the pain caused by spam of the ciliary muscle [11].

Currently, there are three classic combination regimens for the treatment of OT: (1) pyrimethamine, sulfadiazine, folinic acid, and prednisone; (2) pyrimethamine, clindamycin, folinic acid, and prednisone; and (3) pyrimethamine, sulfadiazine, clindamycin, folinic acid, and prednisone [11]. However, in a survey among all members of the American Uveitis Society in 2001, the most commonly used drugs to treat typical cases of OT were pyrimethamine (65%), sulfadiazine (54%), clindamycin (42%), and trimethoprim/sulfamethoxazole (28%). The remaining five antiparasitic agents used in current regimens of choice are all used by no more than 10% of responders; they include atovaquone, spiramycin, azithromycin, minocycline, and pyrimethamine/sulfadoxine. Only 17% of respondents used an oral corticosteroid drug for all immunocompetent patients with OT regardless of clinical findings. For those who do not use corticosteroids for all patients, indications for use of corticosteroids include severe vitreous humor inflammatory reactions (71%), decreased vision (59%), proximity of lesions to the fovea or optic disc or zone 1 (Fig. 6.21) (35%), and large lesions (5%) [58].

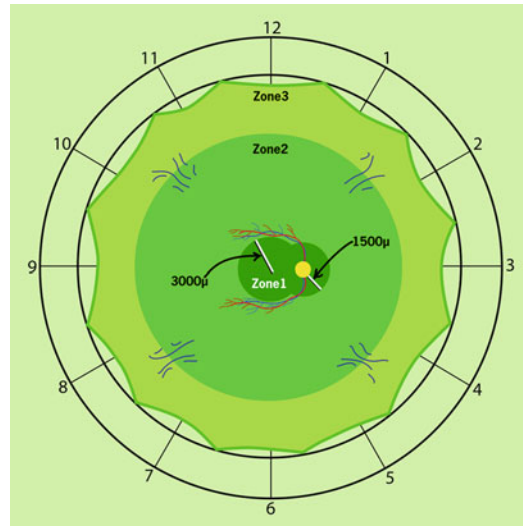

Fig. 6.21 Illustration demonstrates the topographic location of the toxoplasmic retinochoroiditis lesion in the retina. Zone 1: Lesions located in an area between the temporal vascular arcades, affecting an area within 3,000 µm of the center of the fovea or 1,500 µm from the edges of the optic disc. Zone 2: Lesions located outside the boundaries of the zone 1, up to the anterior margins of the vortex veins. Zone 3: Lesions outside the zone 2 up to the ora serrata

Some patients are intolerant and allergic or have infections resistant to systemic therapy. Intraocular drug delivery is one option for these patients. Intravitreal injection of clindamycin alone or in combination with dexamethasone has been reported as an alternative for such patients [59]. We often use intravitreal clindamycin and dexamethasone for the treatment of

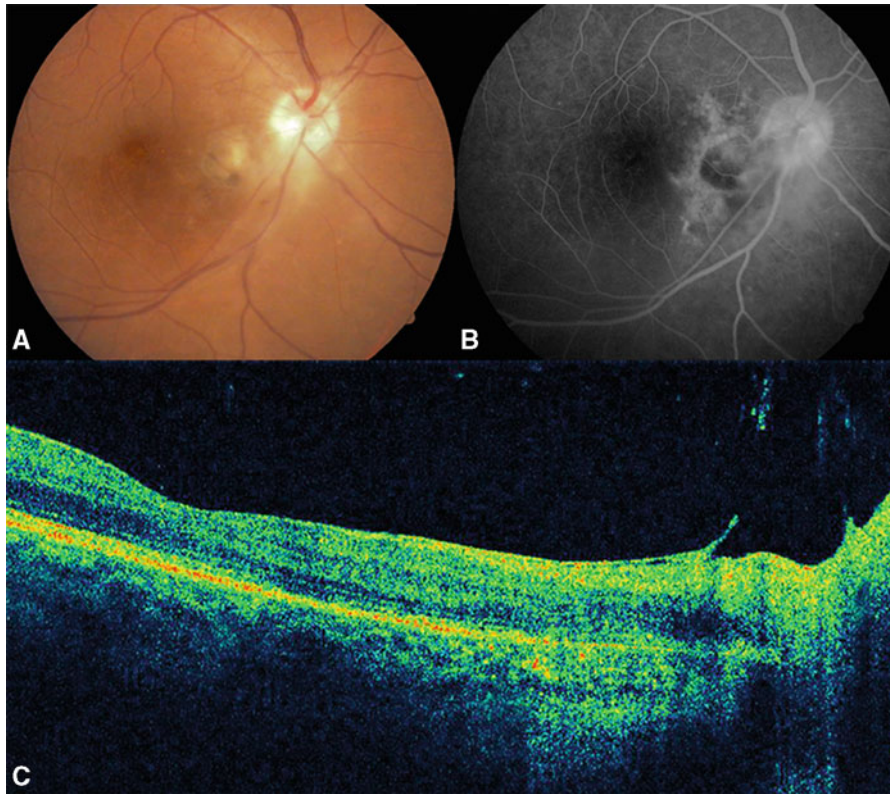

Fig. 6.22 Same patient as in Fig. 6.13 after four weekly injections of intravitreal clindamycin and dexamethasone. (**a**) Color fundus photograph demonstrates resolution, and a large decrease in both the size of the lesion along the inferotemporal vascular arcade and vitreous inflammation. (**b**) Fluorescein angiogram demonstrated a significant decrease of leakage from toxoplasmic retinochoroiditis. (**c**) Optical coherence tomography scan shows normalization of the papillomacular anatomy and a decrease in the height of the peripapillary granuloma. The retina map analysis indicates a central macular thickness of 240 μm. His visual acuity improved to 20/40

zone 1 TRC in pregnant patients, in patients with disease progression despite systemic therapy, or in patients with lesions located at or near the fovea and/or optic disc. Such combined therapy is typically effective at controlling TRC and improving both inflammation and vision (Figs. 6.13 and 6.22). Recently, Sobrin et al. [59] reported a case series of six patients who were treated with a single intravitreal injection of clindamycin alone (1 mg/0.1 mL). Complete resolution of vitreous inflammation was noted within 6 weeks in five of six patients.

Photocoagulation and cryotherapy have been proposed for the treatment of TRC and to decrease relapse rates [60, 61]. These procedures cause destruction of the cysts and the tachyzoites in the retina. However, photocoagulation and cryotherapy of active lesions have been associated with severe complications, including choroidal neovascularization, vitreous hemorrhages, and retinal detachment [62]. Vitreous surgeries should be used if there are vitreal opacities or vitreal membranes that obstruct vision or cause traction on the retina. Vitrectomy should be performed after the inflammatory process is controlled [63].

Controversies and Perspectives

Although serological tests can reliably identify individuals with recent *T. gondii* infections, there are currently no serological techniques to discriminate between patients with congenital

infections and remote postnatally acquired infections. In addition, clinical characteristics do not always reliably distinguish between patients with congenital and postnatally acquired infections.

Ocular fluid analysis shows that intraocular anti–*T. gondii* IgG production is more frequently present in patients with recurrent ocular toxoplasmosis, whereas *T. gondii* DNA is more frequently present in ocular fluid samples from patients with primary OT. The presence of DNA in patients with primary OT and serologic evidence of acute systemic toxoplasmosis is possibly caused by the gradual activation of the intraocular *T. gondii*–specific immune response, which is not yet capable of clearing the infectious agent in the early stage of the disease. Intraocular anti–*T. gondii* IgA antibodies could be detected in patients with both acute and chronic stages of systemic infection and in patients with primary OT as well as in patients with recurrent OT. In contrast, serum IgA antibodies have been noted so far only in the acute phase of primary disease. The intraocular presence of IgA is therefore not a marker of acute disease, but it could be caused by the unique environment of the eye, where the cytokine transforming growth factor-β(beta) is present in relatively high levels [48]. We consider that the combination of serum anti–*T. gondii* IgG, IgM, and IgA to be essential for evaluation of any TRC case. However, most cases are diagnosed clinically.

Proliferating parasites are believed to be responsible for tissue destruction, whereas hypersensitivity reactions to the parasite are responsible for associated inflammatory signs, including retinal vasculitis, anterior uveitis, vitreous inflammatory reactions, and retinal edema. While it has been suggested that intraocular inflammation can occur without necrotizing retinochoroiditis in patients with acquired *T. gondii* infections, there has been little data provided to support such statements. It is known that retinochoroidal scars can first develop after birth in patients with congenital infections and that tissue cyst can exist in normal-appearing retina [7]. Acquired *T. gondii* infection should be considered in the differential diagnosis of patients with the recent onset of nonspecific vitreous humor inflammation and retinal vasculitis, especially in the presence of constitutional symptoms.

Clinicians are cautioned against corticosteroid injections in patients of acquired *T. gondii* infections if there is evidence to suggest systemic toxoplasmosis because the inflammatory reactions may be in response to parasites within the eye and treatment may facilitate proliferation of organisms, leading to necrosis that would otherwise have been prevented by host defenses. On the other hand, low-dose corticosteroid monotherapy has been administered without severe side effects in some reports. However, a well-defined study of the effect of corticosteroid monotherapy in OT as well as the additional value of corticosteroids as adjuvant therapy has not been performed. Thus, the use of corticosteroids for the treatment of OT is controversial, and the timing and dosages during the course of the disease are not well defined [64]. Basically, topical and half-dose (0.5 mg/kg/day) corticosteroids are fine with antimicrobial cover. Depot corticosteroids, both periocular and intraocular, are contraindicated. Intravitreal dexamethasone is fine with antimicrobial cover because it only lasts a day or two. Ocular toxoplasmosis in immunocompromised patients is often treated without the use of corticosteroids, thereby reducing the risk of further suppression of host defenses; clinical series have shown that the signs of OT, including inflammatory signs, can respond rapidly to antiparasitic therapy alone in immunocompromised patients.

A variety of observations suggest that clinical features of OT are related to age of the host. The distribution of active TRC episodes in relation to patient age has been remarkably similar in many reports. Ocular involvement during the acute phase of postnatal toxoplasmosis occurs predominantly in elderly patients [65]. In addition, it has been described a relationship between older age and larger lesions. A relationship between age and scar size could be explained by a history of progressive enlargement in older patients with long-standing disease and multiple reactivations, but this explanation would not account for a relationship to the area of the active recurrence.

The latter relationship may reflect waning immunity with a decreased ability to limit the proliferation of parasites among elderly patients.

Ocular toxoplasmosis is one of the few forms of uveitis in which intraocular pressure (IOP) is elevated during the initial phase of inflammation; others include herpetic anterior uveitis (HSV, VZV, CMV), sarcoidosis, Posner–Schlossman syndrome, and syphilitic uveitis. The cause of elevated IOP in eyes with OT is unknown [26]. Westfall et al. identified a possible relationship between elevated IOP and increased anterior chamber cells, but the relationship was not statistically significant [26, 66].

The source of the original infection in patients with OT has been a subject of debate. For many years, it has been widely accepted that nearly all scars are the residua of congenital infections and that ingestion of undercooked meat is the major source of primary, acquired infection in pregnant women and others. Recent observations have challenged these traditional beliefs [24]. A better understanding of the source of initial infection in patients with recurrent TRC has important implications for prevention of disease transmission and possibly for treatment. If establishment of retinal infections with acquired disease is more common than heretofore believed, it is important to reconsider sources of infection. Ingestion of tissue cysts has traditionally been assumed to be the major route by which infection occurs [17, 24].

Evidence that strain type does indeed affect disease outcome in humans is increasing. We need a more detailed understanding of the population structure for this ubiquitous parasite. Most of the existing information is from a few regions (principally Europe, Brazil, and North America) and a limited number of animals and people with severe disease. Although certain strains appear to dominate in these groups, the numbers analyzed in detail remain small. The use of SAG2 for genotyping *T. gondii* strains is capable of distinguishing all three clonal genotypes at a single locus. This approach works well in North America and Europe where the three major lineages predominate because of extreme linkage disequilibrium. Current findings indicate that most strains from Brazil as well as many other countries do not fit the clonal pattern seen in North America. Consequently, studies that rely solely on *SAG2* typing will necessarily under represent the true genetic divergence in many regions [45].

Further research is required to determine whether virulence factors are associated with prolongation of the tachyzoite phase, which could create a longer therapeutic window before tissue cyst formation when anti-toxoplasmic treatment might be effective [40].

Finally, the factors that affect the epidemiology of ocular toxoplasmosis include endogenous factors such as age, sex, medical history, and immunogenetic background, as well as exogenous factors such as climate, public health, dietary habits, and causative strands. Primary preventive strategies should include children and adults at risk of ocular disease as a result of postnatal infection and should not be confined to pregnant women. Additionally, prophylaxis to prevent recurrence of OT in immunocompetent individuals has been advocated by some groups and is in continual discussion.

Focal Points

The timing of toxoplasma infection leading to ocular disease is rarely known. However, current evidence suggests that many more people are affected by postnatal than by prenatal toxoplasmosis. This has major public health implications. Considerable expertise and expense is concentrated on screening and health information to reduce the risks of toxoplasmosis due to prenatally acquired infection, principally to reduce the risks of ocular morbidity in the long term.

Initial retinal infection may be subclinical, with development of retinal lesions months or years later. Tissue destruction is probably attributable both to proliferation of *T. gondii* and to inflammatory reactions, but the relative importance of each factor may vary between hosts. In some cases, the disease may be predictably self-limiting, and so no intervention is needed. In other instances, aggressive treatment may be warranted. These decisions will probably be most

important in the treatment of maternal infection, in which the developing fetus is especially sensitive to drugs, and so the drugs must be used only when absolutely necessary.

Patients can periodically have mild, transient recurrences of inflammation without evidence of active retinochoroiditis. Attention to these various observations may help to understand disease mechanisms, ultimately with implications for choice of therapy. Reinfection with *T. gondii* might explain some clinical observations and should be investigated with new techniques that can differentiate between parasite types. Disease features are probably more diverse than traditionally taught; yet most, if not all, "atypical" forms of disease appear to be part of a spectrum of the same basic disease process of retinal infection with stimulation of a host immune response.

Although the general approach to management of OT is similar for most uveitis specialists, there is currently no consensus regarding a preferred treatment regimen.

Prognosis of OT is generally good in immunocompetent individuals. Immunosuppressed patients and the elderly may have more chronic disease, and vision loss can occur secondary to macular scar formation, optic nerve involvement, vascular occlusion, retinal detachment, and other potential complications:

- Acquired toxoplasmosis in childhood may lead to severe blinding OT late in life and anti-toxoplasma drugs may be indicated when the infection is diagnosed.
- Most cases of OT are acquired, not congenital.
- The classic clinical presentation for OT is retinochoroiditis, but rarely only vasculitis or small areas of retinal thickening/whitening can be seen.
- Pregnant women can rarely transmit the infection to fetus more than once.
- Cats and meat are not the only source of infection; both air and water sources have been recognized.
- Anti-toxoplasma drugs should be given according to the clinical picture and not just for 4–6 weeks.
- Prevention of recurrence is possible and should be used in high-risk patients.
- Recurrences not just related to retinal cysts (persistency of infectious agent).
- PCR and modern molecular biologic techniques still play a minor role in diagnosis.

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7 Retinal and Choroidal Manifestations in Bartonellosis, Lyme Disease, and Syphilis

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Abstract

Infections with bartonellosis, lyme, and syphilis are not uncommon, especially in selected populations of patients who are at risk. Ocular manifestations, which include retinal and choroidal diseases, are protean and may be initial presentations of the infections or may represent extension of the systemic infectious processes. The diagnosis is often established clinically, with serologic evaluations performed for confirmation. Therapy is targeted with specific anti-infectious agents aiming directly at the underlying infectious organisms. Systemic corticosteroid may be used subsequently to provide complementary control of the inflammation. Ocular involvements, similar to central nervous system disease, mandate intravenous administration of therapeutic agents over sufficient treatment duration.

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Introduction

The human eye can offer critical clues to the presence of systemic diseases, which may be manifested initially as ocular morbidity. In such cases, information obtained from careful ocular examination may aid in the diagnosis. On the other hand, the diagnosis of selected systemic diseases warrants detailed ocular examination, as the eye is often involved. The index chapter will discuss the diverse retinal and choroidal manifestations in ocular Bartonellosis, Lyme disease, and syphilis.

Bartonellosis

The first manifestations of ocular bartonellosis were first described by Henry Parinaud in 1889. Parinaud reported three patients presenting with follicular conjunctivitis, regional lymphadenopathy, and chronic fever, in addition to a prior history of contact with pets [1]. The newly reported manifestations were named Parinaud's oculoglandular syndrome (POGS). Over the following years, the association of POGS and exposure to pets was confirmed in several reports [2, 3]. Several decades later, an association was established between the POGS and cat scratch disease (CSD) [3], an infectious disease that was first described by Debré et al. in 1950 and characterized by tender and swollen regional lymph nodes [4]. An association between CSD and neuroretinitis was first suggested by Sweeney and Dance in 1970 [5] and confirmed 7 years later by Donald Gass [6].

For nearly a century, the etiologic agent of POGS and CSD was not identified; it was not until the evolution of biomolecular technology in the mid-1990s of the past century that allowed the identification of *Bartonella henselae* as the causative agent of CSD [7, 8]. In 1994, Golnik and associates were the first to report a serologic evidence of systemic Bartonella infection in patients with neuroretinitis [9]. Since the early 1990s, *B. henselae* has been incriminated in an increasing list of medical conditions including POGS, CSD, neuroretinitis, focal retinochoroiditis, and bacillary angiomatosis [10, 11].

B. henselae is one of 21, so far identified, Bartonella species. Of these 21, eight species have been found to cause human diseases, four of which (*B. henselae, B. quintana, B. grahamii, and B. elizabethae*) have been linked to ocular complications [12]. In immunocompetent individuals, Bartonella species are capable of causing Oroya fever, Trench fever, endocarditis, myocarditis, bacteremia, cat scratch disease, and neuroretinitis. The list of diseases grows even longer in immunocompromised patients to include chronic fevers, bacteremia, peliosis hepatitis, and bacillary angiomatosis [12].

Epidemiology

The prevalence of CSD has been estimated to be 9.3 per 100,000 population with an annual incidence rate of about 22,000 cases and approximately 2,000 annual hospitalizations and with an annual cost of health care, estimated in 1993, of 12 million US dollars [13].

Over 90% of patients report a history of having been scratched by a cat, often a kitten. Children younger than 10 years of age are particularly susceptible to Bartonellosis, constituting nearly 80% of cases [10].

Cat-to-cat transmission of *B. henselae* is mediated by the cat flea *(Ctenocephalides felis)*. The role of fleas, however, in transmission of infection to humans, is unknown, although flea feces remain infectious for long periods and could transmit *B. henselae* through direct inoculation of open wounds or mucous membranes, such as the conjunctiva [14]. Cat-to-human transmission may occur from trauma (scratch), inhaling materials infected by cats, being licked by infected animals, or rubbing one's eye after contact. Human-to-human transmission has not been reported.

It is estimated that the total population of cats in United States is around 60 million with nearly one-third of all homes having a cat. It is also estimated that 10–40% of domestic cats have asymptomatic bacteremia [15]. Kittens in particular are susceptible to infection with *B. henselae* and may have asymptomatic bacteremia for several weeks, whereas some adult cats have been shown to be chronic carriers. Multiple infections within the same family have been reported [16]. However, removal of the cat from the house is considered unnecessary as the overall rate of human transmission is generally low [17].

Typical manifestations of CSD include conjunctival injection, watery discharge, and foreign body sensation. A granulomatous nodule, usually unilateral, develops in the palpebral conjunctiva, surrounded by follicles, intense chemosis, and injection. The nodule may be single, flat, and large, or multiple and raised. The fornices and bulbar conjunctiva may also be involved. Corneal involvement usually consists of superficial punctate keratitis but rarely causes significant keratitis [18]. The outcome of CSD is usually benign with recurrences uncommon possibly because of lasting immunity [19].

POGS is classified as an atypical manifestation of CSD and occurs in approximately 3–7% of all CSD infections with clinical manifestations occurring, typically, 1–2 weeks post infection [20]. A primary inoculation lesion in the conjunctiva, skin, or mucous membrane has been identified in about 76% of patients [21].

Microbiology

Bartonella, formerly known as Rochalimaea, are a genus of Gram-negative facultative intracellular bacteria. Bartonella belong to the phylum Proteobacteria, to the order Rhizobiales, which makes Bartonella a close relative to the Brucella species [22–24]. Bartonella carried its name after the Peruvian microbiologist Alberto Barton who, in 1905, discovered the etiologic agent of Oroya fever: the *Bartonella bacilliforms*.

Bartonella are fastidious and highly resilient rods requiring long incubation of up to 4 weeks in enriched media. Within their host, Bartonella reside inside erythrocytes or endothelial cells, which can lead to bacteremia, hemolytic anemia, endocarditis, or even an angioproliferative response [25, 26]. Bartonella cannot oxidize glucose; however, they use glutamate and succinate as their sources of carbon. Whereas *B. henselae* colonies tend to be rough and produce pitting of the agar, *B. quintana* colonies are usually smooth, with little or no pitting [27].

Bartonella can cause a necrotizing or focally suppurative response, such as that observed in CSD, in immunocompetent patients. In immunocompromised patients, however, the response typically will be vasoproliferative as seen in bacillary angiomatosis [28]. Analysis of primary skin lesions and affected lymph nodes shows a granulomatous inflammation with a center of necrotic material surrounded by concentric layers of inflammatory cells, most commonly histiocytes, lymphocytes, and nucleated giant cells [29].

The ability of Bartonella to induce a vasoproliferative response (bacillary angiomatosis) in immunocompromised hosts could be partially explained by their ability to parasitize endothelial cells [30, 31]. At the same time, the ability of some Bartonella species, such as the flagellated *B. bacilliformis*, to cause hemolysis and sometimes life-threatening anemia (as in acute infections of Oroya fever) could be explained by their ability to invade the red blood cells. *B. henselae* has also been observed to penetrate human red blood cells in a fashion similar, yet slower, to that observed in cats [32].

Clinical Findings in Cat Scratch Disease

Systemic Manifestations

Cat scratch disease follows, in most cases, a benign course and usually resolute without complications. A lesion at the primary inoculation site, in the form of macule, papule, or pustule, is usually the first manifestation of CSD. The primary lesion is sometimes accompanied by mild to moderately severe flu-like symptoms including headache, anorexia, nausea, vomiting, and sore throat. The flu-like symptoms are usually associated with regional lymphadenopathy, which slowly resolves over the ensuing weeks or months. The affected nodes are frequently tender and may even be suppurative. The lesion at the primary inoculation site occurs in 25–60% of patients, usually 3–10 days following the injury and 1–2 weeks before the onset of constitutional symptoms. Ocular involvement has been estimated to occur in 5–10% of patients with CSD [33].

Other less common systemic manifestations of CSD include encephalitis (1–2%), osteomyelitis (less than 1%), and hepatosplenic disease (less than 1%) [27].

Ocular Manifestations

The eye is the most commonly affected non-lymphatic organ in CSD [33]; however, not all patients experience obvious systemic manifestations, and some patients with systemic *B. henselae* infection fail to provide a history of recent cat or flea exposure. In this sense, recognition of suggestive ocular findings often leads to specific serologic testing and the correct diagnosis (Table 7.1) [27].

Table 7.1 Ocular manifestations of bartonellosis, Lyme, and syphilis

Funduscopic findings	Bartonellosis	Lyme	Syphilis
Retinal vasculitis	+	+	+
Vascular occlusion	+	+	+
Macular edema	+	+	+
Macular pucker	–	+	+
Multifocal retinitis	+	–	–
Diffuse or focal retinochoroiditis	+	+	+
Serous retinal detachment	+	+	–
Retinal pigment epithelial detachment	–	+	–
Ciliochoroidal detachment	–	+	–
Cotton-wool spots only	–	+	–
Retinal bacillary angiomatosis	+	–	–
Optic neuritis	+	+	+
Neuroretinitis	+	–	–
Macular star	+	–	–
Optic atrophy	–	–	+
Choroidal neovascular membrane	–	+	+
Retinal tear	–	+	–
Pseudoretinitis pigmentosa	–	+	+
Mimicking white dot syndrome	+	+	–

Parinaud's Oculoglandular Syndrome (POGS)

In his overview of 1,200 patients with CSD, Carithers, in 1985, found that approximately 4% of patients (n = 48) with symptomatic cat scratch disease suffered from the oculoglandular syndrome of Parinaud (POGS), making it the most commonly encountered ocular complication of cat scratch disease [33]. The typical presentation of POGS includes conjunctival irritation, eye redness, and foreign body sensation. Discharge is usually serous; nevertheless, purulent conjunctivitis with abscess formation may occur. On examination, POGS typically presents with granulomatous conjunctivitis associated with regional lymphadenitis. Lesions may involve the palpebral conjunctiva in the form of either a single flat nodule or multiple raised vegetations with surrounding erythema; necrosis of the overlying conjunctival epithelium and ulceration may ensue. Regional lymphadenitis typically involves preauricular lymph nodes; submandibular and cervical lymph nodes may also be affected [18, 34, 35]. The granuloma disappears over period of weeks, leaving no scar. Lymphadenopathy regresses over weeks or months, depending on the severity of the infection; however, in many cases, the lymphadenopathy progresses to suppuration [33].

The differential diagnosis of unilateral granulomatous conjunctivitis includes, in addition to cat scratch disease, other infections like tularemia, tuberculosis, syphilis, sporotrichosis, and acute Chlamydia trachomatis [36]. At the same time, not all cases of POGS seem to be caused by *B. henselae*; positive serology for *B. quintana* was detected in one patient with POGS, and herpes simplex virus type 1 was detected by culture and PCR testing in another patient [37, 38].

Retinal and Choroidal Manifestations and Complications

Retinal and choroidal manifestations and complications of CSD include neuroretinitis, focal retinitis, focal choroiditis, multifocal retinitis, multifocal choroiditis, intermediate uveitis, vasculitis, vascular occlusions, and bacillary angiomatosis [9, 36, 39–46]. Panuveitis, acute unilateral maculopathy, macular hole, secondary unilateral glaucoma, and serous retinal detachments have also been reported [47–52].

Neuroretinitis (Leber's Neuroretinitis)

Neuroretinitis is a unique form of optic neuropathy characterized by optic disk swelling in the presence of a partial or complete macular star [53]. Leber first described neuroretinitis in 1916 as acute unilateral visual loss associated with optic disk swelling and a macular star [54]. Gass later observed that neuroretinitis was simply a unique form of exudative optic neuropathy with transudation into the macula [6]. Despite being originally described as a unilateral disease, neuroretinitis has been reported to manifest as bilateral optic disk swelling with macular star formation [55, 56].

Among 14 patients with neuroretinitis, Suhler et al., in 2000, found nine patients (64%) to have elevated IgM or IgG for *B. henselae* [44], making CSD the most common cause of neuroretinitis [12]. Despite this high percentage of *B. henselae* seropositivity in patients with neuroretinitis, the true prevalence of neuroretinitis in patients with systemic *B. henselae* infection is unknown. It was proposed, nevertheless, to occur in 1–2% of patients [12]. *B. elizabethae*, *B. grahamii*, and *B. quintana* have also been reported by serology and PCR testing to be associated with neuroretinitis [57–59].

Although uncommon, simultaneous or consecutive retinitis or neuroretinitis in patients with POGS or CSD has been reported [55]. Some cases of neuroretinitis have been accompanied by localized serous retinal detachment [60]. Macular star typically develops 2–4 weeks later; some patients, however, never develop macular star [61]. It has been proposed that the combination of neuroretinitis and serous retinal detachment can be an early indicator of systemic *B. henselae* infection [61].

The optic nerve swelling usually resolves spontaneously in 2–8 weeks, either leaving a normal disk appearance or a mild residual pallor. Macular exudates remain stable for several weeks, after which a gradual regression begins; the most extensive macular exudates may take up to 12 months to resolve [10]. Patients regain most of their visual function; however, some patients sustain functional damage in the form of decreased contrast sensitivity, dyschromatopsia, and reduced optic nerve functions [42].

Other patients developed massive angiomatous inflammatory disk mass associated with subretinal and intraretinal exudates [39, 62]. Cases of neuroretinitis of similar or more severe picture have been reported in HIV patients with CSD [45, 63, 64].

The differential diagnosis of neuroretinitis includes, in addition to cat scratch disease, Lyme disease, syphilis, leptospirosis, sarcoidosis, malignant hypertension, diabetic retinopathy, pseudotumor cerebri, toxoplasmosis, and toxocara [53].

Multifocal Retinitis and Choroiditis

Several forms of choroiditis and retinitis have been reported in CSD, some of which may mimic other retino-choroidal conditions [40, 65–67]. Diffuse choroiditis associated with CSD has been reported to cause multiple pinpoint leaks on fluorescein angiography (FA) mimicking Vogt-Koyanagi-Harada disease [67]. A case of multifocal choroiditis, associated with positive serology for *B. henselae* in a 12-year-old boy,

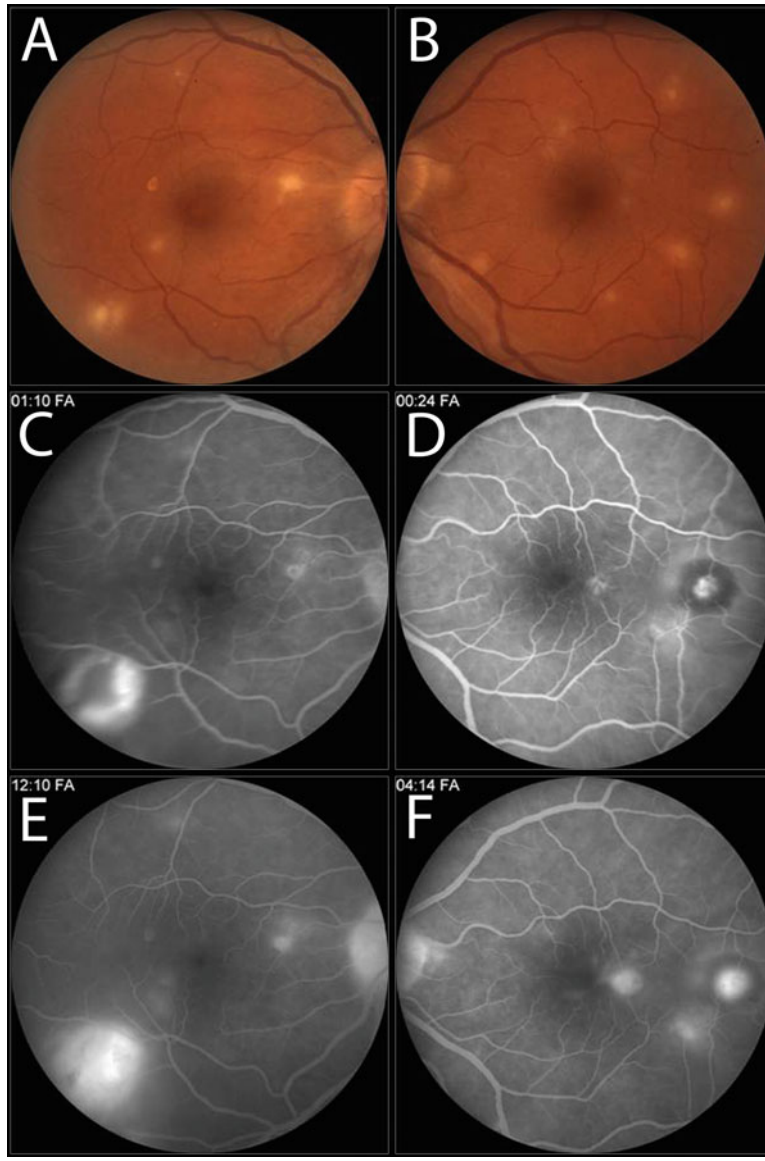

Fig. 7.1 A case of bilateral chorioretinitis mimicking birdshot chorioretinopathy in an immunocompromised patient with *Bartonella henselae* infection. Color fundus photographs from the right (**a**) and left (**b**) eyes showing multiple *creamy yellow* chorioretinal lesions in the macular region. Mid-frames of FA of the right (**c**) showing hyperfluorescent ring inferotemporal to the macula with diffuse leakage in the late frames (**e**). Early frames of FA from the left eye (**d**) showing abnormal hypofluorescent ring with late leakage (**f**)

has been reported mimicking the picture of multiple choroidal metastases [66].

Multifocal retinitis in cat scratch disease may also present as bilateral, multiple, intraretinal white infiltrates, 100–300 μm in size, resembling one of the white dot syndromes, typically multiple evanescent white dot syndrome or acute posterior multifocal placoid pigment epitheliopathy [9, 40, 65]. It may also represent mimicking birdshot choroidopathy (Fig. 7.1) [68]. The white dots usually clear after 2–3 weeks without a trace. CSD-associated

multifocal retinitis/choroiditis should be included in the differential diagnosis of white dot syndrome [40].

Foci of retinochoroiditis have also been observed in the absence of neuroretinitis or macular exudates [40–43, 60]. The presence of multifocal retinitis and/or choroiditis can be a clue to the diagnosis of *B. henselae* infection in cases of optic disk edema when associated with peripapillary serous retinal detachment, especially when subretinal or intraretinal exudates are absent [61].

Vasculitis and Vascular Occlusion

Ocular complications associated with retinochoroiditis in CSD may include vasculitis [46] with arterial [40, 43, 65] and/or venous [10, 65] occlusions causing severe visual loss.

Peripapillary Bacillary Angiomatosis

Bacillary angiomatosis is a dermatological disorder that had been observed in severely immunocompromised AIDS patients and characterized cutaneous vascular proliferations that clinically and pathologically resemble Kaposi's sarcoma [69]. LeBoit and associates have suggested a similarity between the organisms found in CSD and those found in bacillary angiomatosis [70]. That association has been confirmed in subsequent studies [11, 71]. *Afipia felis,* once thought to be the causative agent for CSD, was initially suspected to be the etiologic agent for bacillary angiomatosis [72, 73]. However, several subsequent studies [7, 74–76] have identified *B. henselae* as the more likely causative agent of both cat scratch disease and bacillary angiomatosis.

In 1998, Warren et al. reported a case of an HIV-positive patient presenting with a focal area of hemorrhagic retinal necrosis in one eye and multiple midperipheral intraretinal hemorrhages and several cotton-wool spots in the other eye. Retinal biopsy from the retinal lesion revealed findings similar to those seen in bacillary angiomatosis, with multiple tufts of proliferating vascular endothelial cells with fibroblasts and fusiform-appearing cells. Steiner variation of the Warthin-Starry stain revealed clusters of *B. henselae*. The diagnosis was confirmed using PCR amplification of 16S rRNA of *B. henselae* [64]. Matsuo and colleagues characterized the FA findings in cat scratch disease presenting in four patients with granuloma and abnormal vascular network. In three patients, the granuloma and vascular network arose from the optic disk. They considered this finding a hallmark of fundus manifestation of cat scratch disease [77]. Curi et al. have reported in 2006 similar retinal finding in three HIV-positive patients with peripapillary abnormal vascular networks (tufts). All three patients were seropositive for *B. henselae* [78].

Uveitis

Both intermediate uveitis and panuveitis have been reported in several cases with CSD [79–81]. It has also been presumed that most patients with focal retinochoroiditis or neuroretinitis associated with CSD have a mild to moderate vitritis and sometimes significant non-granulomatous anterior uveitis [10, 62, 82, 83].

In their study on 19 patients with unexplained unilateral uveitis and high positive IgG and/or IgM titers, Kerkhoff and Rothova found six patients to be positive for HLA-B27 (32%). Of these six patients, five patients had severe posterior segment involvement with papillitis, macular edema, and vitritis, with duration of active intraocular inflammation of 6 months or more. Their observation led them to suggest that *B. henselae* infection may be either a trigger or risk factor for anterior uveitis in HLA-B27-positive patients as evidenced by the higher seroprevalence rate for *B. henselae* and by the more severe and chronic course of the posterior segment complications in those patients [84]. In 2004, a vitreous biopsy acquired from a patient with HLA-B27 bilateral panuveitis tested positive for *B. henselae* using enzyme-linked immunosorbent assay and PCR-based testing [85]. Bilateral anterior uveitis has also been reported in HLA-B27-negative 9-year-old girl that was serologically positive for *B. henselae* [86].

Diagnosis

Historically, a skin test for cat scratch disease, Hanger-Rose test, was one of the original diagnostic criteria for CSD. The antigen was obtained from a suppurative lymph node and used as a skin-test antigen. A dose of 0.1 ml of the antigen is inoculated intradermally with a positive reaction creating a central papule or erythema measuring 0.5–1 cm in diameter after 48–72 h. The size of the skin reaction, however, did not correlate with the severity of the illness.

Currently, with the advent of other serological and PCR tests, the risk of using foreign human lymphoid tissue outweighed its benefits [87]. The new diagnostic criteria for cat scratch disease include the following:

1. History of contact with a cat or kitten with presence of a scratch.
2. Primary inoculation site either cutaneous or ocular.
3. Serological tests – Two serologic tests are available for the confirmation of *B. henselae* exposure: indirect immunofluorescence test (IFA) and enzyme-linked immunoassays (ELISA). The sensitivity and specificity of both tests are variable, depending on the laboratory performing the tests; however, the CDC-processed tests yield above 90% for both [88].
   (a) IFA is developed by the Centers for Disease Control and Prevention. In 1992, Regnery et al. described the IFA test for detection of the anti *B. henselae* IgG. The test was reported to have a sensitivity between 88% and a specificity of 97% [75, 88, 89], with titers greater than 1:64 being considered positive.
   (b) ELISA test for *B. henselae* is commercially available from several laboratories. Sensitivity and specificity are variable, depending on the laboratory, which results in greater false-negative results [89].

Both IFA and ELISA tests depend on the robust immune response from the host. Because of that, the accuracy of both tests in immunocompromised patients is significantly lower [27]; the sensitivity and specificity of IFA test may drop below 70% in patients infected with HIV [27, 90]. A single positive IFA or ELISA titer for IgG or IgM antibodies is generally sufficient to confirm CSD. IgG levels rise during the first 2 months after disease onset, followed by a gradual decline [88]. IgM titers provide greater predictability than IgG with the ELISA method; however, in order to achieve high specificity and sensitivity, the results need to be combined with other diagnostic criteria. Moreover, cross-reactivity with other Bartonella species, especially *B. quintana,* is possible and may result in false-positive results [89, 91, 92].

Biopsy and Testing

The specimen can be obtained from the granulomatous conjunctival lesion or the inflamed lymph node. Testing of the specimen may include:

1. Staining
   Direct detection of bacteria in tissue specimens by Warthin-Starry silver stain has traditionally been used [93, 94]; however, this stain is unreliable and lacks species specificity.
2. PCR testing
   PCR amplification of 16S rRNA has been developed by Relman and associates using the *B. henselae* 16S ribosomal RNA gene [95]. PCR testing for *B. henselae* was successfully used to identify *B. henselae* infection in specimens from conjunctiva and from lymph node biopsies and aspirates [96–99]. PCR amplification of 16S rRNA is highly sensitive and specific in detecting Bartonella species; however, PCR-based tests are not yet commercially available [12].
3. Culture
   Bartonella species can be cultured from biopsy specimen by using enriched agar at 35–37°C with 5% CO_2. Different Bartonella species tend, however, to grow better on different culture media; for example, *B. henselae* is cultured more effectively on heart infusion agar with 5% defibrinated rabbit blood [100, 101]. Tissue or blood specimens can take up to 4 weeks before growth is detected on the culture media. Specimens from blood yield better results when

a lysis centrifugation system, in which the blood specimen is lysed before it is inoculated onto the enriched media, is used [22].

With the advent of new biomolecular laboratory techniques over the past few decades, the diagnosis of cat scratch disease now relies heavily on serologic testing and, to a lesser extent, on culture or PCR-based analysis of tissue and/or fluid samples [12].

The diagnosis of CSD can be made when the clinical manifestations of the disease are combined with a serologic or a pathologic confirmation. However, other serious infections such as Lyme disease, syphilis, leptospirosis, toxoplasmosis, and toxocara should be considered and excluded in addition to the noninfectious causes such as sarcoidosis, malignant hypertension, diabetic retinopathy, pseudotumor cerebri, and malignancies, especially lymphoma and tumor metastasis. If diagnosis could not be made using the above mentioned guidelines, a biopsy may be warranted to confirm the diagnosis.

Therapy

With only few publications reporting permanent ocular damage, the overall prognosis of cat scratch disease in immunocompetent patients is generally good. Immunocompetent patients with cat scratch disease tend to have self-limited disease that resolves completely with in 2–4 months in majority of cases, even without treatment. The benign nature of CSD makes the necessity of antibiotic treatment doubtful, and because of that, definitive treatment recommendations for CSD and its ocular complications have not yet been established.

In 1992, before *B. henselae* was recognized as the causative agent in CSD, Margileth presented the therapeutic outcomes of 18 different therapeutic agents in 268 patients with cat scratch disease. Margileth concluded that rifampin, ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole have the most reasonable probability of efficacy, with rifampin 10–20 mg/kg/day every 12–24 h being the most effective in the group [21].

In 1998, however, Bass et al. reported, based on the results of a prospective, randomized study of therapy of CSD, that a single 500-mg dose of azithromycin followed by four daily doses of 250 mg resulted in faster resolution of lymphadenopathy when compared to placebo at 1 month [102].

Due to the risks associated with CSD in HIV-positive patients, antibiotics are often required to control the infection [90]. In 1999, Koehler and Relman reported a dramatic response to treatment either with doxycycline or erythromycin in immunocompromised patients with CSD [90]. Such dramatic success of erythromycin and doxycycline in treating CSD in patients with HIV encouraged the use of antibiotics in treatment of immunocompetent patients with severe ocular or systemic complications of *B. henselae* infection.

Doxycycline is usually given in an oral dose of 100 mg twice daily. Doxycycline has better intraocular and central nervous system penetration than erythromycin and is often preferred to erythromycin in treatment of ocular complications of CSD. Erythromycin, on the other hand, is preferred in children younger than 12 in order to avoid the possibility of tooth discoloration that often occurs with doxycycline treatment. An intravenous combination of doxycycline and erythromycin can be helpful in severe infections [90]. Rifampin, in an oral dose of 300 mg twice daily, can also be added to the combination.

Immunocompromised individuals with CSD can also be treated using azithromycin in a single dose of 500 mg, followed by four daily doses of 250 mg or by doxycycline in a dose of 100 mg three times daily [27, 102].

Antibiotic treatment and observation should continue for several months because of the possibility of recurrence. The duration of treatment is usually 2–4 weeks in immunocompetent patients and up to 4 months for immunocompromised patients [90]. Recurrences in HIV-positive patients have been reported even after prolonged treatment [100]. Long-term use of doxycycline or erythromycin may be useful for preventing recurrences in HIV-positive patients [101].

Oral corticosteroids have been effective in reducing the inflammation and improving the visual function in cases with systemic and posterior ocular manifestations. However, the necessity of corticosteroids therapy in isolated POGS has not been established [103, 104].

Management of pain caused by suppurative lymphadenopathy may include NSAIDs. Although aspiration of the lymph node can be done, it is not recommended because a fistulous tract may develop, and discharge may persist for several months resulting in permanent scarring. Children with CSD should be managed in association with a pediatrician specializing in infectious disease.

Controversies and Perspectives

The method of transmission of Bartonella infection to humans is still unknown. It is controversial whether the cat flea or flea feces is responsible for some cases of cat-to-human transmission. It is controversial whether *B. henselae* is the only causative agent of CSD or some other Bartonella species, as well as other bacteria, are responsible for some cases. Both the safety and the value of the use of foreign human lymphoid tissue to diagnose CSD, through the Hanger-Rose skin test remains controversial, especially after the advent of other serological and PCR tests that make the risk of its use outweigh its benefits. The necessity of treatment with antibiotics in immunocompetent patients with ocular involvement is also controversial given the benign nature of the disease.

Clinical Pearls

- *B. henselae* seropositivity has been associated with nearly two-thirds of all cases of neuroretinitis.
- The infection is transmitted to humans from infected domestic cats, especially kittens.
- Children and adolescents make up 80% of cases of CSD.
- Ocular involvement occurs in only 5–10% of all cases of CSD.
- Ocular involvement in CSD is usually in the form of unilateral granulomatous conjunctivitis with watery discharge and foreign body sensation. The presence of a single, large, and flat nodule in the bulbar or palpebral conjunctiva associated with regional lymphadenopathy helps with the diagnosis of CSD, especially when the primary inoculation site can be identified.
- Retinal and choroidal manifestations of CSD include neuroretinitis, multifocal retinitis and choroiditis, vasculitis and vascular occlusion, intermediate and diffuse uveitis, and retinal bacillary angiomatosis.
- Neuroretinitis may be associated with optic disk swelling, focal serous retinal detachment, and macular star.
- The outcome of the disease is generally benign; however, in some cases, a residual damage, in the form of optic disk pallor, decreased contrast sensitivity, dyschromatopsia, and abnormal visually evoked potentials, may happen.
- The diagnosis of CSD can be made when the clinical manifestations of the disease are combined with a serologic or a pathologic confirmation.
- Biopsy is only required when the clinical manifestations and laboratory confirmations are inconclusive.
- Antibiotic treatment ideally should be reserved for immunocompromised patients and for immunocompetent patients with severe sight-threatening ocular involvement.
- Recurrence of disease is not uncommon in immunocompromised patients due to the lack of long-lasting immunity. Longer courses of antibiotics treatment may be required in such patients.

Lyme Disease

Lyme disease, or borreliosis, first described by Steere in 1977 as an epidemic of oligoarticular arthritis in several Connecticut communities, is a multisystem disease that also involves the eye and its adnexa [105]. Lyme disease is caused by a spirochete belonging to the genus *Borrelia* and is transmitted to humans by the bite of certain infected *Ixodes* ticks in temperate climate zones [106]. Three *Borrelia* species frequently cause Lyme disease in humans: *Borrelia burgdorferi sensu stricto*, *Borrelia garinii*, and *Borrelia afzelii* [107, 108]. *B. burgdorferi sensu stricto* is found primarily in North America and Europe, while *B. garinii* and *B. afzelii* are found throughout Eurasia [107–110].

Lyme disease presents in three stages: localized early, disseminated early, and persistent late. In the first stage (3–30 days following the tick bite, which includes the incubation period), clinical findings include erythema chronicum migrans rash (classic annular skin lesion, target rash) and flu-like symptoms. Clinical findings in the second stage (weeks to months) include signs and symptoms of serious organ involvement, including neurological and cardiac systems and joints. In the third stage (months to years), the skin, joints, heart, and nervous systems are involved; however, the most common disorder is chronic severe relapsing Lyme arthritis, which in some patients may lead to permanent joint disability. The symptoms in all stages can overlap, and many patients do not manifest all stages [111].

Diagnosis

There are two ways to diagnose Lyme disease: one is considered a clinical diagnosis and the other is made as a definitive diagnosis. Clinical diagnosis is based on finding the pathognomonic skin rash (erythema chronicum migrans) in a patient with either a history of tick bite or who has recently been in regions in which Lyme disease is common. In patients who are unaware of tick bite or in a non-endemic area, presence of erythema chronicum migrans and the involvement of two organ systems are enough for diagnosis. For a definitive diagnosis, cultures from the plasma, skin lesions, synovial fluid, and cerebrospinal fluid in Barbour-Stoenner-Kelly medium must be conducted. The probability of diagnosis is high in the early stages of the disease [112].

In the chronic stages, polymerase chain reaction can be used [113]. The enzyme-linked immunosorbent assay (ELISA) and an indirect immunofluorescence antibody test (which is less accurate but may be used when ELISA is not available) are used to detect the presence of specific antibodies to *B. burgdorferi*. The disadvantages of these tests are limited sensitivity and long latency to become positive, decreased response after antibiotic treatment, and cross-reactivity with other spirochetes [114, 115]. Because of these issues, serological testing must be reserved for patients who have uveitis of unknown cause and at least one other manifestation of the disease; if any of these tests are positive or uncertain, they should be followed by the Western immunoblot, which is more accurate and very helpful in confirming the diagnosis.

Other diagnostic tests include antibody capture enzyme immunoassay, lymphocyte antigen stimulation, and detection of antibodies in urine. Studies are underway to create more accurate serological tests for Lyme disease.

The Centers for Disease Control and Prevention made Lyme a reportable disease in 1982, and the current definition of a case of Lyme disease includes any one of the following [116]:

1. Development of erythema chronicum migrans within 30 days of exposure in an endemic area; size of lesion should be ≥5 cm
2. Without erythema chronicum migrans, history of exposure to endemic area, with signs involving one organ system, and a positive laboratory test
3. No history of exposure to endemic area but presence of erythema chronicum migrans as well as involvement of two organ systems
4. No history of exposure to endemic area but with erythema chronicum migrans and a positive serology

Ocular Manifestations

Because many ophthalmologists and general practitioners may not be aware of the clinical ocular features of Lyme disease, ocular Lyme borreliosis is often underdiagnosed. Ocular manifestations can involve any of the ocular structures, and, while generally occurring in stage 2, they can occur at any stage either in the presence or absence of other organ involvement (Table 7.1). Ocular involvement, including conjunctivitis, periorbital edema, and mild photophobia, may be noted in as many as 11% of patients during the first stage of the disease [111]. Severe ophthalmic manifestations and intraocular inflammation first occur during stage 2. A number of conditions have been observed in later periods of stages 2 and 3, including stromal keratitis, granulomatous iridocyclitis with or without uveitis, intermediate uveitis, vitritis, panuveitis, retinitis, retinal vasculitis, choroiditis with or without serous retinal detachment, optic disk edema, optic neuritis, ischemic optic neuropathy, optic atrophy, ocular motor cranial neuropathies, Bell's palsy, Argyll Robertson pupil, Horner's syndrome, temporal arteritis, orbital myositis, and cortical blindness. In this chapter, we will evaluate retinal and choroidal changes in Lyme disease under the following headings:

1. Intermediate uveitis
2. Retinal vasculitis, branch retinal artery occlusion, and cotton-wool spots
3. Neuroretinitis
4. Choroiditis, chorioretinitis with or without serous retinal detachment
5. Miscellaneous: Cystoid macular edema and macular pucker, retinal pigment epithelial detachment, retinitis pigmentosa-like clinical presentation, choroidal neovascular membrane, acute posterior multifocal placoid pigment epitheliopathy (APMPPE)-like clinical presentation, retinal tear, and ciliochoroidal detachment

Intermediate Uveitis

Intermediate uveitis refers to inflammation localized to the anterior vitreous, pars plana, and peripheral retina. Infectious causes of intermediate uveitis are Epstein-Barr virus (EBV) infection, human T cell lymphotrophic virus type1 (HTLV-1) infection, cat scratch disease, hepatitis C, tuberculosis, and Lyme disease [117]. Lyme disease is a causative factor in 0.6% of all intermediate uveitis cases. Patients with intermediate uveitis due to Lyme disease typically present with complaints of floaters, blurred vision, or a vague, ill-defined disturbance of vision [118]. Involvement is usually bilateral, although asymmetric [117, 119]. Symptoms may often wax and wane over many months. The clinical picture most frequently seen is that of a syndrome resembling pars planitis complicated by posterior and granulomatous anterior chamber inflammation, which is inconsistent with classic intermediate uveitis, in which anterior chamber symptoms are not regularly encountered [120]. However, in some cases, the patient may present with mild anterior chamber reactions [121]. The hallmark of the disease is vitritis, which consists of vitreous cells that form aggregates, commonly referred to as snowballs, which are quite common and, although often noted in the inferior vitreous peripherally, may be found throughout the vitreous cavity. Inflammation of the pars plana may progress to form organized exudates called snowbanks. Inflammation-induced fibrovascular proliferation within the vitreous, vitreous base, and pars plana may result in retinal tears and rhegmatogenous retinal detachment [120]. However, intermediate uveitis in Lyme borreliosis can be seen even in the absence of severe ocular complaints [122].

Retinal Vasculitis, Branch Retinal Artery, Retinal Vein Occlusion, and Cotton-Wool Spots

Retinal vasculitis is a sight-threatening inflammatory disease that involves the retinal vessels. Retinal vasculitis may be either symptomatic or asymptomatic. If the retinal vascular changes occur in the periphery of the fundus without vitreous involvement, patients may have minimal or no symptoms. The condition results in sheathing and angiospasm, as well as arterial and/or venous occlusion. Inflammation of macular blood vessels can cause macular edema.

Retinal vasculitis due to Lyme disease was first presented in 1990 by Dr. U. Schonherr and associates at the International Conference on Borreliosis in Stockholm, Sweden, based on observing two individuals with this condition in a case series of ten patients. In 1991, Smith et al. published three cases of retinal vasculitis that were found to be seroreactive for Lyme borreliosis [123]. In the same year, Lang et al. reported a 43-year-old man admitted because of recurrent vitreous hemorrhage, who was diagnosed as bilateral occlusive retinal vasculitis with proliferative retinopathy due to Lyme disease with positive IgM and IgG serology for *Borrelia burgdorferi* [124]. In 1995, Leys et al. reported seven patients with retinal vasculitis due to Lyme disease with clinical and serologic evidence of *Borrelia burgdorferi* infection [125]. Three patients presented with abrupt loss of vision due to acute retinal vasculitis, and all demonstrated engorged veins, hemorrhages, perivenous infiltrates, and retinal white spots. Arterial occlusions were observed in two patients, and leakage was present from the veins, white spots, and the optic disk on fluorescein angiography. Four patients had signs of chronic uveitis with vitritis, cystoid macular edema, and retinal vasculitis, which were associated with neovascularization and vitreous hemorrhage in one patient and with optic neuritis in another patient [125]. Karma et al. reported a case series of ten ocular Lyme borreliosis patients in 1995 [126]. In this study, six of seven patients with uveitis had retinal vasculitis [126]. They extended this series to include an additional ten ocular Lyme borreliosis patients and published the series in 2000 [127]. Among the new patients in this extended series, two patients had evidence of retinal vascular involvement: one had peripheral multifocal chorioretinitis with panuveitis and the other had a branch retinal vein occlusion, possibly caused by a vasculitic mechanism as well [127]. Based on these results, they concluded that retinal vascular involvement in ocular Lyme borreliosis may be more common than previously thought [127].

Lightman et al. reported a branch retinal artery occlusion due to Lyme disease in a 37-year-old Caucasian woman [128]. The patient presented with a scotoma above fixation in her left eye upon awakening. There was no known history of a tick bite or skin rash. The anterior segments were normal, and there was mild bilateral vitritis. The right optic nerve was slightly swollen, the retinal arterioles were irregular in caliber, and a cotton-wool spot was present above the disk. The left posterior segment had an inferotemporal branch retinal artery occlusion, ischemic whitening of the inferior macula, multiple cotton-wool spots, mild disk edema, and focal irregularity of some arterioles. FA demonstrated a branch retinal artery occlusion in the left eye and bilateral disk edema. Positive serological tests and clinical response to antibiotics made the diagnosis of ocular borreliosis [128]. The author proposed that an immunologic response to *Borrelia burgdorferi* causes vasculitis and obliteration of small vessels, as seen in connective tissue diseases, which are known to cause retinal arterial obstruction [128].

The pathogenesis of CWS is an occlusion of a feeder arteriole and capillaries, leading to vacuoles of various sizes and representing accumulated axoplasm in the nerve fiber layer due to ischemia. CWS in uveitis is often found not only in HIV infection but also in cytomegalovirus, tuberculosis, cryptococcal infection, Behcet's disease, leptospirosis, and human T-lymphotropic virus type I. Klaeger et al. observed a 54-year-old woman who presented with recurrent iritis in her right eye and was diagnosed with ocular borreliosis and treated with doxycycline 100 mg bid for 3 weeks. After multiple recurrences of uveitis in her right eye, she presented with CWS in her left fundus (Fig. 7.2) and was treated with pentoxifylline 400 mg three times a day and salicylic acid 100 mg a day. The CWS gradually resolved but without proof that the resolution had been influenced by the therapy [129]. The patient Klaeger et al. presented differs from the Lightman et al. case in the absence of retinal whitening and focal irregularity of arterioles. Therefore, the only fundus finding of the Klaeger et al. case was CWS [129]. As a conclusion, Klaeger et al. advised ruling out ocular borreliosis in patients presenting with otherwise unexplained CWS [129].

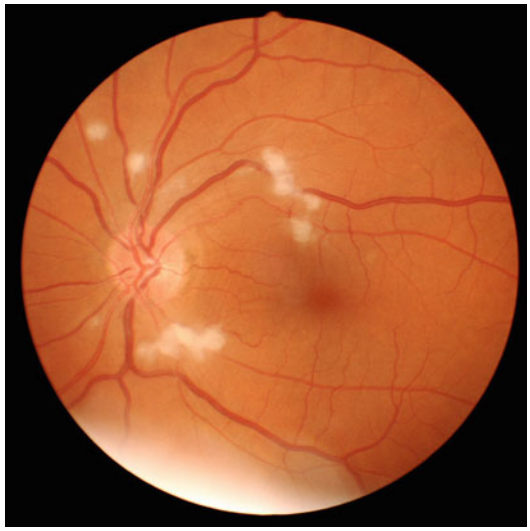

Fig. 7.2 Fundus photograph from a patient with positive serology for Lyme disease showing multiple cotton-wool spots (CWS) in the left eye. All CWS are nearly equidistant from the optic disk, some are confluent, while some overlie major vessels (Reprinted with permission from Klaeger AJ, Herbort CP. Cotton wool spots as possible indicators of retinal vascular pathology in ocular lyme borreliosis. Int Ophthalmol. 2010 Oct;30(5):599–602. Epub 2008 Oct 15)

Neuroretinitis

Neuroretinitis typically presents in the form of white retinal lesions that may vary in size and topography. An associated mild or moderate vitreous inflammation is commonly observed. FA shows early hypofluorescence and late staining of large acute white retinal lesions and isofluorescence or moderate hypofluorescence of small active retinal lesions.

The first case of neuroretinitis due to Lyme disease was reported in a 13-year-old girl by Lesser and colleagues in 1990 [130]. Winterkorn et al. published another case of neuroretinitis due to Lyme in a 21-year-old girl in the same year [131]. Schönherr et al. reported a 22-year-old white female with bilateral Leber's stellate neuroretinitis after a viral-like illness [132]. Seroconversion for *Borrelia burgdorferi* and resolution of symptoms and signs during therapy with 200 mg doxycycline resulted in a diagnosis of Lyme disease [132]. In a case series including ten patients, Karma et al. reported four cases of neuroretinitis, three of which were bilateral and all accompanied by retinal vasculitis [126]. One year later, the same author reported a long-term follow-up of a chronic Lyme neuroretinitis that was unresponsive to systemic antibiotic therapy [133]. In 2001, Lochhead et al. reported a case of neuroretinitis due to Lyme disease in a 7-year-old girl that developed after bilateral papilledema and diagnosed by a positive Lyme IgG/M serology and cerebrospinal fluid PCR [134].

Choroiditis and Chorioretinitis with or Without Serous Retinal Detachment

Choroiditis is the inflammation of the choroid. Inflammation may be diffuse, called multifocal choroiditis, or in patches, known as focal choroiditis. If the inflammation involves both the choroid and retina, it is named chorioretinitis. Typically, the only symptom is blurred vision.

The first case of bilateral multifocal choroiditis due to Lyme disease with exudative retinal detachment was reported by Bialasiewicz et al. in 1988 [135]. This case was a 32-year-old woman who was diagnosed with Vogt-Koyanagi-Harada disease and treated with oral corticosteroids by the referring ophthalmologist. At the presentation, bilateral inflammatory cells in the anterior chamber and vitreous, diffuse choroidal infiltration with exudative retinal detachment that extended peripherally between 4 o'clock and 8 o'clock, cystoid maculopathy, and choroidal thickening on B-scan ultrasonography were noted. However, diagnosis of bilateral diffuse choroiditis with exudative retinal detachment due to Lyme disease was made via demonstration of Lyme IgM antibodies in sera [135]. Wilk et al. also reported two cases of bilateral disseminated choroiditis with exudative retinal detachments in *Borrelia burgdorferi* infection [136]. In a survey of 84 Lyme arthritis patients, Huppertz et al. reported ocular inflammation in three of them [137]. One of the patients, a 13-year-old girl, presented with bilateral intermediate uveitis and right retinal detachment. A diagnosis of Lyme borreliosis was made when antibodies to *Borrelia burgdorferi* were detected in the patient's serum; she was then treated with systemic tetracyclines.

Since arthritis recurred and vision deteriorated further, she was also treated with ceftriaxone and underwent bilateral pars plana vitrectomy. Arthritis disappeared and uveitis abated with permanently reduced visual acuity [137].

In 1993, Niutta et al. reported a unilateral multifocal chorioretinitis due to Lyme disease in a 22-year-old myopic man [138]. Although both anterior segments were normal, multiple foci of chorioretinitis confined to the posterior pole were observed in his right retina while the left fundus was normal. The diagnosis of unilateral multifocal chorioretinitis due to Lyme disease was confirmed via demonstration of Lyme IgM antibodies in sera [138]. A case series reported by Karma et al. in 1995 included a 70-year-old female patient with chorioretinitis in both eyes [126].

Other Ocular Manifestations

Cystoid Macular Edema and Macular Pucker

Cystoid macular edema (CME) associated with Lyme disease is occasionally reported. Breeveld et al. reported a 29-year-old man with bilateral intermediate uveitis with mild anterior chamber reaction without posterior synechiae [121]. The patient had bilateral CME confirmed by FA that responded subsequently to antibiotic therapy [121]. A patient with retinitis pigmentosa-like clinical presentation reported by Karma et al. in 1993 also had CME [139]. Preac-Mursic et al. reported a 24-year-old panuveitis-iridocyclitis patient whose first isolation of *Borrelia burgdorferi* was accomplished with an iris biopsy [140]. In that patient, they reported CME, macular pucker, and an exudative inferior retinal detachment [140]. Guex-Crosier et al. presented a case with CME due to recurrent pars planitis with two episodes of acute pericarditis [141]. Karma et al. reported a 5.5-year follow-up of a Lyme neuroretinitis patient in 1996 [133]. The 29-year-old women had intense hyperfluorescence of cystoid pattern at the juxtapapillary area in both eyes, which extended to the foveola in the left eye at presentation [133]. The patient received oral prednisone, which has no effect either on vision or fundus changes with the diagnosis of idiopathic uveitis. Two years later, the patient was admitted with retinal edema of the same magnitude, but cystoid degeneration was also noted in both maculae. Additionally, a lamellar hole with macular pucker developed in the left macula [133]. Reibaldi et al. treated a case of CME due to Lyme disease that did not respond to antibiotic therapy with intravitreal triamcinolone acetonide injection. One month following the injection, visual acuity was 1.0 and the CME had completely resolved [142].

Retinal Pigment Epithelial Detachment

Koch et al. reported a 41-year-old man who, 6 months following a tick bite, was admitted with the complaint of headache and blurred vision in both eyes due to clover-shaped parapapillary retinal pigment epithelial detachment (PED) in both eyes, which involved the macula in the left eye [143]. Although there was only moderately increased immunoglobulin in the aqueous humor and serum, they initiated 4 g/day ceftriaxone disodium for 14 days; the PEDs disappeared within a few days and visual acuity returned to normal. Although the immunoglobulin values remained unchanged, diagnosis of neuroborreliosis with retinal PEDs was made after considering the history of a tick bite and response to treatment. The author assumed that the tissue around the optic nerve head, which does not have an effective blood–brain barrier, allowed the spirochetes to spread from the central nervous system into the sub-pigment epithelial space, thus causing the observed peripapillary pattern of PED [143]. Wu et al. reported a 7-year-old child who developed bilateral pigment epithelial mottling at the fovea 1 year after resolution of papilledema due to Lyme disease [144].

Retinitis Pigmentosa-Like Retinopathy

Zierhut et al. reported an extensive depigmented choroidal atrophy in the entire anterior retina, accompanied by pigment clumping similar to retinitis pigmentosa, in a patient who had positive serological tests for syphilis and Lyme disease [145]. In 1993, Karma et al. reported a 15-year-old girl who presented with atrophic RPE, attenuated arterioles, equatorial corpuscular pigmentation in the left fundus, and bilateral pale disks [139].

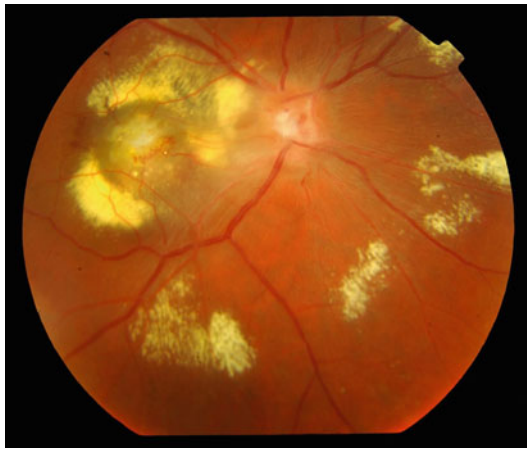

Fig. 7.3 A fundus photograph from the right eye of a patient with persumed ocular Lyme borrelieosis marked optic disk swelling with a *gray-yellow* lesion in the center of the macula surrounded by hard exudates. Similar exudation is also seen around the optic disk (Reprinted with permission from Amer R, Brannan S, Forrester JV. Inflammatory choroidal neovascular membrane in presumed ocular Lyme borreliosis. Acta Ophthalmol. 2009;87:346–348)

Biomicroscopy revealed opacity of the posterior capsule and posterior vitritis in the left eye. A fluorescein angiogram of the left fundus revealed exaggerated choroidal fluorescence in the initial phases, delayed retinal circulation, incomplete filling of the venules, and cystoid macular edema in the late phases. A diagnosis of Lyme disease was made with the aid of CSF and vitreous fluid specimens PCR [139].

Choroidal Neovascular Membrane

Amer et al. described the occurrence of inflammatory choroidal neovascular membrane (CNVM) in two patients with Lyme disease [146]. Both cases had a history of tick bite and responded to IV ceftriaxone treatment; however, because both were seronegative, their diagnosis was clinically based [146]. The first patient, a 16-year-old male, had an elevated gray-yellow lesion in the center of the macula surrounded by subretinal fluid and fine retinal hemorrhages on its surface as well as temporal to it (Fig. 7.3). There were circinate hard exudates surrounding it and similar exudates nasal, superior, and inferior to the optic disk. In the second patient, a

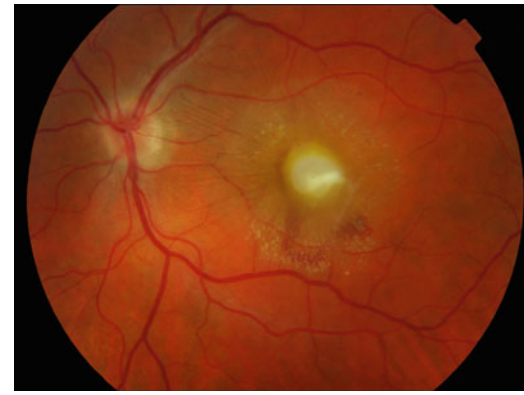

Fig. 7.4 Fundus photograph from a patient with negative serology for Lyme disease showing a *yellow* subfoveal lesion with marked fibrosis of the overlying retina and retinal striae radiating between the lesion and the optic disk. Flat subretinal hemorrhage is noted at the inferotemporal margin of the lesion (Reprinted with permission from Amer R, Brannan S, Forrester JV. Inflammatory choroidal neovascular membrane in presumed ocular Lyme borreliosis. Acta Ophthalmol. 2009;87:346–348)

38-year-old healthy female, fundus examination revealed a subretinal yellow macular lesion with marked overlying retinal fibrosis and retinal striae extending nasally (Fig. 7.4). Small deep retinal hemorrhages were noted on its inferotemporal edge [146].

Acute Posterior Multifocal Placoid Pigment Epitheliopathy-Like Picture

Bodine et al. reported a 32-year-old man who had multifocal choroiditis without vitreous involvement [147]. At presentation, the patient had multiple white lesions at the level of the choroid in both eyes. In FA, patches of hyperfluorescence and hypofluorescence in the macula, with staining in the late transit of the left eye, and patches of hypofluorescence in the inferior retina of the right eye were detected. The other lesions had a central area of staining surrounded by a hypofluorescence halo. During the follow-up, additional white choroidal lesions were noticed in the midperipheral fundus in both eyes, and older lesions had begun to atrophy and become lightly pigmented. Using the serial ELISA of the patient's serum and cerebrospinal fluid specimen, the author suggested the diagnosis of Lyme disease and treated the patient with

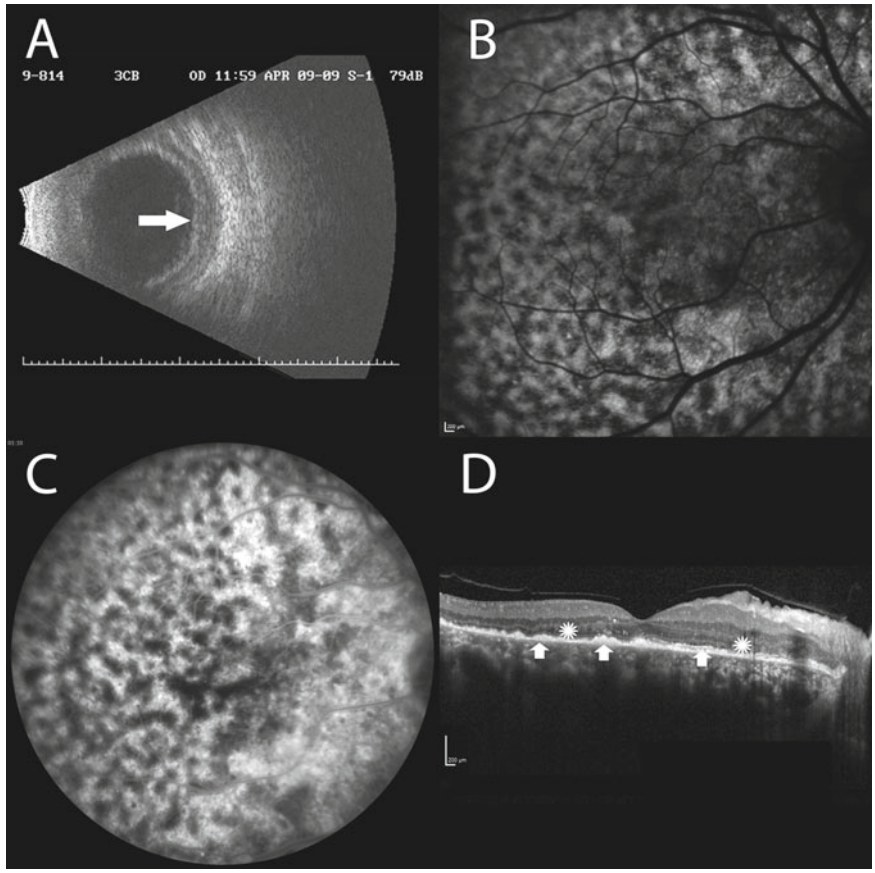

Fig. 7.5 Case of recurrent ciliochoroidal detachment in a patient with positive serology to *Borrelia burgdorferi*. Transverse B-scan ultrasonography (**a**) directed toward the ciliary body nasally in the right eye, showing extensive, shallow elevation of the ciliary body (*arrow*). Autofluorescence (**b**) and mid-phase FA (**c**) images from the same eye showing leopard skin pattern of alternating hypo- and hyperfluorescence, indicating the recurrent and long-standing nature of the detachment. Horizontal section of spectral domain optical coherence tomography across the fovea of the same eye (**d**) showing damage to the retinal pigment epithelium and photoreceptor layers (*arrows*) with attenuation of the outer nuclear and outer plexiform layers of the retina (*asterisks*)

intravenous ceftriaxone. Following that treatment and during the follow-up, no new choroidal lesions appeared and the old lesions became moderately pigmented; the retinal lesions were unchanged. Bodine et al. concluded that some of the cases of APMPPE may actually have been Lyme disease [147]. Wolf et al. screened the sera of 18 patients who possessed all of the characteristic fundus and fluorescein angiographic appearances of APMPPE for *burgdorferi*-specific antibodies. They could not demonstrate any serologic immune response *to burgdorferi* to support an association between these two disorders [148].

Retinal Tear

In 1991, Smith et al. published three cases of retinal vasculitis who were found to be seroreactive for Lyme borreliosis [123]. In one of the cases, a 25-year-old patient presented with a whitish deposit in the preretinal space and a retinal tear in the left eye at 1:30 with whitish exudative material on an attached flap and vitritis [123].

Ciliochoroidal Detachment

We have recently evaluated a 74-year-old man (Fig. 7.5) who presented with bilateral ciliochoroidal detachments and macular edema in the right eye. Slit-lamp examination revealed

no cells or flare in the anterior chambers. Funduscopic examination revealed multiple, bilateral, and symmetrical hypo- and hyperpigmentations resembling a leopard-spot pattern. FA showed patchy areas of hyperfluorescence corresponding to the areas of RPE hypopigmentation, with no leakage or staining. B-scan showed diffuse choroidal thickening and mild vitreous opacities in both eyes, with ciliochoroidal detachment in the right eye. Optical coherence tomography showed macular edema in the right eye and epiretinal membrane in the left. Lyme disease serology was positive for IgG and negative for IgM. Subsequently, the patient was started on IV ceftriaxone (2 g/day) for 28 days. The improvement continued over the following months with complete resolution of the ciliochoroidal detachments in 2 months.

Therapy

In case of acute disease in adults, treatment involves oral 100 mg doxycycline twice daily or 500 mg amoxicillin three times for 14–21 days. In case of doxycycline and amoxicillin allergy, oral cefuroxime 500 mg twice daily or erythromycin 250 mg four times daily for 14–21 days is recommended. In children, treatment of acute disease involves oral amoxicillin 50 mg/kg/day in three divided doses for 14–21 days. In case of penicillin allergy, oral cefuroxime 30 mg/kg/day in two divided doses for 14–21 days is recommended [149, 150].

In case of neurological and/or ocular involvement in adults, treatment involves intravenous (IV) ceftriaxone 2 g once a day or cefotaxime 2 g every 8 h for 14–28 days. In case of ceftriaxone or penicillin allergy, doxycycline 100 mg orally three times a day for 30 days is recommended. In children, treatment involves IV ceftriaxone 75–100 mg/kg/day (maximum 2 g) once a day for 14–28 days or IV cefotaxime 150 mg/kg/day (maximum 6 g) in 3–4 divided doses for 14–28 days [149, 150].

In a case of tick bite, a single dose of 200 mg doxycycline should be given within 72 h for prophylaxis [150, 151].

Controversies and Perspectives

The diagnosis of Lyme disease can be controversial and difficult. The presence of positive titer to *Borrelia burgdorferi* does not necessarily establish a diagnosis of Lyme disease. Appropriate clinical findings and symptoms should also exist at presentation. Most clinicians would agree that once the infection is treated completely (e.g., ocular Lyme disease should be treated with intravenous antibiotics), the infection is eradicated. Unless the patient is re-infected, repeated anti-microbial therapy is not required after initial treatment.

Clinical Pearls

- Lyme disease is a clinical diagnosis. Ancillary tests are performed to confirm the diagnosis.
- Erythema chronicum migrans rash might not always be annular and may occur as a more homogenous pink or red lesion.
- Serological tests are not needed for diagnosis of early Lyme disease. Four or six weeks are needed to develop antibody response.
- During the diagnostic workup, IgM and IgG tests must be ordered first. Western blot testing is ordered as a follow-up test when the initial tests are positive or indeterminate. Do not skip IgM and IgG tests.

Syphilis

Syphilis is an infectious disease caused by the bacterium, *Treponema pallidum* [152]. Treponemas are motile, spiral-shaped bacteria belonging to the Spirochaeta family. Many *Treponema* species are harmless members of the normal flora in humans. However, pallidum, endemicum, and pertenue are some of the pathogenic subspecies causing venereal syphilis, endemic syphilis, and yaws, respectively [153]. Syphilis is a sexually

transmitted disease, most commonly acquired via direct contact with a syphilitic sore [154–156]. It is conventionally divided into three stages: primary, secondary, and tertiary. A chancre is considered definitive for primary syphilis. A rash, with or without constitutional symptoms, indicates secondary syphilis. Cardiovascular disease, gummatous lesions, or neurologic manifestations such as tabes dorsalis, general paresis, seizures, or hemiparesis indicate tertiary syphilis [155].

Ocular Manifestations

Ocular manifestations usually occur in the secondary and tertiary stages of the disease [156] but can potentially occur at any stage (Table 7.1) [157, 158]. A review by Aldave and colleagues categorized ocular manifestations according to the stage of syphilis [156]. Retinal vasculitis and pigmentary mottling in "salt-and-pepper" pattern were seen in congenital syphilis cases. In cases of secondary syphilis, eyes were usually involved after other systemic manifestations had resolved. Retinal manifestations were similar in secondary and tertiary syphilis with necrotizing retinitis, neuroretinitis, retinochoroiditis, and serous retinal detachment, with cystoid macular edema being seen in both [156]. Optic nerve findings were slightly different between the two stages: disk edema was seen in both and optic atrophy and gumma were mainly seen in tertiary syphilis.

After a period of low incidence, there has been a resurgence of syphilis reported across the world [159–165]. In the United States, a decline in syphilis cases was reported between the years 1990 and 2000 [166–168]. However, between 2001 and 2007, the number of cases of primary and secondary syphilis increased from 3.0 to 6.6 per 100,000 of the population. In San Francisco, the number of syphilis cases increased from 44 in the year 1999 to 522 in the year 2003, while in the UK, a 15-fold increase in incidence was noted during the same period. Ocular syphilis is seen most commonly among African-American men [157], with high incidence among men who have sex with men (MSM) and are co-infected with HIV [165, 167–169].

Ocular syphilis can affect any layer of the eye, with uveitis being the most common overall clinical manifestation [170]. Uveitis at times can also be the sole manifestation of the disease and may be seen within 6 weeks of the primary syphilis infection [171]. Chorioretinitis, vitritis, and vascular sheathing have been reported as common posterior segment manifestations of ocular syphilis, with chorioretinitis usually being the most common [156, 157, 172].

There are no pathognomonic ocular clinical presentations of syphilis; therefore, it is important to have a high index of suspicion among the high-risk populations described above, including African-American MSMs who are HIV-positive, and to be vigilant for the presence of systemic signs and symptoms of the disease.

Retina and Choroid

Retinal and choroidal involvement in syphilis usually occurs together. If the neurosensory retina is involved first and choroid and RPE are involved later, the finding is described as retinochoroiditis; if the choroid and RPE are involved first and the neurosensory retinal later, it is known as chorioretinitis [172].

Chorioretinitis has been described as large areas of atrophic scarring bordered by proliferation of the RPE. Choroidal vessels, RPE, and outer retinal layers may be absent within the scarred areas [173, 174]. Two patterns of chorioretinitis have been described in literature: diffuse and localized. The diffuse form usually occurs in secondary syphilis and is characterized by multiple grayish-yellow chorioretinal lesions that may or may not be associated with vitritis, vasculitis, retinal edema, and retinal detachment. The lesions may fuse to give the appearance of general retinal whitening similar to that seen in herpetic retinitis [159]. A localized form usually occurs in the later stages and is characterized by focal pale yellow subretinal lesions at the level of the RPE that typically occur around the optic disk and macula and may be associated with vitritis, shallow retinal detachment, papillitis, or retinal vasculitis [175, 176]. Such presentation

was initially described by Gass as syphilitic lesions mainly involving the RPE and given the name acute syphilitic posterior placoid chorioretinitis (ASPPC) [176]. Gass et al. described six patients who had large, placoid, yellowish lesions with pale centers at the level of the pigment epithelium in the macula and juxtapapillary areas. All eyes had associated vitritis, and FA showed a leopard skin pattern with early hypofluorescence and late staining [176]. The pathogenesis of this clinical lesion is believed to be due to the spread of spirochetes into the RPE. Another hypothesis is that immune complex deposition in the retina leads to this clinical picture [177]. Multiple similar cases have been reported in the literature since then [167, 178–186]. This lesion is thought to be more common among patients with decreased immunity, for example, HIV-positive patients with syphilis and following steroid treatment [179, 181, 182]. However, it has recently been reported in immunocompetent patients as well [178, 183–185]. Menon and colleagues reported "Ganzfeld" electroretinogram (ERG) and multifocal ERG findings in their patient with ASPPC [185]. The readings were markedly reduced and undetectable, respectively; treatment with penicillin led to complete resolution of these functional defects, suggesting reversible loss of function in their patient with ASPPC. Bellamann and colleagues reported increased fundus autofluorescence in the area corresponding to the lesions of posterior placoid chorioretinopathy [186]. Although characteristic of syphilis in the appropriate clinical setting, these placoid lesions are not unique to syphilis; they may also be seen in serpiginous choroiditis, viral retinitis, and acute posterior placoid pigment epitheliopathy.

Morgan and colleagues described two cases of acute syphilitic chorioretinitis [175]. The first patient was a young woman with a history of positive serology for syphilis, who presented with decreased vision in one eye. Examination revealed active inflammation in the anterior chamber and scattered foci of chorioretinal involvement throughout the posterior pole. The second patient also presented with acute unilateral loss of vision. In this case, there were no obvious signs of inflammation in the anterior chamber. Funduscopic examination revealed venous sheathing, shallow macular detachment, and infiltrates in the macula at the level of the RPE. This patient's FA showed staining and leakage of the affected retinal veins and choroiditis localized to the macula. Both patients showed prompt response to IV penicillin with resolution of the lesions and improvement of vision. These cases described two different forms of syphilitic chorioretinitis: one had a diffuse chorioretinitis associated with anterior chamber inflammation, while the other had a more localized chorioretinal involvement with evidence of vasculitis.

Blodi and colleagues studied the histological appearance of four eyes with syphilitic chorioretinitis [173]. In two eyes, there was proliferation of the RPE cells into the choroid through a break in the Bruch's membrane, while in the other two there was proliferation of glial tissue through similar breaks in the Bruch's membrane. The fundus examination of one eye with glial proliferation showed multiple atrophic partly hyperpigmented patches and attenuated and sheathed vessels, while the other case showed macular scarring. Of the two eyes with RPE proliferation, one was a case of congenital syphilis and had inactive chorioretinitis with extensive scarring, while the other eye showed chorioretinal adhesions.

Focal or multifocal chorioretinitis can occur in the secondary or tertiary stages of syphilis. Features more specific to secondary syphilis include isolated vitritis and vascularized iris nodules; gummas are seen in tertiary syphilis [156].

Browning and colleagues described a patient who developed a lesion morphologically and angiographically very similar to that seen in birdshot chorioretinopathy [157]. They reported it as a broad band of pale inflammatory change in the choroid and retina in the absence of vasculitis; vitritis was concomitantly present; FA showed delayed venous return from the site of the lesion. After treatment with penicillin, the inflamed area of choroid became depigmented and FA findings remained the same at 1-month follow-up. Villaneuva and colleagues reviewed the clinical findings of 20 patients diagnosed

with posterior uveitis secondary to syphilis [172]. They categorized the patients as having acute or chronic disease based on whether it had been less than or more than 3 months since disease onset. Diffuse chorioretinitis was found to be the most common manifestation in 11 of the 12 patients with chronic disease; one patient had chronic retinal vasculitis. Among the eight patients with acute disease, multifocal chorioretinitis was seen in four, and one patient had acute retinal vasculitis. Chorioretinitis may be associated with retinal vasculitis, edema of the optic disk, serous retinal detachment [171], or tractional retinal detachment [169]. Lesions are most commonly located in the posterior pole and mid-periphery and may increase in size with time [175].

Ocular syphilis can occur with isolated involvement of the retina in the form of focal retinal edema, vasculitis, or papillitis with minimal to absent involvement of the anterior chamber [155, 171].

Jumper and colleagues described three cases of exudative retinal detachment occurring in association with uveitis and periphlebitis; although vision did not normalize, the detachments resolved completely following antibiotic treatment [187]. The authors suggest that earlier treatment may lead to a better visual outcome. In another case of retinal detachment secondary to syphilis, Treponemas were identified in the subretinal fluid; however, despite aggressive treatment that included penicillin, the patient had a poor visual outcome with recurrence of detachment [188].

In 2003, Anand and colleagues reported a case of multifocal central serous retinopathy occurring bilaterally in a patient with neurosyphilis in the absence of any other signs of ocular inflammation [189]. The RPE detachment resolved slowly over the course of 2 years, and the patient maintained good vision. However, it could not be established with certainty whether these detachments were secondary to syphilis.

Necrotizing retinitis can be caused by a number of etiological agents such as toxoplasma, HSV, and CMV, including *Treponema pallidum*. In HIV-positive MSMs, any of these agents, including *Treponema pallidum*, might be the causative agent, and it may be impossible to distinguish them from each other clinically. However, accurate identification of the etiological agent is important to ensure correct treatment, which in the case of syphilis is associated with an excellent visual outcome. Mendelsohn and colleagues discuss the case of a 32-year-old man who presented with blurred vision, redness, and pain in his right eye [190]. The patient did not fit into the "typical" demographic pattern of a syphilitic patient; the patient revealed a monogamous sexual relationship only with his wife. On examination, there was evidence of anterior uveitis; funduscopy showed a pale optic disk with ill-defined borders, and yellowish-white patches of retinitis were scattered over the posterior pole with evidence of vascular sheathing and some vascular occlusion. There was no evidence of any skin lesions. The presentation was typical of acute retinal necrosis; only a positive VDRL and FTA-ABS directed the authors towards a diagnosis of syphilis. The patient later admitted to homosexual contact and was subsequently treated with penicillin. Apart from a transient worsening of symptoms due to the Jarisch-Herxheimer reaction, the patient had an uneventful clinical course and vision was restored to normal over the course of several weeks. The authors discuss that it may not always be possible to distinguish syphilitic retinitis from CMV retinitis, herpes retinitis, or ARN. In another case series of 20 eyes with ocular syphilis, four patients presented with panuveitis and necrotizing retinitis. These were mistakenly treated initially with acyclovir, which was later switched to penicillin when laboratory testing identified syphilis infection [167].

We recently published a diagnostic challenge that discussed the case of an HIV-positive patient with unknown immune status who presented with a severe anterior uveitis with hypopyon (Fig. 7.6), vitritis, vasculitis, and optic disk edema [191]. The consultants discussed the possible etiologies: agents, acute retinal necrosis, syphilis, as well as noninfectious causes such as sarcoid and malignancy were possible differentials. However, iritis and hypopyon in a patient with retinitis are less likely to be present in a case of acute retinal

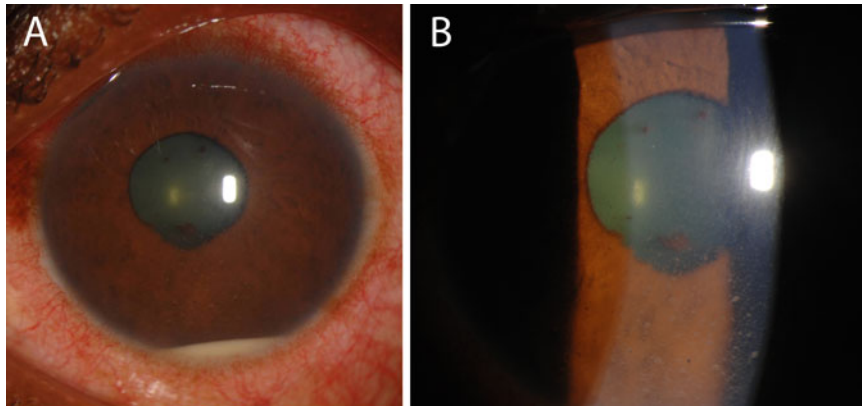

Fig. 7.6 Slit-lamp photograph of the anterior segment of the left eye, illustrating conjunctival injection, posterior synechiae, and hypopyon (**a**) and mutton fat keratic precipitates (**b**)

necrosis versus a case of syphilis. In cases when a patient's CD4 cell count is known, the differential can be narrowed down further. For example, CMV retinitis occurs in patients with very low CD4 counts, while ocular syphilis occurs in patients with comparatively higher CD4 counts. None of the cases of ocular syphilis reported by Shalaby and colleagues had CD4 cell counts less than 70 cells/mm^3; in the case series by Balba, CD4 counts ranged between 388 and 594 cells/mm^3 [169, 192].

There are a few cases reported where morphology may help over serology for the diagnosis of ocular syphilis [159]. Wickremasinghe and colleagues reported a case series of five patients with ocular syphilis who had very similar patterns of involvement; each had areas of inner retinitis with several preretinal/inner retinal dots and retinal arteriolitis. They treated two of their patients empirically with penicillin based on the above described fundus appearance despite negative serology. One of the patients treated empirically was later found to have a positive serology for syphilis.

Retinal involvement may rarely present with a picture very similar in appearance to retinitis pigmentosa (RP). Morgan and colleagues describe a case in which a patient was initially given the diagnosis of RP before being identified as having syphilitic retinopathy [175]. Villanueva described this finding in a case of chronic chorioretinitis causing significant RPE damage [172]. Skalka and colleagues discuss that presence of vitritis, areas of chorioretinal atrophy, and perivasculitis are more likely to be seen in patients with syphilis than in those with RP [193]. The blood vessels in syphilis are less stenosed, and the disease is more likely to be unilateral. In both RP and syphilis, electroretinogram shows reduction in amplitude of the waves depending on the extent of retinal damage. However, in syphilis, A and B wave latencies remain normal, while in RP they are prolonged.

Retinal Vasculature

Retinal arterioles and venules may both be involved, or there may be isolated involvement of either one [175, 194, 195]. Vascular involvement may be limited to staining of vessels only visible on FA, or it may be seen as tortuous vessels with extensive exudation [159]. Vascular involvement may be followed by neovascularization or stenosis of the retinal vessels [159, 175].

Yokoi and colleagues report a case of irreversible damage of retinal vessels due to syphilitic vasculitis occurring in the secondary stage of the disease [196]. They describe a patient who presented with severe loss of vision in his left eye for 3 weeks before presentation. Examination showed minimal presence of uveitis or vitritis. Funduscopic examination showed hemorrhages, white exudates,

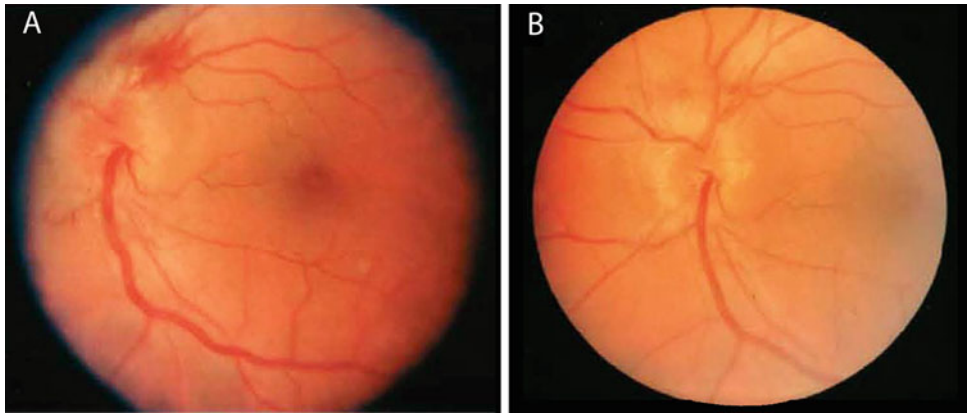

Fig. 7.7 Fundus photograph of the left eye showing optic disk swelling, peripapillary flame hemorrhage, and venous distension; the patient did not have vitritis at presentation (**a**). Twenty-four days after initiation of treatment with intravenous penicillin, there is remarkable resolution of the fundus abnormalities (**b**) (Adapted with permission from Browning D. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy, and the influence of human immunodeficiency virus status on response. Ophthalmology. 2000;107:2015–2023)

and severe edema in the posterior pole with vascular sheathing at the mid-periphery. FA showed delay in filling and hyperpermeability of the vessels; some vessels were completely occluded and showed no filling with dye. Six-month follow-up after treatment demonstrated resolution of the edema, hemorrhages, and exudates. However, the peripheral capillary non-perfusion and occlusion of the sheathed vessels persisted.

Morgan and colleagues described a patient who presented to them with complaint of a scotoma, the presence of which was verified on Amsler grid [175]. Funduscopy revealed multiple cotton-wool spots and one particularly large cotton-wool spot corresponding to the scotoma in his visual field. FA revealed the presence of capillary non-perfusion at that point. No other evidence of inflammation was described in their case. The patient was treated with IV penicillin for 10 days, but no further follow-up was available regarding the resolution of the scotoma.

Optic Disk

The optic nerve may be affected unilaterally or bilaterally, and involvement can occur as perineuritis, optic neuritis, retrobulbar neuritis, or papilledema (Fig. 7.7) [197]. Involvement of the optic disk may manifest as field defects or rapid vision loss, while morphologically it does not appear to be different from any other disease entity involving the optic nerve. Inflammation of the optic nerve may occur in isolation, or there may be concomitant inflammation of the vitreous and aqueous humor [197]. Other syphilitic manifestations include a well-demarcated opacified area of RPE around the disk [157] and a bilateral presence of optic disk edema with surrounding splinter hemorrhages [157, 197] that may even be present at the macula, leading to very poor vision [197].

Prokosch and colleagues compared the visual outcomes of 60 cases of syphilitic optic neuritis reported in literature [197]. They reported better outcomes in HIV-negative patients and in patients who received treatment with corticosteroids in addition to penicillin and probenecid. The benefit of additional steroid treatment did not seem to apply to the HIV-positive population.

Corticosteroids, however, should be used with caution in patients with syphilis. Zamani and colleagues cite a case of a 38-year-old Caucasian male who presented with decreased vision and color sensitivity [179]. Three weeks after treatment with oral prednisone only, his vision worsened and yellow placoid lesions developed around his macula. Discontinuation of steroid treatment

was followed by resolution of the lesions and improvement of vision by the next follow-up visit 5 days later. At this time, the patient was found to be positive for RPR and VDRL and was treated successfully with ampicillin. This case highlights the importance of correctly identifying syphilis at the outset as steroid treatment alone, without antibiotics, can lead to adverse outcomes.

Indocyanine Green Angiography in Ocular Syphilis

Mora and colleagues described the indocyanine green (ICG) findings in 16 eyes with ocular syphilis. Their review of late frames in 11 eyes showed multiple scattered hyperfluorescent areas in the mid-periphery [198], which were later confirmed in another case report [183]; late hyperfluorescence around retinal vessels was identified in one patient in their series[198]; and two eyes in their series showed ICG abnormalities in the absence of findings on clinical examination and FA. These findings suggest the possibility of using ICG as a diagnostic tool when suspicion is high, but funduscopy and FA do not reveal any abnormalities.

Association Between HIV and Syphilis

Before the advent of penicillin, syphilis was identified as one of the most common causes of eye infection [172]. In recent years, there has been a resurgence of ocular syphilis among HIV-infected individuals, with syphilis being identified as the most common bacterial cause of uveitis [169]. HIV co-infection leads to a rapid progression of ocular syphilis [199] with more severe manifestations [168, 200], which are frequently bilateral and involve the posterior segment [169, 176, 197, 201, 202]. In a review of literature of syphilitic optic nerve manifestations, Prokosch and colleagues reported a lower rate of improvement in the HIV-positive versus the HIV-negative population [197]. Historically, CMV retinitis has been the most commonly reported ocular infection associated with HIV [203]; however, ocular syphilis is becoming increasingly common among HIV patients and must be kept in mind as a differential when considering etiological agents of retinitis in this population [192]. Ocular syphilis does not seem to occur only in the immunocompromised state of HIV infection; clinical manifestations have been reported in literature irrespective of CD4 cell count and whether or not the individuals are receiving antiretroviral treatment [167, 169, 192]. Shalaby and colleagues reported that HIV-positive patients who were not receiving antiretroviral treatment experienced severe involvement of the eye with syphilis. Over a 12-year period, ocular syphilis was identified in 0.6% of 2,085 HIV-positive patients [169]. Most of their patients had a CD4 count less than 200 cells/mm^3, but none had a CD4 count lower than 70 cells/mm^3. Later, in 2006, Balba and colleagues compared the occurrence of ocular syphilis before and after the era of HAART [192]. In a retrospective chart review of 453 patients screened for syphilis between 1997 and 2001, 16 cases were identified to have syphilis, but none had ocular manifestations; however, between 2001 and 2002, they identified three cases of ocular syphilis. All three cases were MSMs, and their CD4 counts ranged between 388 and 594 cells/mm^3. They discussed that restoration of the immune system did not protect HIV-positive individuals from ocular involvement with syphilis but instead made it more likely to experience the inflammatory manifestations of the disease [192]. They reported blurred vision to be the most common presenting complaint; bilateral posterior uveitis was observed in all three patients, while one patient also had retinal detachment [192]. Ocular syphilis, in patients who are HIV-positive, has been reported to cause papillitis, optic neuritis, branch retinal vein occlusion, necrotizing retinitis, periphlebitis, and serous and exudative retinal detachment among other manifestations [168, 201, 202, 204].

Clinical Importance of Ocular Syphilis

Ocular syphilis can be the first manifestation of syphilis and HIV status of a patient. In the case

series published by Browning and colleagues, ocular syphilis was the first manifestation of HIV status in three of the five patients who were HIV positive [157]. In another case series of 12 patients (20 eyes), ocular manifestations of syphilis were the first signs of a positive HIV status in three patients [167]. In the retrospective case series reported by Shalaby and colleagues, ocular complaints were the first manifestations of syphilis in half of their patients, some of whom were later identified to have a concomitant rash [169].

Ocular syphilis may go unrecognized, especially in the private practice setting. According to a retrospective chart review of 14 patients by Browning and colleagues, six patients were seen by ophthalmologists prior to presenting to them; syphilis was not identified as the etiological agent in any of the six patients, who were instead treated with different formulations of steroids [157].

Therapy

Ocular manifestations of syphilis are usually associated with neurological involvement and therefore should be treated according to the recommendations for neurosyphilis. The Centers for Disease Control (CDC) recommends aqueous crystalline penicillin G 18–24 million units administered as 3–4 million units IV every 4 h or as a continuous infusion for a total of 10–14 days. If patient compliance is certain, an alternative regimen is procaine penicillin 2.4 million units intramuscular (IM) once daily, plus probenecid 500 mg orally four times a day, both taken for a total of 10–14 days [205].

For penicillin-allergic patients, ceftriaxone 2 g daily IM or IV for 10–14 days can be used. However, there is a possibility of cross-reactivity between cephalosporins and penicillins. In such cases, one may consider skin testing to confirm allergy; if positive, follow with desensitization [205].

Also, if ocular syphilis is suspected or diagnosed, one needs to perform a cerebrospinal fluid (CSF) examination to complete the evaluation. If pleocytosis is detected, one needs to repeat CSF examination every 6 months until the cell count becomes normal. If the cell counts do not decrease after 6 months or remain abnormal after 2 years, consider re-treatment and closely follow the patient [205].

Corticosteroids play an important role in the treatment of ocular syphilis. However, steroid treatment should be initiated at the appropriate time. If continued for long without appropriate antibiotics, it can lead to worsening of the disease with increased treponemal load and development of new lesions. However, initiating steroid treatment in association with antibiotics plays an additive role in combating the infection and also helps to avoid the Jarisch-Herxheimer reaction [156, 178, 179].

Jarisch-Herxheimer reaction is a febrile reaction usually occurring within the first 24 h of initiating treatment for syphilis. It has been reported to cause transient worsening of symptoms [190], but some cases may experience a very severe reaction [206, 207]. Pournaras and colleagues report a case of bilateral giant tears and retinal detachment developing in an emmetropic 45-year-old man 2 weeks after starting penicillin treatment for syphilitic uveitis [207]. The inflammation associated with severe vitritis may have been exacerbated by the inflammatory changes associated with the Jarisch-Herxheimer reaction, leading to giant retinal tears in this patient. Danesh-Meyer and colleagues recommend pretreatment with corticosteroids a few hours before commencing penicillin treatment to avoid having a severe Jarisch-Herxheimer reaction [208].

The Center for Disease Control (CDC) guidelines state that antibody titers of the non-treponemal tests, for example, VDRL or RPR, are reflective of disease activity [152]. However, cases have been reported in the literature that have severe eye disease despite having low titers [209]. Manifestation of ocular symptoms occurring after previous treatment for syphilis may account for the low antibody titers in some patients with ocular involvement of the disease [172]. Also, VDRL and FTA-ABS should both be performed for accurate diagnosis as VDRL alone without an FTA-ABS test may cause one to miss many cases of ocular syphilis [209].

Controversies and Perspectives

The incidence of ocular syphilis is increasing and the disease can present in many different ways. Morphology of the lesions is generally not believed to be helpful in the diagnosis of the disease; however, as mentioned in the text, cases where morphology rather than serology pointed to the diagnosis have been reported in literature. We have discussed most of the retinal and choroidal manifestations reported in the literature. However, there may be newer ways in which syphilis may present. As co-infection with HIV continues to modify the progression of this disease, it is important to be vigilant for the presence of syphilis when patients from high-risk populations present with ocular inflammation. However, in some cases, patients simply may not give history of high-risk behavior. Therefore, demographics, history, examination, laboratory tests, including treponemal and non-treponemal antibody tests, imaging modalities, and in some cases retinal function tests should all be used effectively to allow one to make the correct diagnosis. Posterior segment involvement should not be looked at in isolation as a concomitant anterior chamber inflammation as well as systemic signs and symptoms may direct one toward the diagnosis. Prompt identification and treatment can lead to rapid and full recovery in most cases.

There are debates regarding the significance and the correct timing of performing the CSF examination in patients with syphilis. The CSF-VDRL test is not very sensitive for detection of antibodies, and in HIV-positive patients, CSF protein levels and cell counts are usually abnormal without actual invasion of the CNS by the Treponemas. Also, CSF pleocytosis persists for long periods of time in patients who are co-infected with HIV. Therefore, the presence of cells on follow-up CSF examination is not necessarily an evidence of treatment failure. Close clinical correlation is required. CSF examination is recommended for cases of ocular syphilis. However, for infection limited to the anterior chamber, its significance is debatable. Although the CDC does not recommend a different treatment regimen for HIV-positive versus HIV-negative patients with syphilis, it is likely that HIV-positive patients may have higher rates of treatment failure and complications, and in some cases, a more aggressive treatment approach may be needed.

Clinical Pearls

- Ocular syphilis is frequently associated with neurosyphilis; CDC recommends CSF examination in these patients.
- For diagnosis of ocular syphilis, both the non-treponemal (i.e., VDRL, RPR) and treponemal tests (i.e., FTA-ABS) should be performed to avoid missing the diagnosis.
- CDC recommends testing for HIV infection in patients diagnosed with neurosyphilis; strongly consider HIV testing in any patient presenting with ocular syphilis.
- Ocular infection with *Treponema pallidum* is considered tertiary syphilis and requires complete therapeutic course of 10–14 days with intravenous therapy; treatment with intramuscular antibiotics is often not sufficient.
- Syphilis has no pathognomonic manifestations; one needs to consider the diagnosis in patients who have risk factors for acquiring the infection.
- One needs to rule out infectious causes of inflammation before initiating treatment with steroids; appropriate treatment of ocular syphilis with intravenous penicillin often yields excellent visual outcome.

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Retinal and Choroidal Manifestations of Viral Diseases

8

Nathaniel C. Sears and Careen Yen Lowder

Abstract

Several viral infections may involve the retina and choroid. These viruses include herpesviruses, rubella, rubeola, influenza, Epstein-Barr virus, human immunodeficiency virus (HIV), and West Nile virus. The predominant causes of viral retinitis and choroiditis are viruses of the Herpesviridae family. Classic findings of infection include vitritis, periarteritis, necrotizing retinitis, and optic neuropathy.

Keywords

Choroiditis • Cytomegalovirus • Herpes simplex • Herpesviridae infections • Influenza • Retinitis • Varicella zoster • West Nile virus

Introduction

Several viral infections may involve the retina and choroid. These viruses include herpes viruses, rubella, rubeola, influenza, Epstein-Barr virus, human immunodeficiency virus (HIV), and West Nile virus. The predominant causes of viral retinitis and choroiditis are viruses of the Herpesviridae family. Classic findings of infection include vitritis, periarteritis, necrotizing retinitis, and optic neuropathy. The central questions regarding the diagnosis and management of viral infections of the retina include identification of the best method of rapid and specific treatment, the optimal surgical approach for repair of secondary retinal detachment, and the primary etiology of ocular infection and reactivation especially in the case of latent virus within the central nervous system.

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Acute Retinal Necrosis

In Japan, in 1971, Urayama et al. reported six cases of a novel form of uveitis and named the disease Kirisawa's uveitis. Later, Willerson reported a necrotizing vaso-occlusive retinitis and named this syndrome acute retinal necrosis (ARN) [1]. In 1982, Culbertson identified the

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causative organism of ARN as herpesvirus, first by demonstrating the presence of intraocular herpesvirus particles by electron microscopy and later by culturing varicella-zoster virus (VZV) from an affected eye [2].

ARN is an ocular emergency as it rapidly leads to blindness if not promptly recognized and treated. It is characterized by peripheral necrotizing retinitis, retinal arteritis, and intraocular inflammation. ARN syndrome is caused by a primary infection with [3] or reactivation of a latent herpes simplex virus (HSV-1 or HSV-2) or varicella-zoster virus (VZV). While advances have been made in the diagnosis of ARN syndrome, specifically with the detection of viral DNA in intraocular fluids using polymerase chain reaction (PCR), recognition of the disease remains based on clinical appearance.

In 1994, the American Uveitis Society published a set of diagnostic criteria for ARN (Fig. 8.1): (1) one or more foci of retinal necrosis with discrete borders in the peripheral retina, (2) rapid progression in the absence of antiviral therapy, (3) circumferential spread, (4) occlusive vasculopathy with arteriolar involvement, (5) prominent vitritis and anterior chamber inflammation, and (6) optic neuropathy or atrophy, scleritis, and pain (supportive but not required). It should be noted that this definition does not depend on the extent of necrosis, viral etiology, or immune status of the host. When these criteria are not met in the setting of necrotizing retinitis that additionally does not resemble cytomegalovirus (CMV) retinitis or progressive outer retinal necrosis (PORN), the term "necrotizing herpetic retinopathy" is suggested. Necrotizing herpetic retinopathy can occur early after the initial infection. However, in this circumstance, the retinal lesion is usually localized and slowly progressive, whereas in ARN the lesions are rapidly progressive [4].

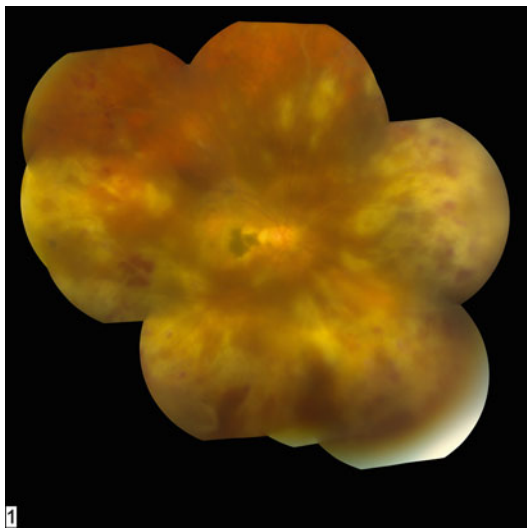

Fig. 8.1 Acute retinal necrosis. Photograph demonstrates retinal necrosis, vitritis, and perivascular infiltrates

Causative Virus

The causative agents in ARN are the alpha herpes viruses HSV-1, HSV-2, VZV, and rarely CMV [5]. These viruses have been isolated from the choroid [6], retina [6], lens, and vitreous body [6–8]. Antigen for HSV-1 had been detected in the inflammatory infiltrate and also in the retina and vitreous body [9, 10]. Antigen for HSV-2 has been detected in the vitreous [11] and also in the spinal fluid and serum [12, 13]. DNA for HSV-1 and HSV-2 has been amplified by PCR in several ocular biopsies [14–18]. Interestingly, a study measuring the serum anti-HSV antibody titers by enzyme-linked immunosorbent assay (ELISA) revealed a positive anti-HSV-2 antibody and negative anti-HSV-1 antibody in the sera of a group of Japanese patients with HSV-2 DNA–positive ARN syndrome [12]. This finding that patients who are positive for HSV-2 ARN only possess anti-HSV-2 antibodies suggests that the absence of preexisting HSV-1 infection may play an important role in the development of HSV-2 ARN syndrome.

Epidemiology

ARN is a rare condition. A study from the United Kingdom demonstrated an incidence of 1 in every 1.6–2 million people per year [19]. Additionally, a 2002 study revealed that only 41 (1.3%) of 3,060 Japanese uveitis patients had ARN [20].

There is controversy regarding the discrepancy of sex with the development of ARN. One study reports no sex difference for all types of ARN and the prevalence of ARN is nearly equal between the sexes [16]. HSV-2-associated ARN tends to occur at a younger age than HSV-1- and VZV-associated ARN. In one report, the mean age of onset was 20 years (6 cases) for HSV-2–ARN, 47 years (7 cases) for HSV-1–ARN, and 57 years (13 cases) for VZV–ARN syndrome [16].

Virological Diagnosis

Virological analysis of the aqueous humor or vitreous is required for diagnostic confirmation and for identification of the specific herpes virus. The highest sensitivity and specificity are obtained through the detection of viral DNA by PCR. Real-time quantitative PCR has allowed monitoring of viral titer and treatment response throughout the clinical course of ARN. There have been reports of patients with ARN in whom real-time PCR documented a decrease in the HSV DNA copy number in aqueous humor following the initiation of treatment [21, 22].

Since most adults have a history of infection by herpes virus, the presence of viral antibodies in the peripheral blood is not a specific finding. Additionally, the serum antibody level does not necessarily correlate with clinical activity of the virus, specifically with ARN [23]. However, comparison between the antibody load in serum and intraocular fluids may be measured and compared to monitor intraocular viral infection. The ratio of specific antibody (aqueous or vitreous)/total IgG (aqueous or vitreous) to specific antibody (serum)/total IgG (serum) makes up the Goldmann-Witmer coefficient. If the coefficient is 1 or greater, theoretically, there is intraocular production of antibody, indicating an intraocular propagation of the virus. In practice, a coefficient of 4 or above is interpreted as intraocular infection, whereas a coefficient between 1 and 4 is suspected infection and any coefficient below 1 is regarded as negative. In general, these strategies are mired by complexities in the course of antibody production, which is weak in early infection and therefore calculations must be normalized against IgG production. PCR should be chosen as the initial test for suspected cases, and antibody titers should be reserved for cases with a time lapse from onset. It is important to note, though, that treatment should never await diagnostic confirmation when there is strong suspicion based on clinical examination.

Clinical Course

ARN is predominantly unilateral, but the contralateral eye occasionally becomes involved, usually within 1–6 weeks following onset in 9–36% of patients. A national population-based study from the United Kingdom revealed that 9.7% of subjects had progression to the contralateral eye [19]. While Palay et al. reported that prolonged acyclovir treatment decreases the involvement of the contralateral eye, another study reported that 9 of 80 patients (11.3%) had contralateral involvement despite adequate antiviral therapy [24, 25].

The cardinal symptoms of ARN include acute onset of ocular pain, external vasodilatation, unilateral loss of vision, photophobia, and floaters. The classic triad of symptoms includes vitritis, multifocal yellow-white peripheral retinitis, and retinal arteriolitis. In some cases, early manifestations of choroiditis can be observed as opacification of the choroid/retinal pigment epithelium (RPE) with hypoperfusion then late staining of the choroid followed by the classic findings [26]. Heavy anterior chamber and vitreous inflammation is frequently observed during the acute phase. Vitreous inflammation soon resolves following treatment initiation, but opacity can recur 3–4 weeks after onset due to fibrous organization of the vitreous. This can lead to incomplete posterior vitreous detachments, proliferative vitreoretinopathy, and persistent vitreous traction of vitritis, periarteritis, necrotizing retinitis, and optic neuropathy.

Multifocal, small, white-yellow granular lesions develop in the peripheral retina, considered to be a result of active viral proliferation and excessive recruitment of immune response in outer retinal layers. These lesions are usually discontinuous

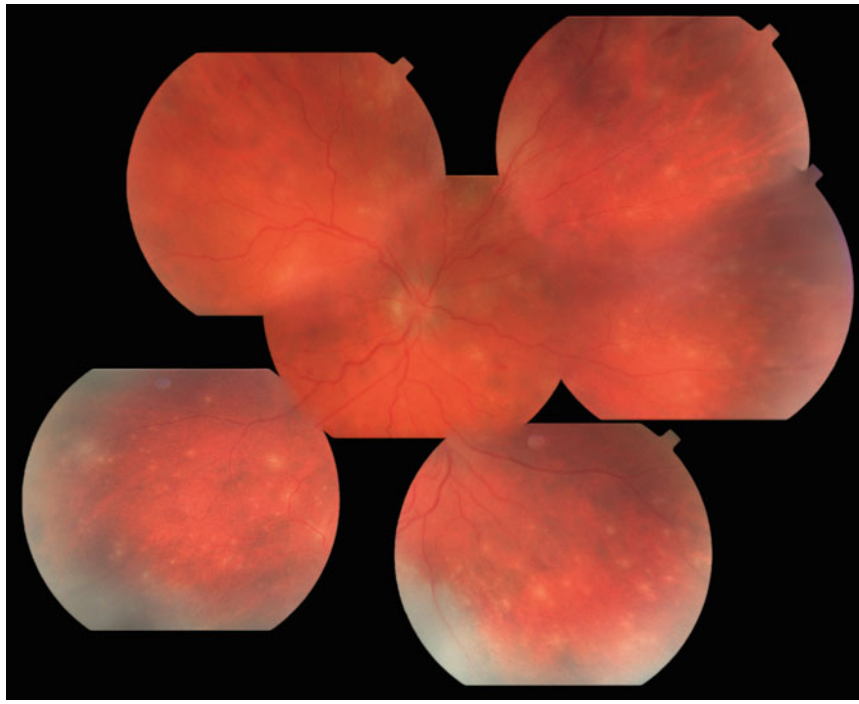

Fig. 8.2 Multifocal posterior necrotizing retinitis. Montage demonstrates punctate multifocal lesions that will coalesce to confluent areas of retinitis. This variant of ARN is often associated with varicella zoster

with scalloped edges. As the disease progresses, these lesions enlarge and coalesce to become confluent, dense, creamy opaque lesions which eventually spread toward the posterior pole. Periarteritis and occlusive retinal vasculitis are also commonly observed, sometimes associated with the development of ghost vessels and club-shaped hemorrhages along the vasculature [27]. As the disease advances, full-thickness retinal necrosis develops. Circulatory impairment in the retinal tissue surrounding the early granular lesions likely occurs early in the clinical course. Even with the initiation of treatment, these lesions may expand, leading to a several-day lag time between treatment initiation and disease regression. As the vitreous contracts from chronic inflammation, even weak traction on the retina can create breaks where necrosis has occurred. In the final stages and even after regression, retinal detachment occurs at rate of 50–75% secondary to breaks in these areas of retinal necrosis. Margolis et al. reported herpetic retinitis presenting as a rapidly progressive multifocal posterior necrotizing retinitis caused mostly by varicella-zoster virus. Patients with this clinical presentation had a 100% incidence of rhegmatogenous retinal detachment (Fig. 8.2) [28].

Treatment

Treatment of ARN has three general principles: rapid administration of antiviral therapy, protection of the uninvolved eye, and surveillance/repair of retinal detachment. The most important action is immediate initiation of intravenous (IV) acyclovir (10 mg/kg body weight every 8 h), usually with the assistance of infectious disease consultation. This medication may lead to reversible elevations in serum creatinine and liver function tests, and dosage should be reduced in the presence of renal insufficiency. Additional therapy with intravitreal injection of ganciclovir (0.2–2.0 mg/0.1 mL) or foscarnet (1.2–2.4 mg/0.1 mL) is recommended at presentation. This should immediately follow vitreous aspirate for PCR studies but should not await laboratory confirmation. These drugs have a short

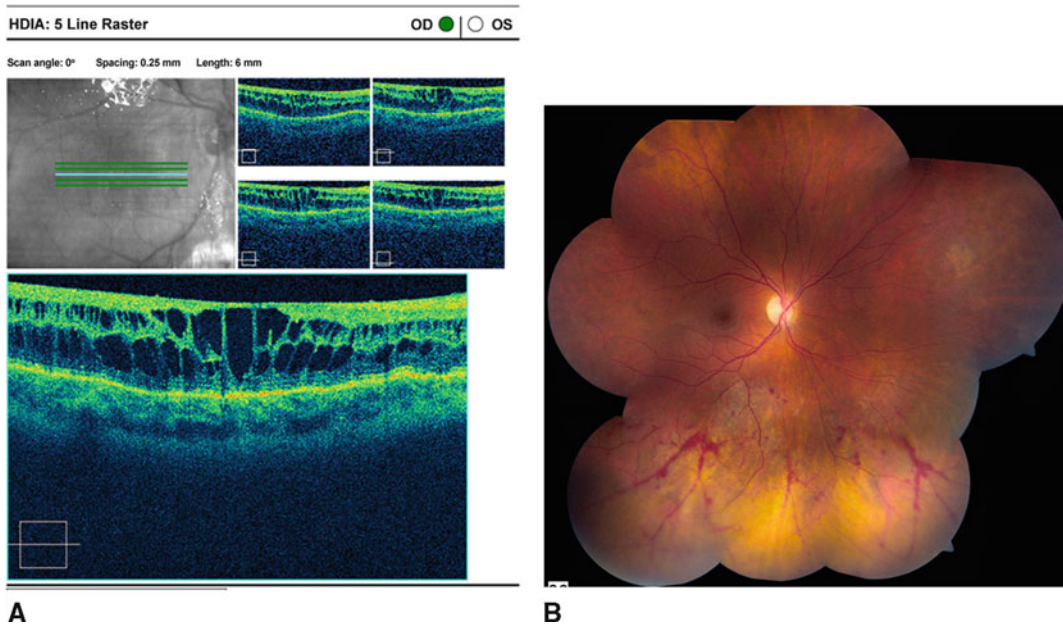

Fig. 8.3 Optical coherence tomography (**a**) shows massive cystoid macular edema in a patient with acute retinal necrosis (**b**). At presentation, the patient had received 2 weeks of intravenous acyclovir for herpes simplex encephalitis

half-life and intravitreal injection may need to be repeated twice weekly until adequate control has been obtained. With the advent of intravitreal injections, initial combination therapy with the oral prodrug, valacyclovir (1–2 g orally three times daily), has been used as first-line therapy or in patients who fail to respond to IV acyclovir. There is currently no randomized trial that compares IV to oral therapy, and presently, the cost of the oral prodrug is 10–100 times the cost of generic acyclovir. Hence, 2 weeks of outpatient IV therapy followed by oral acyclovir may be more cost effective. Following 24–48 h of systemic antiviral therapy, systemic corticosteroid, predominantly prednisone (1 mg/kg/day), is initiated to treat the associated inflammation.

The second area of controversy is the optimal timing for conversion to oral therapy when IV therapy is used and the general time period for maintenance therapy. Usually following a 10–14-day course of IV acyclovir with or without weekly intravitreal antiviral injections, treatment may be changed to oral therapy if adequate regression of retinitis is observed. Oral acyclovir is rarely used secondary to its poor bioavailability. Instead, valacyclovir (1 g three times daily for VZV; 500 mg daily for HSV) or famciclovir (500 mg three times daily for VZV; 250 mg three times daily for HSV) is initiated for at least 3 months following infection. If central nervous system manifestations are noted that are consistent with viral meningitis or encephalitis, management requires a longer course of IV therapy and perhaps even long-term viral suppression with oral antiviral therapy.

Even following "resolution" of ARN, there is nearly a 75% risk of retinal detachment. Prophylactic barrier laser photocoagulation should be applied to areas of healthy retina posterior to necrosis as soon as vitreous inflammation clearance permits an adequate view. Additionally, early pars plana vitrectomy along with endolaser treatment has been postulated to have better response secondary to removal of contributing vitreous traction. Generally, in the presence of multiple retinal breaks with or without detachments, reattachment by vitrectomy with either C3F8 or silicone oil injection is usually necessary. Although the rate of reattachment approaches 98%, by either gas or silicone, a visually limiting complication of ARN is cystoid macular edema (CME) (Fig. 8.3a, b), which can be difficult to treat secondary to the threat of viral reactivation with intensive steroid

treatment. In severe circumstances, one may consider the placement of a sustained-release ganciclovir implant (Vitrasert®, Bausch & Lomb, Madison, NJ, USA) with continued oral antiviral treatment if intravitreal triamcinolone acetonide is necessary to resolve the CME or if a retinal detachment repair is necessary. The Vitrasert® implant can be used in conjunction with either silicone oil or C3F8.

The prognosis for ARN is generally poor. The majority of patients have less than 20/200 vision in the affected eye. However, the prognosis may significantly improve with early recognition, aggressive antiviral therapy, and laser photocoagulation. In severe cases, especially with retinal detachment, hypotony is an infrequent but serious complication.

Cytomegalovirus

Cytomegalovirus (CMV) is a herpes virus containing double-stranded DNA. Systemic infection is common and causes an antibody-negative mononucleosis syndrome. CMV retinitis is the most common ophthalmic manifestation of CMV, occurring as a congenital infection in infants or as an opportunistic infection in the immunocompromised host. Adults commonly affected include those individuals with acquired immunodeficiency syndrome (AIDS), oncology patients, and patients on immunosuppressive/immunomodulatory therapy post-organ transplantation or for autoimmune disorders. Specifically, AIDS patients with a CD4+ count lower than 50 cells/μ(mu)L are considered at highest risk and make up the most commonly affected population of patients. Ocular CMV infection is an especially rare cause of ARN in immunocompetent adults. The advent of highly active antiretroviral therapy (HAART), though, has significantly reduced incidence of CMV retinitis and its complications in AIDS patients.

Diagnosis

The diagnosis of CMV retinitis is primarily based on clinical findings in the immunocompromised host, with observation of characteristic hemorrhagic, full-thickness retinitis (Fig. 8.4a, b, c).

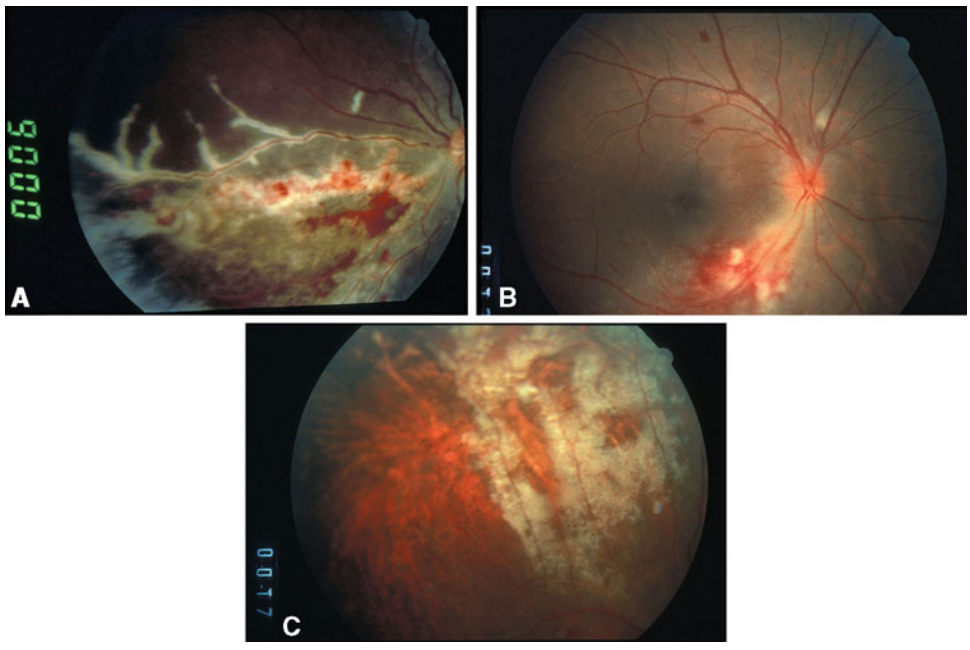

Fig. 8.4 Cytomegalovirus can present as a pattern of (**a**) frosted branch angiitis, (**b**) hemorrhagic retinitis, or (**c**) granular infiltrate

Early CMV may appear as a small white retinal infiltrate mistaken for a cotton-wool spot of HIV-related microvasculopathy. However, this focal edema quickly expands without treatment. The healthy retina becomes sharply demarcated from spreading infected retinal cells. Histopathology of infected retina reveals pathognomonic large eosinophilic intranuclear inclusions and small basophilic cytoplasmic inclusions and few surrounding inflammatory cells. Active retinitis has a faint granular border of intraretinal infiltrates that represent foci of viral activity in the normal retina. Infected cells lyse, leaving an area of full-thickness necrosis with underlying choroiditis. Released virus particles and cell-to-cell transmission allow infection of adjacent retinal cells. A diminished inflammatory response is observed secondary to the immunocompromised state of the host.

The identification of these clinical features relies on fundus photography, fluorescein angiography, optical coherence tomography, and electrophysiological testing. Fundus autofluorescence imaging can be helpful in highlighting areas of active CMV retinitis. A hyperautofluorescent signal has been correlated with flagrant advancing CMV retinitis, and a hyperautofluorescent border is helpful in the detection and localization of subtle CMV reactivation. In one of nine patients in a recent study, diffuse, punctate hyperautofluorescence after intravitreal ganciclovir and foscarnet was associated with medication-related toxicity [29].

Congenital CMV retinitis has a similar clinical appearance on ophthalmoscopic exam. However, it is additionally associated with systemic findings of jaundice, hepatosplenomegaly, ventriculomegaly with periventricular calcifications, petechial rash, seizures, microcephaly, fever, thrombocytopenia, anemia, and pneumonitis.

Staging and Progression

CMV retinitis staging is tied closely with the nature of CMV retinitis progression. The broadest staging classification focuses on the differentiation of active infectious retinitis from necrosis. There are three distinct variants of CMV retinitis: (1) classic or fulminant retinitis with large areas of retinal hemorrhage along a whitened, edematous, or necrotic retina, usually in the posterior pole in the distribution of the nerve fiber layer along the vascular arcades; (2) granular or indolent retinitis without retinal edema, hemorrhage, or vascular sheathing, progressing along active borders in the retinal periphery; and (3) perivascular CMV or frosted branch angiitis with retinal perivasculitis. Active CMV retinitis progresses in two modes. First, new discontinuous hemorrhagic skip lesions can appear, presumably through hematogenous spread. Second, and more commonly, lesions may expand and coalesce with nearby lesions via cell lysis and cell-to-cell transmission.

CMV retinitis may also be described by the zone of involvement. Zone 1 lies within 1,500 μ(mu)m of the optic nerve or 3,000 μm of the fovea, zone 2 extends from the edge of zone 1 to the vortex veins ampullae, and zone 3 extends from the edge of zone 2 to the ora serrata. Zones 2 and 3 are the most common sites of initial retinal involvement.

CMV retinitis lesions expand relatively slowly at 250–350 μm/week, and therefore, the center of the lesions will have time to progress from hemorrhagic to fully necrotic while the border remains active. This is an important contrast to ARN lesions which expand more rapidly usually without an identifiable atrophic center. When the central area progresses to necrotic tissue, the lesion evolves from an edematous hemorrhagic appearance to a glial scar with underlying retinal pigmented epithelium apparent. Therefore, special attention should be given to the edges of the lesions, inspecting for advancing retinitis, rather than central areas of atrophic and inactive infection, when monitoring for progression of infection.

Although this disease is destructive, prompt recognition and treatment of this slowly progressive infection can allow for visual preservation. The progression of CMV retinitis may be monitored by repeated clinical examinations or by serial fundus photography [30, 31]. Peripheral and/or central vision loss occurs predominantly

secondary to the development of an absolute scotoma due to retinal necrosis. It is common for patients to be asymptomatic until there is macular involvement with central vision loss. This may be secondary to necrosis involving the macula or to macular edema associated with nearby lesions. Additionally, if the optic nerve is involved, visual loss can be severe even with a minimal degree of retinitis.

Retinal detachment occurs in 5–29% of eyes in various case series, predominantly secondary to vitreous traction [32]. In those patients with retinal detachment in one eye, 50% will develop a detachment in the contralateral eye if involved in the disease course. The probability of retinal detachment increases, in a nonlinear manner, with the extent of retinal involvement. There is a fivefold increase in detachment incidence when the retinitis involves 25% of the retina compared to 10% involvement [33]. The risk of detachment is substantially less among patients receiving HAART, with an associated 60% reduction in retinal detachment rate ($P < .001$) [34]. The greatest benefit was observed among patients who developed an immunologic response with the initiation of this therapy. This is attributed to better control of infection, resulting in smaller, inactive lesions and therefore better healed and more adherent scars [35, 36]. In one study, a significant difference in the rate of retinal detachment was additionally found between eyes treated with systemic therapy only and those treated with implants, whether used as primary therapy or subsequent to using systemic anti-CMV therapy [37].

Laboratory Findings

The most important risk factor for CMV retinitis is immune dysfunction. The CD4+ count is used as a marker of immune dysfunction in patients infected with HIV, and patients are deemed at highest risk when CD4 count falls below 50 cells/uL. Because these patients may be asymptomatic with regard to CMV retinitis, scheduled ophthalmic screening, with frequency of dilated fundus exams (Table 8.1) based on CD4 count, should be performed.

Table 8.1 Scheduled ophthalmic screening for ocular CMV based on CD4 count

CD4+ >100 cells/uL	Little risk; screen yearly
CD4+ 50 to 100 cells/uL	At risk; screening examination every 6 months
CD4+ <50 cells/uL	High risk; 35% incidence of CMV retinitis; median time to diagnosis of CMV retinitis is 13 months; screen every 3 months

The presence of atypical features can sometimes make clinical diagnosis more difficult. As noted above, initial signs of CMV retinitis may resemble cotton-wool spots commonly observed in HIV retinopathy. Additionally, it may be clinically difficult to distinguish CMV retinitis from intraocular lymphoma, complicating diagnosis in some patients [38]. Patients with an atypical presentation or those individuals nonresponsive to antiviral therapy may undergo aqueous or vitreous biopsy with subsequent PCR analysis to confirm the diagnosis and differentiate infection from other herpetic etiologies as well as toxoplasmosis. This diagnostic evaluation, though, is rarely practiced. Systemic specimens can be obtained from blood buffy coat, semen, or urine. Detection of CMV in the blood by DNA PCR is most predictive of developing CMV disease [39]. Patients with AIDS who test positive will have over a 60% chance of developing CMV end-organ disease. An important consideration is that responders to ganciclovir prophylaxis convert to PCR negative with treatment. Compared to non-responders, survival is increased 2.4 times at 12 months. In congenital CMV infection, identification of viral inclusion bodies, a positive CMV culture, and supportive PCR analysis of urine, saliva, and subretinal fluid may be helpful in the diagnosis.

Treatment

Pharmacologic

There are two main objectives in the treatment of CMV retinitis. First, vigorous anti-CMV medication must be initiated to stop viral propagation.

Second, the host's immunologic status must be corrected. This almost always entails the initiation or adjustment of HAART therapy because the majority of the CMV patients are AIDS patients. The initiation of HAART and anti-CMV therapy simultaneously will prevent immune reactivation uveitis while HAART-induced immunologic recovery is taking place. If the patient is suffering from other systemic infectious diseases, such as tuberculosis, HAART initiation or alteration is often delayed until treatment for the infection is started. This serves to reduce the risk of systemic inflammatory reactions against the other pathogen.

In general, current therapies use a high induction dose of the anti-CMV medication to halt active disease followed by the introduction of HAART. Following response to therapy, the patient's anti-CMV therapy may be lowered to an effective maintenance dose. This maintenance dose may be continued indefinitely if the patient remains persistently immunocompromised. However, if the patient exhibits a stable immune recovery, discontinuation of maintenance anti-CMV medication is possible.

CMV retinitis itself, independent of CD4 count, viral load, and presence of HAART therapy, is associated with a higher mortality in AIDS patients. There is a clear mortality benefit with the initiation of anti-CMV therapy [40]. There are five medications that are approved for CMV infection: ganciclovir (intravenous, intravitreal, intraocular implant), foscarnet (intravenous, intravitreal), cidofovir (intravenous, intravitreal), fomivirsen (intravitreal), and valganciclovir (oral). Routes of delivery and adverse effect profiles vary. Ganciclovir is a prodrug which is triphosphorylated intracellularly to allow inhibition of viral DNA polymerase. Ganciclovir is virostatic so eradication of the infection relies on a functional immune system. Several studies have shown that a 14-day course of intravenous ganciclovir (5 mg/kg twice daily) can halt CMV retinitis with 90% of the patients reverting to a less active lesion [41]. Neutropenia is an important adverse side effect of treatment with ganciclovir. Until the development of granulocyte colony-stimulating factor as an adjuvant therapy, it was a dose-limiting toxicity. Neutropenia typically occurs during the second week of therapy, and dosing should be adjusted to maintain neutrophil counts of at least 500 cells/uL.

Valganciclovir is the L-valyl ester prodrug of ganciclovir. After oral administration, it is rapidly converted to ganciclovir by intestinal and hepatic esterases. Valganciclovir is the most common choice for initial therapy secondary to its convenience, lower cost, and absence of complications associated with intravenous administration. Current standard of care consists of an induction phase with valganciclovir (900 mg PO bid for 2–3 week) or ganciclovir (5 mg/kg IV bid for 2–3 week) followed by maintenance with valganciclovir (900 mg PO qd) until the CD4+ count is above 100 cells/uL.

Foscarnet also inhibits viral DNA polymerase, but in a different manner than ganciclovir. It is effective against herpesviruses, and it also inhibits reverse transcriptase and therefore is inhibitory on the replication of HIV. It is administered intravenously (2×90mg/kg daily or 3×60mg/kg daily). Although it is not as toxic to bone marrow as ganciclovir, it is nephrotoxic and leads to abnormalities in serum calcium, phosphate, and magnesium levels. It cannot be used with other nephrotoxic drugs, such as amphotericin B. The systemic and ocular complications of AIDS trial (SOCA) have demonstrated that foscarnet and ganciclovir are equally effective in preventing CMV retinitis [42].

Cidofovir is effective in the treatment of CMV retinitis, but it has an increased adverse effect profile and is not orally bioavailable. Cidofovir is additionally associated with immune reactivation uveitis.

Intravitreal ganciclovir, foscarnet, and cidofovir are additionally available. However, while these modes of treatment are extremely effective for local retinitis, they do not cover extraocular systemic CMV, which may additionally be debilitating. In one of nine patients in a recent study, diffuse, punctate hyperautofluorescence after intravitreal ganciclovir and foscarnet was associated with medication-related toxicity [29].

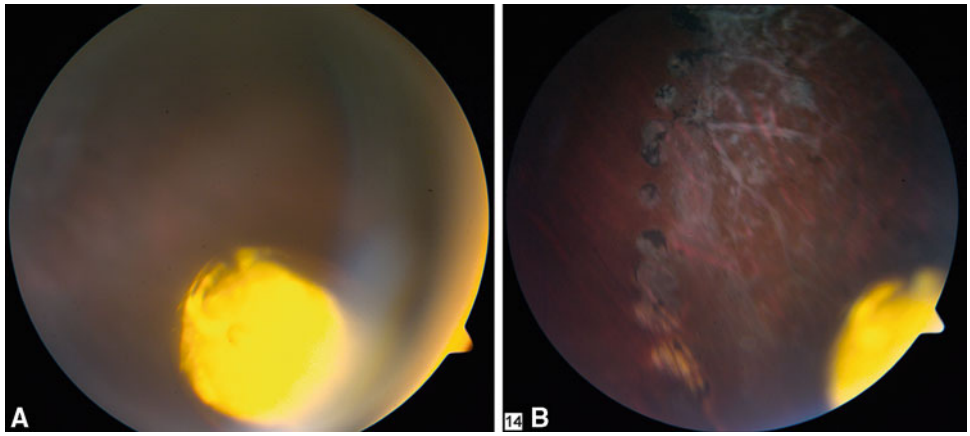

Fig. 8.5 Pars plana ganciclovir implant, Vitrasert (**a**) provides sustained delivery of intravitreal ganciclovir. (**b**) Laser was placed intraoperatively posterior to the broad temporal area of retinitis

Surgical

Intravitreal ganciclovir implant is used in patients who have reactivation of retinitis despite systemic treatment, or in those that cannot tolerate other treatments. The intravitreal ganciclovir implant (Vitrasert®) is an effective surgical modality for CMV treatment (Fig. 8.5a, b). It provides a 1 μg/h sustained release of ganciclovir over the course of 8 months [43, 44]. The implant is extremely important in patients who cannot tolerate systemic therapy, but does not address prophylaxis of the companion eye or systemic CMV viral load. Individuals with CMV retinitis commonly require surgical intervention for repair of a retinal detachment, and in this setting, concomitant vitrectomy and scleral buckle can be combined with ganciclovir implant. Retinal detachment occurs in 5–29% of eyes in various case series (Fig. 8.6) [32]. The total reattachment rate is 76%; macular attachment occurs in 90%. Mean postoperative visual acuity is 6/18. The risk of detachment is substantially less among patients receiving HAART. This is attributed to better control of infection, resulting in smaller, inactive lesions and therefore better healing.

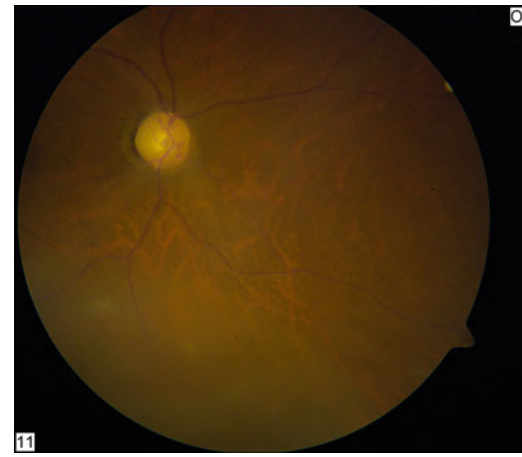

Fig. 8.6 Inferior, macula on, retinal detachment in a patient with CMV retinitis

CMV Retinitis and Therapy in the HAART Era

Highly active antiretroviral therapy (HAART) refers to the strategic combination of different classes of antiretroviral drugs which effectively suppress HIV replication. Treatment is marked by nearly complete clearing of HIV from the blood (decreasing viral load) and subsequent repletion of circulating CD4+ T lymphocytes. Immune recovery may require several months of therapy, during which time patients remain at risk for opportunistic infections. There are now approximately 30 FDA-approved antiretroviral drugs and fixed-drug combinations, summarized by the International AIDS Society-USA [45–47]. Before HAART became standard of care in HIV patients, CMV patients were required to take long-term maintenance doses of anti-CMV treatment and still unfortunately progressed relentlessly toward

blindness. For example, when patients were being treated with ganciclovir, median time to progression was 2 months. When patients were treated with intravenous foscarnet, median progression time was 4 months. The most effective treatment was intravitreal ganciclovir implant, increasing the time to progression to 7 months. Immune recovery has allowed for CMV patients to be taken off of maintenance therapy [45–47]. Reactivation can occur, especially if patients CD4+ counts fall back below 50 cells/uL [47]. It appears that the CD4+ count is the best predictor of an effective immune response against CMV. Other laboratory values including HIV viral load and CMV culture data have not been correlated with a particular outcome. One area of active research is the correlation between CMV viral load and CMV-specific CDR T-cell response with the ability to promote an effective host immune response.

The widespread use of HAART has been attributed to an over 50% decrease in the number of new cases of CMV retinitis. A large retrospective review of over 1,200 HIV patients who had at least one CD4+ count below 100 cells/uL revealed a decrease in the incidence of three major opportunistic infections including CMV from 22 per 100 person-years to 3.7 per 100 person-years when HAART was instituted [41, 48]. Another study found the incidence of new CMV retinitis in the HAART era to be 5.6/100 person-years [45–47].

CMV retinitis remains a major problem, however. Many HIV-infected individuals had CMV retinitis prior to the introduction of HAART and have suffered permanently impaired vision, specifically secondary to retinal detachments and scarring following clearance of the infection. There additionally continue to be new cases occurring in HAART-failure patients who have low CD4+ T-lymphocyte count, and there are patients who despite successful HAART therapy still contract CMV retinitis [49]. Finally, CMV retinitis is expected to rise as HIV resistance to antiretroviral drugs increases and as HIV-infected individuals remain poorly informed about the HIV or have limited access to healthcare information. In addition, there are non-CMV-related ocular complications for HIV patients which persist. For example, retinal hemorrheologic abnormalities are found despite use of HAART. The pattern is changed from what is found in severely immunodeficient individuals, however. Cotton-wool spots, a feature often seen in severely immunodeficient individuals, become rare after immune recovery. For this reason, factors other than blood flow are thought to contribute to the findings in these patients. The remodeling of the microvasculature is thought to be a possibility [50, 51].

HAART has allowed the management of CMV retinitis to shift from previous short-term treatment to the long-term management of what has become, for many individuals, a chronic disease. There has been a paradigm shift of treatment objectives from slowing of disease progression to long-term suppression of disease activity altogether. The guidelines for management of CMV after the introduction of HAART have been summarized by the International AIDS Society-USA [52].

Discontinuation of Anti-cytomegalovirus Treatment

Immune recovery allows eventual discontinuation of specific anti-CMV therapy without reactivation of infection. A decision to discontinue anti-CMV drugs usually is based on several factors: a sustained rise in CD4+ T-lymphocyte count, a drop in HIV viral load, duration of HAART that is sufficient to effect immune recovery, and inactivity of CMV retinitis lesions. The Center for Disease Control (CDC) has stated that patients receiving HAART should have CD4+ T-lymphocyte counts of more than 100–150 cells/μL for at least 3–6 months prior to discontinuation of anti-CMV therapy [53]. However, Macdonald and colleagues observed that most patients for whom discontinuation of anti-CMV drugs was successful had values that far exceeded those guidelines [54].

Some clinicians require the additional evidence that the HIV viral load has dropped to fewer than 200 copies/uL [55]. However, Macdonald and colleagues further noted that the value of HIV viral load as a criterion for discontinuation of anti-CMV drugs was unclear [54]. Others have subsequently reported patients who have sustained CMV inactivity without maintenance treatment

despite HIV viral loads of greater than 30,000 copies/mL [55]. Regardless, HIV viral load may be a useful marker for eventual reactivation.

Patient Follow-up

Following effective discontinuation of anti-CMV therapy, CMV retinitis may reactivate. Studies have estimated that the risk of recurrence is approximately 0.02 events/person-years [55, 56]. For this reason, continuous monitoring of affected patients is essential. Additionally, with each relapse, the time to the next reactivation decreases. Putative laboratory measures are CD4+ T-cell count, HIV viral load, and CMV serum antigen or DNA [49, 57, 58].

As a nonspecific measure of immune function, CD4+ T-lymphocyte count is the most commonly followed parameter. While impaired CMV immunity is usually reflected in low CD4+ T-lymphocyte counts, some cases do not follow this rule, with development of CMV retinitis despite an adequate CD4 count. A number of studies have demonstrated a selective impairment of immune reactions against CMV present in patients with AIDS and CMV retinitis. Although tests of CMV immunity may provide an increased understanding of CMV retinitis in this setting, they are not yet commercially available and their ability to predict development or reactivation of CMV retinitis has not yet been demonstrated. For example, Sinclair and associates have shown that cytokine response of CD4+ T lymphocytes and CD8+ T lymphocytes to CMV antigen, as well as characteristics of CD8+ T-lymphocyte profiles, differs between patients receiving HAART who have prolonged inactivity of CMV retinitis and those with active infections [59].

Serial ophthalmic examinations and patient education regarding symptoms of CMV retinitis are additional components of effective screening programs. Because patients who are "at risk" may develop CMV and suffer substantial visual impairment within a 6-month time frame, it is critical to educate at-risk individuals about the symptoms of CMV retinitis and necessity of timely follow-up. With an increasing percentage of asymptomatic patients in the HAART era, the need for rigorous screening programs is growing, as even small peripheral lesions can progress quickly without treatment and result in visual disturbance. Because CMV retinitis occurs in immunocompromised individuals, treatment of underlying disease is the most important prevention of retinitis. Untreated retinitis will progress to blindness from retinal necrosis, optic nerve involvement, or retinal detachment. It is also important to note that retinitis can relapse despite ongoing treatment. Reinduction, a change in medication, combination drug therapy, or an ocular implant are alternatives for management.

Acquired Immunodeficiency Syndrome (AIDS)

The first era in the study of ocular HIV was a short period of rapid discovery, in which the spectrum of ophthalmic disorders associated with AIDS was identified. Most of these disorders had been identified prior to the epidemic; however, they were quite rare before the rise of HIV and AIDS. Examples of this phenomenon include the increased prevalence of Kaposi sarcoma, progressive outer retinal necrosis (PORN), and choroidal pneumocystosis. Kaposi sarcoma, for example, is associated with infection of human herpes virus 8 and has become the most common AIDS-associated eyelid and conjunctival tumor [60]. PORN is a unique variant of herpetic retinitis only seen in immunocompromised patients (Fig. 8.7a, b) [61].

HIV

HIV-1 is a lentivirus. As a retrovirus, it has only RNA in its genome and relies on reverse transcriptase for its replication. HIV-1 was initially discovered and termed LAV (lymphotropic adenovirus). Relative to HIV-2, which has been identified primarily in western Africa, HIV-1 is more virulent, is more infective, and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 compared to

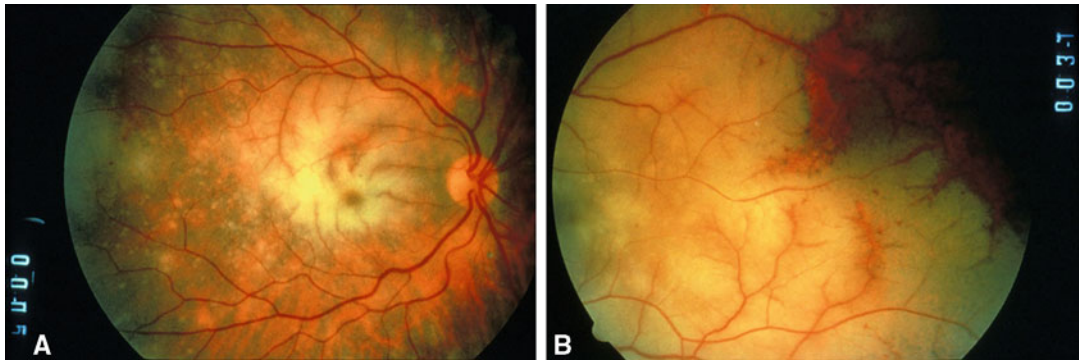

Fig. 8.7 Progressive outer retinal necrosis occurs in a severely immunosuppressed patient is notable for sparing of the inner retinal circulation and lack of associated vitritis (**a**). Typical perivascular clearing in PORN (**b**)

HIV-1 implies that fewer of those exposed to HIV-2 will be infected per exposure. HIV has predilection for infecting CD4+ T lymphocytes, a cell type that is crucial for proper immune response. As HIV infection propagates, the CD4+ T cells lyse and the host experiences a severe immunosuppression.

Epidemiology

As of 2007, the prevalence of HIV has been documented at over one million people in the United States and 33 million people worldwide [62]. In 2005 alone, there were more than 40,000 new cases of AIDS in the United States reported to the CDC. The demographics of the AIDS epidemic have changed in the United States over the past 25 years. HIV is predominantly spread through sexual transmission. Homosexual activity was responsible for most transmission until the mid-1990s, but now, heterosexual activity accounts for the major route of transmission in developed countries. Intravenous drug abuse is another common route of disease transmission. Women now account for one quarter of HIV infections. Transmission from mother to child may occur prenatally, during parturition, or postnatally during breast feeding. Professional healthcare workers are also at risk for hematogenous transmission via needlestick injury. Seroconversion for this incident is about 0.3%, which is nearly 100 times less than that for hepatitis C or hepatitis B [63].

Diagnosis

HIV infection can be detected by the presence of antibody to viral antigens by ELISA, 2–8 weeks following inoculation, and diagnosis is confirmed by Western blot for gag, pol, and env proteins. Immunoassays for HIV detection perform better than other serological assays, and most short comings are related to user error [64]. ELISA tests are 100% sensitive, although there are rare false-positive results. The HIV virus has been identified in the cornea, vitreous, and retina.

HIV Disease

There is an acute retroviral syndrome which occurs 1–6 weeks following inoculation. This consists of fever, rash, myalgias, headache, and/or gastrointestinal symptoms. The CD4+ count is reduced and, unless treatment is initiated, the count continues to reduce by approximately 75 cells/uL/year [63]. Individuals with HIV loads greater than 30,000 copies/mL have an 80% likelihood of developing AIDS within 6 years, whereas individuals with 500 copies/mL have a 5% likelihood. Typically, AIDS develops 10 years following initial HIV exposure and infection and generally occurs when the CD4+ count falls below 200 cells/uL. It is at this point that opportunistic infections may occur, most notably Pneumocystis carinii, Cryptococcus neoformans, and Cytomegalovirus. Susceptibility to the

various opportunistic infections occurs at different CD4+ count thresholds, with *P. carinii* occurrence below 200 cells/uL and CMV occurrence below 50 cells/uL.

HIV Therapy

The rate of the decline in CD4+ count and rise of HIV viral load are two important factors in determining treatment plans. There are differing opinions on the process, but one general rule focuses on treatment initiation for all patients in whom CD4+ count falls below 350 cells/uL. When therapy is started, a HAART regimen is used, consisting of one protease inhibitor and two nucleoside inhibitors. Lack of compliance on the part of the patient can lead to failure of therapy secondary to rapid development of resistance.

Ocular Manifestations of HIV

While HIV may be isolated from every layer of the eye, clinically relevant ocular manifestations are limited to the posterior segment. HIV-associated microvasculopathy, for example, causes retinal nerve fiber layer infarcts observed as cotton-wool spots (Fig. 8.8). The incidence of these superficial white fluffy infarcts increases with the degree of immunosuppression, secondary to an underlying microvasculopathy likely associated with increasing immune complex formation [65].

Progressive Outer Retinal Necrosis

Initially described in immunocompromised patients, progressive outer retinal necrosis (PORN) is a rapidly progressive syndrome. Although both are caused by herpesviruses, PORN may be differentiated from ARN based on its distinctive clinical appearance with the absence of vitreous inflammation. Secondary to its high incidence of retinal detachment as well as affinity for bilateral involvement, PORN carries a very poor prognosis.

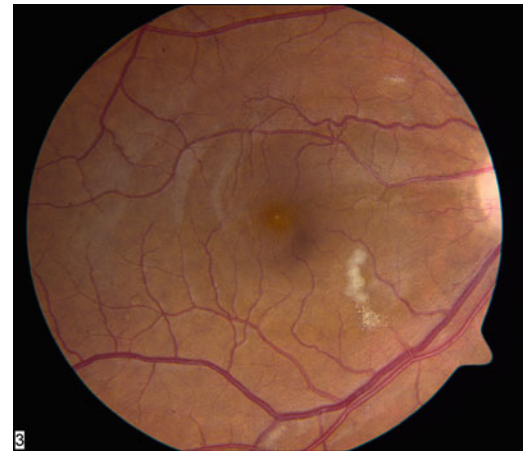

Fig. 8.8 Cotton-wool spots in HIV retinopathy

Diagnosis

PORN syndrome was originally described in two HIV patients and is thought to be a variant of ARN in a immunocompromised host [66]. Margolis described a similar syndrome in VZV patients with AIDS and also noted a rapidly progressing relentless necrotizing retinitis [67]. While PORN commonly occurs in association with cutaneous zoster infection or zoster ophthalmicus, it may occur in the absence of these disease entities as well. Macular lesions were noted in 21 of the 65 eyes in another study, with multifocal deep retinal lesions typically found in the periphery [68]. Most patients were unilaterally affected by these macular lesions, but 25% demonstrated peripheral disruption in the other eye. In addition, asymptomatic disease was noted in 11% of the 65 eyes. The lesions rapidly progress to confluence, and although the syndrome is described as involving the outer retina, pathologic examination suggests that the disease can lead to significant destruction of the inner retina [66].

The differential diagnosis for PORN is similar to that of ARN, but it is important to differentiate between the two infections. Unlike typical ARN, there is little or no vasculitis, less vitritis, and early posterior pole involvement and bilateral disease is more common. Furthermore, the retinal lesions in PORN involve in the deep retinal tissue, whereas full-thickness involvement predominates

in ARN. The lesions are nearly uncontrollable in PORN and often progress to confluence.

Etiology

Varicella-zoster virus and herpes simplex virus have been implicated in the cause of PORN. Most patients with PORN have impaired immune status [69]. In one study, the median CD4+ T-cell count was 21 cells/uL [66].

Therapy

PORN is associated with an extremely poor prognosis despite vigorous treatment protocols. As in ARN, combinations of intravitreal and intravenous ganciclovir and foscarnet may be used. Unlike ARN, though, these medications appear to be more effective than intravenous acyclovir.

Retinitis/Choroiditis Following Other Systemic Illnesses

Measles: Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a subacute encephalopathy affecting unvaccinated children and young adolescents arising approximately 6–8 years following primary infection. It infrequently affects adults and pregnant women. SSPE is caused by an aberrant measles virus, known as the SSPE virus, which differs from wild-type measles viruses by several mutations in the matrix gene. The characteristic clinical manifestations of SSPE include visual impairment, behavioral changes, cognitive decline, myoclonic jerks progressing to spastic paresis, seizures, bilateral pyramidal signs, dementia, coma, and death [70].

Visual impairment occurs in up to 50% of patients secondary to maculopathy with focal retinitis and RPE changes, involvement of the optic nerve with papilledema or disc pallor, or visual cortex damage leading to cortical blindness [71]. Additional ocular manifestations include nystagmus, gaze palsies, and ptosis. These symptoms may precede the neurologic manifestations by a several weeks up to 2 years [72–74]. It has been suggested that measles virus–acquired virulent neurotropism develops in the retina before involvement of the central nervous system [75]. Ultrastructural examination of the retina in an affected patient demonstrated numerous filamentous microtubular intranuclear viral inclusions consistent with the measles virus in the retinal nuclear layers [76]. While diagnosis is made based on this unique constellation of clinical manifestations, it is important to consider the diagnosis of SSPE in cases with acute vision loss resulting from cortical blindness even when other classical findings of SSPE are absent [77]. Further diagnostic clues can be given by periodic electroencephalographic discharges, identification of raised anti-measles IgG antibody in the serum or cerebrospinal fluid, or by the observation of panencephalitis with histopathology as described above on brain biopsy.

At present, there is no effective treatment for SSPE. Oral isoprinosine and intrathecal or intraventricular alpha-interferon may prolong survival to some extent. Immunization against measles is currently the most effective strategy against SSPE.

Rubella

Rubella infection is caused by a highly contagious virus of the Togaviridae family. It is a single-stranded RNA virus that is surrounded by a lipid envelope. German measles, or acquired infection, is associated with mild systemic symptoms in adults and children. The most frequent ocular finding is conjunctivitis, although keratitis and retinitis may infrequently occur [78]. The retinitis resolves spontaneously with return to normal vision.

Unlike acquired infection, congenital rubella is a devastating syndrome. It occurs when virus crosses the placenta during maternal viremia approximately 10–12 days following primary infection [79]. The frequency and severity of congenital infection is related to gestational age at the onset of maternal infection. The risk is

greatest, reported at 81–100%, when maternal infection occurs during the first trimester or in the final month of pregnancy [80].

As a result of immunization programs instituted in the United States in 1969, congenital rubella is rare. Five to twenty-five percent of women of child-bearing age in the United States lack rubella-specific antibodies and are susceptible to infection [80]. Congenital rubella syndrome presents with a chronic infection beginning in the neonatal period and continuing through infancy. The most common systemic manifestation of congenital rubella syndrome is hearing loss [81]. Cardiac malformations have been reported in 67–69% of infected patients [82]. Systemic manifestations include thrombocytopenia, hepatosplenomegaly, low birth weight, failure to thrive, psychomotor and mental retardation, and microcephaly [83].

Ocular manifestations occur in 30–78% of infants and children, most commonly chorioretinitis (25–50%), followed by cataract (15%) and glaucoma (10%) [79, 82]. Chorioretinitis leads to a classic rubella retinopathy consisting of salt-and-pepper pigmentary changes with a mottled, blotchy, irregular pigmentation, usually deep to normal retinal vasculature. The foveal reflex is usually absent, and the optic nerve may be pale. The condition may occur focally in only one quadrant or unilaterally and may be stationary or progressive after birth [84]. Despite these abnormalities, vision is usually normal or minimally affected by rubella retinopathy. However, rubella proliferation at the level of the RPE leads to RPE atrophy and rarely subsequent choroidal neovascular membrane formation, resulting in a significant decline in visual acuity [85].

Because maternal infection is often subclinical, the diagnosis of congenital rubella is suspected based on the observation of associated congenital anomalies. Diagnosis is confirmed by a fourfold increase in rubella-specific IgG in paired sera 2 weeks apart or the new appearance of rubella-specific IgM in the neonate [86].

The most effective treatment is prevention of maternal rubella infection with immunization programs. There is no specific antiviral therapy of either acquired or congenital rubella infection, and treatment is supportive. While rubella retinopathy does not require treatment, the rare complication of choroidal neovascularization may require photocoagulation, photodynamic therapy, or anti-angiogenic treatment. Rubella retinitis with acquired infection or postvaccination optic neuritis may respond to systemic steroids.

West Nile Virus

West Nile virus (WNV) was first isolated in 1937 in the West Nile district of Uganda. Later, in 1957, it was recognized as a cause of meningoencephalitis during an outbreak in an Israeli nursing home. Since then, several outbreaks have been reported worldwide, including a Canadian epidemic which extended to five provinces [87–91]. The first reported human WNV infection in the United States was in 1999 during an outbreak of meningoencephalitis in New York City [92]. It has subsequently spread throughout the country.

WNV is transmitted to humans through the bite of an infected Culex mosquito. The mosquito acquires the virus through feeding on infected birds, which typically are the natural host of the virus and have a high-level viremia. Crows and blue jays of the family Corvidae are particularly susceptible to infections with WNV. Corresponding to the mosquito season, the majority of human infections occur in August and September [93].

There are three clinical categories of systemic WNV infection: (1) asymptomatic, (2) West Nile fever, and (3) West Nile meningoencephalitis. Most individuals remain asymptomatic with only 20% of patients developing symptoms and only 1 in 150 infected patients developing meningoencephalitis [94]. Clinical features of WNV fever include sudden onset of high-grade fever, headache, myalgias, gastrointestinal symptoms, pharyngitis, arthralgias, fatigue, and maculopapular rash on the chest, back, and lower extremities. Following an incubation period ranging between 2 and 14 days, the acute illness is self-limiting, typically lasting less than a week [95]. Presenting

ocular complaints include ocular pain, photophobia, conjunctival injection, and blurred vision. Garg and Jampol have identified five categories of intraocular manifestations of WNV infection [94]: (1) multifocal chorioretinitis with lesions either widely scattered or in linear arrays, (2) uveitis without focal lesions, (3) occlusive retinal vasculitis, (4) congenital chorioretinal scarring secondary to intrauterine transmission, and (5) optic neuritis.

WNV chorioretinitis most commonly presents with associated uveitis, and although most of the patients have uveitis in association with chorioretinitis, Kuchtey et al. described a patient with vitritis and iritis in the absence of chorioretinitis [96]. Acuity on presentation ranges from 20/25 to counting fingers vision and most cases demonstrate bilateral involvement. The chorioretinal lesions during the active phase are deep, flat, and whitish yellow in color, ranging from 200 to 1,000 μm in diameter. The lesions soon become pigmented, sometimes as early as 2 weeks after initial presentation. Fluorescein angiography demonstrates hyperfluorescent lesions which display late leakage when active and late staining when inactive or quiescent. Usually, inflammation resolves and vision returns to near baseline within several months. However, there have been rare reports of development of choroidal neovascular membrane underlying a WNV chorioretinal scar [97–100].

Three cases of bilateral optic neuritis have been reported in association with WNV meningoencephalitis [70]. However, although all three patients had lumbar punctures performed, opening pressures were not reported. Thus, increased intracranial pressure may have been responsible for the observed bilateral optic nerve swelling associated with papilledema [101–103].

There is currently no proven treatment for WNV infection. It usually follows a self-limiting disease course. However, concurrent diabetes mellitus has been linked to WNV-associated death. When needed, therapy is supportive, with hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections. The mainstay of WNV infection control is prevention. Public health measures to reduce the number of mosquitoes include draining water from breeding sites and use of mosquito larvicides or methoprene, a mosquito-maturation inhibitor. Antiviral agents such as ribavirin and interferon-2B, although effective in vitro, were found clinically ineffective [104]. Vaccination, a long-term solution, is still in the research phase [105].

Other Systemic Illnesses

There are several additional viral infections suspected to cause choroiditis. For example, the influenza virus has been implicated in the etiology of acute posterior multifocal placoid pigment epitheliopathy (APMPPE). This disorder is usually diagnosed in young patients following a prodromal viral illness. Azar and colleagues demonstrated adenoviral infection in one patient [106]. The average age of onset is 20–50 years and presents with rapid visual loss in one or both eyes. The characteristic findings include the presence of creamy, yellow-white lesions at the level of the RPE with sparing of the retina. The lesions are circumscribed and discreet, frequently coalescing to large confluent areas that typically fade within weeks to become hypo-/hyperpigmented. Gass initially described this entity in 1968 [107]. Visual acuity is better than 20/30 in >90% of affected eyes. The diagnosis is confirmed by the characteristic angiographic finding of early blockage and late staining which strongly suggests that the choriocapillaris is the primary site of infection.

Controversies and Perspectives

What Is the Best Method of Providing Rapid and Specific Treatment for Infectious Retinitis?

PCR studies should be obtained from vitreous aspirates when a patient presents with a rapidly progressive necrotizing retinitis, but treatment should not await laboratory confirmation. Traditional treatment for ARN consists of induction therapy with

intravenous acyclovir for 7–10 days followed by oral antiviral medications for approximately 3 months. Newer intravitreal and oral antiviral regimens have emerged over the past decade, but a recent analysis of current treatment practices at four tertiary eye care centers identified no single treatment strategy as the standard of care for ARN. Fortunately, the variation in initial antiviral strategy did not affect final outcome, suggesting that the physician may use his or her own judgment on the basis of available resources.

The same study also revealed variation in long-term oral antiviral treatment strategies. Treatment duration varied greatly, ranging from 1.5 to 75.7 months, and usually consisted of valacyclovir. Unfortunately, the ideal duration and relative efficacy of these long-term oral antiviral regimens remain unclear, and the visual outcome was generally poor [43].

When Should Patients' CMV Antiviral Treatment Be Discontinued After Onset of Immune Recovery Uveitis?

Immune recovery allows eventual discontinuation of specific anti-CMV therapy without reactivation of infection. A decision to discontinue anti-CMV drugs usually is based on several factors: a sustained rise in CD4+ T-lymphocyte count, a drop in HIV viral load, duration of HAART that is sufficient to effect immune recovery, and inactivity of CMV retinitis lesions. The Centers for Disease Control (CDC) has stated that patients receiving HAART should have CD4+ T-lymphocyte counts of more than 100–150 cells/μL for at least 3–6 months prior to discontinuation of anti-CMV therapy [53].

What Is the Best Surgical Approach for Repair of Secondary Retinal Detachment?

The basic principle of viral-associated retinal detachment repair is to elevate the posterior hyaloid and remove vitreous as completely as possible. It is often not prudent to be aggressive with the hyaloid in areas of necrosis as this induces more retinal tears. In these areas, a close shave of vitreous is effective. Laser is applied in confluent burns in the area of necrosis with overlap onto healthy retina. A scleral buckle may or not be necessary and is used to protect healthy retina from tearing. A buckle is often not helpful when retinal necrosis extends too posteriorly to be supported, and therefore, the buckle can help protect uninvolved retina. Patients can be left phakic or pseudophakic. Finally, the choice of vitreous tamponade can either be silicone oil or C3F8. The previous use of silicone only reflected the fact that most patients with CMV secondary to HIV perished within 6 months of CMV detachment, but HAART has dramatically changed this finding. C3F8 works equally as well as silicone, even in cases with multiple necrotic holes. Finally, a Vitrasert® is a nice adjunct to herpes-related detachment and can be used with gas or silicone oil.

What Causes Reactivation of HSV in Retinal Tissue?

Although primary infection with HSV can involve ocular and adnexal sites and can manifest as blepharitis, conjunctivitis, or corneal epithelial keratitis, it is not known precisely why secondary ocular HSV retinal infection occurs after latency is established within the central nervous system. The latent infection occurs in the trigeminal ganglia and can remain latent during the lifetime of the host. One observation is that during latency, there is abundant transcription at the region encoding the latency-associated transcript, which may play significant roles in the maintenance of latency as well as neuronal reactivation. Many host and viral factors have been implicated in HSV reactivation from latency. Additionally, HSV DNA is shed into tears and saliva of most adults, but in most cases, this does not result in lesions. Finally, recurrent disease occurs as HSV is carried by anterograde transport to the original site of infection, or any other site innervated by the latently infected ganglia and can reinfect the ocular tissues [108].

Focal Points

Viral infections of the retina and choroid are rare but important causes of visual loss. The nearly uniform involvement of choroidal and retinal vessels demonstrates the likely hematogenous spread of systemic viral infection to the eye. The retina provides a good substrate for viral infection because of its relatively immunoprivileged status and its connection to the central nervous system where latent virus can become activated. The principles of management of viral-associated retinitis are:

1. Prompt diagnosis
2. Immediate intraocular and then systemic (intravenous or oral) treatment
3. Close surveillance at weekly intervals early to see treatment effect in at least 2 weeks followed by monthly intervals late for progression to retinal detachment
4. Systemic evaluation for presence of immunosuppression
5. Close inspection of the companion eye

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Retinal and Choroidal Manifestations of Fungal Diseases

9

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Abstract

An increased number of fungal infections of the eye have been reported in the past few decades, in part because of increased clinical awareness and improved laboratory techniques. The increase reflects more significantly the widespread use of antibiotics, immunosuppression, chemotherapy, and ocular prosthetic devices. Despite their ubiquitous nature, only a limited number of fungal species produce infections of the eye, and an even smaller number cause fungal retinitis or endophthalmitis. The major causes of fungal retinitis are *Candida* species, *Aspergillus* species, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Sporothrix schenckii*.

Keywords

Amphotericin B • Antifungal agents • *Aspergillus* • *Blastomyces dermatitidis* • *Candida* • Candidemia • Chorioretinitis • *Coccidioides immitis* • *Cryptococcus neoformans* • Endophthalmitis • Fluconazole • Fungal infection • *Histoplasma capsulatum* • *Sporothrix schenckii* • Voriconazole

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Introduction

Fungi are wide in nature and constitute a prominent and diverse group of microorganisms; however, a relatively small number of fungal species cause serious primary and opportunistic human diseases, and an even smaller number cause fungal retinitis or endophthalmitis. Fungal infections can be endogenous or exogenous. Endogenous fungal infections of the choroid, retina, and vitreous cavity are a complication of disseminated fungal diseases, and the fungi may infect the eye through the bloodstream [1]. On reaching the eye, fungi usually lodge in the choroid or retina, producing choroiditis, retinitis, or chorioretinitis. When this initial focus of infection extends into the vitreous to produce inflammation, which may involve the entire internal structure of the eye, endophthalmitis results. Ocular involvement occurs in 10–29% of patients with fungemia. Risk factors include systemic antibiotics and corticosteroid therapy, bacterial sepsis, prolonged hyperalimentation, recent abdominal surgery, alcoholism, hemodialysis, intravenous drug abuse, immunosuppression (burned patients; acquired immunodeficiency syndrome [AIDS]; patients with lymphoma, leukemia, or cancer; patients on chemotherapy), and diabetes. Exogenous fungal infections of the eye are a complication of penetrating ocular trauma and intraocular surgery; fungi may infect the eye by extension from periocular and orbital tissues [2].

Fungi can be divided into yeasts and molds. They are eukaryotic organisms, differing from bacteria in ribosome structure, nuclear structure, cell wall composition, and size. They lack chlorophyll, are nonmotile (except for certain spore forms), and may grow as single cells (yeast) or as long, branched, filamentous structures (mycelia). Virtually all fungi reproduce by forming spores through mitosis.

The most common organisms that produce fungal infections are the *Candida* species, followed by the *Aspergillus* species, and *Cryptococcus neoformans*. Other much less commonly encountered fungi include *Sporothrix schenckii*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* (Fig. 9.1). Table 9.1 depicts characteristics of fungal infections.

Causative Organisms

Candidiasis

Candida species can cause devastating visual loss. Ocular candidiasis frequently follows an indolent course, progressing from chorioretinitis to vitritis and endophthalmitis (Fig. 9.2). *Candida* species is the fourth most common cause (9%) of nosocomial infections and is even more prevalent (10%) in the intensive care unit [3].

The incidence of nosocomial candidemia has increased approximately tenfold over the last 20 years [4]. In contrast, the incidence of ocular candidiasis has been decreasing among inpatients with candidemia. Historically, the rate of ocular candidiasis has been reported between 9% and 45%. More recent estimates, however, have shown an incidence of less than 2% [5]. It has been suggested that this trend is related to earlier identification and treatment of candidemia.

Candida species are part of the normal flora of the respiratory, gastrointestinal, and female genital tracts. They constitute commensal yeasts of usually low virulence. However, *Candida* species may become pathogenic and can cause serious disease in immunocompromised patients.

Candida albicans is the most frequently isolated fungus from ocular infection [6]. Other less common *Candida* species, including *C. parapsilosis* (Fig. 9.3) and *C. glabrata*, may also produce ocular infections [7]. One theory for the greater tendency of *C. albicans* to produce chorioretinitis compared with other *Candida* species is because of the differences in the patterns of phospholipase and protease production [8]. Another theory of the different degrees of *Candida* pathogenicity can be because *C. albicans* rapidly produces germ tubes in serum, whereas other *Candida* species do not. It is possible that the

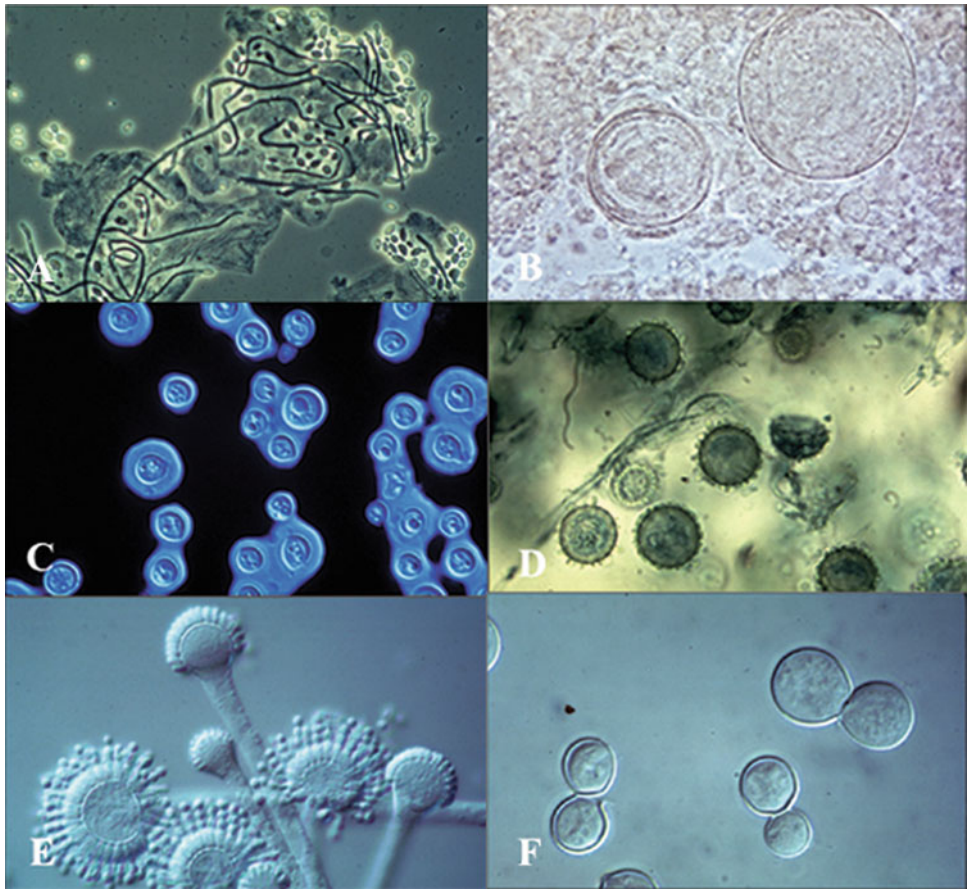

Fig. 9.1 Differential interference contrast microscopy. (**a**) *Candida albicans* (yeast cells and pseudohyphae; KOH preparation). (**b**) *Coccidioides immitis* (spherules; KOH preparation). (**c**) *Cryptococcus neoformans* (the round yeast cells surrounded by polysaccharide capsules; India ink). (**d**) *Histoplasma capsulatum* (rough-walled macroconidia; Sabouraud glucose agar). (**e**) *Aspergillus* (stages in development of fruiting bodies). (**f**) *Blastomyces dermatitidis* (broad-based budding and thickened cell walls, and globose shape). (Modified and reprinted with permission from http://www.doctorfungus.org)

germ tubes of *C. albicans* lodge in the choriocapillaris more easily and frequently than those of other species.

Risk Factors

Factors affecting the increase in fungal disease include [9]:

- Increase in the number of immunocompromised individuals
- Intravenous drug abuse
- Use of broad-spectrum antibiotics
- Immunosuppressive agents
- Intravenous hyperalimentation
- Indwelling intravenous pressure-monitoring devices
- Organ transplantation
- Implantation of prosthetic cardiac valves
- Recent major surgery, especially if involving the gastrointestinal system
- Low birth weight and normal neonates undergoing prolonged hospitalization
- Induced abortion

Pathogenesis

Microscopically, *Candida* can be found in the inner choroid and later extend into the subretinal space and retina. *Candida* may produce an acute necrotizing process and a chronic granulomatous reaction by histiocytes and round cells. Rupture of the inner limiting membrane may occur with

Table 9.1 Characteristics of fungal infections (postsurgical and endogenous)[a]

Organism	Risk factor	Ocular features
Candida sp.	IV drug use Chronic IV therapy Surgery	Yellow-white chorioretinal lesions, vitreous fluff balls
Aspergillus sp.	IV drug use Immunosuppression Surgery	Yellow-white chorioretinal lesions, vitreous fluff balls
Blastomyces dermatitidis	Systemic blastomycosis	Panuveitis
Cryptococcus neoformans	Immunocompromised Lymphoma	Yellow-white chorioretinal lesions, vitreous fluff balls
Coccidioides immitis	Southwest United States	Punched-out choroidal lesions, yellow chorioretinal lesion

[a]Modified from Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis; Fundamentals and Clinical Practice. 2nd ed. St Louis: Mosby Year Book; 1996

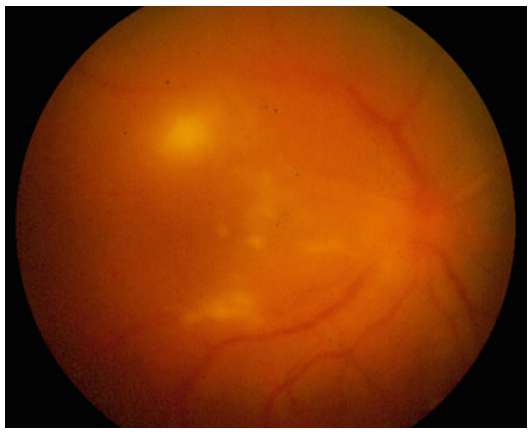

Fig. 9.2 Fundus photography of *Candida* endophthalmitis infection with multifocal chorioretinitis and vitreous involvement

vitreous invasion. Budding yeast forms (pseudohyphae) may be found (Fig. 9.4). Abscesses in the retina, choroid, and vitreous and extensive tissue necrosis characterize late stages of infection (Fig. 9.5) [10].

Clinical Features

Common presenting symptoms include a subacute history of blurred vision with low-grade pain, photophobia, and injection [11]. Early extramacular or peripheral fundus lesions (Fig. 9.6) produce little or no visual symptoms. With macular lesions or significant vitreous (Fig. 9.7) involvement, most patients become symptomatic, unless they are too ill to respond [7]. Progression of the disease leads to visual loss, pain, and redness of one or both eyes.

In candidemia, new visual symptoms—typically floaters and blurred vision—are also correlated with ocular involvement. Donahue and colleagues report normal fundi in 92% of patients with candidemia capable of denying symptoms. These data suggest that the lack of symptoms carries a strong negative predictive value [12].

Signs may include single or multifocal, yellow-white, fluffy retinal and choroidal lesions from one to several disk diameters in size. These lesions can be unilateral or bilateral, isolated or confluent, and may exist in a satellite pattern. Lesions may increase in size and spread into the vitreous, appearing as "cotton balls" (Fig. 9.8). Vitreous opacities are typically yellow-white and may be connected by strands, producing a "string of pearls" appearance. Vitritis may be so severe as to obscure the view of the fundus, which makes clinical diagnosis difficult. Other signs include lens abscess (Fig. 9.9), vitreous abscesses (Fig. 9.10), intraretinal hemorrhages (Fig. 9.11), and white-centered hemorrhages (Roth's spots) [1, 13]. Vitreoretinal membrane formation and contraction combined with focal retinal necrosis and scarring are the major causes of permanent visual loss [14].

Diagnosis

The diagnosis of *Candida* retinitis should be considered in patients who present with vitritis accompanied by a chorioretinal focus in the clinical setting of a recent or current debilitating illness or other risk factor for candida infection. Clinical suspicion plays an important role in identifying patients who may have *Candida* endophthalmitis [15]. Isolation of *Candida*

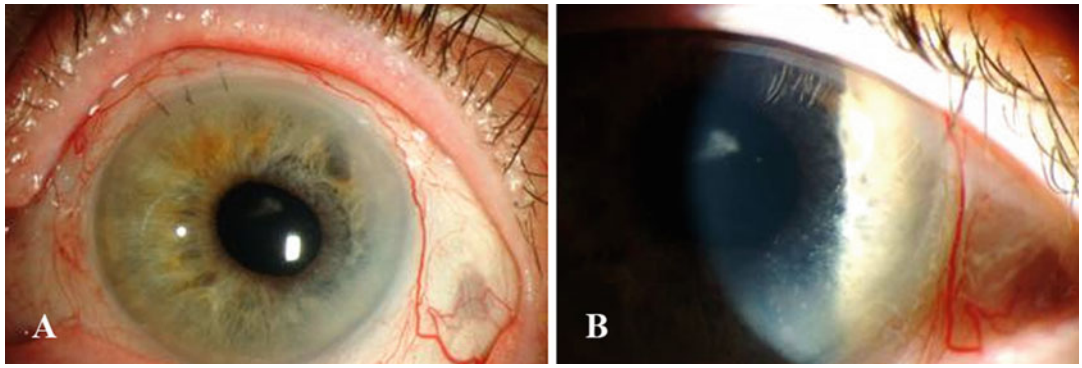

Fig. 9.3 (**a**) Photography of the anterior segment after uneventful cataract surgery showing persistent corneal infiltrate and inflammation; the culture was positive for *C. parapsilosis*. (**b**) Higher magnification of corneal infiltrate and retrokeratic precipitates

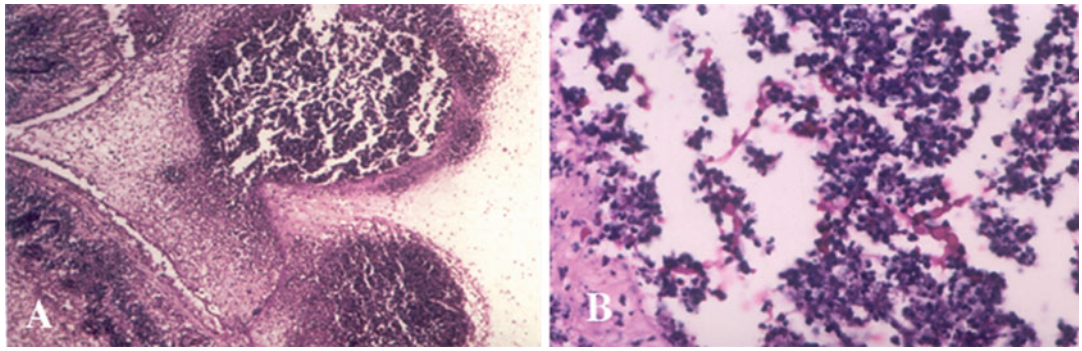

Fig. 9.4 Light microscopy. (**a**) Granuloma containing *Candida albicans*. (**b**) Higher magnification reveals *Candida* organisms. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier; 2006; 366–774)

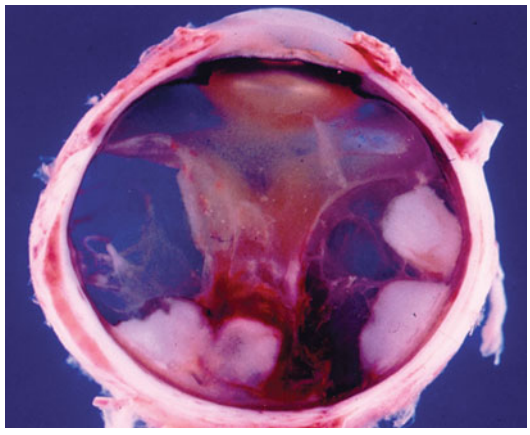

Fig. 9.5 Gross anatomy shows multifocal candidal retina abscess with "cotton ball" vitreous opacities. (Reprinted and modified with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier; 2006; 366–774)

species directly from the eye confirms the diagnosis of ocular candidiasis. However, the fungus may not always be detected, even clinically, in certain cases or in cases where the fungus has grown from another site. Fungal cultures can be positive in 44–70% of patients diagnosed clinically. Vitrectomy samples are more sensitive for fungal cultures than vitreous needle biopsies [16]. Anterior chamber aspirate is a poor diagnostic technique; however, anterior chamber taps may prove useful for detecting local production of anti-*Candida* antibodies [17].

The laboratory should be alerted when a vitrectomy specimen is expected so as to ensure that the specimen is handled appropriately and that culture media for fungi are used. *Candida* species can be cultured directly on blood agar, but room-temperature Sabouraud agar without cyclohexamide is recommended when this organism is

clinically suspected. A pasty white colony appears in the culture media (Fig. 9.12). In addition, direct examination of fungi with Giemsa, Gomori methenamine silver (GMS), and periodic acid Schiff (PAS) stains should be obtained.

Culture has been used as the gold standard in the diagnosis of fungal endophthalmitis, but its true sensitivity is not known. Also, it is time consuming. The main reasons for the lack of sensitivity of conventional methods are the small number of organisms in the eye, the small sample size of the intraocular specimen collected, and a greater tendency for the organisms to be loculated, thus being absent in the collected material. Hence, the collection of a small amount of vitreous by a tap is likely to be subject to greater sampling error in fungal cases. All these factors may contribute to a significant number of culture-negative specimens from cases of fungal endophthalmitis.

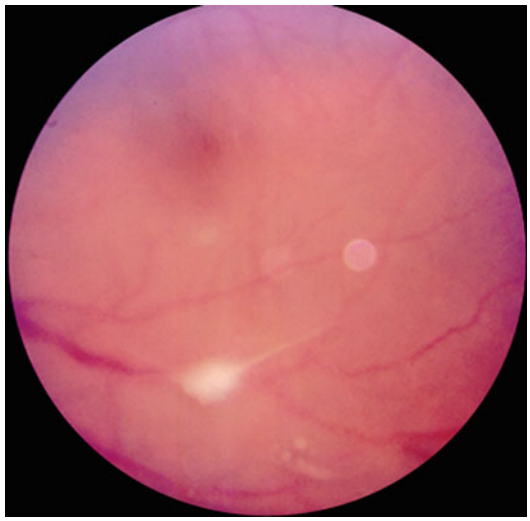

Fig. 9.6 *Candida* chorioretinitis lesion in the inferotemporal arcade. (Reprinted and modified with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal Infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier; 2006; 366–774)

A useful, recently introduced diagnostic tool for fungal endophthalmitis is the polymerase chain reaction (PCR). The main advantages of PCR over conventional fungal cultures are the higher sensitivity and the rapid results obtained with PCR. Although PCR does not replace conventional mycologic methods, it helps to make an early differentiation between bacterial endophthalmitis and fungal endophthalmitis. PCR has been used successfully to identify *Candida* species from an intraocular sample. The major drawback of fungal culture is the prolonged period of time (3–4 days and up to 3 weeks) required for the growth of fungus, whereas the results of PCR are available in less than 24 h [18].

Fluorescein angiography shows hyperfluorescence in the late phases from choroidal neovascularization that may develop in numerous inflammatory and infectious conditions of the posterior segment, including ocular candidiasis. Optical coherence tomography has been useful to demonstrate the development of a macular hole under a *Candida albicans* "cotton ball" (Fig. 9.13).

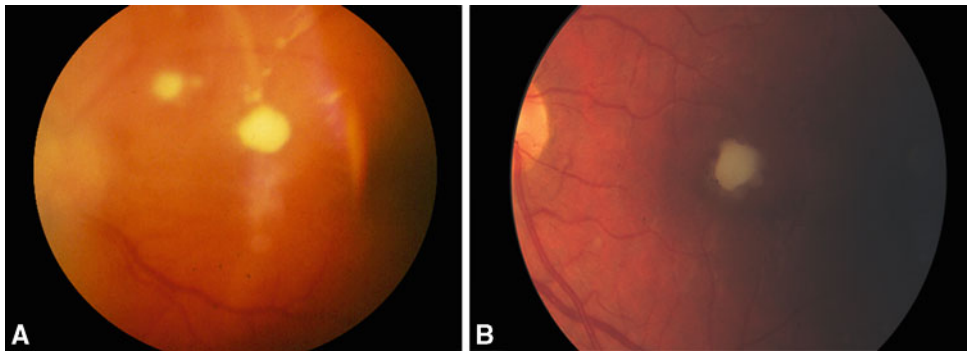

Fig. 9.7 (**a**) Fundus photography of *Candida* endophthalmitis with vitreous involvement. (**b**) *Candida* retinal abscess in the macula. (Part B: Reprinted with permission from Davis JL. Infectious chorioretinal inflammatory conditions. In: Regillo C, Brown G, Flynn HW, eds. Vitreoretinal Disease: The Essentials. New York: Thieme;1998: 393–415)

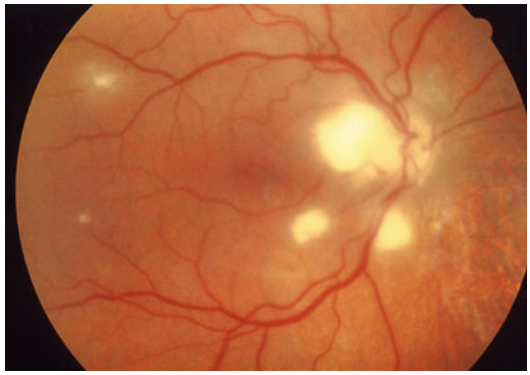

Fig. 9.8 Several large and small *Candida* chorioretinitis lesions with vitreous invasion are noted temporal to the optic nerve head in the right eye. In addition, healed cytomegalovirus retinitis is seen inferonasal to the optic nerve head in this AIDS patient. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: ®. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

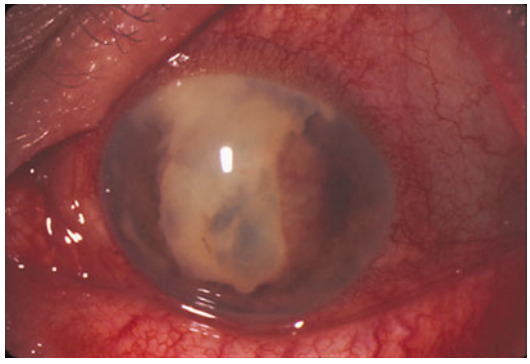

Fig. 9.9 Photography of the anterior segment showing *Candida* endophthalmitis with intralenticular lens abscess

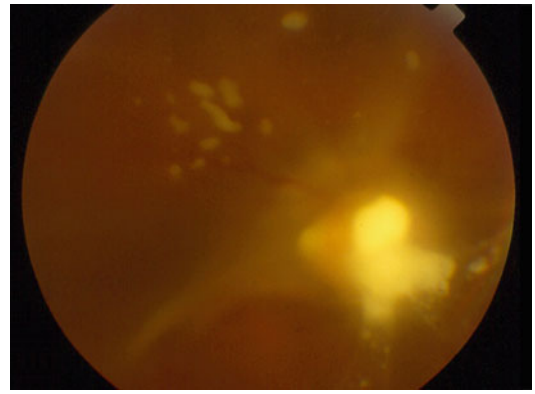

Fig. 9.10 Vitreous inflammation and snow ball in the vitreous in a patient with *Candida* endophthalmitis

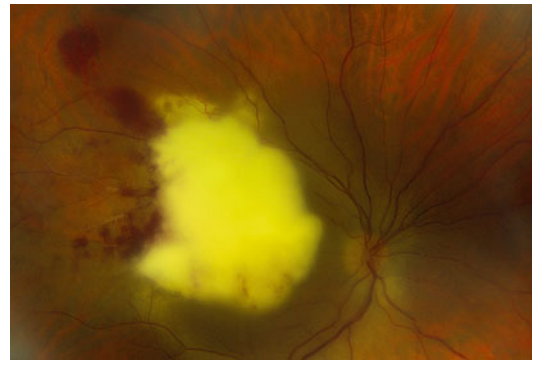

Fig. 9.11 Vasculitis, intraretinal hemorrhages, and retinochoroiditis lesion in the macula in a patient with candidiasis diagnosed as toxoplasmosis and treated with corticosteroids

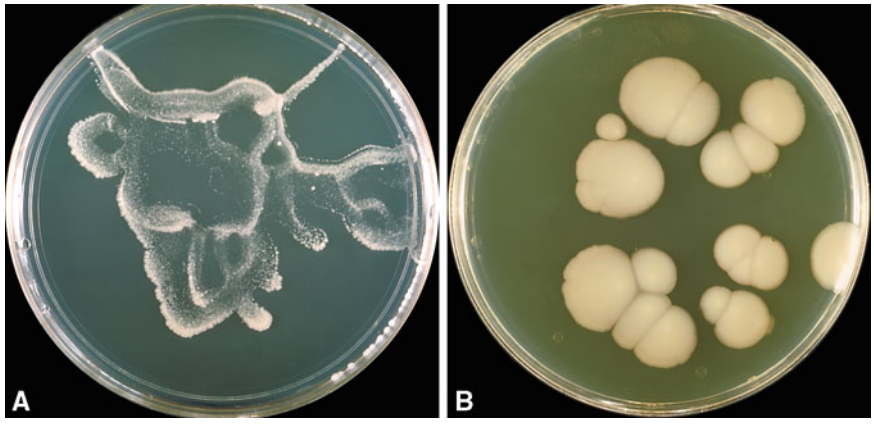

Fig. 9.12 (**a**) Plate culture of *Candida albicans*. (**b**) SABHI agar plate culture of the fungus. (Figures courtesy of the CDC/Dr. William Kaplan)

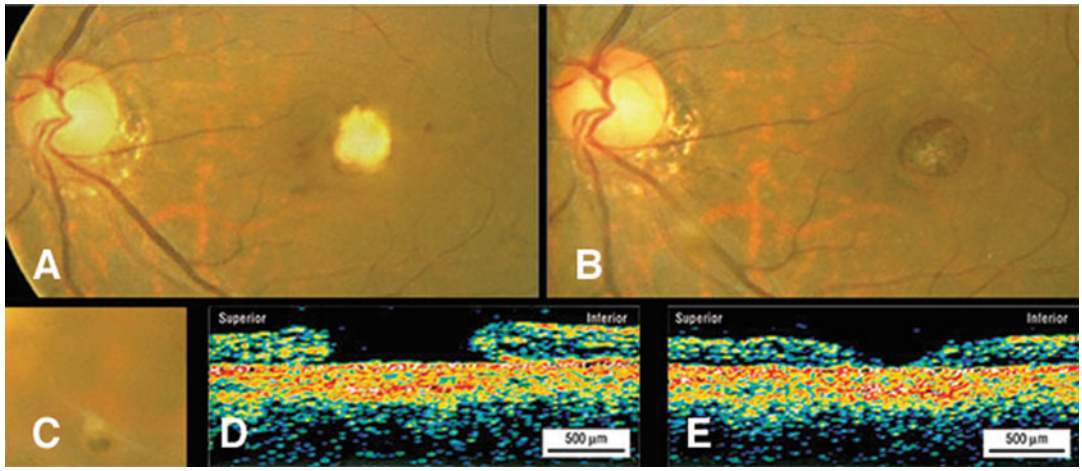

Fig. 9.13 (**a**) Fundus photograph of the left eye at the initial visit showing a focus with surrounding hemorrhage. (**b**) Fundus photograph of the left eye on the second visit showing a large macular hole that had developed at a previous site of a focus. (**c**) Fundus photograph of the left eye at the second visit showing an operculum on the posterior vitreous surface. (**d**) An optical coherence tomographic (OCT) image through the center of the macular hole, showing swollen edges on both sides, with a vertical diameter of 920 μ(mu)m. (**e**) Postoperative OCT images through the center of the macula showing flattened edges. (Modified and reprinted with permission from Kusaka S, Hayashi N, Ohji M, Ikuno Y, Gomi F, Tano Y. Macular hole secondary to fungal endophthalmitis. Arch Ophthalmol. 2003; 121:732–733)

Treatment

Therapy of ocular fungal infections represents a challenge for the ophthalmologist. The first step is to suspect the proper diagnosis. Prompt recognition and early treatment have enhanced anatomic and visual results [19]. Treatment strategies include administration of antifungal agents (systemic or intravitreal) and pars plana vitrectomy.

Amphotericin B is a polyene antibiotic with prominent antifungal activity. It works by directly bonding to ergosterol, a sterol unique to fungal cell membranes, thereby disrupting fungal cell membrane integrity and ultimate cell death [20]. The intravenous dose of amphotericin B is 0.3–1 mg/kg/day, administered in 500 ml of 5% dextrose over a period of 4–6 h. An initial test dose of 1 mg of the drug dissolved in 20 ml of 5% dextrose is given intravenously over a period of 30 min. For cases of chorioretinitis without vitreous involvement, treatment is initiated using 0.3–0.7 mg/kg/day of amphotericin B until a minimum cumulative dose of 200 mg is achieved; if no significant side effects occur such as severe hypotension or cardiac arrhythmia, therapy is continued. The total dose of amphotericin B is between 1,000 and 1,500 mg in the case of severe vitreitis or poor therapeutic response to initial treatment. Total daily dose in neonates should not exceed 0.5 mg/kg/day. Other side effects include anemia, hypotension, convulsions, anaphylaxis, phlebitis, fever, thrombocytopenia, headache, and cardiac arrhythmia [21].

The intravitreal dose of amphotericin B is 5–10 μ(mu)g [22]. To avoid retinal toxicity, amphotericin B must be injected slowly into the central vitreous, as far from the retina as possible. The rate of clearance of amphotericin B from the vitreous cavity is more rapid in vitrectomized eyes (2 days) than in nonvitrectomized eyes (11 days). Intravitreous amphotericin B is an adjunct rather than an alternative to systemic antifungal therapy.

Flucytosine is recommended combined with amphotericin B. Such combination therapy is indicated in cases with threatened macular involvement, extensive inflammatory response, or rapidly progressive disease [23]. Unlike amphotericin B, the gastrointestinal absorption of flucytosine is excellent and its vitreous penetration is good following oral administration. The selective antifungal action of flucytosine is because of its unique property of conversion to fluorouracil in fungal cells but not in host cells. The recommended daily dose of flucytosine is 50–150 mg/kg/day orally in four divided doses.

Side effects include nausea, vomiting, diarrhea, thrombocytopenia, anemia, leukopenia, hepatotoxicity, and, rarely, bowel perforation.

Fluconazole, miconazole, ketoconazole, and itraconazole are azole derivates. Intraocular penetration is highest for fluconazole and lowest for itraconazole [24]. Fluconazole has excellent oral bioavailability and a relatively long half-life (mean, 25 h) in humans, permitting once-a-day administration. Its clinical toxicity (rigors, fever, vomiting, and renal failure) is less than that of amphotericin B. With its broad-spectrum antifungal activity, fluconazole is effective in the treatment of experimental cryptococcal meningitis, systemic and ocular *Candida* infection, and systemic aspergillosis. The dose of fluconazole for treatment of fungal chorioretinitis without endophthalmitis is 200–400 mg/day in two divided doses. Several species of *Candida* other than *C. albicans*, such as *C. krusei* and *C. glabrata*, as well as *Aspergillus* and *Fusarium* species, are known to be resistant to fluconazole. In these cases, itraconazole may be used. Itraconazole has a low toxicity profile and is active against *Candida*, *Aspergillus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis* [25]. Available data suggest that none of the azole derivatives are as effective as amphotericin B. Furthermore, antagonism occurs in the anti-*Candida* effect of amphotericin B and ketoconazole when these two drugs are used in combination. The use of ketoconazole in combination with amphotericin B is not recommended because exposure of *C. albicans* to ketoconazole may make the organism resistant to amphotericin B [26].

The indications for vitrectomy in patients with fungal chorioretinitis and endophthalmitis are advanced cases with extensive vitreous involvement and poor response to systemic antifungal therapy [27].

Although vitrectomy poses some risks, it does have potential benefits, such as:

- Debulking of inflammatory and infectious material from the vitreous
- Acquisition of a larger sample for laboratory study
- Potential for concentrating the sample by centrifugation or filtration to give a better yield on culture
- An opportunity for intravitreal injection of antifungal agents
- Removal of the scaffolding for vitreoretinal traction bands and epiretinal membranes that can contribute to late-developing macular pucker and retinal detachment

Aspergillus Retinitis

Aspergillus is second in frequency to *Candida* as a cause of fungal intraocular inflammation. *Aspergillus* species exists as a saprophytic fungus common in soil and decaying organic matter. Although more than 100 species have been identified, the majority of human illnesses are caused by *Aspergillus fumigatus* and *Aspergillus niger* and, less frequently, by *Aspergillus flavus* and *Aspergillus clavatus*. Even though exposure to *Aspergillus* is universal, infection in humans is uncommon. *Aspergillus* can normally be isolated from the skin and mucous membranes including the conjunctiva. The most common mode of transmission of fungal spores to the human host is via inhalation into the pulmonary alveoli and paranasal sinuses [28]. In the debilitated patient, however, *Aspergillus* invades and disseminates and may produce lesions in the lung, brain, kidney, gastrointestinal tract, myocardium, liver, spleen, and occasionally the eyes. Reported ocular involvement includes subretinal, serous retinal detachments; choroidal, subretinal, and vitreoretinal granulomas; and abscess formation. Primary anterior segment involvement is rare. Exogenous *Aspergillus* endophthalmitis can occur following penetrating ocular wounds or ocular surgery.

Risk Factors

- Intravenous drug abuse is the most common risk factor associated with endogenous *Aspergillus* endophthalmitis (EAE). The organisms enter the bloodstream directly from contaminated drugs, needles, or syringes [29].

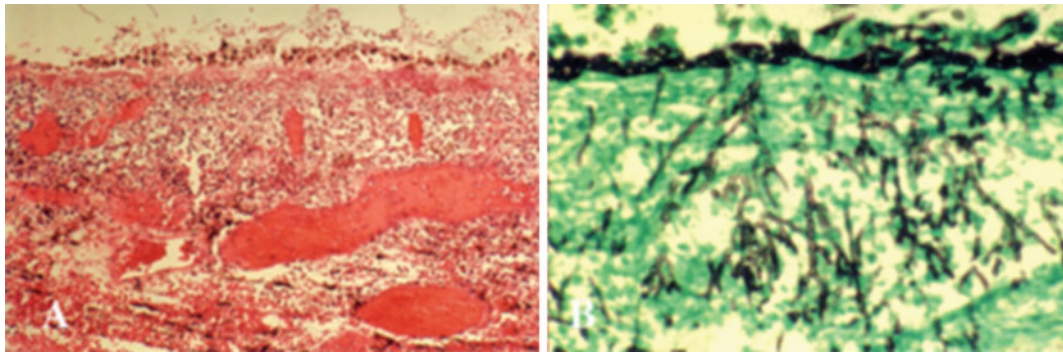

Fig. 9.14 (**a**) Histopathology of *Aspergillus* chorioretinitis. (**b**) Special stains revealed evidence of *Aspergillus*. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

- Immunosuppression and debilitating diseases, such as [30]:
  - Organ transplantation
  - Myeloproliferative disorders
  - Bronchopulmonary aspergillosis and chronic bronchitis in chi1dren
  - Bronchial carcinoid and systemic corticosteroid use
- Prematurity.
- Miliary tuberculosis.
- Alcoholism.
- Goodpasture syndrome.
- *Aspergillus* endocarditis on prosthetic or natural cardiac valves.

Pathogenesis

Aspergillus has a predilection for invasion of blood vessels producing thrombosis, hemorrhage, infarction, and suppuration (Fig. 9.14). Vascular involvement is the major cause of death. Hematogenous dissemination to the eye can occur following hyphal penetration of blood vessels with an initial choroidal lesion. The infection then spreads to the overlying retina, with progressive abscess formation. Eventually the vitreous is invaded, and finally the anterior segment becomes involved [31]. Septate dichotomously branching hyphae can be found throughout the eye. This also explains the recalcitrance of infection to intravenous amphotericin B, given the absence of patent ocular vessels for drug delivery and the poor intraocular penetration of the drug.

Clinical Features

The ocular presentation and findings are often characteristic and provide possible diagnostic clues. The patients come to the office with rapid onset of pain and severe visual loss. Photophobia, pain, and iridocyclitis may occur, although the anterior segment is often quiet. Some patients present as a marked vitreous haze, a white mass in the vitreous, or a white pupil. The chorioretinal compromise characteristically involves the central macula. A large macular abscess and retinal pseudohypopyon formation are suggestive of the diagnosis (Fig. 9.15). A confluent yellowish macular infiltrate begins in the choroid and subretinal space. The retinal involvement may range from subretinal or subhyaloid infiltrates to full-thickness retinal necrosis (Fig. 9.16). Serous or exudative retinal detachment, intraretinal hemorrhages, choroidal or vitreous abscess, intravitreal granulomata, and posterior scleritis (Fig. 9.17) are also frequent [32].

Diagnosis

Disseminated aspergillosis is often a difficult clinical diagnosis to confirm. High clinical index of suspicion assisted by microbiological and histopathological evaluation helps in arriving at a correct diagnosis, thereby aiding successful treatment. Serologic tests are unreliable whereas blood cultures are usually negative even in fulminant cases. Even in patients with pulmonary involvement, sputum cultures are rarely positive. Invasive culture techniques (e.g., biopsies)

are helpful. Early recognition of intraocular aspergillosis may hasten diagnosis and improve prognosis. Awareness of *Aspergillus*' propensity to cause retinal and choroidal infarction may improve the ophthalmologist's ability to diagnose this vision- and life-threatening event.

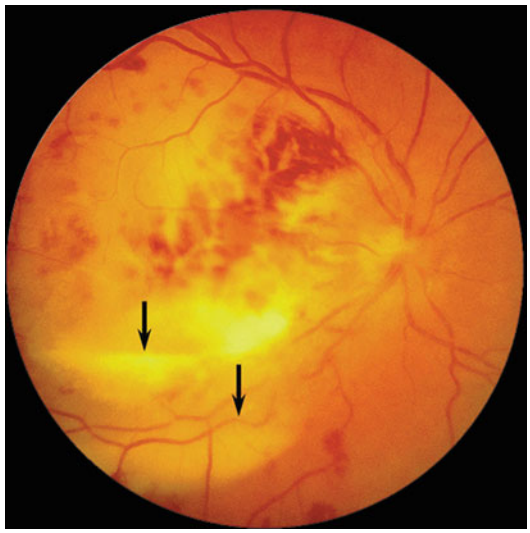

Fig. 9.15 Man with a history of intravenous drug abuse had vitritis and retinal pseudohypopyon formation due to *Aspergillus*. (Reprinted with permission from Weishaar PD, Flynn HW Jr, Murray TG, et al. Endogenous Aspergillus endophthalmitis. Clinical features and treatment outcomes. Ophthalmology. 1998;105:57–65)

Intraocular infection with *Aspergillus* species is difficult to distinguish from the other causes of endophthalmitis on the basis of clinical appearance alone [33]. In addition, *Aspergillus* species cannot be differentiated, with certainty, from other fungi on histopathological examination.

It has been suggested that a definitive diagnosis of *Aspergillus* infection is possible only by isolating and identifying the organism after culturing. In culture, all *Aspergillus* species have septate, dichotomously branching hyphae with conidiophores (stalks) bearing conidia at their ends. They are best identified using periodic acid Schiff or Gomori methenamine silver stain, but may also be seen with Gram stain or hematoxylin and eosin. *Aspergillus* species rapidly grow on Sabouraud agar and Czapek solution agar. Colonies are initially flat, white, and filamentous but become pigmented within 48 h with the production of conidia (Fig. 9.18).

Anterior chamber aspirates are usually of no value for isolation of the fungus. Despite the presence of hyphae on the surface of the iris, negative anterior chamber aspirates can be reported [34]. Direct examination and culture of vitreous specimens provide a better chance for isolation of the fungus, confirming the role for early vitrectomy in cases of *Aspergillus*

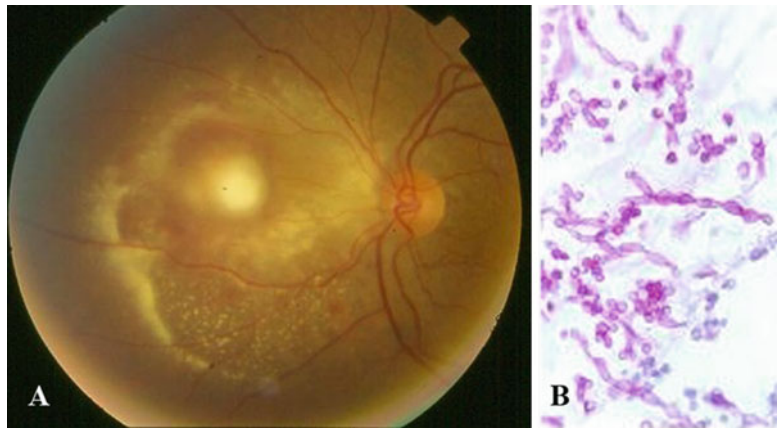

Fig. 9.16 (**a**) Yellowish subretinal lesion nasal to the optic disk surrounded by fluid secondary to *Aspergillus* infection in chronic leukemia. (**b**) Histology of the fellow enucleated eye confirming *Aspergillus* infection. (Reprinted and modified with permission from Machado Od Ode O, Gonçalves R, Fernandes EM, et al. Bilateral Aspergillus endophthalmitis in a patient with chronic lymphocytic leukemia. Br J Ophthalmol. 2003;87:1429–1430)

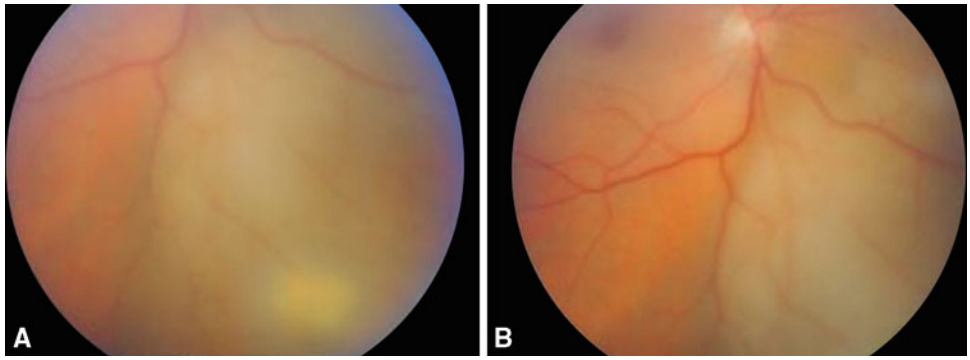

Fig. 9.17 (**a**–**b**) Fundus photography showing serous retinal detachment with yellowish subretinal lesions secondary to *Aspergillus* posterior scleritis

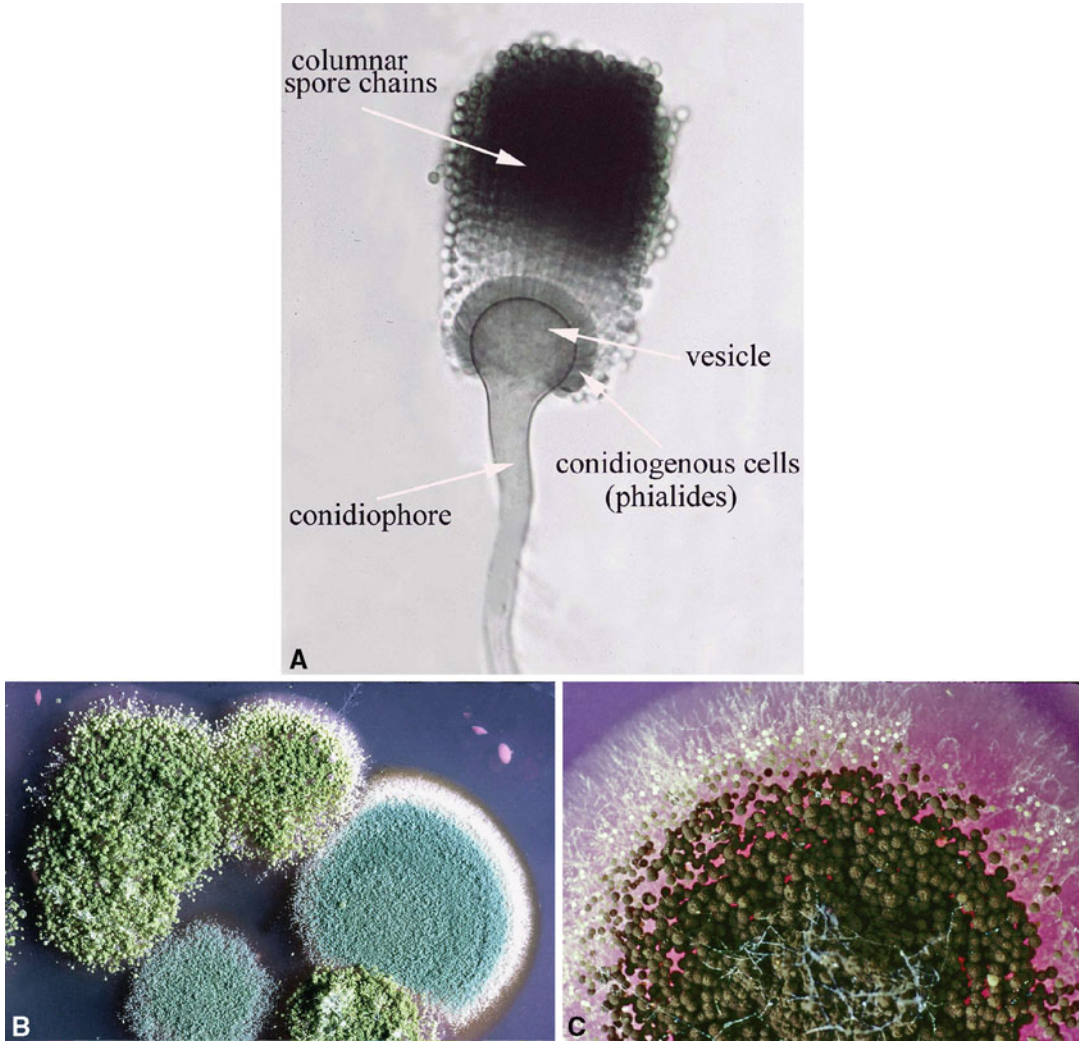

Fig. 9.18 (**a**) *Aspergillus fumigatus* – columnar head. (**b**) *Aspergillus flavus* and *Penicillium*. (**c**) *Aspergillus niger*. (© George L. Barron. Figures reproduced by permission of George L. Barron, Ph.D., D.Sc.)

endophthalmitis for both diagnostic and therapeutic purposes [32].

Treatment

Despite treatment, which generally includes pars plana vitrectomy (PPV), intravitreal amphotericin B, systemic amphotericin B, and oral antifungal agents, the visual prognosis remains grave, and the risk of mortality high. Amphotericin B is currently the only antifungal agent approved for injection into the vitreous. However, even at low concentrations it may cause focal retinal necrosis. Furthermore, a variety of fungal species, particularly *Aspergillus*, have shown resistance to amphotericin B [35]. Voriconazole, a second-generation triazole, was developed for the treatment of life-threatening infections. It has potent in vitro activity against *Aspergillus* species and has been found to be more effective than amphotericin B for the treatment of invasive aspergillosis. Voriconazole is used orally, intravenously, or by intravitreal injections (100 μ[mu] g/ 0.1 ml) to treat endogenous *Aspergillus* endophthalmitis [36].

The use of intravitreal dexamethasone remains controversial, but some protocols recommended using this adjunctive medication to reduce the marked intraocular inflammation in many of these eyes. In patients with persistent vitreous infiltrates and suspected recurrent disease after initial treatment, repeat intravitreous injections of amphotericin B and possibly repeat vitrectomy may be considered.

Cryptococcal Chorioretinitis

Cryptococcus neoformans is a budding, spore-forming, yeastlike fungus, with a polysaccharide capsule, ranging in size from 5 to 10 μ(mu)m. *Cryptococcus neoformans* has two varieties: var neoformans and var gattii. *C. neoformans var gattii* is associated with a higher incidence of visual impairment, as compared to *C. neoformans var neoformans*. The organism has a worldwide distribution. The most common source of infection is droppings from pigeons and other birds. The fungus has also been isolated from soil, fruit, and milk. *Cryptococcus neoformans* can enter the body through inhalation and spread hematogenously to end organs, most commonly the brain. The most common ophthalmic manifestation of cryptococcosis is secondary to cryptococcal meningitis or meningoencephalitis [37].

Risk Factors

A normally functioning host immune response is capable of eliminating *C. neoformans* infection, or can sequester *C. neoformans* into sites where it can remain controlled via fungistatic and fungicidal host defense mechanisms. The humoral system is activated through the complement cascade. Therefore, the clinical manifestations of this infection can range from an asymptomatic colonization of the respiratory tract to a widespread dissemination depending on the host immune factors.

Most cases of intraocular cryptococcosis reported in the literature are the result of:

- Cryptococcal septicemia associated with severe meningeal infection
- Immunocompromised patients
- Malignant lymphoma, Hodgkin's disease, and other malignant diseases
- Acquired immunodeficiency syndrome (AIDS)
- Systemic lupus erythematosus

Pathogenesis

The primary lesion of cryptococcal infection is usually in the lung through inhalation of airborne spores, with dissemination most frequently to the meninges and brain or spinal cord. Other reported sites of cryptococcus include the skin, bones, and liver. Direct cryptococcal involvement of the eye is rare and usually associated with disseminated disease [37]. Cryptococcus organisms reach the eye through either direct extension from the optic nerve sheath or hematogenously from a distant focus.

Histological studies show that endogenous ocular cryptococcosis is primarily a choroidal disease, with secondary invasion of the sensory retina and other intraocular structures. *Cryptococcus neoformans* has also been reported to cause endophthalmitis, uveitis, and retinitis [37]. The histological reaction caused by the organism in the choroid and retina can range from minimal to

no inflammatory reaction or necrosis to granulomatous changes [38].

Clinical Features

Patients sometimes do not complain of visual symptoms; however, a detailed visual perimetry assessment can show dramatic and generalized concentric diminution of visual field in both eyes. Patients sometimes present with visual loss. *C. neoformans* usually presents intraocularly as a multifocal chorioretinitis characterized by discrete multiple, yellowish white, slightly elevated chorioretinal lesions of different sizes. Retinal necrosis accompanied by retinal hemorrhage (Figs. 9.19 and 9.20) and exudative retinal detachments also have been known to occur [39]. Retinal vessels may be sheathed; vitreitis of variable intensity and papilledema, optic atrophy, and ophthalmoplegia may develop (Figs. 9.19, 9.21, and 9.22). Without treatment, the condition progresses to endophthalmitis [37]. Clinically, this appears as a diffuse vitritis with haze, debris, and fluffy white vitreous exudates that progressively enlarge to involve the entire vitreous [37]. An unusual presentation is a solitary retinovitreal abscess (Figs. 9.23 and 9.24) [40]. A mild inflammatory reaction is usually present in the anterior segment. If treatment is not instituted, iris neovascularization and cataract may result. Visual outcomes are very poor in most cases.

Diagnosis

The diagnosis in a patient with a suspected cryptococcal chorioretinal or retinal lesion is complicated by the frequent association between direct intraocular cryptococcal involvement and the disseminated form of the infection, which frequently involves the central nervous system. Fluorescein angiography typically reveals hypofluorescent spots located under the neural retinal without significant leakage in late stages of the angiogram in cryptococcal choroiditis (Fig. 9.25). Multifocal pattern and irreg-

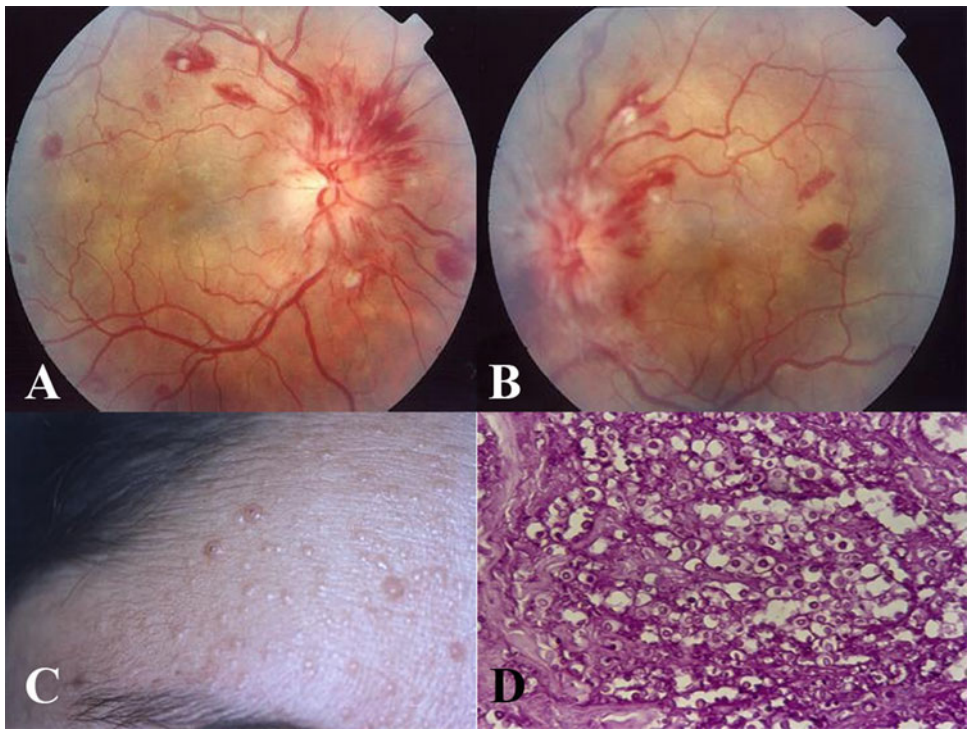

Fig. 9.19 (**a**–**b**) Fundus photography showing disk edema associated with multifocal choroiditis and retinal hemorrhages in a patient with disseminated cryptococcus neoformans infection. (**c**) Umbilicated skin lesions in an HIV-positive patient. (**d**) Histology study of skin lesion showing the presence of *Cryptococcus neoformans* (PAS/Grocott)

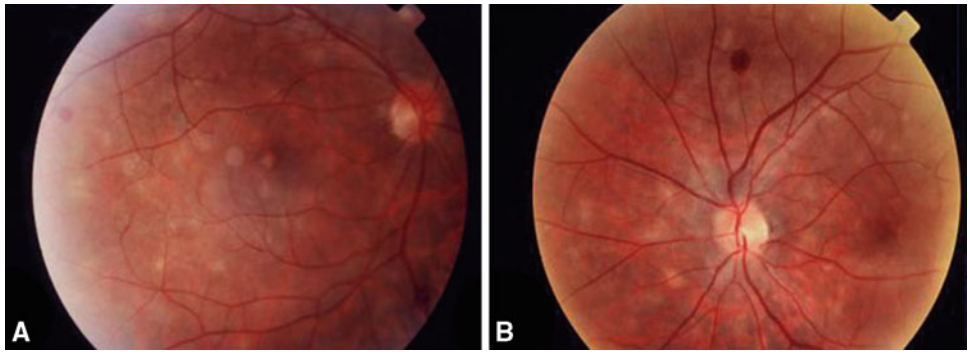

Fig. 9.20 (**a**–**b**) Multifocal cryptococcal choroiditis. Right (**a**) and left (**b**) eye photographs show multiple, yellowish lesions at the level of the retinal pigment epithelium and choroid (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

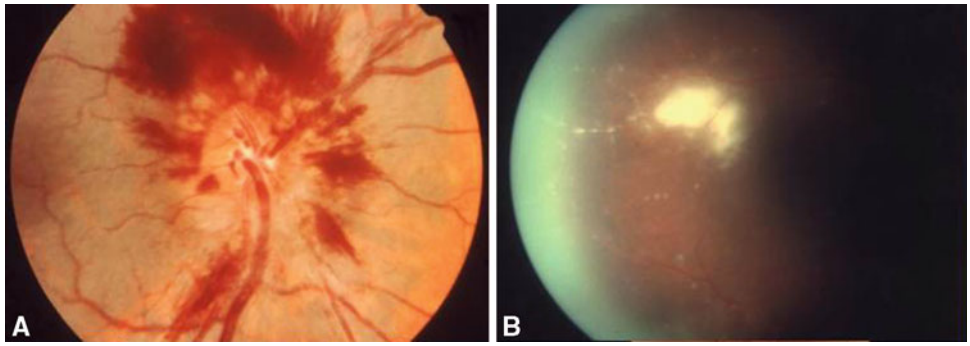

Fig. 9.21 (**a**) Hemorrhagic papilledema associated to cryptococcal meningitis. (**b**) Cryptococcal retinochoroiditis with vasculitis. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal Infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier; 2006; 366–774)

ularly shaped hypofluorescent spots on indocyanine green video-angiography are observed in choroiditis for *Cryptococcus neoformans* [41]; they have a tendency to be confluent. This finding may be related to an active disease stage than may have involved the choriocapillaris (Fig. 9.26).

If the causative organism is not known, an early diagnostic vitreous tap or vitrectomy may be performed. Identification of the encapsulated organism in cerebrospinal fluid (CSF) stained with India ink is sufficient for making a presumptive diagnosis and initiating treatment pending culture results. India ink preparations are negative in 50% of cases involving the central nervous system. In suspected cases, the urine, CSF, blood, and sputum should be cultured even in the absence of evidence suggesting genitourinary or pulmonary infection. *Cryptococcus neoformans* grows well on both blood agar and Sabouraud medium. Growth usually occurs within 24–48 h, producing mucoid, cream or pink colonies. *Cryptococcus neoformans* is a budding, spore-forming yeast. The organism can be found within histiocytes as well as free in the extracellular matrix in the choroid, either with or without involvement of the overlying retina (Fig. 9.27).

Several serological tests for *Cryptococcus* have been developed including complement fixation, tube agglutination, immunodiffusion, and an indirect immunofluorescence test. The latex agglutination test for detection of antigen on the cryptococcal polysaccharide capsule is the

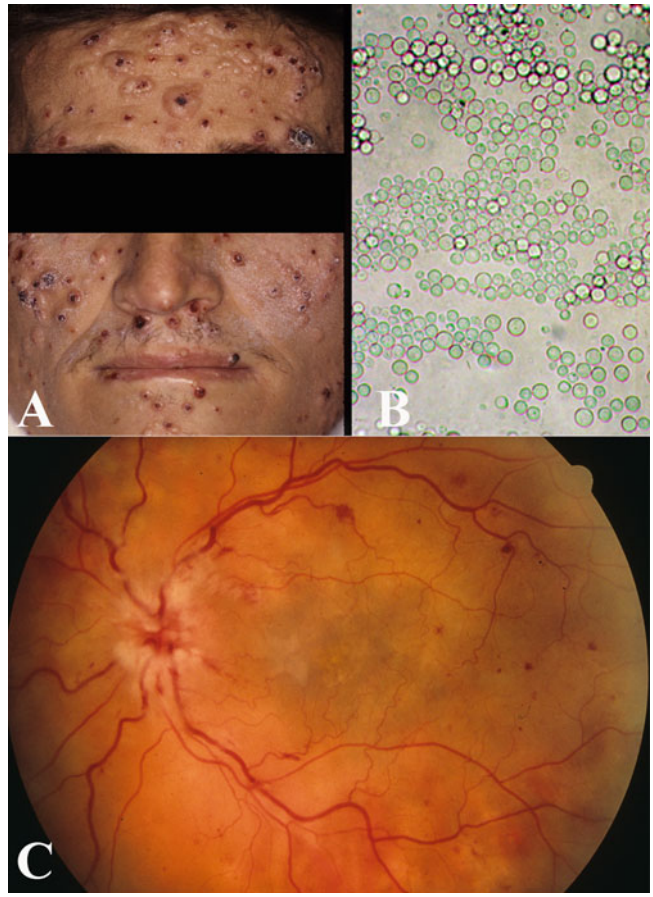

Fig. 9.22 (**a**) Umbilicated skin lesions in a patient with cryptococcal meningitis and disseminated *Cryptococcus neoformans* infection. (**b**) Histology study of skin lesion showing the presence of *Cryptococcus neoformans*. (**c**) Fundus photography showing direct nerve invasion associated with multifocal choroiditis and retinal hemorrhages in the same patient with cryptococcal meningitis

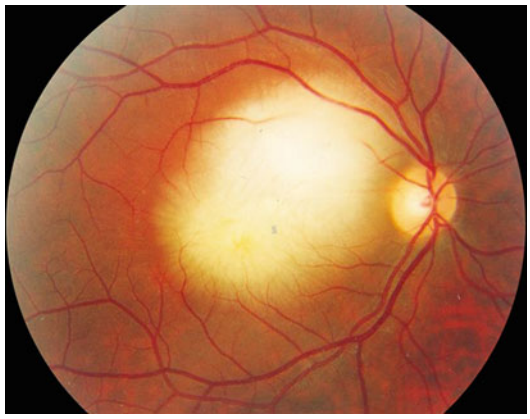

Fig. 9.23 Fundus photography showing a large subretinal lesion in the macula due to *Cryptococcus* infection in a patient with Hodgkin's lymphoma

most commonly used commercially available test. A titer greater than 1:8 is an indication for treatment. The presence of the antigen should be tested in blood, urine, and CSF if the diagnosis is suspected but not proved.

Morphological characteristics of the organism that allow identification are apparent with periodic acid Schiff (PAS) or methenamine silver stains. Mayer's mucicarmine will stain the polysaccharide capsule of red, which differentiates *Cryptococcus neoformans* from other organisms and artifacts (see Fig. 9.27).

Treatment

Treatment usually consists of amphotericin B or flucytosine, and therapeutic failure or relapse

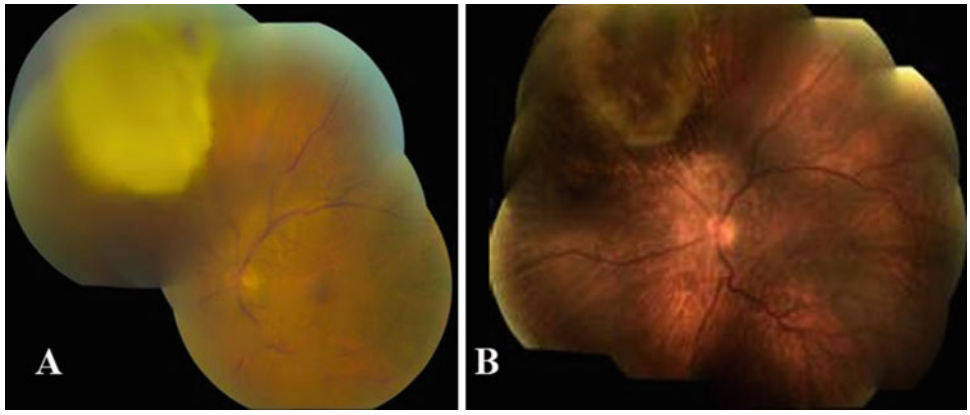

Fig. 9.24 (**a**) Fundus photography showing large solitary cryptococcoma in an elderly man with chronic lymphocytic leukemia. (**b**) Same patient after cryptococcoma resolution

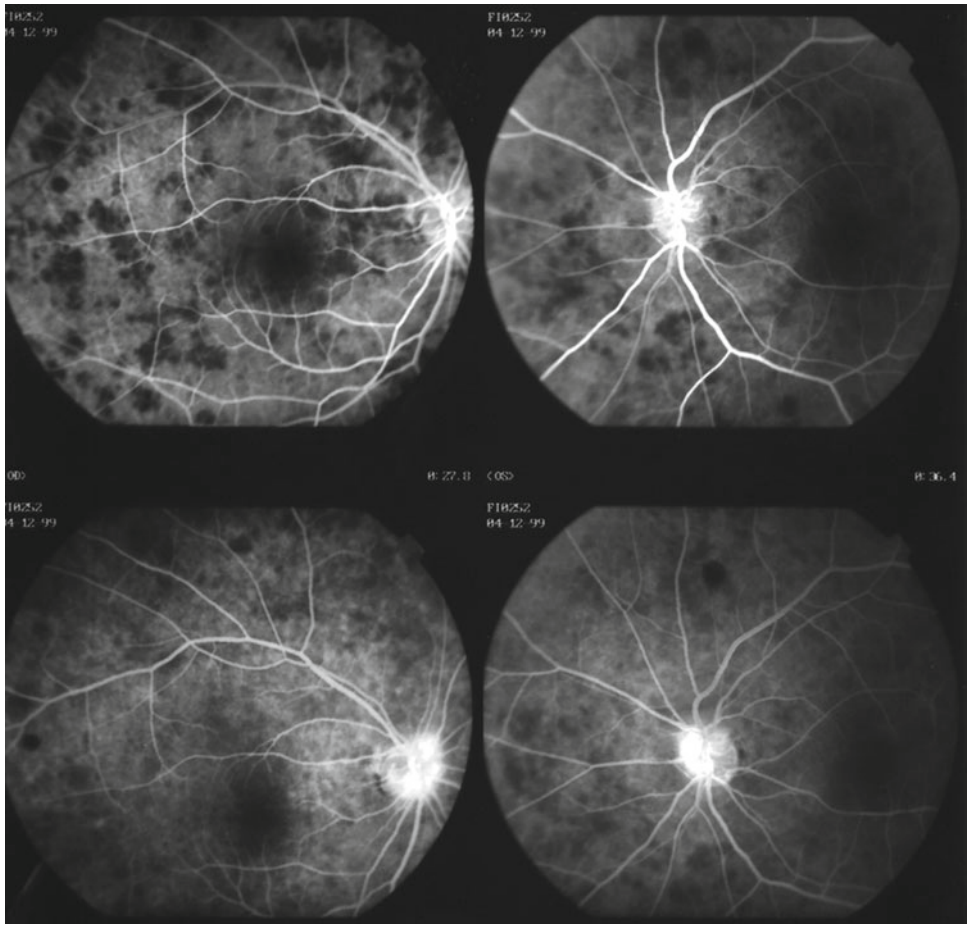

Fig. 9.25 Fluorescein angiogram of same patient in Fig. 9.20 shows the presence of rounded lesions that were located underneath the neuroretina in an AIDS patient with multifocal cryptococcal choroiditis. These lesions masked fluorescence early during the study (*top* pictures). There was no significant leakage in the late stages of the angiogram although some late hyperflourescence may be seen on the nasal aspect of the optic disk in both eyes (*bottom* pictures). (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

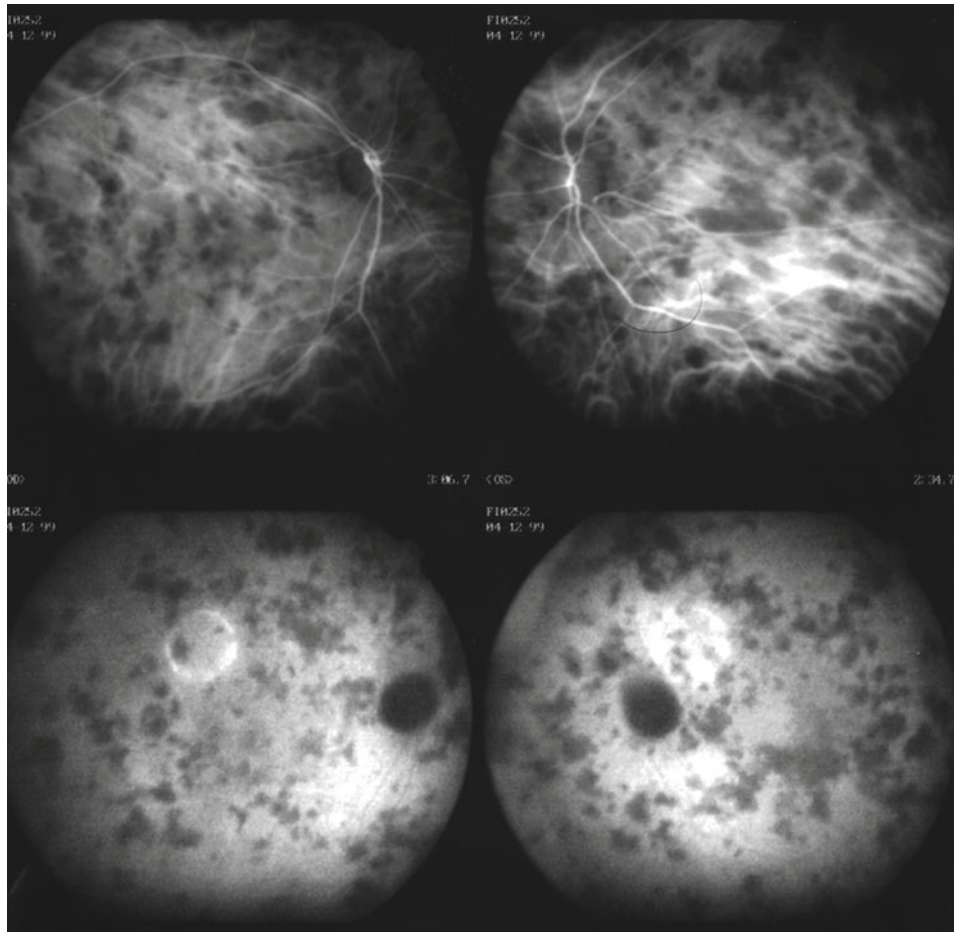

Fig. 9.26 Indocyanine green video-angiography (ICG-V) of same patient in Fig. 9.20 and Fig. 9.25 confirmed the presence of lesions that were at the level of the choroid. These lesions masked fluorescence throughout the study. Most of these hypofluorescent dark spots were already visible at the early phase of the ICG-V, became more sharply delineated in the intermediate angiographic frames (*top* pictures), and remained hypofluorescent in the late frames (*bottom* pictures) of the retinal pigment epithelium and choroid. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

has been reported in approximately 33% of cases. Agents like fluconazole have also been used. Voriconazole is a synthetic derivative of fluconazole, but it has a significantly broader spectrum of activity. Compared with amphotericin B, fluconazole, and itraconazole, voriconazole has the lowest minimum inhibitory concentration for *Cryptococcus neoformans*, and time-kill assays demonstrate its fungicidal activity. When administered systemically, voriconazole shows excellent bioavailability, penetrating well into the eye and reaching intravitreal concentrations of 1.0–1.5 mg/mL. It has no significant toxicity in vitro cell cultures when administered in therapeutic concentrations up to 250 mg/ml. Intravitreal voriconazole may therefore be a promising regimen for treatment of cryptococcal endophthalmitis. Early vitrectomy is recommended if severe vitritis fails to clear or worsens under antifungal therapy [37]. Enucleation is considered if the outcome is a blind, painful eye.

Coccidioides immitis Chorioretinitis

Coccidioides immitis is a dimorphic fungus. The disease is endemic in the semiarid areas of the southwestern United States and Mexico. The area affected most heavily is the San Joaquin valley of central California. Cases of coccidioidomycosis, however, have been found in almost every state in the United States in persons who have at one time lived or traveled through an endemic area. The disease has also been reported in Hawaii, Canada, Central and South America, Italy, and the Balkan countries. The disease is transmitted to humans by inhalation of the arthroconidia stages in the saprophytic phase of the organism's life cycle from dry dust arising from contaminated soil [42]. *Coccidioides immitis* has rarely been proved to cause ocular disease.

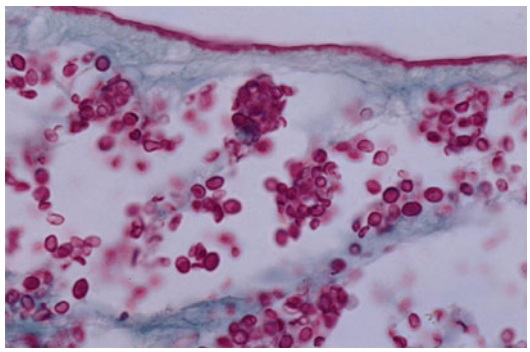

Fig. 9.27 Light microscopy reveals cryptococcal organisms with their characteristic mucopolysaccharide capsule. (Reprinted with permission from Khodadoust, AA, Payne JW. Cryptococcal "torular" retinitis: a clinicopathologic case report. Am J Ophthalmol. 1969,67:745–750)

Risk Factors

The general population is susceptible to coccidioidomycosis because the major risk factor is exposure to the arthroconidia of the mycelial phase of *C. immitis*. However there are some risk factors for ocular compromise including:

- Dissemination of primary coccidioidal lesion. Systemic coccidioidomycosis becomes manifest as an asymptomatic subclinical infection, an acute self-limited pulmonary flu-like disease (primary pulmonary), a chronic pulmonary disease (persistent pulmonary), or a disseminated condition with involvement of the lungs and extrapulmonary lesions in skin, joints, bones, and meninges.
- Pregnant women contracting coccidioidomycosis are at significant risk of developing severe or disseminated disease.
- Patients with immunosuppression [43].

Pathogenesis

Coccidioides immitis produces pyogenic, granulomatous, and mixed reactions [44]. Fibrosis, necrosis, and calcification can occur. Miliary retinal and choroidal granulomas may result by distribution of the endospores via the ophthalmic artery (Fig. 9.28).

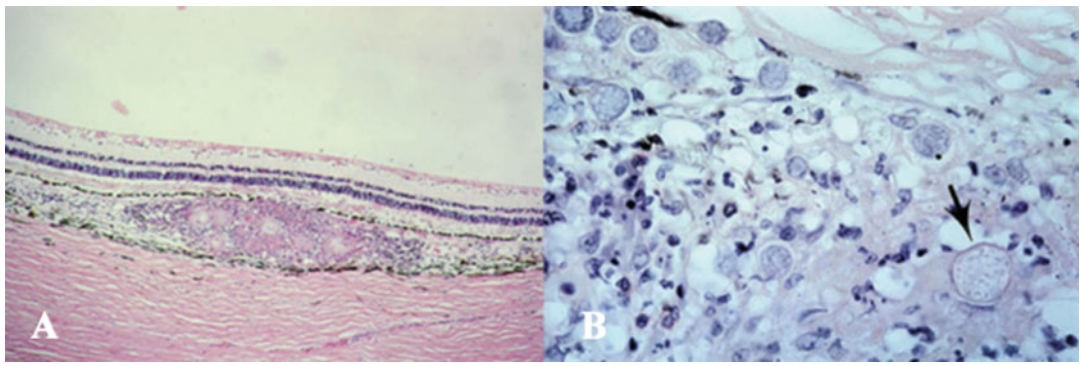

Fig. 9.28 (**a**) Focal granuloma in the fundus of a man who died of disseminated coccidioidomycosis. (**b**) Multiple spherule-containing endospores (*arrow*). (Modified and reprinted with permission from Boyden BS, Yee D. Trans Am Acad Ophthalmol Otolaryngol, 1971; 75:1006–1100)

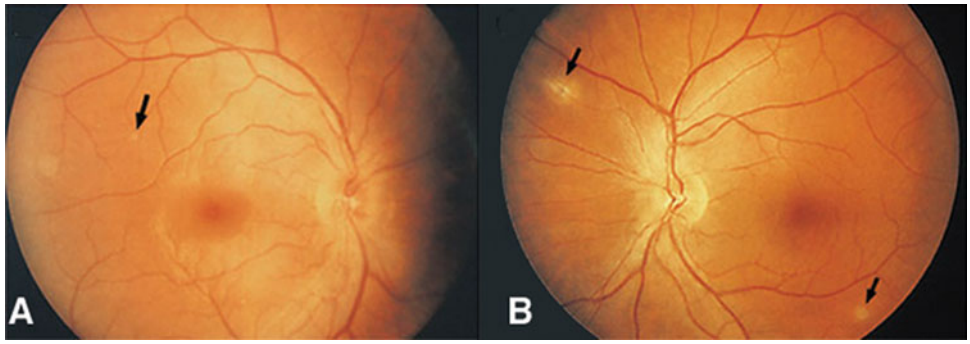

Fig. 9.29 (**a**) *Right* fundus photograph shows a small choroidal lesion superotemporal to the fovea (*arrow*) and mild papilledema. (**b**) *Left* fundus photograph shows two choroidal lesions, one superonasal to the optic nerve head and one inferotemporal to the fovea (*arrows*). Mild papilledema is also evident. (Modified and reprinted with permission from Cunningham ET Jr, Seiff SR, Berger TG, et al. Intraocular coccidioidomycosis diagnosed by skin biopsy. Arch Ophthalmol. 1998;116:674–677)

Clinical Features

Approximately 40% of infected individuals are symptomatic. The vast majority of symptomatic patients present upper respiratory tract infection. Ocular coccidioidomycosis is rare and may affect either the anterior or posterior segment of the eye producing blepharitis, phlyctenular conjunctivitis, episcleritis, scleritis, iridocyclitis, choroiditis, and chorioretinitis. The typical posterior infection is a multifocal choroiditis with numerous scattered, discrete, yellow-white lesions less than a disk diameter in size [44]. Large juxtapapillary choroidal infiltrates with variable involvement of the overlying retina may be associated with retinal edema and hemorrhage, and small peripheral chorioretinal scars with central hypopigmentation resembling presumed ocular histoplasmosis scars (Fig. 9.29). Miliary retinitis with multiple retinal granulomata has also been reported. Vitritis may be associated with vitreous cells and infiltrates overlying the chorioretinal lesion. *C. immitis* may also primarily affect the optic nerve.

Diagnosis

A history of travel to an endemic area may provide a clue to the diagnosis. If the diagnosis is highly suspected, the laboratory workup includes characterization and quantification of anticoccidioidal antibodies in serum and a coccidioidin skin test. Skin and serologic testing provide strong evidence for prior exposure to *C. immitis* but alone do not confirm the presence of disseminated or intraocular disease.

Histopathologic or culture identification of *C. immitis* in anterior chamber, vitreous, or chorioretinal specimens is the most direct method to diagnose intraocular infection, but intraocular biopsy is not without risk. In contrast, biopsy of skin lesions has low morbidity and can provide definitive evidence for disseminated disease [45].

Antibodies to two antigens of *C. immitis* are of particular interest: a tube-precipitating (TP) reacting seroprotein (an IgM) and a complement fixing (CF) antibody (an IgG). The level of CF antibody is directly proportional to the extent of the disease. A positive CF antibody test in dilutions greater than 16-fold indicates extrapulmonary disseminated disease. Rising titers of both antibodies indicate a worsening prognosis, and falling titers indicate improvement.

Treatment

Amphotericin B is the drug of choice for treatment of chronic pulmonary and disseminated coccidioidomycosis [45]. With isolated vision-threatening ocular infections, more aggressive treatment may be warranted, including intracameral or intravitreal injection of amphotericin B and pars plana vitrectomy. Ketoconazole, fluconazole, and itraconazole can also be used in combination with or following treatment with amphotericin B.

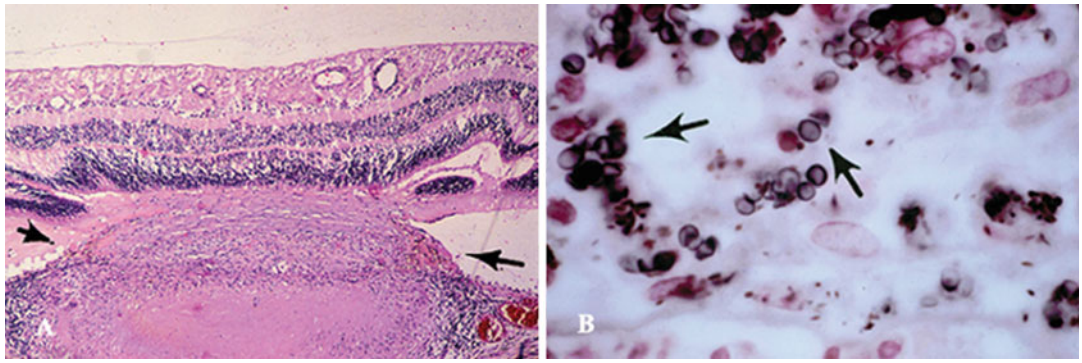

Fig. 9.30 (**a**) Large focal choroidal granuloma (*arrows*) secondary to histoplasmosis. (**b**) Special stains showed *Histoplasma capsulatum* (*arrows*). (*Panel A* reprinted with permission from Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol. 1967;63:Suppl:1–139; and Maumenee AE, Ryan SJ. Photocoagulation of disciform macular lesions in the ocular histoplasmosis syndrome. Am J Ophthalmol. 1973;75:13–16. *Panel B* reprinted with permission from Klintworth GK, Hollingsworth AS, Lusman PA, Bradford WD. Granulomatous choroiditis in a case of disseminated histoplasmosis. Histologic demonstration of Histoplasma capsulatum in choroidal lesions. Arch Ophthalmol. 1973;90:45–48)

Histoplasma Chorioretinitis

Histoplasma capsulatum is a dimorphic unencapsulated fungus with mycelial and yeastlike phases that often grows in soil around old chicken houses and areas harboring bats, such as caves [46]. The organism is endemic in southeastern and central United States and many parts of Central America and Asia. The organism gains access to the body by way of the respiratory tract through inhalation of spores.

Acute histoplasmosis is usually a benign subclinical or self-limited pulmonary illness [47]. Disseminated histoplasmosis is a rare condition in which the organism spreads by way of the bloodstream, producing lesions throughout the body.

Presumed ocular histoplasmosis syndrome (POHS) is a distinct clinical entity that is characterized by peripheral atrophic chorioretinal scars, peripapillary scarring, and maculopathy. This condition is believed to be secondary to exposure to *Histoplasma capsulatum*, although this fungus rarely has been isolated or cultured from an eye with the typically associated clinical findings.

Risk Factors

Rarely, disseminated infection occurs in normal adults without any immunologic defect [48]. Risk factors for histoplasmosis infection are:

- Residents or visitors to endemic areas
- Prior exposure to chickens, parakeets, or pigeons
- Incomplete development of immune defense mechanisms in infants [47]
- AIDS
- Iatrogenic immunosuppression, especially after kidney transplantation
- Immunocompromised patients

Pathogenesis

In a normal host, the initial infection is usually asymptomatic or feels like influenza. In a few patients, a chronic cavitary pulmonary disease may follow. In immunocompromised patients, a progressive, life-threatening, disseminated form can occur. Following initial infection, hematogenous spread to the rest of the body, including the eye, can occur. *Histoplasma capsulatum* may eventually seed the choroid to produce a multifocal granulomatous chorioretinitis that heals as atrophic histo scars (Fig. 9.30).

Clinical Features

The classic ocular disease is manifested with a triad of disseminated choroiditis (histo spots), maculopathy that may be associated with episodes of exudation and may occur with subretinal neovascularization, and peripapillary atrophy with pigmentary changes (Fig. 9.31) [49].

Ocular involvement in cases of disseminated histoplasmosis may manifest as retinitis, optic neuritis, or uveitis. The retinitis appears as multiple,

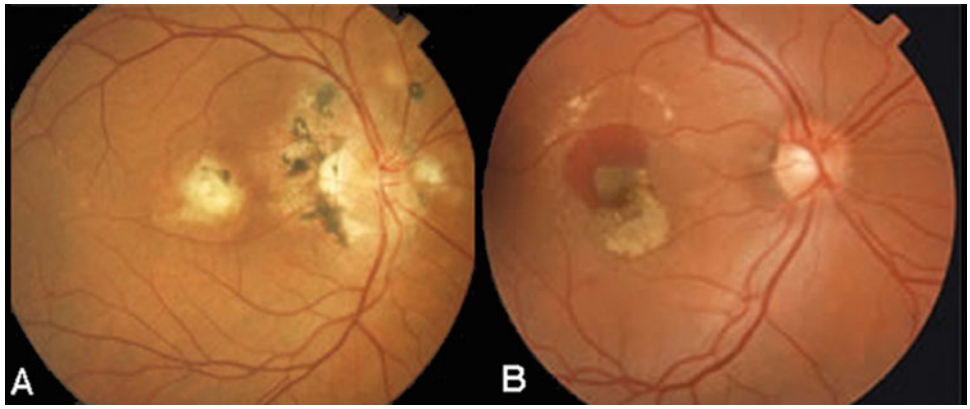

Fig. 9.31 (**a**) Disseminated choroiditis (histo spots), maculopathy, and peripapillary chorioretinal degenerative changes in a patient with the presumed ocular histoplasmosis syndrome. (**b**) Fundus photographs revealed serosanguinous retinal detachment with faint pigment halo in right macula of a patient with the presumed ocular histoplasmosis syndrome. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

creamy white intraretinal and subretinal infiltrates and intraretinal hemorrhages (Fig. 9.32 panels A, B, and C). Active choroiditis appears as discrete, round, yellowish choroidal lesions. With time, the lesions resolve, leaving the typical "punched-out" atrophic scars that disrupt Bruch's membrane. Reexposure to the histoplasmin antigen may account for the enlargement of old scars and the emergence of new scars (Figs. 9.33 and 9.34).

Diagnosis

Diagnosis is made by histology and culture of tissue specimens. The organism exists as yeasts within the host tissues, usually located within macrophages, and surrounded by granulomatous inflammation. Organisms are best visualized by stains specific for fungal elements such as periodic acid Schiff, Gomori methenamine silver, or Grocott silver stain. The morphology of the yeast is suggestive, but not diagnostic, as it can be confused with other fungi such as *Candida glabrata*, *Blastomyces dermatitidis*, *Penicillium marneffei*, or *Coccidioides immitis*.

Culture is performed on routine fungal culture medium such as Sabouraud glucose agar (Fig. 9.32 panel D) or brain heart infusion agar. At 28–30°C, the organism grows as a white mold, with typical tuberculated macroconidia on microscopy. However, conversion to a yeast form after subculture at 35–37°C is required for diagnosis. Microscopy then shows elliptical yeast cells, budding from the small end by a narrow base. Confirmation can also be made by immunofluorescent techniques, which detect specific exoantigens or nucleic acid probes, which detect *Histoplasma*-specific DNA. Serology is positive in as many as 75% of patients 6 weeks after the onset of acute disease, but antibodies can also be detected in up to 10% of asymptomatic individuals in endemic areas. Immunocompromised individuals often do not mount an antibody response. Skin testing using histoplasmin antigen is mainly used as an epidemiological tool. The organisms may also be isolated from vitreous aspirates obtained during pars plana vitrectomy.

Fluorescein angiography can show hyperfluorescence in the late phases of the study from choroidal neovascularization in patients with histoplasmosis (Fig. 9.35) [50]. Optical coherence tomography is useful in the identification of different types of choroidal neovascularization (type 1 or 2), accumulation of subretinal fluid, macular edema, and epiretinal membranes (Fig. 9.36). Chest radiography may show calcified lesions by histoplasmosis infection (Fig. 9.37).

Treatment

Amphotericin B or ketoconazole generally is recommended for treatment of disseminated histoplasmosis. Pars plana vitrectomy with

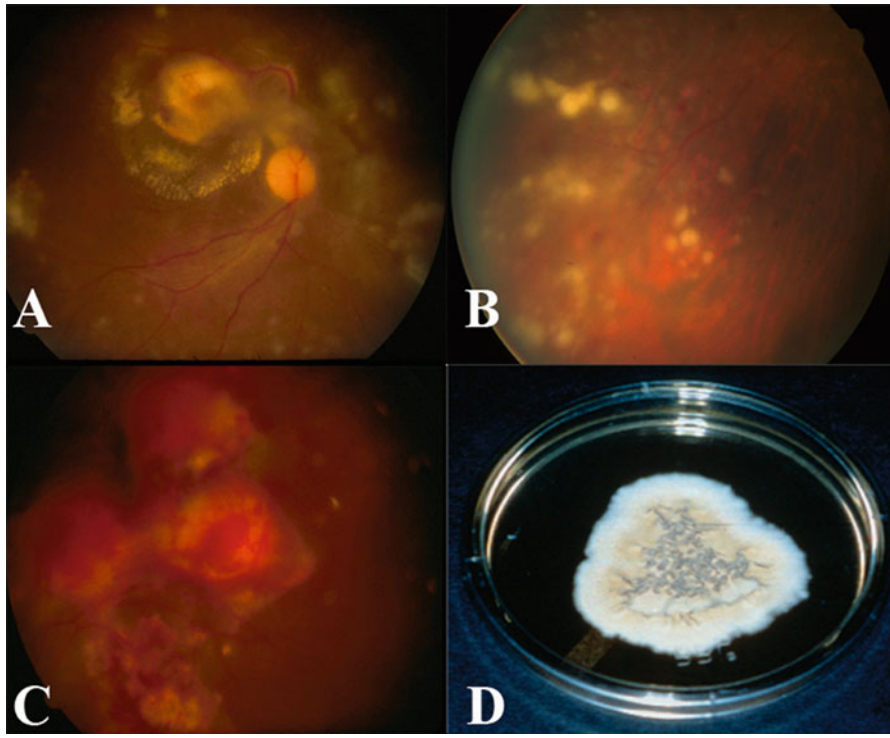

Fig. 9.32 Patient with ocular histoplasmosis. (**a**–**b**) Multiple, creamy white intraretinal and subretinal infiltrates. (**c**) Intraretinal and subretinal hemorrhages. (**d**) *Histoplasma capsulatum*. Yeast colonies in Sabouraud glucose agar. (Part D, reprinted with permission from Gonzales CA, Scott IU, Chaudhry NA, Luu KM, Miller D, Murray TG, Davis JL. Endogenous endophthalmitis caused by Histoplasma capsulatum var. capsulatum: a case report and literature review. Ophthalmology. 2000;107:725–729)

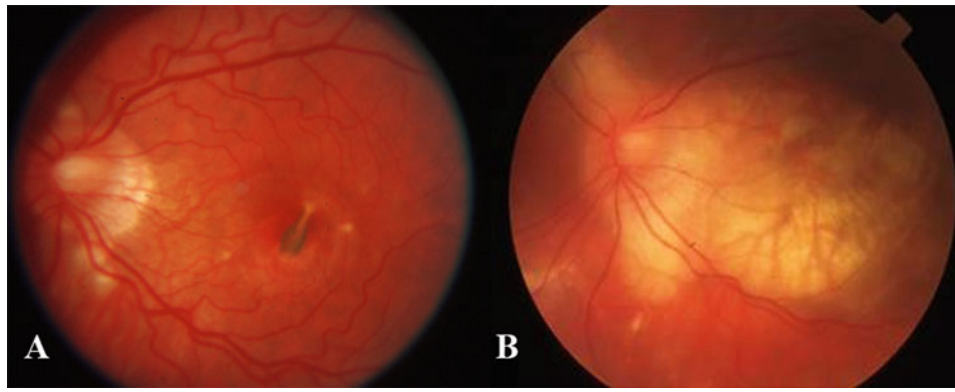

Fig. 9.33 (**a**) Choroidal neovascular membrane in a patient with a diagnosis of presumed ocular histoplasmosis syndrome. (**b**) Progressive lesion enlargement through 10 years

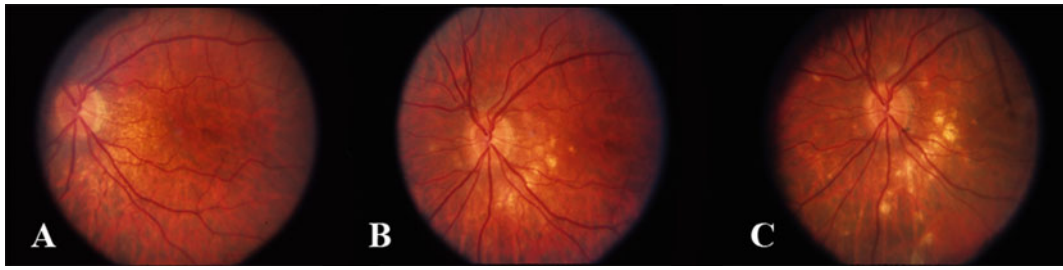

Fig. 9.34 (**a**–**c**) Progressive "punched-out" atrophic scar enlargement in a patient with presumed ocular histoplasmosis syndrome

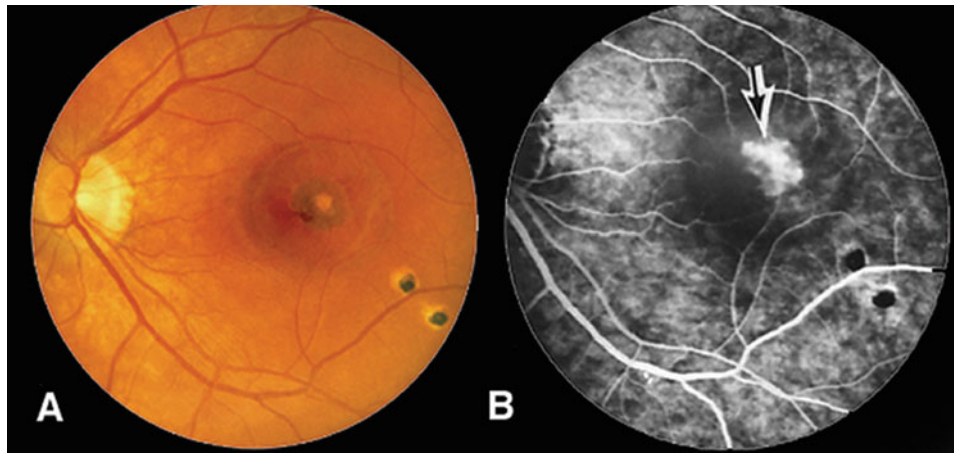

Fig. 9.35 (**a**–**b**). Hyperfluorescence in the late phases of the fluorescein angiogram from choroidal neovascularization in patient with the presumed ocular histoplasmosis syndrome. (Modified and reprinted with permission from Gass JDM. Stereoscopic Atlas of Macular Diseases; Diagnosis and Treatment. 4th ed. St. Louis: Mosby, Inc. 1997)

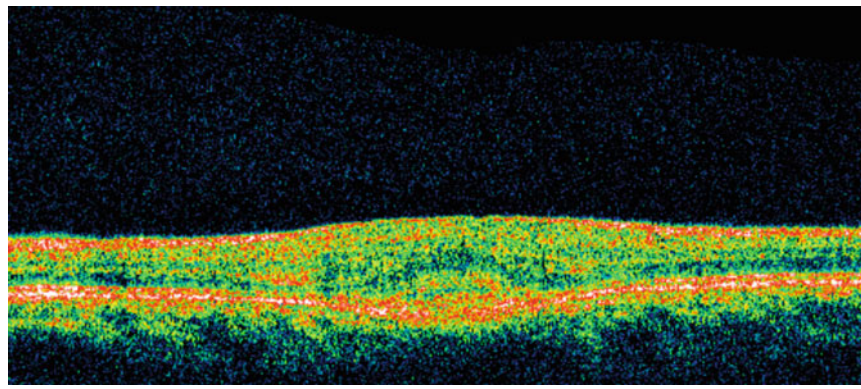

Fig. 9.36 Type 2 choroidal neovascular membrane in a patient with a diagnosis of presumed ocular histoplasmosis syndrome. Fusiform hypereflectivity between the retina and the retinal pigment epithelium complex on optical coherence tomography

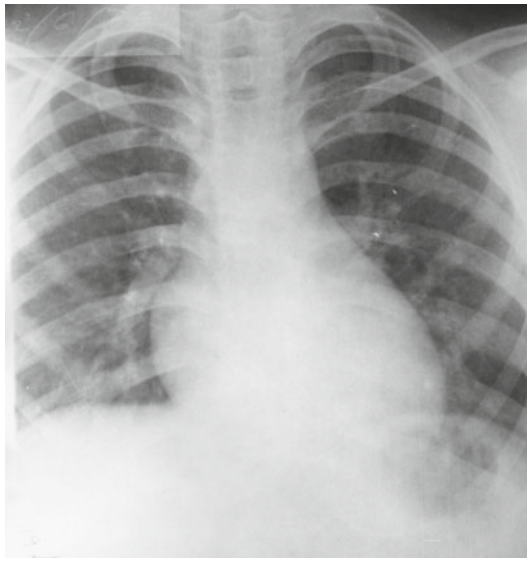

Fig. 9.37 Chest X-ray showing calcified lesions due to histoplasmosis infection. (Reprinted with permission from Arévalo JF, Fernández CF, Mendoza AJ. Chapter 41: Fungal Infections. In: Retinal Imaging. Huang D, Kaiser PK, Lowder CY, Traboulsi EI, eds. Philadelphia: Mosby Elsevier: 2006; 366–774)

intravitreal injection of antifungal drugs may be indicated in cases with dense vitreous exudates or fulminant retinitis [51].

Blastomyces Dermatitidis Chorioretinitis

Blastomyces dermatitidis is a thermally dimorphic fungus that grows in mycelial form. The geographic distribution of reported blastomycosis cases is fairly widespread in the United States. The disease has also been reported in Canada, Africa, the Middle East, India, and Poland. Although the incidence of ocular involvement is low, blastomycosis has been reported to involve essentially all the intraocular and periocular tissues [52].

Risk Factors

- Persons in areas with endemic disease with exposures to wooded sites (e.g., farmers, forestry workers, hunters, and campers)
- Immunocompromised individuals, such as those on chronic steroid therapy, organ transplant recipients, and patients with human immunodeficiency virus (HIV)

Pathogenesis

Except for rare cases of cutaneous inoculation caused by laboratory accidents or infected animal bites [53], the most common route of infection of blastomycosis is by inhalation of airborne spores that arise from the soil. Inside the body or when incubated at 37°C, the organism converts to the yeast form, which reproduces by budding. The pulmonary lesion may resolve, leaving no signs of previous infection. Hematogenous dissemination can produce cutaneous blastomycosis, blastomycosis of the bone marrow, blastomycosis of the male genitourinary system, or ophthalmic blastomycosis. *Blastomyces dermatitidis* causes a combination of acute suppurative and granulomatous inflammation.

Clinical Features

Ocular symptoms of blastomycosis include pain, redness, photophobia, and blurred vision. The ophthalmic manifestations include eyelid infection, conjunctivitis, keratitis, iritis, choroiditis, endophthalmitis, panophthalmitis, and orbital cellulitis.

Choroidal involvement in blastomycosis is unusual and can be seen clinically as one or more yellowish-white choroidal lesions (Fig. 9.38) and perivascular infiltrates [13].

Diagnosis

Hematoxylin–eosin, Gomori methenamine silver, periodic acid Schiff, and auramine are the stains used for *B. dermatitidis* identification. The organism grows well on Sabouraud agar, producing white to tan colonies. *Blastomyces derma*titidis is dimorphic (septate mycelia and conidia). The organism grows almost exclusively in the yeast form, with hyphae only rarely found (Fig. 9.39).

Because of variations in both the systemic and the ocular manifestations of blastomycosis, diagnosis is based on a high index of suspicion. *B. dermatitidis*

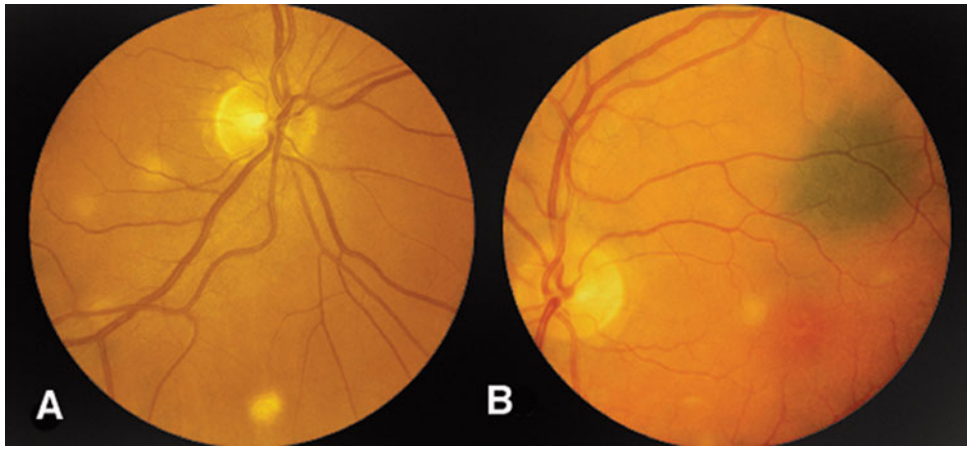

Fig. 9.38 (**a**–**b**) Fundus photographs show multifocal blastomycosis choroiditis. Biopsy of skin revealed blastomycosis. (Modified and reprinted with permission from Gass JDM. Stereoscopic Atlas of Macular Diseases; Diagnosis and Treatment. 4th ed. St. Louis: Mosby, Inc. 1997)

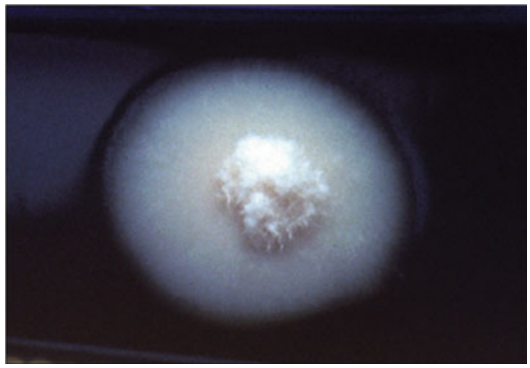

Fig. 9.39 Colony of *Blastomyces dermatitidis* on mold-inhibitory agar (Modified and reprinted with permission from http://www.doctorfungus.org)

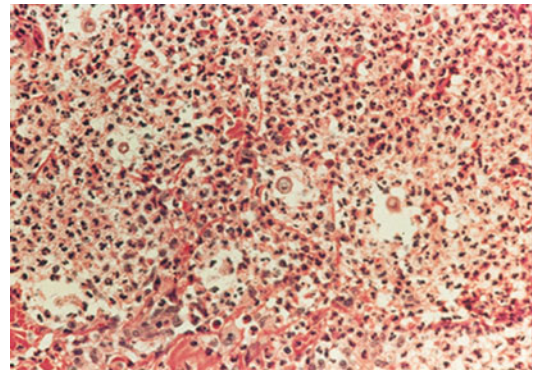

Fig. 9.40 Granuloma containing *Blastomyces dermatitidis* (Reprinted with permission from Lewis H, Aaberg TM, Fary DRB, et al. Latent disseminated blastomycosis with choroidal involvement. Arch Ophthalmol 1988; 106:527–530)

does not colonize, so detection by histologic analysis or culture confirms the diagnosis [54].

B. dermatitidis produces granulomatous reactions with choroidal and retinal involvement (Fig. 9.40). The fungus is identified commonly by microscopy of exudate, sputum, tissue after cell digestion, or aqueous and vitreous aspirates using 10% potassium hydroxide, but fine-needle aspiration cytologic analysis can be used.

Treatment

In addition to amphotericin B and ketoconazole, itraconazole currently is the accepted form of therapy for blastomycosis. Pars plana vitrectomy together with intravitreous injection of amphotericin B must be performed if significant vitreous inflammation is present.

Sporothrix schenckii Chorioretinitis

Sporothrix schenckii is a saprophytic, dimorphic fungus worldwide. The organism can be found in soil associated with plant organic matter (e.g., thorns, dry leaves, and wood), water,

and decomposing organic matter, among others. Natural infection of rats, dogs, mules, and horses also has been reported [55]. *Sporothrix schenckii* affects humans in three distinct forms: cutaneous, pulmonary, and disseminated sporotrichosis. Most cases of intraocular involvement of disseminated sporotrichosis have been endophthalmitis, which shows poor response to therapy.

Risk Factors

- Farmers, gardeners, laborers, and certain types of miners [55]
- Renal transplant patients
- Patients with debilitating or immunosuppressive diseases

Pathogenesis

Most cases of sporotrichosis start as primary cutaneous lesions following inoculation with contaminated soil or other vegetable material. This stage is followed by centripetal lymphatic spread, which appears as multiple subcutaneous nodules creeping up an extremity. Intraocular infections may be due to direct extension from the lid or conjunctiva, but most are endogenous, owing to systemic infection, and usually lead to loss of the eye.

Ocular (and other monofocal sites) infections without an antecedent history of trauma or evidence of systemic disease are rare but may be more common with *S. schenckii* than with other causes of fungal endophthalmitis [56].

Clinical Features

The presenting features of intraocular sporotrichosis are nonspecific and include pain, decreased vision, and redness. Ocular manifestations of sporotrichosis include lesions of the eyelids and lacrimal apparatus, conjunctivitis (Fig. 9.41), keratitis, scleritis, nongranulomatous anterior uveitis with small white keratic precipitates or granulomatous anterior uveitis with iris nodules [57], endophthalmitis, and chorioretinitis that appears as fluffy, white, necrotic retinal lesions with overlying vitreous haze (Fig. 9.42). The condition may progress over several months [58].

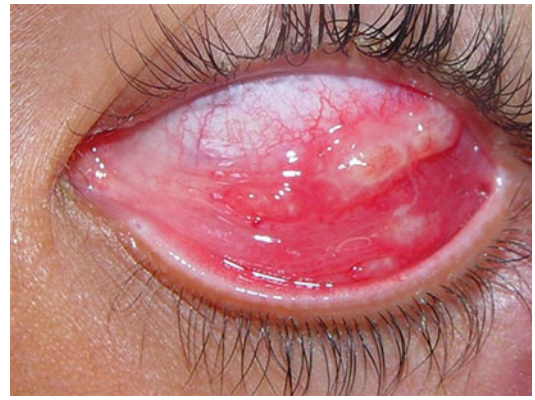

Fig. 9.41 Follicular conjunctivitis with conjunctival granuloma secondary to *Sporothrix schenckii* infection

Diagnosis

The histopathological diagnosis of *S. schenckii* is often difficult. In primary lesions, the free yeast forms are rarely found in tissue sections stained with hematoxylin and eosin and may not be identified despite stains with periodic acid Schiff or glyceryl monostearate, making recovery in culture the diagnosis. Repeated aqueous and vitreous aspirates may be necessary to isolate the organism. In patients with other sites of infection, such as skin or joints, biopsy or aspiration of that site, with culture, also may be helpful. In culture it grows in a yeastlike form at incubation temperatures and filamentous form at room temperature. Sabouraud agar is a satisfactory culture medium, in which cream-colored to black leathery colonies develop within 3–5 days [55].

Treatment

For disseminated sporotrichosis or extraocular sporotrichosis, intravenous amphotericin B is usually used. Early vitrectomy and intravitreal injection of amphotericin B in cases of *S. schenckii* endophthalmitis are important. Also, itraconazole can be used for disseminated and ocular sporotrichosis [59].

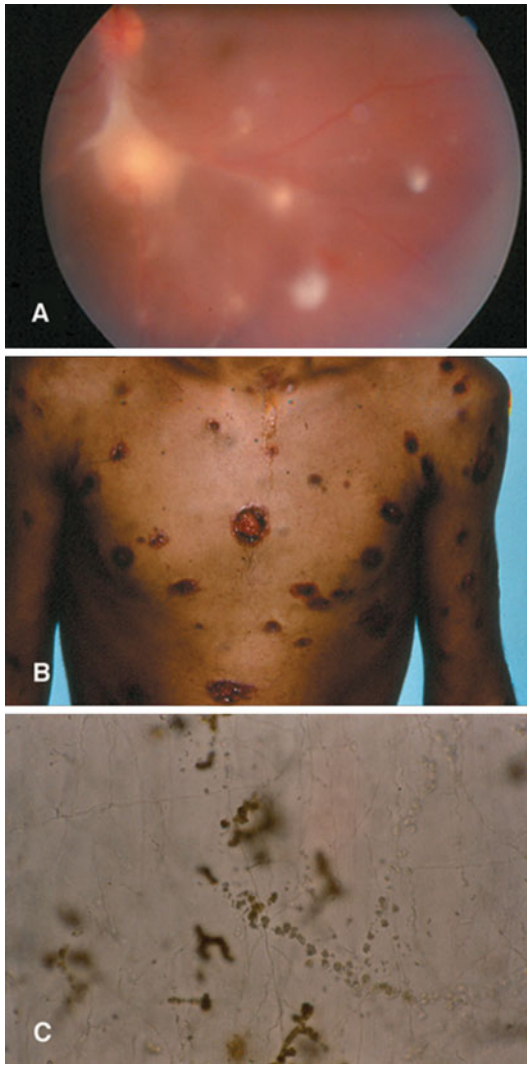

Fig. 9.42 *Sporothrix schenckii*. (**a**) Fundus photography showing retinal granuloma and fluffy opacities in the vitreous in the left eye. (**b**) Ulcerated skin lesions. (**c**) Positive culture for *Sporothrix schenckii*. (Modified and reprinted with permission from Curi AL, Felix S, Azevedo KM, et al. Retinal granuloma caused by Sporothrix schenckii. Am J Ophthalmol. 2003; 136:205–207)

Controversies and Perspectives

The last few decades have seen significant changes in health care with increasing numbers of heavily immunocompromised patients. Because of new and more aggressive treatments, patients with severe immune defects are surviving longer and the spectrum of fungal pathogens is increasing. Until relatively recently, *Candida albicans* and *Aspergillus fumigatus* were considered the only important nosocomial fungal pathogens. However, non-albicans *Candida* species and other yeasts, together with an increasing range of molds apart from *A. fumigatus* are now reported to cause nosocomial fungal infections. The widespread use of azoles for prophylaxis and treatment has been linked with the emergence of non-albicans *Candida* species and other yeasts. Therefore prevention of nosocomial fungal infections is an increasingly important aspect of infection control.

Despite enormous advances in the field of infectious diseases, the identification of fungi as the cause of an infection is difficult to establish in cases of presumed fungus infection because of the nonspecific clinical signs and symptoms and the difficulties encountered in the isolation of these microorganisms in the microbiology laboratory. Delays in identification of fungal pathogens often lead to advanced disease and delay in the use of targeted antifungal therapy. To further compound the dilemma, treatment of fungus infection can be difficult given the paucity of commercial antifungal ophthalmic agents and the not-well-established criteria for antifungal sensitivity testing.

New classes and newer generations of antifungal therapies are being developed and may be important in combating this sight-threatening infectious disease.

The role of corticosteroids and its proper use in the treatment of fungal infections continues to be debated among experts. The controversy arises because there are two goals in the treatment of fungus infection that are inherently incompatible: (1) to get rid in the affected tissue of the replicating microorganisms causing the infection and (2) to limit the degree of structural damage caused by the infectious process.

Focal Points

- Fungal infections can be exogenous (postsurgical or posttraumatic) or endogenous.
- Fungal endophthalmitis usually presents as a chronic panuveitis.
- Fluffy deep yellow-white retinal or choroidal lesions are frequently present, and the vitreous often contains "fluff balls."
- The patient may not be symptomatic for days or even months until he or she develops blurred vision or floaters.
- Later in the course, redness, pain, hypopyon, and dense vitreitis may occur.
- *Candida* species are the most common organisms responsible for endogenous (as well as exogenous) fungal endophthalmitis.
- *Candida* endophthalmitis usually occurs in chronically ill patients with an indwelling catheter. It is also a frequent complication of intravenous drug use.
- *Aspergillus* species are the second most common cause of endogenous fungal endophthalmitis.
- Diagnosis is confirmed unequivocally by culturing the fungus from patient specimens on appropriate media and by specific laboratory methods, including the finding of fungi on direct microscopic examination of specially stained tissue sections.
- Histological features can be more rapidly diagnostic than culture when mycoses are caused by slow-growing fungi.
- The time saved by allowing appropriate introduction of antifungal therapy can be critically important to preserving ocular structures.
- Biopsy may provide proof that the fungus is invading tissue and that it is not merely a contaminant or saprophyte.
- Histological examination and culture ideally are performed together.
- For fungus infections that are limited to the eye, vitrectomy combined with intravitreal antifungals are the treatment of choice.

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Endogenous Endophthalmitis

10

J. Fernando Arévalo, Janet L. Davis, Emilio Dodds, and David G. Zeballos

Abstract

Endogenous endophthalmitis is the result of hematogenous spread of organisms to the eye from a site of infection elsewhere in the body or from contaminated catheters or needles. The prognosis in endophthalmitis is dependent on culture results, time of onset of the endophthalmitis, and the virulence of the pathogen. Biopsy of intraocular fluid/tissue is the only method that permits reliable diagnosis and treatment. Successful management of infectious endophthalmitis depends on timely diagnosis and institution of appropriate therapy. The different presenting clinical settings, a rational approach to diagnosis, and the treatment of infectious endophthalmitis are reviewed.

Keywords

Biopsy • Endogenous endophthalmitis • Intravitreal antibiotics • Metastatic infection • Vitrectomy

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DOI 10.1007/978-1-4614-3646-1_10,

Introduction

Endophthalmitis is a rare but potentially devastating intraocular infection that can result from exogenous spread following intraocular surgery, a complication of ocular trauma, or from an adjacent ocular interface, resulting in a poor visual prognosis for the majority of patients [1]. Endophthalmitis is divided into endogenous endophthalmitis, resulting from hematogenous spread from a focus of infection elsewhere in the body, and exogenous endophthalmitis, resulting from primary inoculation of the eye. Few patients with endogenous endophthalmitis are able to maintain good visual acuity.

Endogenous endophthalmitis, also termed metastatic endophthalmitis, occurs when organisms reach the eye via the bloodstream and enter the internal ocular spaces by crossing the blood-ocular barrier. Endogenous bacterial endophthalmitis (EBE) is less common than exogenous bacterial endophthalmitis and accounts for only 2–6% of all cases of endophthalmitis [2]. Several large series estimate that endogenous endophthalmitis accounts for 2–15% of all cases of endophthalmitis [3].

The possible range of infectious agents is broad and includes gram-positive bacteria, gram-negative bacteria, and fungi. However, there is considerable variation in the frequency of these pathogens between different geographical areas. Previously published series of patients with endogenous endophthalmitis have reported the most common bacterial organism as *Staphylococcus aureus* and the most common fungal organism as *Candida* species [4].

Endogenous endophthalmitis has been associated with many systemic risk factors, including chronic immune-compromising illnesses (diabetes mellitus, renal failure), indwelling or long-term intravenous catheters, immunosuppressive diseases and therapy (malignancies, human immunodeficiency virus [HIV] infection, chemotherapeutic agents), recent invasive surgery, endocarditis, gastrointestinal procedures, hepatobiliary tract infections, intravenous drug abuse, organ transplantation, and genitourinary and dental procedures [5]. In most cases, the diagnosis of endophthalmitis is made on clinical grounds, and treatment is usually initiated empirically while awaiting results from intraocular and/or blood cultures.

Advances in medical technology, a longer life span of patients with chronic diseases and a rising prevalence of long-term intravenous access, may lead to the disease becoming more common in clinical practice. Endophthalmitis is the most dreaded ocular infection and carries one of the worst visual prognoses of all ocular infections. Recognition of the different clinical settings in which endophthalmitis occurs and awareness of the highly variable presentation it may have facilitate timely diagnosis. Biopsy of intraocular fluid/tissue is the only method that permits reliable diagnosis and treatment.

In this chapter, we review the epidemiology, clinical findings, management, and prognosis of endogenous endophthalmitis.

Clinical Settings, Causative Organisms, and Epidemiology

Endophthalmitis is the term used for a severe inflammation of the intraocular structures always involving the ocular fluids (either the vitreous or the aqueous humor or both). The cause of the inflammation may be infectious or noninfectious (also called sterile endophthalmitis).

Infectious endophthalmitis can be classified on the basis of the clinical setting and the time of onset of clinically apparent inflammation. General categories include postoperative endophthalmitis, posttraumatic endophthalmitis, endogenous endophthalmitis, and miscellaneous noninfectious causes of endophthalmitis, e.g., sterile uveitis, phacoanaphylactic endophthalmitis, and sympathetic ophthalmia. It most commonly occurs as a postoperative complication of cataract surgery and in 70% of cases is caused by coagulase-negative *Staphylococci*. Such infections are rare, with an incidence of 0.07–0.32% [6]. Postoperative fungal endophthalmitis is usually seen in clusters due to the use of contaminated intraocular irrigation solution, intraocular

Table 10.1 Classification of endophthalmitis

Infectious endophthalmitis
Postoperative
• Acute postoperative endophthalmitis
• Delayed-onset endophthalmitis (onset > 6 weeks postoperatively)
• Conjunctival filtering bleb–associated
Endogenous
Posttraumatic
Noninfectious endophthalmitis
Sterile uveitis
Phacoanaphylactic endophthalmitis
Sympathetic ophthalmia

lenses, ventilation system, and hospital construction activities (Table 10.1) [7].

Endogenous endophthalmitis comprises only a minority of endophthalmitis cases. Whereas endophthalmitis occurs at an average annual incidence of 5 in 10,000 hospitalized cases, only 2–15% are endogenous [7]. Endogenous endophthalmitis, also termed metastatic endophthalmitis, occurs when organisms reach the eye via the bloodstream and enter the internal ocular spaces by crossing the blood-ocular barrier. Endogenous endophthalmitis is associated with several medical conditions such as diabetes, lymphoproliferative disease, malignancy, immunosuppression, parenteral alimentation, recent extended surgical procedure, alcoholism, or intravenous drug abuse [8, 9].

Endogenous bacterial endophthalmitis is a rare but a visually devastating disease. It may occur at any age and has no sexual predilection. The right eye is involved twice as often as the left eye because of the more proximal and direct blood flow to the right carotid artery [10]. Bilateral involvement occurs in approximately 25% of cases. Organisms spread hematogenously to the eye from a site of infection elsewhere in the body or from a contaminated catheter in the body. Retinal damage is caused partly by microbial toxins and exacerbated by the ischemia caused by septic emboli. Immunocompromised states such as diabetes mellitus, malignancy, and chemotherapy are associated with a reduced host defense and constitute risk factors for developing endogenous endophthalmitis.

The most common causes of bacterial endogenous endophthalmitis include *Streptococcus* species, *S. aureus,* and, in some studies, *B. cereus*. Whereas *B. cereus* was being increasingly recognized in exogenous, posttraumatic endophthalmitis, numerous cases of endogenous endophthalmitis relating to *B. cereus* had already been reported in the literature. The infections were linked with the transfusion of contaminated blood products and the use of illicit intravenously administered drugs [11].

Streptococcus pneumoniae and *S. viridans* are common causes of bacterial endogenous endophthalmitis secondary to meningitis and endocarditis, respectively, but other *Streptococcus* species have been isolated as well. Group G streptococcal endophthalmitis has been reported in elderly patients with skin wounds or malignant neoplasms, and group B streptococcal endophthalmitis has been noted in neonates with meningitis and in immunocompromised adults [12, 13]. *Acinetobacter baumannii* is emerging as a common cause of hospital-acquired infections especially in the very ill patients. Fortunately, *Acinetobacter* endogenous bacterial endophthalmitis is still a rare occurrence [14]. Other infrequently encountered organisms include *Citrobacter* [15], *Aeromonas hydrophila* [16], and nontuberculous *mycobacteria* [17].

Gram-positive bacteria are the most common cause of bacterial endogenous endophthalmitis. *Listeria monocytogenes* has been described as causing a fairly indolent infection that is characterized by a brownish hypopyon and should be considered if this finding is present without corneal involvement. Endophthalmitis caused by anaerobic *Clostridium* species has also been reported in association with bowel carcinoma, and because of its particularly aggressive nature, this infection often results in enucleation [18].

Enteric gram-negative microorganisms (e.g., *Escherichia coli, Klebsiella pneumoniae, H. influenzae, P. aeruginosa,* and *Serratia* species) are the most common causes of gram-negative bacterial endogenous endophthalmitis. *Pseudomonas aeruginosa* is an especially virulent organism that may result in an accelerated presentation with rapid vision loss. *Pseudomonas aeruginosa* endophthalmitis has

been reported in few cases since 1935 [19]. The age range is variable with cases reported in a 21-day-old infant and in an 86-year-old man. Males appear to be more commonly affected than females. Predisposing factors for *Pseudomonas aeruginosa* endogenous endophthalmitis appear to be endocarditis [20], bacteremia from any source, immunosuppression [21], and cystic fibrosis [22].

Neisseria meningitidis was a common cause of bacterial endogenous endophthalmitis, but it is rarely the cause today. *Haemophilus influenzae* infection can present in a manner similar to that of meningococcus with bacteremia, meningitis, and eye infection. *Nocardia asteroides* is an acid-fast bacterium that may lead to bacterial endogenous endophthalmitis secondary to dissemination from a pulmonary focus and has increasingly been associated with endogenous endophthalmitis in immunocompromised patients [23]. Among other acid-fast bacteria, *Actinomyces* species and *Mycobacterium tuberculosis* have also been reported infrequently [24].

The most common organisms responsible for endogenous bacterial endophthalmitis differ in different parts of the world. In Western countries, the proportion of gram-positive organisms is about six times that of gram-negative organisms [25]. On the other hand, *Klebsiella pneumoniae*, which is an uncommon cause of endogenous bacterial endophthalmitis in the West [26], continues to be an important causative organism in Asia especially in Taiwan, being responsible for about 80% of the endogenous bacterial endophthalmitis cases [27].

Wong et al. [28] reported the East Asian experience of predominantly gram-negative organisms, in particular *Klebsiella pneumoniae*. In East Asia, endogenous bacterial endophthalmitis was overwhelmingly caused by gram-negative organisms, particularly *Klebsiella* spp. Cases reported from outside that region were more likely to be caused by gram-positive organisms. Unusual organisms may be more likely to get reported, but Wong's own case series considered all patients presenting with endogenous bacterial endophthalmitis and found that gram-negative organisms were responsible for 70% of infections. *Klebsiella* spp. accounted for about 90% of endogenous bacterial endophthalmitis cases from that region, and 80% of cases in that review were from East Asian hospitals. The reason for this apparent predisposition to *Klebsiella* endogenous bacterial endophthalmitis is not clear, but there is also a high incidence of *Klebsiella* liver abscesses in this population. Patients with *Klebsiella* liver abscess have a 3% risk of developing endogenous bacterial endophthalmitis [29]. A comparable large series from North America found that only 32% of cases were caused by gram-negative organisms [30]. Most cases of *Klebsiella pneumoniae* endophthalmitis also occur secondary to urogenital and respiratory tract infections or, less commonly, in association with brain abscesses or meningitis [28].

Gram-positive organisms are responsible for 40% of cases. The most common gram-positive organisms were *Staphylococcus aureus*, group B *streptococci, Streptococcus pneumoniae*, *Listeria monocytogenes*, *Nocardia asteroides,* and group G *streptococci* [4]. In the West, gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus pneumoniae* are responsible for most cases [30]. *N. asteroides* choroidal abscesses (Fig. 10.1a, b) may also be mistaken for fungal endophthalmitis or, alternatively, neoplastic choroidal metastases. All three conditions may have a similar fundal appearance, abnormal cells in the vitreous, and extraocular manifestations of disease. In this setting, transvitreal fine needle aspiration of a choroidal abscess has been used to establish the diagnosis [31].

Endogenous fungal endophthalmitis has emerged as a visually threatening complication in intravenous drug abusers and in patients with immune deficiency of various causes. In immunocompromised patients, intraocular infection represents dissemination of invasive diseases caused by *Candida* species, *Aspergillus* species, *Fusarium* species, *Cryptococcus neoformans*, *Pseudallescheria boydii*, *Coccidioides immitis*, and others [32, 33]. Among these, *Candida* species is the most common, and *Candida albicans* is the most frequent cause and accounts for 75–80% of cases of fungal endophthalmitis, followed by *Aspergillus* infection.

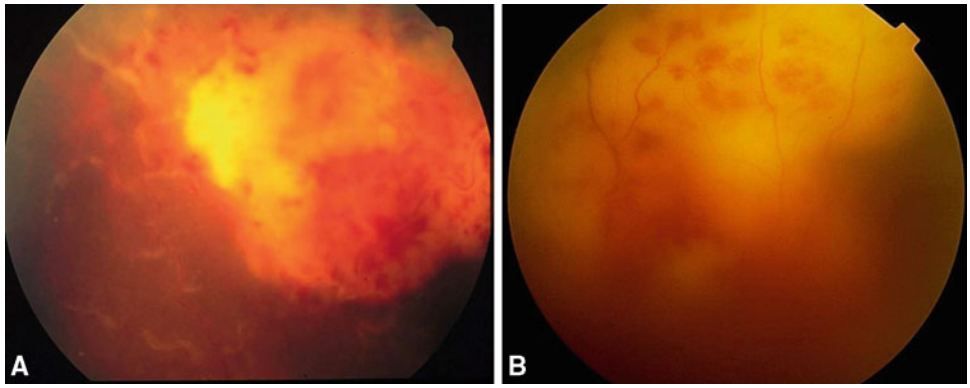

Fig. 10.1 *Nocardia asteroides* choroidal abscesses. (**a**) Fundus photography demonstrating yellowish appearance of subretinal abscess with overlying retinal hemorrhages. Moderate vitritis and vasculitis are present. (**b**) Fundus photography demonstrating yellowish appearance of subretinal abscess with overlying retinal hemorrhages. Moderate vitritis is present

Table 10.2 Causative organisms of endogenous endophthalmitis

Bacteria	Fungi
Streptococcus sp.	*Candida albicans*
Staphylococcus sp.	*Aspergillus* sp.
Clostridium septicum	*Histoplasma*
Bacillus aureus	*Coccidioides*
Coagulase-negative *Staphylococcus*	*Blastomyces*
Escherichia coli	*Cryptococcus*
Klebsiella pneumoniae	*Sporothrix*
Serratia marcescens	*Pseudallescheria boydii*
Pseudomonas aeruginosa	*Bipolaris hawaiiensis*
Neisseria meningitidis	
Listeria monocytogenes	

Candida albicans is the most common cause of endogenous endophthalmitis. Other *Candida* species such as *C. tropicalis*, *C. glabrata*, and *C. parapsilosis*, as well as other fungi such as *Aspergillus*, *Coccidioides*, *Cryptococcus*, *Blastomyces*, and *Sporothrix*, also may cause an endogenous intraocular infection (Table 10.2) [34]. The prevalence of endogenous chorioretinitis and/or endophthalmitis in patients with *Candida* fungemia is reported to range from 2.8% to 45% [35].

Risk factors associated with intraocular *Candida* infection include *Candida albicans* species' multiple positive blood cultures, indwelling catheters, parenteral hyperalimentation, hemodialysis, chronic exposure to antibiotics, immunosuppression, surgery, intravenous (IV) drug use, liver disease, malignancies, and states of debilitation [36].

Aspergillus endophthalmitis, a relatively rare condition, has a devastating course, with blindness as its usual outcome. *Aspergillus* endophthalmitis has been reported to occur following ocular surgery, trauma, and, less frequently, from hematogenous spread from extraocular sites. Disseminated aspergillosis occurs typically in patients with a compromised immune system related to organ transplantation, hematologic malignancy, or use of immunosuppressive agents [37]. In addition, there have been several case reports of *Aspergillus* endophthalmitis in intravenous drug abusers [38]. The diagnosis of *Aspergillus* endophthalmitis should be entertained in all patients with a systemic predisposition or *Aspergillus* disease elsewhere in the body. The help of ancillary investigations such as ultrasonography, lactate dehydrogenase activity of aqueous and serum, aqueous humor cytology, and fungal culture should be utilized to establish a diagnosis.

Cryptococcus spores can survive up to 2 years in pigeon droppings. Spores gain access to the human body through inhalation. From the lungs, the fungus is disseminated hematogenously and

preferentially affects the central nervous system. It is the most common cause of fungal meningitis. *Cryptococcus* organisms reach the eye through either direct extension from the optic nerve sheath or hematogenously from a distant focus. Cryptococcal endophthalmitis is a rare condition that is most often diagnosed by examining enucleated specimens or at autopsy [39].

Coccidioides endophthalmitis results from the inhalation of *C. immitis* arthroconidia, which are found in the dust of endemic areas such as the San Joaquin Valley of central California, Arizona, New Mexico, Texas, and in parts of Venezuela, Honduras, and Colombia. Agricultural workers and construction crews are at particular risk. In most patients, the inhalation of the spores leads to a self-limited respiratory disease. In a few patients who are reexposed to the fungus, a chronic respiratory disease ensues. Hematogenous dissemination to the eye can occur in both immunocompetent and immunocompromised patients [40].

Clinical Findings

A high degree of suspicion is necessary to make an early diagnosis of endogenous endophthalmitis. Blurred vision is the most common symptom at presentation, occurring in 94.3% of patients. It has been suggested that pain is an important indicator of endophthalmitis, but only 74.3% of patients presented with pain, indicating that the absence of pain does not rule out the diagnosis of endophthalmitis. Hypopyon (Fig. 10.2a, b) is the most common sign of endophthalmitis, occurring in 85.7% of patients; but as is the case with pain, its absence does not preclude the diagnosis of endophthalmitis. Poor media clarity is the next best indicator, with 79.1% of patients having no view of any retinal vessels and 68% having no red reflex. Second-order retinal vessels were seen in only 10% of patients. Earlier signs include retinal changes such as Roth's spots and retinal periphlebitis. Slit lamp examination and ocular ultrasonography should be performed to look for anterior vitreous haze echoes and retinochoroidal thickening. Patients who present at a later stage in the disease may have obvious signs such as chemosis, proptosis, and hypopyon.

Endogenous bacterial endophthalmitis generally occurs within a week after the onset of systemic illness, but may occasionally develop a month or more after the onset of sepsis [28]. The systemic symptoms of sepsis are often nonspecific and include malaise, nausea, loss of appetite or weight, and abdominal discomfort. Endogenous bacterial endophthalmitis may be classified as anterior, posterior, or panophthalmitis. The anterior and posterior forms may further be subdivided into focal or diffuse [10]. Anterior focal disease, where the infection is confined to one or more discrete foci that may appear as iris nodules or microabscesses, is rare. The anterior segment inflammation is mild to moderate. In the diffuse type, the inflammation tends to be more severe, with chemosis, lid swelling, corneal edema, fibrin in the anterior chamber, and hypopyon. The intraocular pressure (IOP) is often elevated.

Posterior focal disease manifests as whitish nodules or plaques, usually in the choroid, that rapidly involve the retina. Infections caused by gram-positive organisms such as *Staphylococcus aureus* may be multifocal, associated with Roth's spots and retinal vasculitis, and tend to be severe (Fig. 10.3a, b, c). Gram-negative infections usually cause a single large choroidal abscess involving the posterior pole. There may only be minimal injection of the conjunctiva with a relatively clear cornea and mild to moderate anterior chamber reaction.

Diffuse disease is a more severe condition characterized by intense vitreous inflammation, which usually obscures the fundus. This may arise from virulent organisms such as Group B *Streptococcus* or from posterior focal infection, especially if these are misdiagnosed as autoimmune uveitis and treated with periocular steroid injections. Perivascular hemorrhages, inflammatory infiltrates, and arterial emboli [41] have been noted in cases where the fundi could be visualized. Ultimately, retinal necrosis occurs. Globe perforation may occur at the site of an abscess, especially if the infection is accompanied by a marked rise in IOP. In panophthalmitis, the infection involves the entire globe and may spread to the orbital tissues resulting in lid edema,

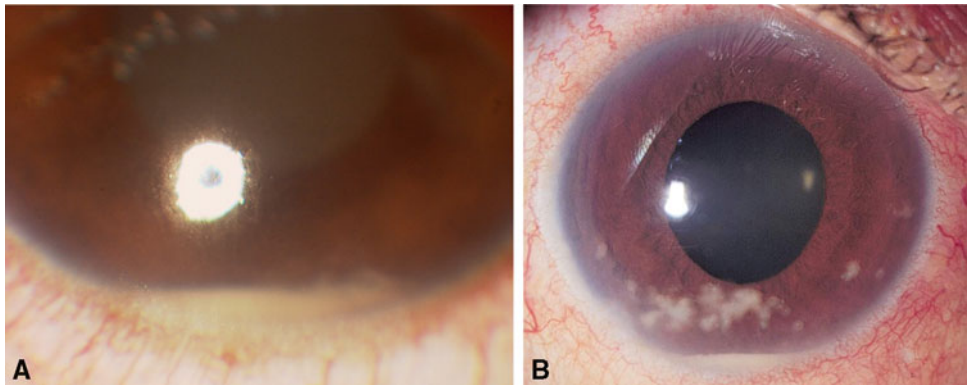

Fig. 10.2 *Candida* endophthalmitis. (**a**) Clinical features of a 22-year-old woman with endogenous endophthalmitis. Marked intraocular inflammation with hypopyon and conjunctival congestion. (**b**) Anterior focal endophthalmitis

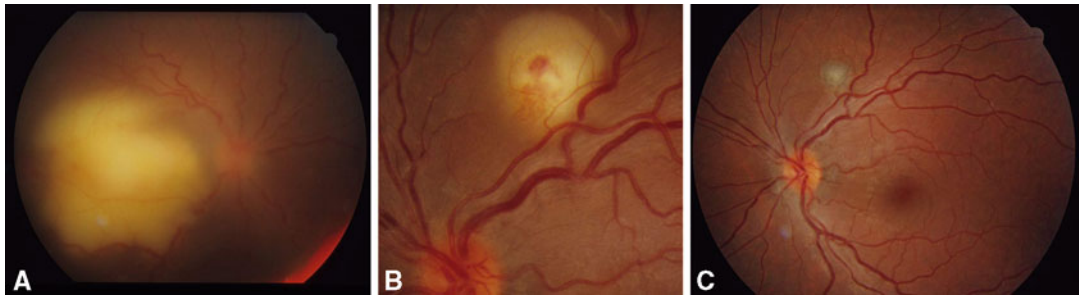

Fig. 10.3 (**a**) *Staphylococcus aureus* abscess diagnosed by transvitreal biopsy. (**b**) *Staphylococcus aureus* abscess in the contralateral eye. (**c**) *Staphylococcus aureus* abscess in the contralateral eye resolved after antibiotic treatment

chemosis, proptosis, and limited ocular movements. This may be caused by *Klebsiella* (Figs. 10.4 and 10.5) and *Pseudomonas* species.

O'Day and colleagues outlined three features common to cases of exogenous *B. cereus* endophthalmitis. Firstly, there was a penetrating injury with vitreous involvement. Secondly, perforation was caused by a low velocity metallic fragment. Finally, there was the possibility of soil contamination. The interval between injury and deterioration of vision was typically less than 48 h. Severe pain often develops within 24 h. This occurs in conjunction with a drastic reduction in visual acuity, chemosis, periorbital swelling, and proptosis. Classically, a corneal ring abscess develops in association with the reduction of vision. Some authors have indicated that this is pathognomonic; however, it has been described in other cases of endophthalmitis including those caused by *Pseudomonas* and *Proteus* species [42]. The other important distinguishing feature is that *B. cereus* endophthalmitis often produces associated systemic symptoms. The patient develops fever, leukocytosis, and malaise.

Candida chorioretinitis is the most common cause of endogenous endophthalmitis with a characteristic clinical ocular appearance. Endogenous *Candida* endophthalmitis often starts as a focal choroiditis, and then the infection spreads into the retina and breaks into the vitreous. The presence of white vitreous opacities forming a string-of-pearls appearance is a very typical feature (Fig. 10.6a, b). Among the mechanisms postulated to explain the predilection of *C. albicans* to infect the eye is the ability to form germ tubes in serum that embolize and lodge in the choriocapillaris.

Aspergillus infections of ophthalmic interest usually cause keratitis or orbital cellulitis, and less commonly conjunctivitis and canaliculitis.

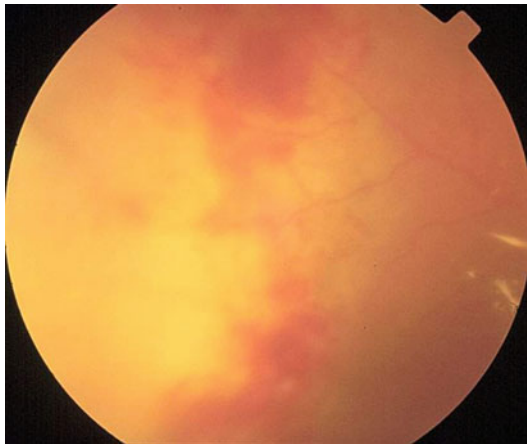

Fig. 10.4 *Klebsiella pneumoniae* endophthalmitis. Fundus photo depicting a unilateral subretinal mass at the posterior pole

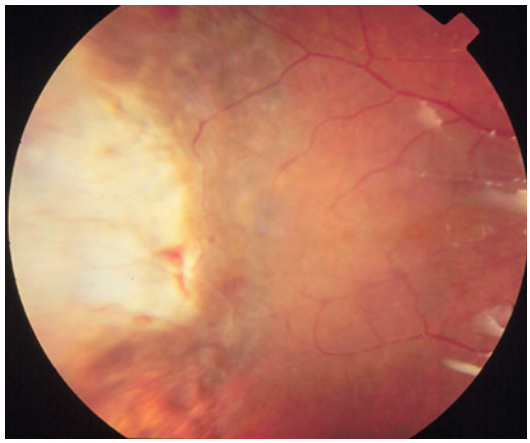

Fig. 10.5 Same patient as in Fig. 10.4. The unilateral mass has resolved after treatment

[43] On review the authors found that the presenting complaint in the cases reported so far was a diminution of vision in 16 cases, a red eye in seven, ocular pain in four, and acute proptosis in two. Clinically, 12 cases presented with signs of iritis, five of whom had a hypopyon, and 18 showed marked chorioretinitis. A yellowish white mass with an abscess in the posterior segment was seen in 15 cases, while superficial retinal hemorrhages were present in three and a retinal detachment was observed in four. One case [44] presented with an anterior chamber mass, quite akin to the picture presented in the left eye by the same patient.

C. neoformans usually presents intraocularly as a multifocal chorioretinitis characterized by discrete yellow-white lesions of different sizes [39]. The inflammatory reaction is somewhat mild, in contrast to *Candida* or *Aspergillus*. Retinal vessels may be sheathed, and vitritis of variable intensity may develop [45]. Retinal necrosis accompanied by retinal hemorrhage and exudative retinal detachments also have been known to occur. If the central nervous system is involved, papilledema is present. A mild inflammatory reaction is usually present in the anterior segment.

In *Coccidioides* endophthalmitis, the uvea is the most common site of intraocular infection [46]. A granulomatous uveitis can ensue, with mutton-fat keratic precipitates and iris nodules with or without posterior involvement. Multifocal choroiditis with small yellow-white lesions

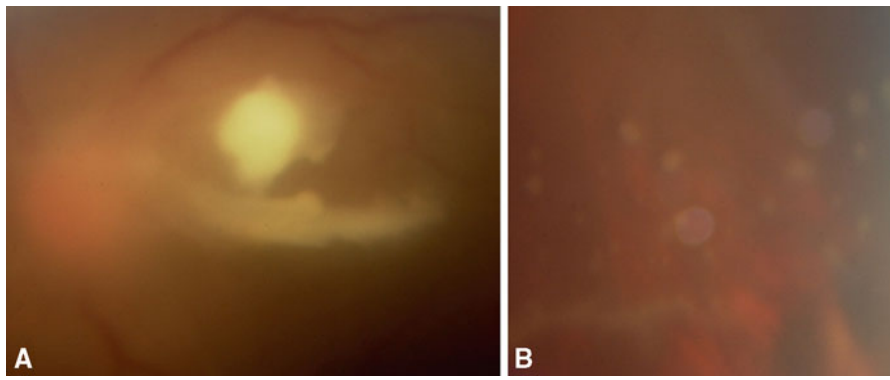

Fig. 10.6 Same patient as in Fig. 10.2a with *Candida* endophthalmitis. (**a**) Fundus photography shows a central macular yellow-white preretinal abscess or "fluffy ball" extending into the vitreous chamber. Vitreous chamber haze resulted in reduced fundus view. The retina was attached. (**b**) Snow balls in the inferior periphery of the same patient

measuring less than a disk diameter in size and most commonly located in the peripapillary area has been described. Occasionally, vascular sheathing, vitreous haze, serous retinal detachment, and retinal hemorrhage may also be seen [47].

Diagnosis

In addition to initial diagnostic laboratory tests, testing for HIV infection should be considered in otherwise healthy persons with endophthalmitis. Routine radiographs may reveal a primary pulmonary infection. Echocardiography is also warranted to assess the possibility of endocarditis. Other tests like chest radiographs, echocardiography, and ultrasonography or computed tomography (CT) scan of the abdomen may be useful to help locate the source of infection. In addition, a Gallium-67 scan may help to reveal foci of inflammation [48]. Computed tomography and magnetic resonance imaging of the orbits have been proposed both for the diagnosis as well as monitoring of response to treatment of endogenous bacterial endophthalmitis in eyes with opaque media. However, this may not be an economically viable option in developing countries, and ultrasonography is an equally sensitive and specific but more cost-effective diagnostic imaging tool [49]. Cultures obtained from blood (72%), urine (28%), and cerebrospinal fluid (50%) allow for early and reliable identification of microorganisms in at least 80% of cases of endogenous bacterial endophthalmitis [30] and should preferably be obtained before initiation of antibiotic therapy.

How to Culture

When any type of endophthalmitis is suspected, intraocular cultures and gram stains should be performed. Both vitreous and aqueous humor from the anterior chamber should be cultured because occasionally organisms are isolated from one but not the other. Aqueous material can be obtained with a 5/8-in. 30-gauge needle attached to a tuberculin syringe through a limbal stab incision, and 0.1–0.2 ml of fluid should be aspirated (Fig. 10.7). Vitreous biopsy is best performed via a 25-gauge transconjunctival sutureless pars plana one-, two-, or three-port vitrectomy (Figs. 10.8, 10.9, and 10.10) [50]. A single-port vitreous biopsy can be performed in the office with a 23-gauge vitrectomy probe. If an automated vitrectomy probe is not available, a biopsy specimen of the vitreous can be obtained with a 5/8- to 1-in., 25–27-gauge needle attached to a tuberculin syringe. Use of a vitrectomy probe probably results in less vitreoretinal traction than aspiration with a syringe, and it does not increase the likelihood of obtaining

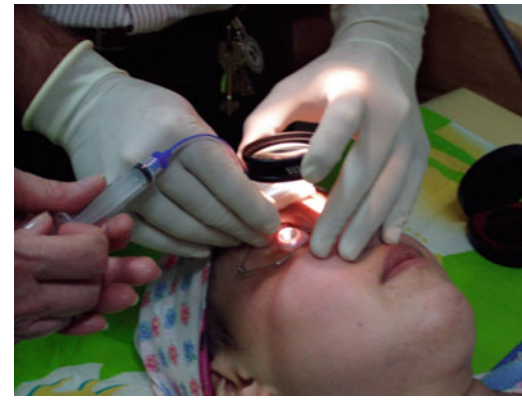

Fig. 10.7 Aqueous material can be obtained with a 5/8-in. 30-gauge needle attached to a tuberculin syringe through a limbal stab incision, and 0.1–0.2 ml of fluid should be aspirated

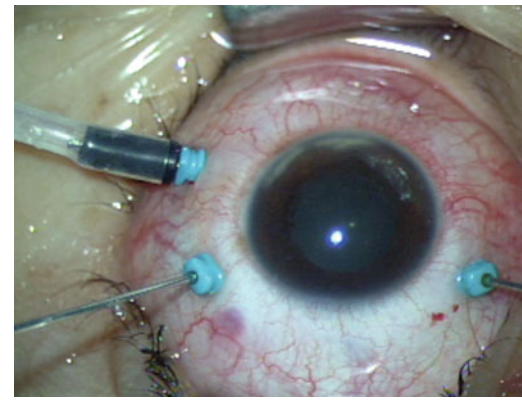

Fig. 10.8 After insertion of the first microcannula, the infusion cannula is directly inserted into the external opening of the microcannula. The infusion cannula should be close (turned off), and two other microcannulas are inserted in the superotemporal and superonasal quadrants

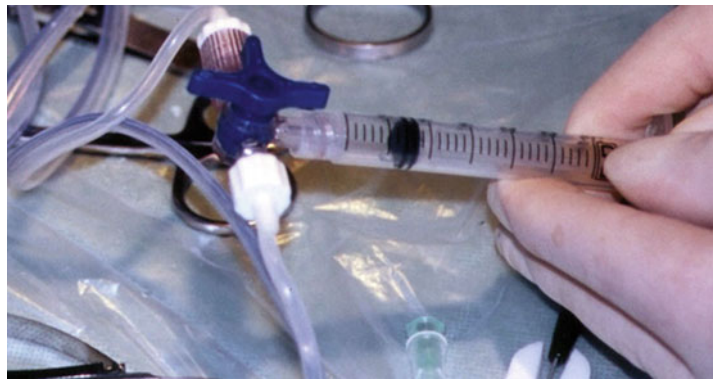

Fig. 10.9 A 10-ml syringe is spliced via a three-way stopcock into the aspiration line. The vitrectomy handpiece is placed in mid-vitreous cavity with the infusion turned off. Automated cutting and manual aspiration of the vitreous without concurrent infusion is then performed. The vitrector is withdrawn from the eye, and the vitreous specimen is aspirated into the syringe

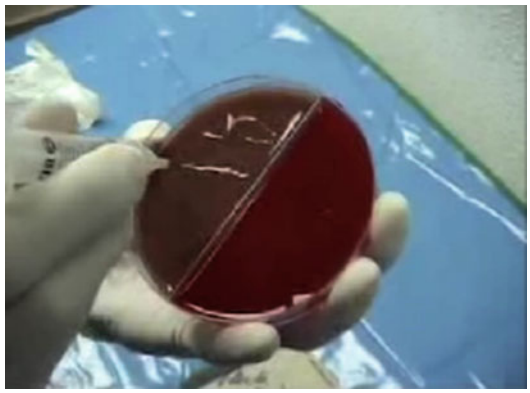

Fig. 10.10 At least 1 ml of undiluted vitreous is aspirated into the collection syringe and distributed for studies

false-positive culture results [51]. Vitreous specimens (0.1–0.2 mL for aspirate, 0.5 mL for vitrectomy probe–assisted vitreous biopsy, 1 mL for three-port vitrectomy) should be sent to the laboratory undiluted to increase the yield. If a two- or three-port vitrectomy is done, one should consider submitting the cassette fluid for culture.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) is becoming increasingly utilized in the diagnosis of endophthalmitis and has a number of potential advantages [52]. PCR greatly amplifies the quantity of bacterial DNA available for analysis, and this may enable the detection of a single organism [53]. The process of DNA replication can also be performed within a few hours.

Although PCR is a rapid and highly sensitive test, it also has disadvantages. The high sensitivity may lead to false-positive results, and specimens need to be carefully collected and processed to avoid exogenous or cross-contamination. False-negative results are also possible, particularly with unusual organisms [54]. Careful control experiments are therefore required if the results of PCR are to be meaningful. PCR may be used to rapidly establish the presence of bacterial infection but may take 48–72 h for final species identification [55], and unlike traditional culture techniques, it does not detect the ability of an organism to replicate, or its antibiotic sensitivity. In addition, PCR is not yet routinely available and is of limited use in mixed infections. For these reasons, PCR is likely to become a useful adjunct to microbiology and culture, rather than replacing it.

Treatment

A patient with hand motions or better vision should have an immediate tap or biopsy, followed by injection of antibiotics. It is reasonable to perform vitreous taps because they can be done more quickly, decreasing delay in administration of antibiotics. Specimens should be obtained

from both the vitreous and the anterior chamber. If an adequate specimen is not obtained, vitreous biopsy should be performed. Undiluted vitreous provides the best specimen for cultures, but a specimen should also be obtained from the anterior chamber because 4.2% of patients in the Endophthalmitis Vitrectomy Study (EVS) had positive cultures from an anterior chamber specimen only [56].

Patients with light perception vision should have immediate vitrectomy. At the beginning of the procedure, a 0.3–0.5-mL specimen of undiluted vitreous should be obtained. After turning on the infusion, an anterior chamber tap should be done, and the specimens should be plated immediately. The vitrectomy is then completed. Often, there is a fibrin membrane covering the anterior surface of an intraocular lens; it is necessary to manipulate the vitreous cutter into the anterior chamber and remove the fibrin membrane, which can markedly improve visualization. Once the vitrectomy is completed, the fundus should be examined with indirect ophthalmoscopy and scleral depression to rule out any retinal breaks. After closing the sclerotomies, antibiotics are injected.

Systemic Antibiotics

Prompt administration of antibiotic therapy is key in the acute management of endogenous endophthalmitis. This condition is particularly responsive to intravenous antibiotics. Systemic antibiotics also treat distant foci of infection and prevent continued bacteremia, thereby reducing chances of invasion of the unaffected eye. Intravenous benzylpenicillin is indicated in cases of suspected meningitis in children and young adults. Subsequent therapy can be tailored according to culture and sensitivity results and response to treatment. In all cases, prolonged intravenous therapy is usually required for 2–4 weeks to ensure complete eradication of the systemic infection. Empiric broad-spectrum antibiotic therapy with vancomycin and an aminoglycoside or a third-generation cephalosporin is warranted (Table 10.3) [57].

Table 10.3 Treatment of endogenous bacterial endophthalmitis

- Admit the patient to the hospital
- Broad-spectrum IV antibiotics including vancomycin and an aminoglycoside or third-generation cephalosporin
- Consider adding clindamycin in IV drug users until *Bacillus* infection can be ruled out
- Intravitreal antibiotics are indicated
- Cycloplegics may be administered
- Topical steroids may be considered
- Vitrectomy may be needed for virulent organisms

IV Intravenous

Third-generation cephalosporins penetrate ocular tissues and are effective against gram-negative organisms. The nature of the clinical presentation, as well as the presumed (or confirmed) source of infection, can be used to guide the decision about which antibiotic to use. In cases of documented gastrointestinal or genitourinary infection, second- or third-generation cephalosporins and aminoglycosides are considered the drugs of choice. Vancomycin should be given to patients known to abuse drugs, covering the possibility of infection with *Bacillus*. In the presence of wounds, oxacillin or a first-generation cephalosporin should be used. If the patient's history, stains, or culture results suggest a fungal infection, amphotericin B, fluconazole, or itraconazole should be included in the regimen [57].

Confirmation of a presumptive diagnosis of fungal endophthalmitis frequently implies a pars plana vitrectomy (Figs. 10.8, 10.9, and 10.11). Vitrectomy has the advantage of eliminating microorganisms and inflammatory mediators from the vitreous cavity and provides material for microbiological examinations. Because patients frequently carry a variety of yeasts, culture from the ocular tissue is the only sure method of establishing the etiology of endophthalmitis.

Intravitreous Antibiotics

At the outset of the Endophthalmitis Vitrectomy Study (EVS), it was recognized that severe retinal vascular nonperfusion could result from

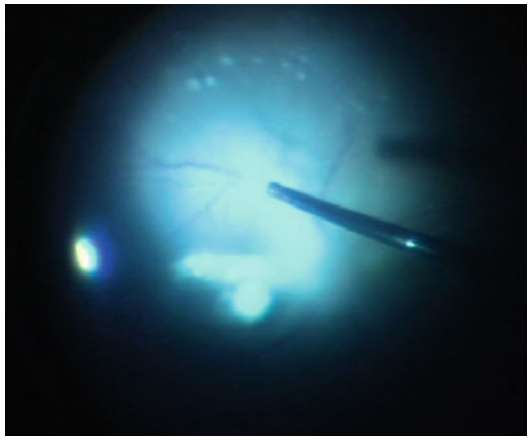

Fig. 10.11 Same patient as in Fig. 10.6. After the undiluted sample is taken, the therapeutic three-port vitrectomy can then be completed if necessary

intraocular injection of gentamicin and that the macula was frequently involved, resulting in severe loss of vision [58].

The organizers of the EVS, however, apparently believed that amikacin did not cause the same sort of toxicity, and, therefore, 0.4 mg of amikacin and 1 mg of vancomycin were selected for intravitreal injections. Other investigators believed that this was an assumption because amikacin, like gentamicin, was known to have neurotoxicity, and amikacin had been implicated in cases of macular infarction [59]. The EVS organizers considered switching from amikacin to ceftazidime but decided against it because patients who developed macular infarction after intravitreal amikacin had also received a subconjunctival injection of gentamicin, and they remained unconvinced that amikacin was toxic [60]. Subsequently, several cases of unequivocal amikacin-induced retinal nonperfusion were reported, and it was demonstrated that decreased visual acuity could range from mild to severe, depending on the location and amount of retinal nonperfusion [61].

Some investigators continue to doubt the potential toxicity of amikacin apparently because in their personal experience they have never recognized such toxicity. They continue to use amikacin and cite the results of the EVS to justify their position, because only one case of macular infarction was recognized out of 392 eyes treated with amikacin [62]. Based upon in vitro sensitivity studies in the EVS, ceftazidime was found to be equally efficacious as amikacin [63], and because ceftazidime has a better safety profile, Campochiaro [64] strongly recommends that ceftazidime be used instead of amikacin for intravitreous injections.

As the organisms that cause endophthalmitis and its virulence are not known, initially we always recommend taking a vitreous sample for culture and antibiogram; after that, we inject ample spectrum antibiotic combination in the cavity vitreous: vancomycin 1 mg in 0.1 ml + amikacin sulfate 0.4 mg in 0.1 ml or vancomycin 1 mg in 0.1 ml + ceftazidime sodium 2.25 mg in 0.1 ml. Antibiotics are sometimes injected into the vitreous cavity as the only intravitreal therapy, whereas on other occasions they are combined with pars plana vitrectomy.

Given the low permeability of pigmented epithelium to systemically administered drugs, intravitreal antifungals are used in cases in which systemic treatment is ineffective or following procedures such as vitrectomy and vitreous tap. For antifungal treatment, we include intravitreal amphotericin B (5 μ[mu]g/0.1 mL). Other primary antifungal treatments include intravitreal injection of voriconazole (100 μ[mu]g/0.1 mL), intravitreal injection of fluconazole (10 μ[mu]g/0.1 mL), intravitreal injection of miconazole (25 μ[mu]g/0.1 mL), and a combination of oral (amphotericin B 20 mg/day, fluconazole 400 mg/day, fluconazole 200 mg/day, or itraconazole 200 mg/day), topical, and subconjunctival antifungal agents, up to 6 months for endogenous fungal endophthalmitis. Despite poor vitreous penetration, systemic therapy of amphotericin B, fluconazole, or itraconazole may help in endogenous endophthalmitis.

The outcome of posterior diffuse endophthalmitis or panophthalmitis is frequently blindness, regardless of treatment measures. Vitrectomy and intravitreal antibiotics may, however, prevent ocular atrophy or the necessity for enucleation. Some damage may also be related to inflammatory mediators.

Corticosteroid Therapy

To reduce the destructive effect of the significant inflammation that coexists with infection in endophthalmitis, many ophthalmologists use systemic, topical, subconjunctival, and intravitreal corticosteroids in combination with antibiotics, provided that no contraindications exist (e.g., diabetes mellitus, tuberculosis, fungal infection).

The use of intravitreal and systemic steroids in the management of endophthalmitis remains controversial, with systemic steroids being contraindicated in patients with inadequately controlled sepsis. Intravitreal steroids, however, may have a protective effect on the retina in curbing the severe inflammation induced by destruction of the bacteria within the eye [65].

We commonly prescribe prednisone, 1 mg/kg orally each morning for 3–5 days. In addition, we recommend intravitreal dexamethasone (400 μ[mu]g/0.1 mL) [66]. It is given at the time of vitreous biopsy or vitrectomy. It is important to use preservative-free drugs to avoid potential retinal toxicity. Vancomycin, ceftazidime, and dexamethasone are physically incompatible and, if mixed in the same syringe, may precipitate. Therefore, separate slow injections to ensure proper mixing in the vitreous cavity are advised [67].

Vitrectomy

The theoretical advantages of vitrectomy include removal of the infecting organisms, endotoxins, exotoxins, and vitreous membranes that could lead to retinal detachment, clearing of vitreous opacities, collection of abundant material for culture, and possibly better distribution of intravitreal antibiotics. The disadvantages of vitrectomy include the added cost and inconvenience, and the risk of anesthetic and surgical complications, such as cataract formation.

The role and timing of vitrectomy remains unclear in endogenous bacterial endophthalmitis. Some reports suggest that combining medical therapy with early surgical intervention is beneficial [68]. Other studies found no significant benefit in performing vitrectomy [69]. However, all these studies have all been limited by the small number of cases and the variability with respect to multiple other factors including timing of surgery and the offending organisms. Vitrectomy will be useful in posterior diffuse disease as adequate material can be obtained for microbiology and it may have additional beneficial effects by reducing the number of organisms. Endogenous bacterial endophthalmitis complicated by retinal detachment is another indication for vitrectomy combined with scleral buckling. Silicone oil fill is usually necessary in these eyes. However, operating on a severely inflamed eye with an ischemic and necrotic retina increases the risk of hypotony, retinal breaks, and phthisis bulbi. When the infection has been controlled by systemic and or intravitreal antibiotics, vitrectomy is also useful in removing residual vitreous opacity and hastening visual rehabilitation

Prognosis

The visual outcome of endogenous bacterial endophthalmitis has not improved in 55 years. Review of the literature from 1976 to 1985 showed that 41% of patients had count fingers vision or better, 26% were blind, and 29% required evisceration or enucleation [10]. Similar figures were reported over the preceding 30 years [70]. Review of the literature since 1986 also indicates a poor outcome, with equivalent figures of 32% (count fingers vision or better), 44% (blind), and 25% (evisceration or enucleation). The studies that investigated prognostic factors in endogenous bacterial endophthalmitis (EBE) [11] were retrospective, and although selection bias cannot be excluded, they identified several factors that adversely affect prognosis. These included delay in diagnosis [10]; use of inappropriate antibiotics [71]; diffuse infection of the vitreous and retina, or panophthalmitis; infection with virulent organisms [30]; and gram-negative infection [70].

Fungal endophthalmitis may occur as a complication of intraocular surgery; as a manifestation of systemic fungal infection, secondary to trauma; or as an extension of an adjacent focus of infection. Its diagnosis requires a high degree of suspicion. PCR testing may reduce the delay in making the diagnosis. The prognosis of fungal endophthalmitis depends on the virulence of the organism, the extent of intraocular involvement, and the timing and mode of interventions. Prompt therapy with systemic antifungals, pars plana vitrectomy, and intravitreal antifungals following early diagnosis helps to reduce significant visual loss in all forms of fungal endophthalmitis.

Controversies and Perspectives

Intravitreal antibiotic therapy has become a commonly utilized standard for endophthalmitis treatment [3]. The intraocular concentration of antibiotics after intravitreal injection is far greater than that achieved by any other modality [62]. Therefore, intravitreal antibiotics are the most important component of therapy in eradicating infection in an eye with endophthalmitis. In the EVS, all patients received intravitreal amikacin (0.4 mg/0.1 cc) and vancomycin (l.0 mg/0.1 cc), but other antibiotics combinations have been suggested.

In the treatment of endophthalmitis, intraocular vancomycin is considered to be the drug of choice for gram-positive organisms and is nontoxic in the clinically recommended dose of 1 mg/0.1 cc [72]. In the EVS, all gram-positive organisms were susceptible to vancomycin, including methicillin-resistant *Staphylococcus aureus* (MRSA) [62]. Prior to vancomycin, cefazolin was used as a first-line choice for the treatment of gram-positive organisms, but frequent resistance to cefazolin made it a less desirable choice [73]. Among gram-positive organisms causing endophthalmitis, resistance to vancomycin is rare.

Continued controversy remains regarding the best antimicrobial against gram-negative organisms. Most clinicians have been using either an aminoglycoside, such as gentamicin or amikacin, or ceftazidime, a third-generation cephalosporin. Intravitreal aminoglycosides are a reported cause of macular toxicity [59]. Aminoglycoside-induced macular infarction is thought to be partially due to the gravity-induced settling of drugs on the macula in a supine patient. This may result in a higher concentration of drug locally at the macula [61].

Ceftazidime has been suggested as an alternative antibiotic to cover gram-negative organisms because of its broad therapeutic index, lower risk for retinal toxicity, and its in vitro sensitivities that are as effective as the aminoglycosides.

The EVS found that only patients with perception of light or worse visual acuity benefited from formal vitrectomy, although it should be noted that a significant selection bias existed in the EVS patients. All EVS patients also received intensive topical steroid and cycloplegia, and because significant anterior segment inflammation exists, higher doses of topical steroids are needed than would normally be given after cataract surgery. In fact the EVS visual results were even better than the Moorfields results quoted [74], with 53% of patients achieving 6/12 or better and 74% achieving 6/30 or better [62]. This reinforces the fact that with prompt and effective treatment endophthalmitis patients can achieve a reasonable result, and unless other contraindications exist, all patients should be given systemic steroids. There has been one paper that reported poorer visual outcomes following the use of intravitreal steroids (albeit a retrospective review) [4]. If intravitreal steroids are contemplated, then the dosage typically recommended for dexamethasone is 0.4 mg in 0.1 mL [75].

One author of a recent paper [76] suggested the use of a 21-G needle, which might not leave a self-sealing wound via pars plana along with potential for vitreous incarceration. It is often possible to obtain an adequate sample using a 23-G needle. Direct visualization of pars plana sampling as suggested by one author is also not necessary [76]. Most eyes do not require anterior chamber washout or other intraocular manipulations that may delay the injection of the relevant antibiotics while a more complex surgical procedure is organized. Similarly changing syringes to

inject antibiotics via the same needle can be technically difficult, and it is typically easier to inject antibiotics as two separate injections. Half-inch 27-G or 30-G needles are sufficient for this purpose, and the shorter length means that damage to intraocular structures is less likely in a soft eye setting.

Focal Points

- The outcome of endogenous endophthalmitis can be optimized by maintaining a high index of suspicion, especially in susceptible patients. However, the possibility of endogenous endophthalmitis in healthy patients and iatrogenic endogenous endophthalmitis also must be borne in mind.
- Poor prognostic factors include infection by more virulent organisms; poor host defense; misdiagnosis; and delayed, inappropriate, or inadequate treatment.
- Prompt diagnosis and intensive intravenous antibiotics are the most critical steps in the treatment of endogenous bacterial endophthalmitis. An important feature of this disease that needs emphasis is the potential risk to the unaffected eye. This means that intravenous antibiotics need to be administered very quickly, and patients should not be treated as if they have a unilateral eye problem.
- Current recommendations for empirically treating suspected bacterial endophthalmitis involve combination therapy targeting both gram-positive and gram-negative organisms. Therapeutic combinations of antibiotics should be tailored to the clinical scenario in which endophthalmitis develops and should target the most common causative organisms. Fungal therapy is considered when clinical history and ocular features justify this approach.
- Due to the low permeability of pigmented epithelium to systemically administered drugs, intravitreal antibiotics or antifungals are used in cases in which systemic treatment is ineffective or following procedures such as vitrectomy and vitreous tap. Regarding optimized therapy in such patients, further studies are required.
- Intravitreal therapy and vitrectomy are effective treatment modalities in fungal and bacterial infections.

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Retinal and Choroidal Manifestations of Sarcoidosis

11

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Abstract

Sarcoidosis is an enigmatic systemic inflammatory disease that can affect any ocular structure, potentially causing significant ocular morbidity and visual loss. Definite diagnosis is based on the demonstration of noncaseating epithelioid-cell granuloma in the affected organs. A wide range of retinal and choroidal manifestations of the disease can frequently simulate other ocular conditions. Corticosteroids are the mainstay of treatment, but several immunomodulatory agents, such as methotrexate, have shown efficacy and steroid-sparing properties. Complications of sarcoidosis must be managed early, given the potential for a decrease in vision. All sarcoidosis patients need comprehensive and periodic eye examinations.

Keywords

Sarcoidosis • Diagnosis • Treatment • Uveitis • Noncaseating granuloma • Corticosteroids • Immunomodulatory agents

Introduction

Sarcoidosis is a multisystem granulomatous disease, characterized by the presence of noncaseating granulomas in involved organs. The disease usually presents with bilateral hilar adenopathy, pulmonary infiltrates, and skin or eye involvement. It affects people of all racial and ethnic groups, typically developing before the age of 50 years, with a peak incidence at 10–39 years. The incidence varies widely among geographical regions, and it is highest in northern European countries (5–40 cases per 100,000 people). Sarcoidosis is approximately three times more common in black Americans than white Americans (35.5 cases per 100,000, as compared with 10.9 per 100,000). A slight preponderance of cases in women is consistent in different ethnic groups throughout the world [1].

The first case of the disease was described in 1869 at the Blackfriars Hospital for Skin Diseases

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by Jonathan Hutchinson [2]. Ocular involvement in sarcoidosis was first recognized by Schumaker in 1909. In the same year, the Danish ophthalmologist Heerfordt described uveoparotid fever (Heerfordt's syndrome), which was later characterized as a variant of sarcoidosis [3].

The eyes and ocular adnexa are involved in up to 80 % of affected patients during the course of the disease and may even predate the development of systemic signs of sarcoidosis. Uveitis precedes systemic disease in 30 % of cases. Although anterior segment involvement is more common (conjunctival granulomas, episcleritis, scleritis, nonspecific conjunctivitis, anterior uveitis), posterior segment involvement, which may include vitritis, vasculitis, choroidal lesions, and optic neuropathy, has been reported to occur in nearly 30 % of the patients with ocular sarcoidosis and may be accompanied by central nervous system (CNS) disease [4, 5].

Etiology

The etiology remains unknown, and the immune reaction in sarcoidosis is thought to be triggered by infectious organisms or exposure to environmental substances. Susceptibility to the disease also depends on genetic factors.

Exposure to irritants found in rural settings—such as tree pollen, insecticides, and emissions from wood-burning stoves—has been linked to sarcoidosis. Environmental exposure to certain elements (aluminum, beryllium, zirconium) is also thought to have a role in the pathogenesis of the disease. Several occupations have been associated with sarcoidosis, including fire fighters, metal workers, service in the US Navy, and the handling of building supplies [6, 7].

Some authors have identified antibodies to mycobacterial antigens in the serum of sarcoid patients. Detection of DNA from *Propionibacterium acnes* in lymph nodes of sarcoid patients has also been reported. Viruses, *Nocardia*-like organisms, have been proposed as potential causative agents [8].

Interferon-alpha, used in the treatment of different viral, autoimmune, and malignant diseases, has been implicated to induce systemic and ocular sarcoidosis [9].

Genetic Features

Although no formal twin study has been reported, the concordance of sarcoidosis seems to be higher in monozygotic twins than in dizygotic twins [1]. A significant elevated risk of the disease has been observed among first- and second-degree relatives of sarcoid patients, particularly in Caucasians [10].

Class I HLA-B8 antigens have been associated with sarcoidosis [11]. Several studies have also shown an association between HLA-DRB1 and the susceptibility and prognosis of the disease [12, 13].

Genes encoding for tumor necrosis factor-α(alpha) (TNF-α), interferon-γ(gamma), and chemokine receptors have not been confirmed to be related to sarcoidosis [14].

Two genome scans have been reported in sarcoidosis: one in German families, reporting linkage to chromosome 6, and the other in African-Americans, reporting linkage to chromosome 5 [15].

Most investigations suggest that genetic susceptibility to sarcoidosis is complex and polygenic in nature. Future studies on large, clinically defined cohorts may help elucidate the genetic impact on sarcoidosis [16, 17].

Immunopathogenesis

Sarcoidosis is a chronic granulomatous condition characterized by the presence of noncaseating granulomas. Histologically, epithelioid cells, radially arranged, with pale-staining nuclei, enclose the inner circle. A few multinucleated cells are present, and activated T cells surround the outer border of the granuloma (Figs. 11.1 and 11.2).

There have been remarkable advances in the past few years in understanding general immunologic and molecular aspects of the mechanisms leading to granuloma formation in sarcoidosis.

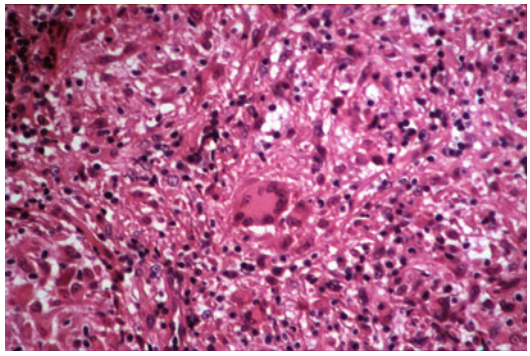

Fig. 11.1 Conjunctival biopsy demonstrating noncaseating granuloma. A Langhans giant cell is present in the center of the granuloma

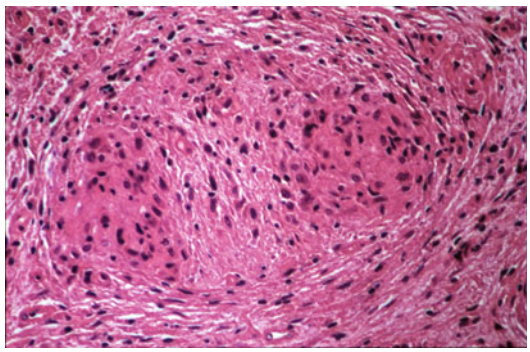

Fig. 11.2 Noncaseating granuloma in a patient with sarcoidosis

A cardinal feature is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of the granulomas [18]. The disease may be manifest clinically by an inverted CD4/CD8 ratio. Activated CD4+ cells differentiate into type 1 helper T cells and secrete interferon-γ(gamma) and IL-2, augment macrophage TNF-α(alpha) production, and amplify the local cellular immune response. TNF receptors are also increased. There is also evidence of B cell hyperreactivity and immunoglobulin production [19, 20].

The evolution of the granuloma results from a complex interplay between diverse cells types, chemokines and cytokines. The efficiency of antigen processing, presentation, and cytokine release is probably under the influence of different genes. Sarcoidal granulomas may persist, resolve, or lead to fibrosis [20].

Diagnosis

The diagnosis of sarcoidosis may be challenging in some cases, due to the wide variety of presentations affecting different organs. A definite diagnosis is established on the basis of compatible clinical and radiologic features, supported by histological evidence of noncaseating granulomas on biopsy of involved organs. Material for biopsy can be collected from the lungs, hilar and peripheral lymph nodes, liver, skin lesions, conjunctiva, and salivary and lacrimal glands. Endoscopic ultrasound-guided, fine-needle aspiration of intrathoracic lymph nodes has been reported to provide a diagnostic yield of up to 94 % [21, 22]. In some cases, physicians rely on less invasive blood and imaging studies to obtain a presumptive diagnosis of sarcoidosis [4, 5].

Macrophages within sarcoidal granulomas produce angiotensin-converting enzyme (ACE), which has been shown to be elevated in approximately 60 % of patients with sarcoidosis. The test is not useful in patients taking ACE inhibitors. Several series have shown that measurement of ACE level alone has poor sensitivity and specificity as a diagnostic tool and is a poor therapeutic guide. Romer et al. found it to be more frequently elevated in patients with chronic active sarcoidosis (duration more than 2 years) [23, 24].

Serum lysozyme levels have been demonstrated to have better sensitivity and specificity than ACE levels. Hosoya et al. studied 125 patients with sarcoidosis, and serum lysozyme levels were elevated in 76 % of them [25].

Bilateral hilar lymphadenopathy is the most frequent radiologic finding in systemic sarcoidosis and may be found in 50–89 % of the cases by chest radiography. Chest computed tomography (CT) imaging has been shown to be helpful in patients with normal or equivocal chest X-rays (Fig. 11.3). Paratracheal, subcarinal, and periaortic lymph node chains can be completely masked by large vessels and the trachea, and lymphadenopathy may be missed by chest X-rays alone. Moreover, chest CT is useful to rule out certain conditions and to guide bronchoscopy to obtain

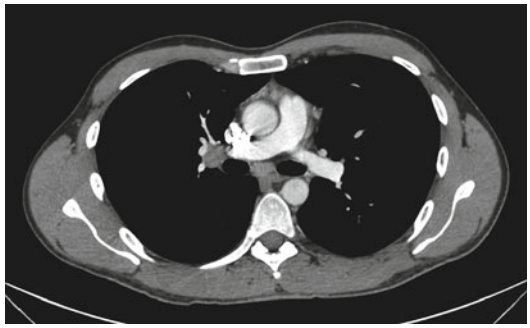

Fig. 11.3 Chest CT scan demonstrating paratracheal and hilar lymphadenopathy

tissue for histopathologic analysis and definite diagnosis [1, 26–28].

One of the most important conditions that may present with findings similar to ocular sarcoidosis is tuberculosis. Interferon-γ(gamma) release assays, such as the QuantiFERON-Gold test, may help the clinician distinguish between the two entities [29].

An International Workshop on Ocular Sarcoidosis, held in Japan in October 2006, aimed to reach a consensus on diagnostic criteria for intraocular sarcoidosis. A group of seven signs of intraocular inflammation were labeled as signs suggestive for the diagnosis, as follows: [30]

1. Mutton-fat/granulomatous keratic precipitates and/or iris nodules (Koeppe/Busacca)
2. Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae
3. Snowballs/string of pearls vitreous opacities
4. Multiple chorioretinal peripheral lesions (active and/or atrophic)
5. Nodular and/or segmental periphlebitis and/or retinal macroaneurysm in an inflamed eye
6. Optic disk nodule(s)/granuloma(s) and/or solitary choroidal nodule
7. Bilaterality

The following investigations were considered important to support the diagnosis of sarcoidosis in patients presenting with suggestive signs [30]:

1. Negative tuberculin test in a patient who previously received bacillus Calmette-Guérin (BCG) or had a positive purified protein derivative (PPD) test in the past
2. Elevated serum angiotensin-converting enzyme and/or elevated serum lysozyme
3. Chest X-ray (presence of bilateral hilar adenopathy)
4. Abnormal liver enzyme tests
5. Chest CT scan in patients with a negative chest X-ray

The consensus conference in Japan also determined four levels of certainty for the diagnosis of ocular sarcoidosis. A prerequisite was that the diagnosis of all other causes of uveitis, particularly tuberculosis, had been excluded.

Definite ocular sarcoidosis was attributed to patients with a biopsy-supported diagnosis with a compatible uveitis.

Presumed ocular sarcoidosis was considered for patients with a compatible uveitis, whose imaging studies showed the presence of bilateral hilar adenopathy, but no biopsy was performed.

Patients who had no biopsy performed and had no evidence of bilateral hilar adenopathy on chest X-ray but presented with three suggestive intraocular signs and two supportive investigations were labeled as *probable ocular sarcoidosis*.

The final category, *possible ocular sarcoidosis*, referred to patients with a negative lung biopsy who had at least four suggestive intraocular signs and at least two positive laboratory results.

Posterior Segment Findings

Posterior segment involvement has been observed in up to 30 % of patients with ocular sarcoidosis and may be the only manifestation of the condition in 11 % of cases. Studies have not shown a relationship between the severity of radiologic grading of pulmonary disease and the degree of ocular involvement [31].

Posterior segment disease has been shown to be more common in whites. European studies have reported a higher incidence of posterior segment involvement when compared to series from the United States. This dissimilarity, however, has been related to different racial patterns among the studies, with European studies tending to include a higher proportion of white patients than American studies [32].

The presence of posterior uveitis in patients with ocular sarcoidosis is one of the strongest

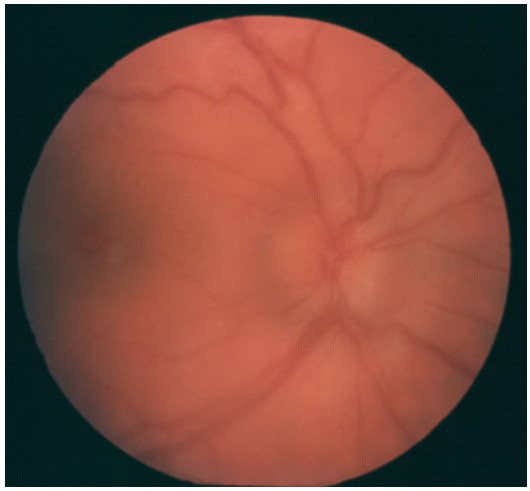

Fig. 11.4 Fundus photograph of the right eye showing vitritis and blurred optic disk margins due to an optic nerve granuloma

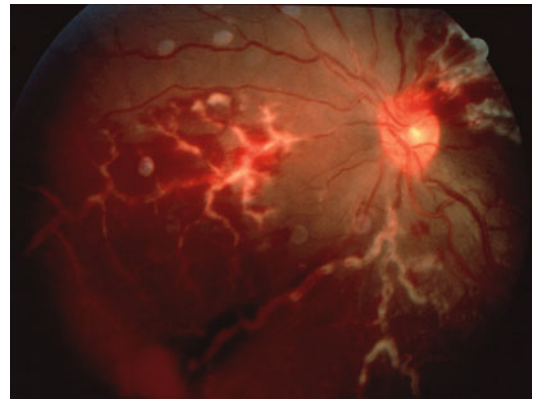

Fig. 11.6 Severe vasculitis extending to the periphery in a sarcoid patient

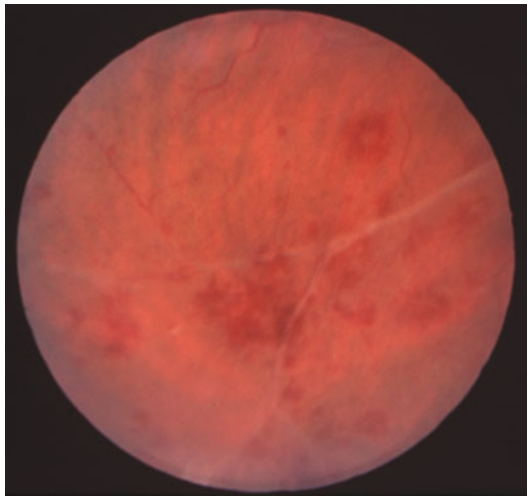

Fig. 11.5 Vasculitis and intraretinal hemorrhages

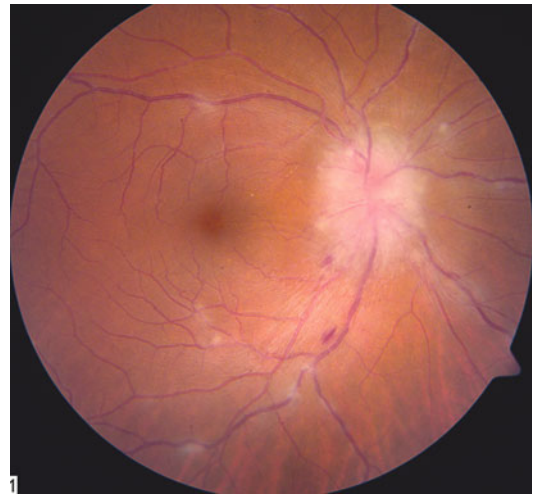

Fig. 11.7 Fundus photograph of the right eye demonstrating blurred disk margins and areas of segmental periphlebitis and white perivenous retinal exudates

parameters associated with a lack of visual acuity improvement (odds ratio, 8.33) [33].

According to several studies, vitritis and vasculitis are among the most common posterior segment findings (Figs. 11.4, 11.5, and 11.6). Vitreous opacities were first characterized by Landers in 1949, as grayish white bodies frequently found in the inferior vitreous and occurring in chains like a "string of pearls." [34]

Segmental periphlebitis typically involves the midperipheral or peripheral venules, resulting in focal vascular narrowing. In more severe cases, patients may present with waxy, yellow, or white perivenous retinal exudates, described as "candle-wax drippings" or "taches de bougie" (Figs. 11.7 and 11.8). This finding, although not pathognomonic, suggests the diagnosis of sarcoidosis [35]. There are reports of occasional occurrence of occlusive retinal vascular disease, particularly branch retinal vein occlusion [36, 37].

The diagnosis of ocular sarcoidosis is particularly challenging in patients with no evidence of

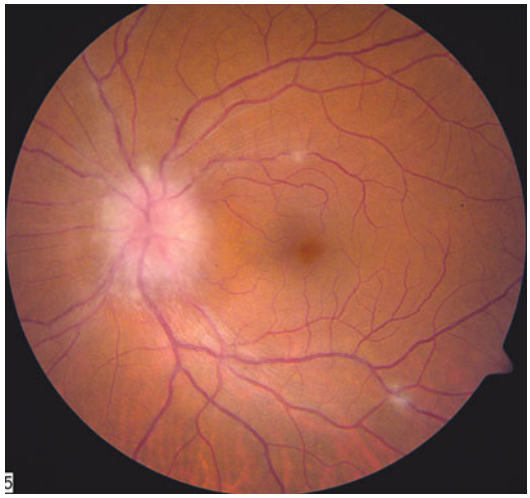

Fig. 11.8 Fundus photograph of the left eye of the same patient, with similar findings

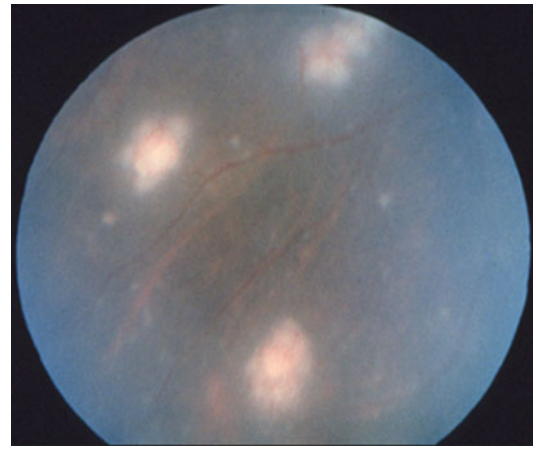

Fig. 11.9 Peripheral retinal granulomas

systemic disease who present with atypical findings. DeRosa et al. described a patient whose initial manifestation was a unilateral hemorrhagic retinopathy. The diagnosis of sarcoidosis in this particular patient was delayed for over a year, due to the atypical retinal findings and normal systemic work-up. Surgical enucleation of the eye once it was blind demonstrated a large noncaseating granuloma of the ciliary body, and inflammation and thrombosis of several large caliber retinal veins were found [38].

Retinal neovascularization may also be seen, particularly in the periphery. It has been reported to occur in less than 5 % of patients with ocular sarcoidosis but may be associated with prominent visual loss due to vitreous hemorrhage. The peripheral neovascular lesions may simulate a sea fan, as seen in sickle cell disease. Neovascularization of the disk may also develop, mainly in association with a branch or central vein occlusion [4, 35, 39].

Two hypotheses have been proposed to explain the etiology of the proliferative changes seen in sarcoid uveitis. One theory is based on the idea that sarcoid granuloma and inflammatory cells may infiltrate the retinal vascular walls, causing vascular occlusion and retinal ischemia, being a predisposing factor for retinal neovascularization. Another is that the development of neovascularization is accelerated by severe inflammation in the eye.

Duker et al. reviewed the clinical features in 11 eyes with retinal neovascularization secondary to sarcoid. In all cases, the new retinal vessels were associated with concomitant peripheral retinal capillary nonperfusion. The authors postulated that capillary nonperfusion secondary to microvascular shutdown, rather than a direct effect of inflammation, was the stimulus for the formation of retinal neovascularization [40].

Retinal arteriolitis has also been linked to sarcoidosis, resulting in weakening of the arterial wall and ectasia. Systemic arterial hypertension appears to play a role in the pathogenesis of the ectasias by increasing the pressure on the arterial wall weakened by inflammation [41, 42].

High-resolution optical coherence tomography may be useful in the documentation of retinal granulomas, which may break through into the vitreous cavity, as demonstrated by Wong et al. (Fig. 11.9) [43].

The appearance of choroidal lesions is variable, and they may mimic other conditions, such as ocular tuberculosis. Sarcoidosis may present as multifocal choroiditis, consisting of small, discrete creamy lesions in the inferior or nasal periphery (Fig. 11.10). It may also mimic birdshot chorioretinopathy with larger, posterior, pale yellow-orange streaks.

Deeper chorioretinal lesions have also been described (Figs. 11.11 and 11.12). They can vary from large choroidal nodules simulating a metastatic tumor to small “Dalen-Fuchs-like” granulomas

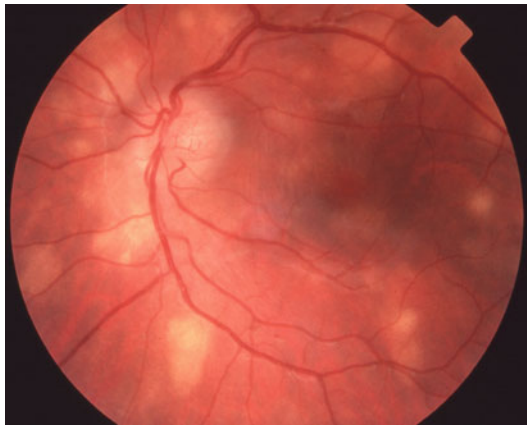

Fig. 11.10 Multifocal discrete creamy choroidal lesions

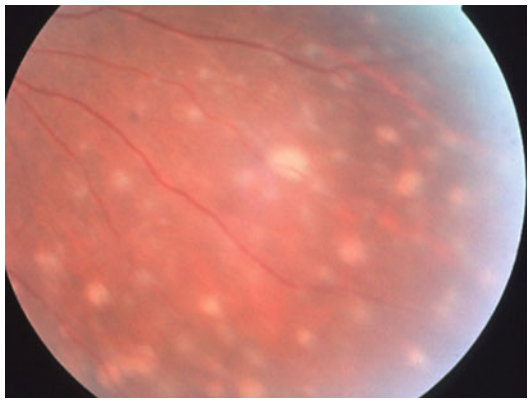

Fig. 11.11 Inferior atrophic choroidal lesions

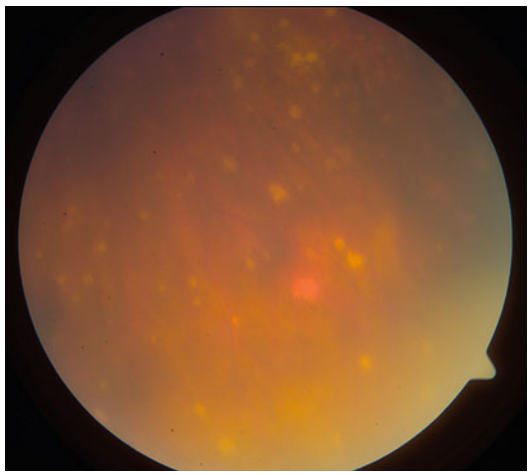

Fig. 11.12 Multiple peripheral atrophic lesions in a patient with sarcoidosis

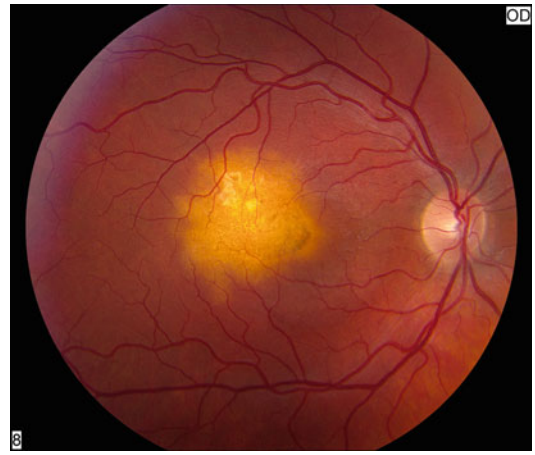

Fig. 11.13 Fundus photograph of the right eye showing a solitary choroidal granuloma

that also occur in sympathetic ophthalmia and Vogt-Koyanagi-Harada syndrome. These lesions might be vision threatening if located in the macular region.

Large nodular chorioretinal granulomas may be complicated by exudative retinal detachments, which appear to be an overlying detachment of the neurosensory retina [44]. An uncommon form of ocular sarcoidosis is a solitary choroidal granuloma (Fig. 11.13). It can simulate a choroidal neoplasm, such as amelanotic melanoma, choroidal metastasis, or lymphoma.

Watts et al. reported an unusual case of serous retinal detachment at the macula in a patient with a history of sarcoidosis, without any other ocular features [45].

Salchow and Weiss described the case of a 54-year-old Hispanic man, with biopsy-proven sarcoidosis, who was found to have multiple retinal pigment epithelium (RPE) detachments on fluorescein angiography, confirmed by optical coherence tomography. The RPE detachments were followed for several years without any treatment, and the visual acuity remained stable. It is uncertain whether the RPE detachments represented small inner choroidal granulomata, which could only be confirmed by histology [46, 47].

Optic nerve involvement, in particular granuloma of the optic nerve head, has been reported to affect up to 7 % of patients with ocular sarcoidosis.

The condition can present as papilledema, secondary to increased intracranial pressure, papillitis, optic neuritis, and optic atrophy. The involvement may also be retrobulbar or chiasmatic. In this situation, progressive visual loss and visual field defect may occur, in the setting of a normal-appearing optic disk. Disturbance in color perception and contrast sensitivity is usually seen [48–51].

Posterior uveitis in sarcoid patients has been linked to CNS abnormalities in some studies. A study by Gould in 1961 showed a much higher rate of neurosarcoidosis in patients with fundus abnormalities when compared to all patients with sarcoidosis [52–54]. However, Desai et al. did not disclose any evidence of CNS involvement by clinical examination and magnetic resonance imaging (MRI) scanning in a group of patients with choroidal granulomas. Therefore, it is unclear if routine neuroimaging should be advocated in patients with posterior segment disease [55].

Some authors have implicated cystoid macular edema (CME) as a major cause of visual loss in ocular sarcoidosis. CME may occur as a result of chronic inflammation in association with anterior, intermediate, or posterior uveitis [56, 57]. Different utilization of ancillary tests among institutions, such as fluorescein angiography, could affect the detection rates of certain posterior segment findings, such as CME. A retrospective study by Khalatbari et al. found a higher rate of CME and worse visual acuity in females when compared to males. In the same study, patients older than 53 years were noted to have higher rates of CME compared to younger age groups [58].

Fluorescein angiography (FA) results in sarcoidosis are generally nonspecific and similar to other inflammatory diseases of the eye. The study may show retinal neovascularization, hyperfluorescent chorioretinal spots, leakage and late staining of the retinal vessels, cystoid macular edema, retinal nonperfusion, and optic nerve inflammation. A diagnosis of sarcoidosis-related granuloma cannot be made solely on angiography. FA may be useful to monitor response to therapy in patients with neovascularization.

Altan-Yaycioglu et al. described FA findings in a series of patients with ocular sarcoidosis. Candle-wax drippings and vasculitis appeared hyperfluorescent in the early phases, increasing in intensity through the late phases. Another patient, who presented with papilledema, showed bilateral papillary hyperfluorescence in early phases, which increased in intensity through the arteriovenous phase [59].

The clinical usefulness and relevance of indocyanine green angiography (ICG) in the investigation of chorioretinal disorders was reviewed by Stanga et al. The authors did not recommend routine use of ICG in ocular sarcoidosis, because in most patients with retinal vasculitis, it did not provide additional information over FA. The group pointed that ICG may be helpful in monitoring the effect of treatment in some patients [60].

Nevertheless, a study by Wolfensberger et al. described ICG findings in a series of 19 patients with posterior ocular sarcoidosis. All patients were found to have choroidal involvement by ICG, but eight of them had no clinical or FA evidence of retinal involvement. Four distinct ICG features were described, as follows: [61]

1. Hypofluorescent dark dots with an irregular zonal distribution
2. Fuzziness of the choroidal vasculature
3. Late diffuse hyperfluorescence
4. Focal pinpoint hyperfluorescent spots appearing in the later phases of angiography

The first three features have been described in conditions such as sympathetic ophthalmia, birdshot chorioretinopathy, multiple evanescent white-dot syndrome, and Vogt-Koyanagi-Harada disease. Choroidal vessel fuzziness is believed to represent choroidal vasculitis, as it was observed near zones of active inflammation [59]. The last feature might be rather specific for sarcoidosis, as it was not found in seven patients with ocular inflammation in whom sarcoidosis had been excluded [61].

Choroidal lesions can underlie sarcoidosis even in the absence of fundoscopic changes. Machida et al. described a 20-year-old woman diagnosed with ocular sarcoidosis with choroidal filling delay, manifested as punctate hypofluorescence in the early phases of ICG, without accompanying fundoscopically detectable retinal lesions or retinal functional disturbance [62].

Management

Systemic corticosteroids are the mainstay of treatment of posterior uveitis in sarcoid patients. They inhibit the inflammatory process by suppressing the arachidonic acid metabolism and activation of complement.

Depending on the severity of the disease, oral prednisone is started at an initial dose of 1 mg/kg/day for 8–12 weeks, followed by a slow taper over few months to establish the minimal effective dose. In some cases, intravenous high-dose methylprednisolone therapy may be necessary.

A meta-analysis of randomized, controlled clinical trials of systemic steroid therapy in pulmonary sarcoidosis failed to show alteration on long-term disease progression, but there was radiologic improvement following 6–24 months of treatment and a small improvement in vital capacity and diffusing capacity [63]. It is unclear if the absence of long-term disease modification also applies to ophthalmic involvement, due to the lack of adequate studies. Moreover, in cases of chronic disease, prolonged corticosteroid therapy is often poorly tolerated, necessitating other steroid-sparing medications. Alternative therapies have therefore been sought [64].

Methotrexate is the most common immunosuppressive agent used. It was introduced in 1958 for the treatment of leukemia and acts as an inhibitor of dihydrofolate reductase, the enzyme responsible for the conversion of dihydrofolate to tetrahydrofolate. This process inhibits the production of thymidylate, which is essential for DNA synthesis and cell division. The exact mechanism of methotrexate in ocular inflammatory diseases is not currently completely understood. It has the added benefit of potentially helping to control other systemic manifestations of sarcoidosis. In 1999, Dev et al. reported the successful use of low-dose methotrexate in 11 patients with chronic sarcoid panuveitis. All patients showed response to the medication (defined as an improvement in visual acuity or a decrease in inflammation), although some required incrementally increased dosages before a response was achieved. The side-effect profile was fairly mild and included mainly gastrointestinal symptoms [65]. Other series have also shown a high response rate with methotrexate in the management of ocular sarcoidosis [35, 66].

Whether methotrexate provides a better visual prognosis than that obtained with corticosteroids in patients with sarcoid-associated posterior uveitis is currently unknown, and randomized clinical trials are necessary to assess and compare the outcomes.

Methotrexate has also been combined with azathioprine. The purpose of combination therapy is to minimize the toxicity while increasing the immunosuppression by multiple mechanisms of action [5].

Leflunomide, an immunomodulatory drug that inhibits dihydroorotate dehydrogenase, with anti-inflammatory effects, has been shown in small series to have similar efficacy to methotrexate in ocular sarcoidosis and may be better tolerated in some patients [67].

Mycophenolate mofetil, an immunosuppressant which acts as a reversible inhibitor of inosine monophosphate dehydrogenase in purine biosynthesis, has also been used in sarcoid patients. In a recent retrospective study by Bhat et al., it was shown to be effective in controlling sarcoidosis-related ocular inflammation with a manageable side-effect profile. The best corrected visual acuity improved in all 14 eyes studied [68].

Since tumor necrosis factor-alpha (TNF-α) plays an important role in granuloma formation, agents that inhibit TNF-α(alpha) could potentially be useful in treating sarcoidosis. However, etanercept, a biologic tumor necrosis factor antagonist, demonstrated disappointing results in chronic ocular sarcoidosis in a series by Baughman et al. It appeared not to be steroid sparing, and despite being well tolerated, it was not associated with a significant improvement of chronic sarcoid uveitis [69].

Cases of refractory ocular sarcoidosis responsive to infliximab, a monoclonal antibody to TNF-α(alpha), have been reported including resolution of retinal vasculitis and optic neuropathy [70, 71]. Another study by Baughman et al. enrolled seven patients with ocular sarcoidosis and persistent inflammation despite systemic

immunosuppressive therapy. All patients demonstrated significant improvement in ocular inflammation with infliximab [72]. The molecular structure of infliximab allows it to initiate the classical complement pathway and cause cell lysis, which does not occur with etanercept. Moreover, infliximab may also lead to apoptosis of TNF-expressing T cells and macrophages [73].

In selected uveitic patients, bevacizumab may be an option for managing neovascularization. Among varied factors involved in sarcoidosis, vascular endothelial growth factor (VEGF) has been reported to be associated with prognosis in systemic disease. This knowledge was the basis of Kurup et al. in attempting anti-VEGF therapy in a sarcoid patient with prominent peripapillary neovascularization. The patient demonstrated dramatic resolution in the subretinal fluid and decrease in the intraretinal hemorrhage associated with the neovascularization over a period of a week [74].

Photocoagulation has also been used in the treatment of neovascularization secondary to sarcoidosis. Spalton et al. have emphasized that ocular inflammation should be well controlled before laser therapy is attempted [48].

It has been suggested that intravitreal triamcinolone injections may be effective in controlling cystoid macular edema in patients with posterior uveitis. It has the advantages of achieving a high therapeutic drug level for maximal local anti-inflammatory effects. Larsson et al. reported the clinical course of two patients with sarcoid uveitis and refractory macular edema, who improved only when intravitreal injections of triamcinolone were given. It was possible to discontinue systemic treatment in both patients [75].

Chan et al. reported a case of a 29-year-old man with retinal periphlebitis and retinal granulomas that responded well to oral corticosteroids. The patient also had a choroidal granuloma, which grew slowly in size and threatened the fovea, despite systemic steroids. Intravitreal triamcinolone acetonide (4 mg) was injected three times at 2-month intervals. The choroidal mass began to shrink after the second injection and became a scar, with no angiographic leakage. The patient's visual acuity improved and remained stable during a 6-month follow-up period. Further studies are necessary to evaluate the long-term efficacy of intravitreal triamcinolone in cases refractory to systemic therapy [76].

Surgical interventions, such as vitrectomy for vitreous opacities, have been reported as beneficial in restoring vision, stabilizing vitreous inflammation, and reducing systemic corticosteroid requirements, in a small number of patients with refractory ocular disease [77].

Controversies and Perspectives

The cause of sarcoidosis remains obscure, despite much research in the last few years. Several new agents with immunosuppressive properties have shown efficacy and an acceptable side-effect profile. However, the long-term impact of the new drugs in altering the course of sarcoidosis, particularly in ocular disease, remains unknown. Developing randomized, controlled trials to test and compare new therapies is paramount.

Future studies will help clarify and provide a better understanding of the genetics of sarcoidosis and allow for the development of new diagnostic, prognostic, and therapeutic modalities that may decrease systemic and ocular morbidity further.

Focal Points

- Sarcoidosis is a multiorgan systemic disease capable of producing a wide variety of ocular manifestations, being one of the greatest mimickers in ophthalmology.
- A combination of signs of intraocular inflammation and systemic studies can be used for the clinical diagnosis of ocular sarcoidosis.
- Posterior segment manifestations of the disease are numerous and may include vitritis, vasculitis, chorioretinitis, retinal neovascularization, and the presence of granulomas in the retina, choroid, or optic nerve.
- All sarcoidosis patients need comprehensive and periodic eye examinations, as untreated ocular disease may lead to poor visual prognosis.

- Corticosteroids are the mainstay of treatment of sarcoidosis. Alternative immunomodulatory therapies have been developed, but their impact on long-term disease progression remains unclear.

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Posterior Pole Manifestations of Behçet's Disease

12

Pelin Atmaca-Sonmez and Leyla S. Atmaca

Abstract

Behçet's disease is among the chronic-relapsing, multisystemic inflammatory disorders that is characterized by obliterative vasculitis. The key clinical manifestations are recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. The uveitis is recurrent and non-granulomatous, and most commonly panuveitis in type. Vitritis, retinal vasculitis, macular edema, retinitis, and retinal hemorrhages are common findings of ocular Behçet's disease. The aim of the treatment in ocular Behçet's disease is to achieve a rapid resolution of inflammation, reduce frequency and severity of attacks, and to avoid complications. There is not a standard treatment protocol. However, combination therapy is necessary in most cases.

Keywords

Behçet's disease • Uveitis • Retinal vasculitis • Macular edema • Treatment • Corticosteroids • Immunosuppressants

Introduction

Behçet's disease (BD) owes its name to a Turkish dermatologist Hulusi Behçet, who described recurrent oral and genital ulcers and iridocyclitis as a separate clinical entity in 1937 [1], although symptoms similar to those of Behçet's disease have been described as early as the time of Hippocrates and later by several others [2, 3]. The disease was later recognized to affect almost all systems or organs including pulmonary, gastrointestinal, genitourinary, nervous systems, as well as joints and large vessels, which suggests that it may rather be a syndrome than a disease. Nevertheless, the major characteristics of the disease is a systemic vasculitis with mucosa, skin, and eye being predominantly involved.

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Epidemiology

Prevalence and Incidence

Although found worldwide, BD has a distinct geographic distribution and is most prevalent along the ancient Silk Route, extending from Eastern Asia to the Mediterranean. Turkey has been reported to have the highest prevalence: 80–420 cases per 100,000 population, followed by Japan: 7–8.5/100,000 [4–6]. Nevertheless, it should be noted that the study of Azizerli et al. from Turkey with the highest prevalence consisted of the population aged 12 and older [4]. Its prevalence has been reported to be 2–30/100,000 in the Asian continent and 0.1–7.5/100,000 in Europe and the USA [6]. While its prevalence in Germany was reported to be 20.75 per 100,000 Turkish descendants, it was only 0.42 per 100,000 German origin [7]. The incidence per 100,000 inhabitants is reported to be 0.75–0.89 in Japan [8], 0.24 in Northern Italy [9], and 0.12–0.33 in the United States [10].

Of all uveitis cases, BD constitutes 15.3% in Israel and around 20% in Japan [11–13].

Age of Onset

Most patients with BD first report their symptoms during the second or third decade of their life [14, 15]. However, juvenile onset is more common in countries with a higher prevalence of the disease [16, 17].

The Gender Factor

Earlier studies from the Middle East and Turkey have shown a male preponderance contrary to the ones from Asia and the United States [7, 18]. Recent studies, however, suggest a more even male-to-female ratio [19]. The gender factor also seems to affect the clinical manifestations and prognosis. The disease has generally a more severe course in men with a younger age of onset.

Etiopathogenesis

Although the etiology is still unclear, some currently unknown triggering factor(s) in the presence of a genetic susceptibility seem to play a major role in the pathogenesis of BD. Recently, some authors suggest that BD is an autoinflammatory disorder [20–23]. Whatever the triggering factor is, endothelium is the most likely target tissue with resulting vasculitis and/or thrombosis as the consequences of inflammation. The quite frequent coexistence of thrombosis and arterial aneurisms implicates a primary vascular pathology rather than a major coagulation defect in BD. Furthermore, many immunological abnormalities related with both innate and acquired immunity have been reported in BD, most of which still await for explanation, interrelation, and confirmation. The most closely associated risk factor for BD, and in some countries for disease severity, is human leukocyte antigen HLA-B51 and especially its allele HLA-B51 01 positivity [24–26]. The role of HLA class I antigens such as B51 is the presentation of endogenous antigens synthesized within the cell to CD8+ cytotoxic-suppressor T cells. It is not yet clear whether B51 is a marker of susceptibility or severity in BD. However, it must be emphasized that the presence of HLA-B51 is not enough to cause BD. Many people may have genetic predisposition, but relatively few develop the disease.

Clinical Features and Diagnosis

Although Behçet's disease may affect almost any system of the body with exacerbations and remissions of inflammation, the key clinical manifestations are recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions.

The diagnosis of Behçet's disease may be challenging since there are no specific laboratory tests and pathognomonic findings. In addition, the presentation and the course of the disease may vary due to ethnic, geographical, and individual characteristics. It may be more difficult to

diagnose incomplete or atypical forms. On the other hand, some of the symptoms may present later in the course of the disease which may challenge the diagnosis. Various sets of diagnostic criteria have been proposed, the two most commonly used ones being the criteria by the Behçet's Disease Research Committee of Japan [27] and the International Study Group Criteria for the Diagnosis of Behçet's Disease [28]. The Behçet's Disease Research Committee classifies the disease into complete and incomplete types according to major and minor diagnostic criteria (Table 12.1). On the other hand, the diagnostic criteria of the International Study Group for Behçet's Disease is briefly summarized in Table 12.2 and requires the presence of oral aphthous ulcers for the diagnosis. Although these criteria are primarily intended to define and classify Behçet's patients for participation in research studies, their sensitivity and specificity are high, being 91% and 96% for The International Study Group for Behçet's Disease and 92% and 89% for The Behçet's Disease Research Committee criteria, respectively.

Table 12.1 The Behçet's Disease Research Committee diagnostic criteria

Major
1. Recurrent oral aphthous ulcers
2. Skin lesions
Erythema nodosum-like lesions
Folliculitis, acneiform lesions
Thrombophlebitis
Cutaneous hypersensitivity
3. Genital ulcers
4. Ocular disease
Iridocyclitis
Posterior uveitis
Minor
1. Arthritis
2. Epididymitis
3. Intestinal symptoms attributed to ileocecal ulcerations
4. Vascular symptoms
5. Neurologic symptoms attributed to nervous system involvement
Complete type: The presence of all four major criteria
Incomplete type:
1. The presence of three major criteria
2. Two major and two minor criteria
3. Ocular disease plus one major criteria
4. Ocular disease plus two minor criteria

Table 12.2 The International Study Group for Behçet's Disease diagnostic criteria

Recurrent oral ulceration
Plus 2 of:
Recurrent genital ulceration
Eye involvement *(anterior, intermediate, posterior uveitis)*
Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules consistent with Behçet's disease)
Positive pathergy test

Recurrent oral ulcers are reported in almost all patients and are the most common presenting feature of the disease [29]. Only the oral ulcers that recur at least three times over a 12-month period are considered as a manifestation of Behçet's disease. A study showed that 52.2% of patients developed overt manifestations of Behçet's disease at an average of 7.7 years after the onset of oral ulcers [30]. The frequency of recurrence was 9.8 times per year in progressive cases.

Genital ulcers are larger, deeper, and more painful than oral ulcers. Unlike oral ulcers, they heal slowly and leave a scar due to associated necrotizing vasculitis.

The *skin lesions* seen in BD are erythema nodosum-like lesions, pseudofolliculitis, papulopustular lesions, acneiform nodules in post-adolescent patients not receiving corticosteroids observed by a physician, cutaneous hypersensitivity, and thrombophlebitis which is usually found on the extremities. Other described skin lesions include pyoderma gangrenosum, Sweet's syndrome, extragenital ulcers, purpura, erythema multiforme, and vesicles. The incidence of skin involvement varies greatly in the literature but is approximately seen in 80% of patients [21].

Pathergy (cutaneous hypersensitivity) is the upregulated inflammatory response to a minor trauma, is not unique to the skin, and can be observed in large vessels, joints, and eyes in

Behçet's disease [29]. Pathergy is tested using the "prick test" in which a 20-g needle is inserted 5 mm obliquely into the skin of the forearm. The test is considered to be positive when sterile erythematous papules or pustules that are a minimum of 2 mm in diameter form 24 to 48 h later. A positive pathergy test is helpful in the diagnosis of Behçet's disease since there are only a few other rare diseases with pathergy positivity; however, it is not 100% specific or pathognomonic.

Recurrent nonmigrating and nondestructive arthritis episodes, mostly affecting the knees, ankles, wrists, and elbows, occur in approximately half of the patients with Behçet's disease.

Vascular involvement: Vessels of all sizes in any organ or system can be affected, and the venous system is more commonly affected than the arterial system.

Nervous system involvement usually occurs late in the course of the disease and carries a poor prognosis. Central nervous system involvement is more common than the peripheral. The most common neurologic symptom in Behçet's disease is headache, which is related to widespread vasculitis [31]. There are a variety of neurologic findings including pyramidal and extrapyramidal signs, cranial nerve palsies, seizures, venous sinus thrombosis, stroke, aseptic meningitis or meningoencephalitis, intracranial hypertension, vertigo, and hearing loss as well as psychiatric disorders [32].

Gastrointestinal system involvement also carries a poor prognosis and presents as single or multiple erosions in any part of the gastrointestinal tract, most commonly at the ileocecal region.

Cardiac system involvement in BD is rare; however, interatrial septum aneurysm, mitral valve prolapse, mitral regurgitation, and aneurysmal dilatations of sinus of Valsalva and ascending aorta are observed in higher incidences in the Behçet's disease patients than in the normal subjects [33]. Pericarditis, coronary vessel thrombosis, endomyocardial fibrosis, and silent myocardial infarction may also be seen.

Pulmonary involvement includes pulmonary artery aneurysm, pulmonary thromboembolism, infarct, pleural effusion, recurrent pneumonia, and pulmonary hypertension.

The *genitourinary system* may be affected as epididymitis, cystitis, urethritis, nephrotic syndrome, glomerulonephritis, or renal vein thrombosis.

Ocular Involvement

Behçet's disease is characterized by recurrent attacks of intraocular inflammation, which resolve over several weeks. Uveitis in Behçet's disease may be anterior, intermediate, posterior, or panuveitis, which is the most frequent type (around 60%) in both sexes [15]. Although various frequencies of ocular involvement have been reported, it is generally observed in more than 50% of the patients with Behçet's disease [21]. Ocular manifestations usually follow the onset of oral and genital ulcers by a few years [34]. Ocular involvement is bilateral in the majority of cases but may be asymmetrical. Males are usually more frequently involved, have an earlier disease onset, and have a more severe disease [15, 19].

The uveitis is recurrent and non-granulomatous. Hypopyon, which is composed primarily of neutrophils, is termed as "hot" in the presence of ciliary injection and "cold" with no signs of ciliary injection. Hypopyon (Fig. 12.1), once considered a hallmark of Behçet's disease, is seen

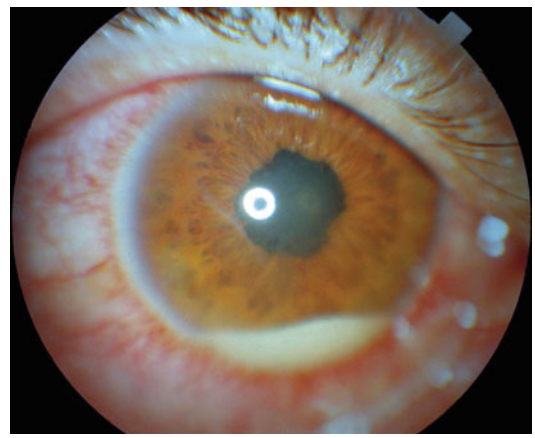

Fig. 12.1 Iridocyclitis with hypopyon

much less commonly than fundus lesions. It was noted in only 12% of 1,567 eyes [15].

Posterior Segment Involvement

The incidence of posterior segment involvement is reported to be 50–93% [35]. In a study of 880 patients with Behçet's disease, vitritis and retinal vasculitis were the most common (89%) findings of uveitis [15]. Retinitis, also described as deep retinal exudates, was the second most common finding of Behçet's uveitis. While hypopyon, vitritis, retinal vasculitis, retinitis, and retinal hemorrhages were more common in male patients, papillitis was more common in females.

Posterior segment examination may show a wide variety of findings:

- *Vitreous*: Vitritis, haze, hemorrhage, posterior vitreous detachment, pars planitis (Fig. 12.2)
- *Retina*: Edema, macular edema especially cystoid type, yellow-white exudates (Fig. 12.3), hemorrhage, retinal neovascularization (Fig. 12.4), chorioretinitis, macular hole (Fig. 12.5), epiretinal membrane, exudative or tractional retinal detachment (Fig. 12.6), retinal pigment epithelial atrophy
- *Optic disc*: Optic nerve head edema, papilledema (Fig. 12.7), disc neovascularization (Fig. 12.8), optic atrophy (Fig. 12.9)
- *Vascular*: Venous and capillary dilation, venous tortuosity (Fig. 12.10), sheathing (Fig. 12.11),

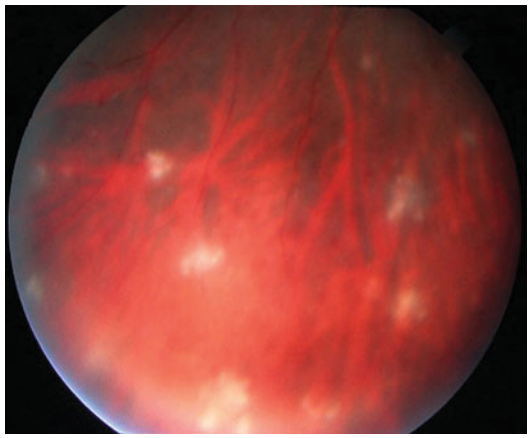

Fig. 12.2 *Yellow-gray* exudates at the ora serrata

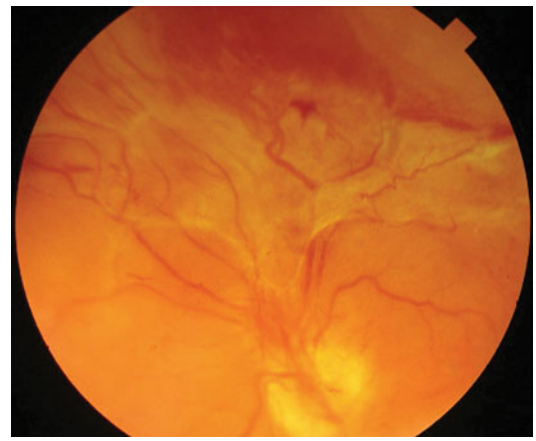

Fig. 12.4 Retinal neovascularization and proliferative changes

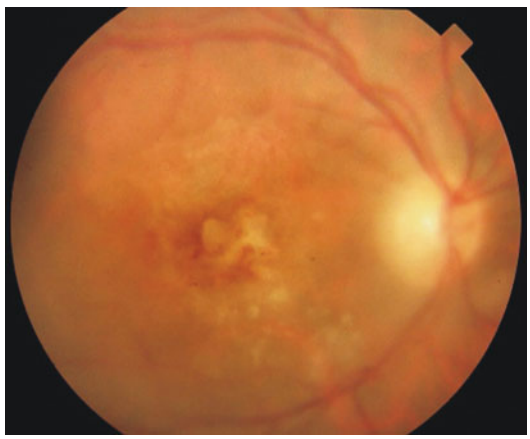

Fig. 12.3 Retinal edema and exudates

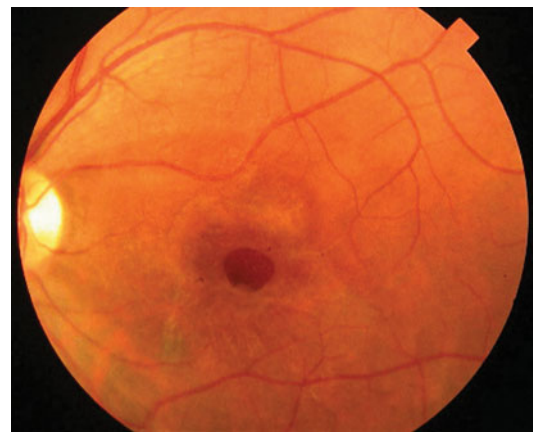

Fig. 12.5 Macular hole in a patient with Behçet's disease

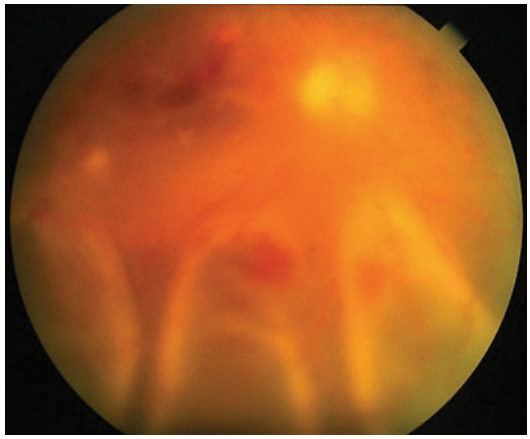

Fig. 12.6 Tractional retinal detachment

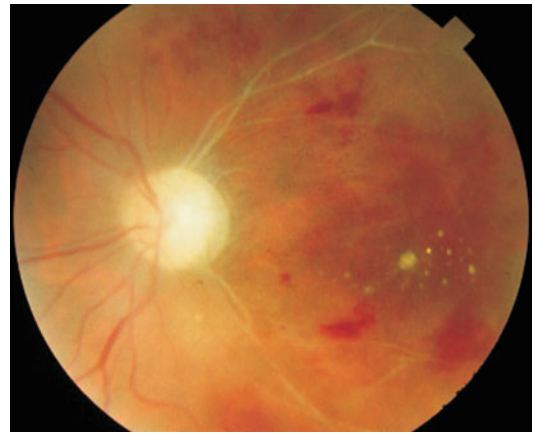

Fig. 12.9 Optic atrophy, ghost vessels, and retinal hemorrhages

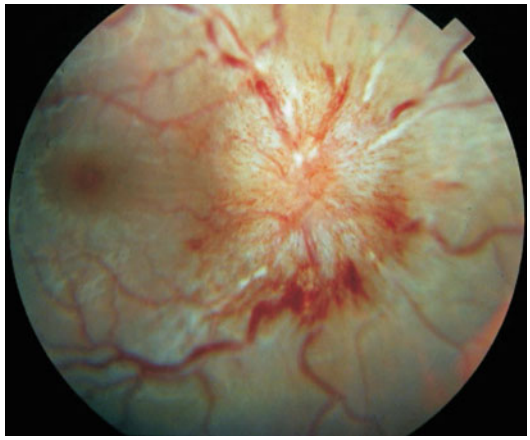

Fig. 12.7 Papilledema due to Behçet's disease

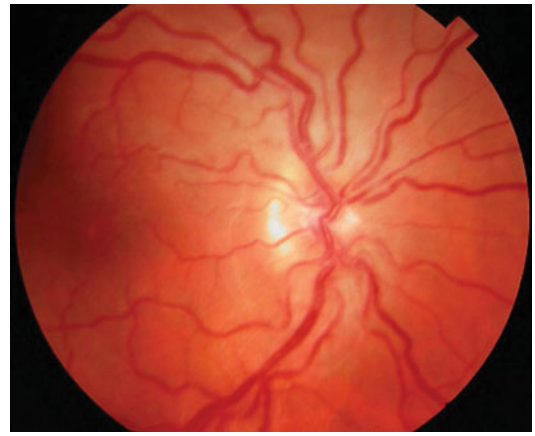

Fig. 12.10 Venous dilation and increased tortuosity

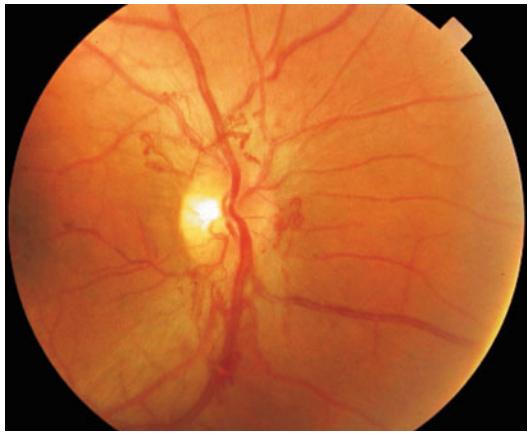

Fig. 12.8 Disc neovascularization

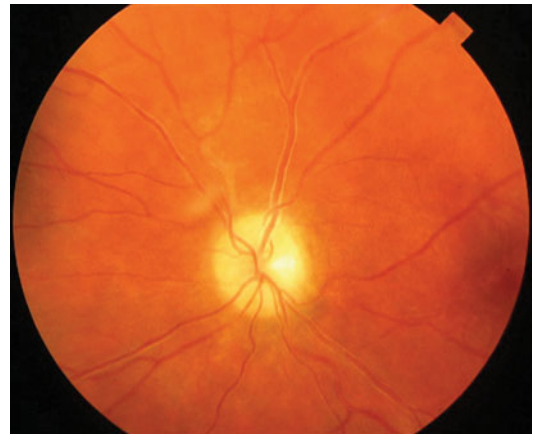

Fig. 12.11 Vascular sheathing and optic atrophy

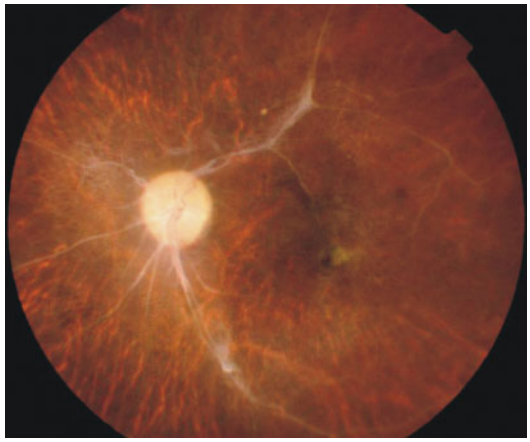

Fig. 12.12 Optic atrophy, ghost vessels, and fibrous proliferation

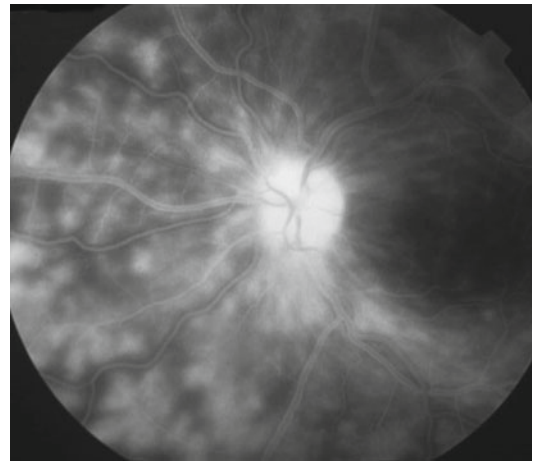

Fig. 12.14 Dye leakage from the papillary and retinal capillaries on fluorescein angiography

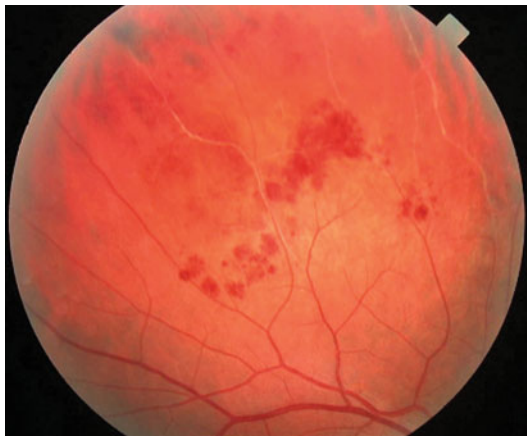

Fig. 12.13 Retinal hemorrhages and ghost vessels due to obliterative vasculitis

vasculitis, attenuated arteries, ghost vessels (Fig. 12.12), central or branch retinal vein occlusion, central retinal artery occlusion

Obliterative vasculitis (Fig. 12.13), which affects both arteries and veins, is characteristic in Behçet's disease leading to retinal edema and retinal exudation. The recurrent nature of this condition leads to severe visual impairment and irreversible alterations in the retina. Episodes of retinal vaso-occlusion may lead to areas of capillary non-perfusion which may result in retinal and/or disc neovascularization. Retinal vascular occlusion has been correlated with three main factors: vascular stasis, thrombotic abnormalities, and vascular wall abnormalities [29].

The effect of obliterative vasculitis can be detected by color Doppler ultrasonography in patients with Behçet's disease, which reveals significant reductions in the blood flow values of the orbital arteries that are more evident in those with ocular involvement [36, 37].

Fluorescein Angiography

Fluorescein angiography (FA) contributes greatly to the early diagnosis of the disease and is essential in the long-term care of the patients. Fluorescein leakage from retinal vessels and other signs of vasculitis may be seen before there are obvious ophthalmoscopic signs of vasculitis [35]. Dye leakage from the papillary and retinal capillaries (Fig. 12.14), vascular wall staining (Fig. 12.15), retinal vein and arterial occlusions, cystoid macular edema (Fig. 12.16), vascular remodeling as a result of capillary non-perfusion (Fig. 12.17), and retinal and/or disc neovascularization (Fig. 12.18) are well documented by FA.

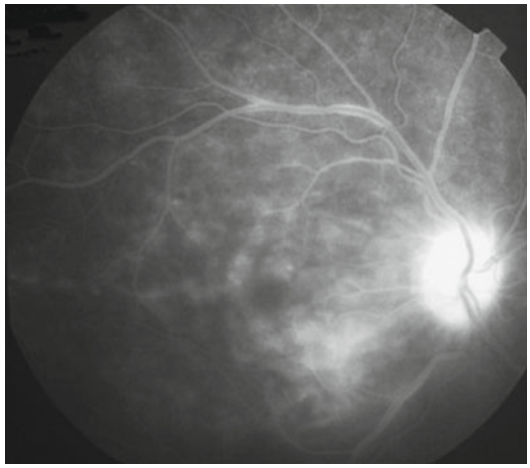

Fig. 12.15 Vascular wall staining on the superior arcuate vein and capillary dye leakage on fluorescein angiography

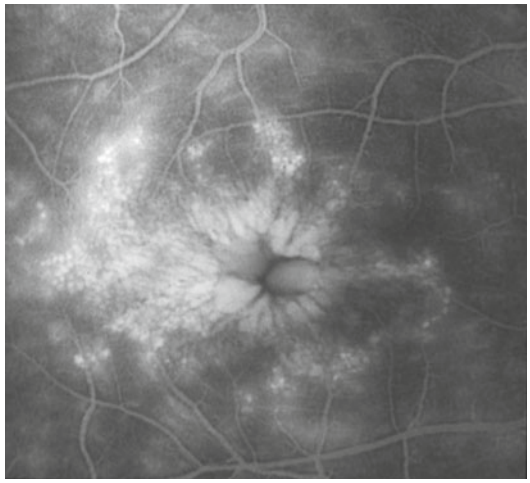

Fig. 12.16 Fluorescein angiography shows cystoid macular edema in a patient with Behçet's disease

Indocyanine Green Angiography

Although the retina is known to be the predominantly affected site of inflammation in posterior Behçet's disease, studies on indocyanine green angiography (ICGA) strongly suggest choroidal involvement shown by hyper- and/or hypofluorescent lesions, ICG leakage from choroidal vessels (Fig. 12.19), choroidal vascular wall staining, irregular ICG filling of the choriocapillaris, and choroidal filling defects (Fig. 12.20) [38, 39]. ICGA may also give additional information on the optic nerve head.

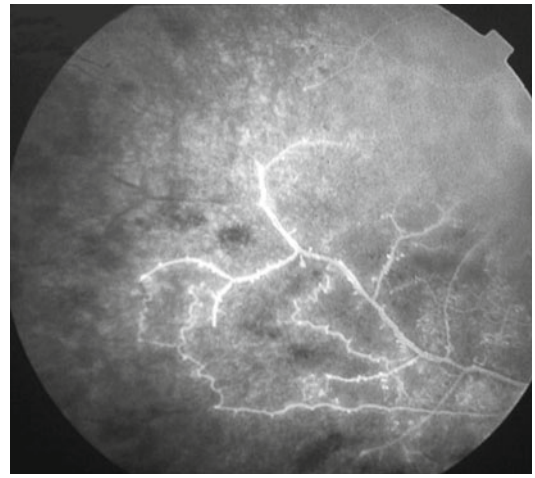

Fig. 12.17 Vascular remodeling on fluorescein angiography: retinal telangiectasias, collateral venous channels, and dilated capillary nets, as a result of capillary nonperfusion

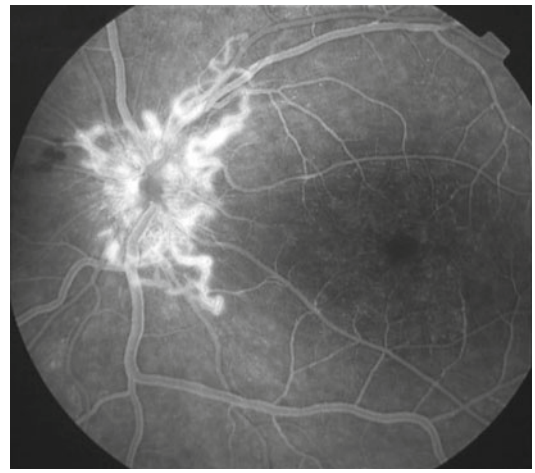

Fig. 12.18 Dye leakage from disc neovascularization on fluorescein angiography

Optical Coherence Tomography

Optical coherence tomography (OCT) is very useful in detecting and documenting the macular changes. Macular edema, especially cystoid type, is frequently seen in Behçet's disease (Figs. 12.21 and 12.22). Chronic edema may lead to macular hole formation, and OCT is especially valuable in the follow-up and management of such conditions (Fig. 12.23), as well as documenting the efficacy of treatment for macular edema [40].

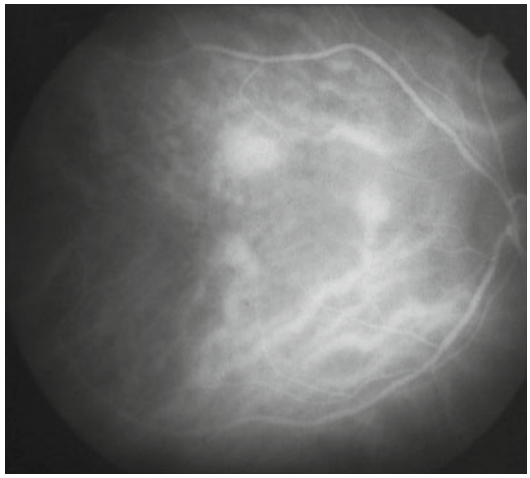

Fig. 12.19 Indocyanine green (ICG) leakage from choroidal vessels in early-phase ICG angiography

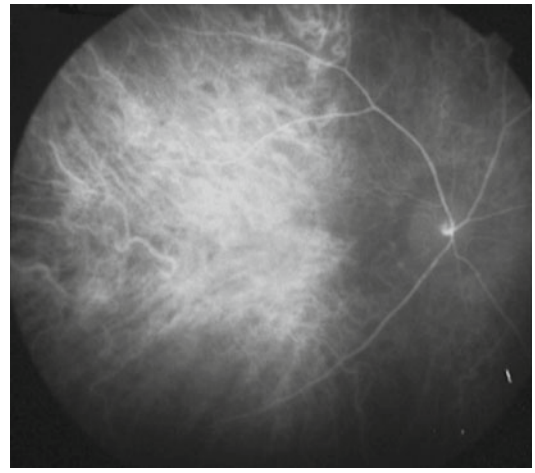

Fig. 12.20 Choroidal filling defect in early-phase indocyanine green angiography

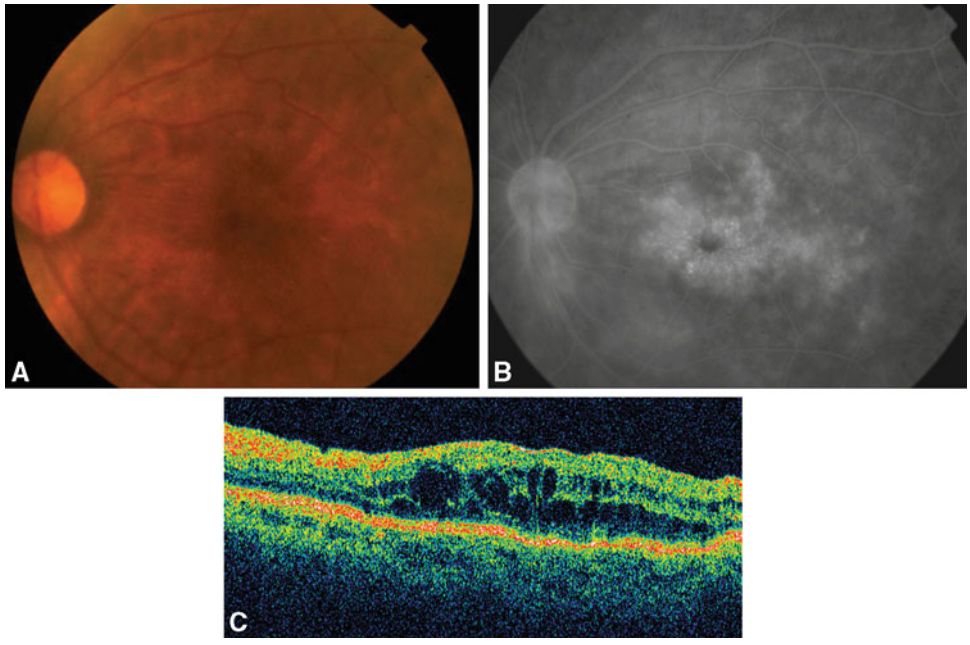

Fig. 12.21 (**a**) Color fundus photography. (**b**) Fluorescein angiography. (**c**) Optical coherence tomography shows cystoid macular edema

Other Ocular Manifestations

Scleritis, episcleritis (Fig. 12.24), recurrent conjunctivitis, conjunctival ulcers, filamentary keratitis, marginal sterile corneal ulcers, and extraocular muscle paralysis may occur.

Complications

Recurrent attacks of inflammation lead to numerous intraocular complications. Posterior and/or peripheral anterior synechiae, cataract (Fig. 12.25) due to inflammation and/or

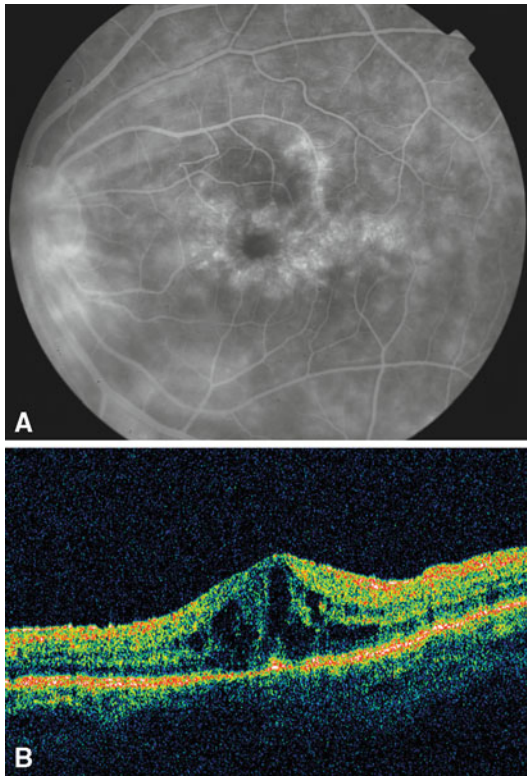

Fig. 12.22 (**a**) Cystoid macular edema, disc hyperfluorescence and retinal vasculitis on fluorescein angiography. (**b**) Cystoid macular edema on optical coherence tomography

medication, iris atrophy, and secondary glaucoma may develop. In the very late stages of the disease, an atrophic retina, optic atrophy, sheathed vessels, chorioretinal scars, and/or proliferative vitreoretinopathy (Fig. 12.26) are often observed. Neovascular glaucoma may occur in as many as 12% of patients and often results in phthisis bulbi [41].

Histopathology

Histopathological studies on eyes with Behçet's disease showed a non-granulomatous uveitis and necrotizing, leukocytoclastic, and obliterative vasculitis, which affect arteries and veins of all sizes [42–44]. Retinal detachment, and diffuse or focal infiltration of the choroid with inflammatory cells were detected. Immunoglobulin and complement deposition in choroidal veins have been reported [45]. During acute inflammation, there is severe vasculitis with marked infiltration of leukocytes in and around blood vessels. Retinal vessels have thickened basement membranes with swollen endothelial cells, which can lead to thrombus formation and vascular obliteration [46]. In addition, the iris,

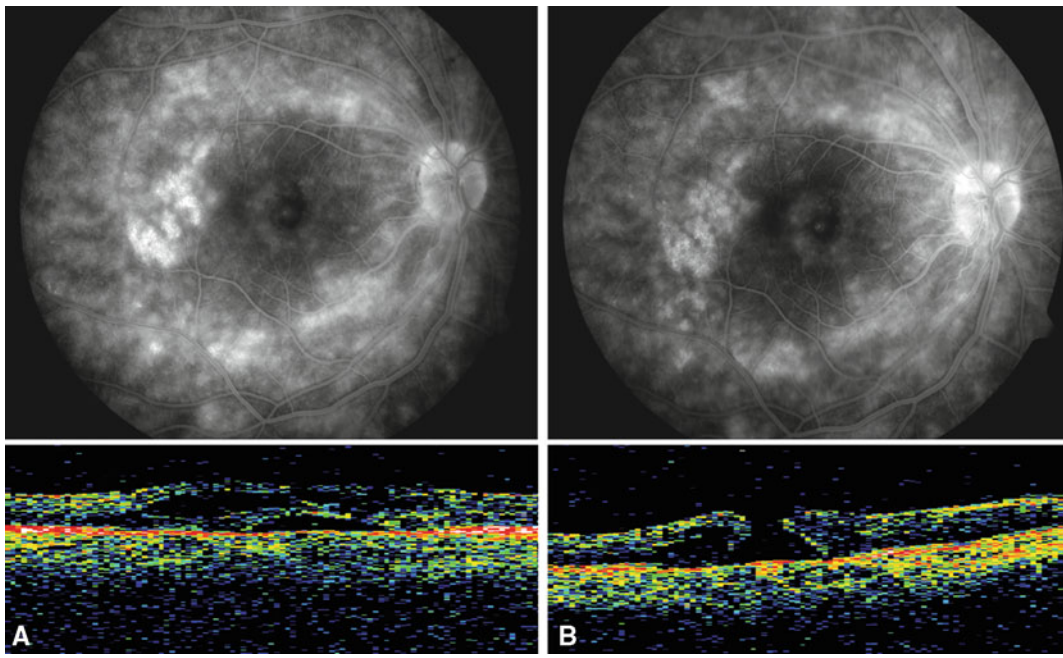

Fig. 12.23 (**a**) Cystoid macular edema, (**b**) developed into full-thickness macular hole

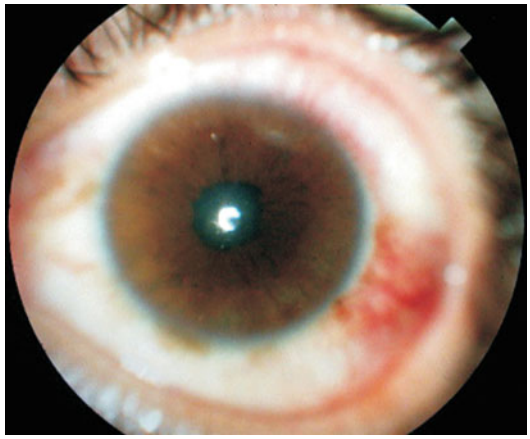

Fig. 12.24 Episcleritis

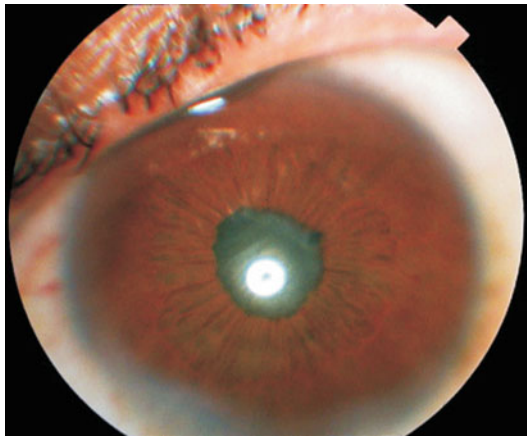

Fig. 12.25 Cataract and posterior synechia

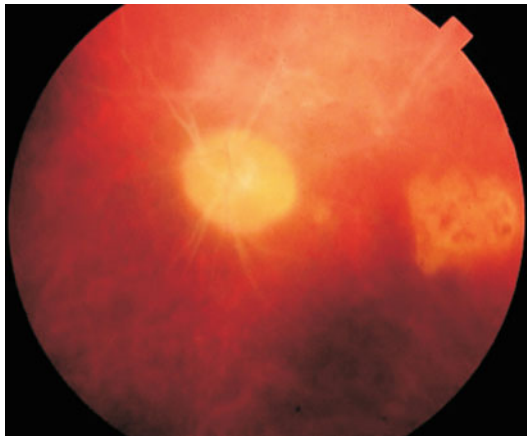

Fig. 12.26 End-stage Behçet's disease

ciliary body, and choroid show diffuse infiltration with neutrophils. In the late stages, there is proliferation of collagen fibers, thickening of the choroid, formation of cyclitic membrane, and sometimes hypotonia and phthisis bulbi. Lymphocytic and plasma cell infiltration occurs during remission. Of all ocular tissues, the retina suffers the most damage.

Prognosis of Ocular Disease

Ocular and central nervous system involvements are the main prognostic determinants in Behçet's disease [19]. The ocular inflammatory episodes in Behçet's disease are characteristically associated with a sudden severe onset of visual loss that may gradually improve with remission. The severity and number of repeated inflammatory attacks involving the posterior segment determine the extent of permanent structural changes and the resultant rate of irreversible visual loss [15]. Therefore, anterior uveitis alone carries the best prognosis in ocular involvement. A study from 1970 reported that 73% of patients with ocular disease developed permanent loss of vision within an average time of 3.5 years [47]. Similarly, another study from 1986 reported that 74% of treated patients lost useful vision 6–10 years after the onset of symptoms [48]. However, increased awareness of the disease, a more aggressive treatment approach, and the availability of several immunosuppressive agents seem to have improved the prognosis of Behçet's disease in the last decade [15, 48].

The clinical course of the disease shows individual variability even in the same family [49]. Nevertheless, male patients in general have a higher risk of eye involvement, younger age at disease onset, more severe disease, and a higher risk of visual loss compared to female patients [15, 19]. In Japan, more than 50% of male patients lose visual acuity to less than 0.1 in 5 years, but this is the case in only 10% of female patients [11]. Consequently, Behçet's disease is the cause of blindness in about 12% of acquired blindness in adults in Japan.

In the majority of studies, early age at onset is found to be associated with a more severe disease

regardless of the gender [50]. The frequency and severity of the attacks tend to diminish as the patients get older.

The role of HLA-B51 positivity and a positive family history on the prognosis of Behçet's disease is uncertain. While some studies found poorer prognosis in HLA-B5-positive patients [7], in other studies, neither HLA-B51 positivity nor a positive family history was found to be significant [50, 51].

Juvenile Behçet's Disease

The diagnosis of Behçet's disease in children may be challenging due to the long interval before the onset of enough manifestations to satisfy the diagnostic criteria. The prevalence of juvenile Behçet's disease and the rate of ocular involvement range widely in published studies.

The clinical spectrum is similar to that of adults; however, the prevalence of certain manifestations varies: less genital ulceration, less vascular thrombosis, more gastrointestinal signs and symptoms, and more arthralgia have been observed in juvenile Behçet's disease. Perianal aphthosis, reported in 7% of patients in one study, was suggested to be a specific feature of juvenile Behçet's disease [52]. Posterior uveitis was the most common ocular manifestation, detected in about 75% of the cases [53].

The frequency and ocular prognosis of juvenile Behçet's disease compared to adult cases vary among the studies. While some studies found ocular complications to be less frequent in juvenile cases [54, 55], others found the contrary [16]. There are also conflicting reports on the ocular prognosis in juvenile patients. Some studies report it to be better [16, 55, 56], whereas in an international collaborative study of 86 cases of childhood Behçet's disease, uveitis was reported to have a very severe course, especially in male patients [52].

Common features of childhood Behçet's disease reported by the majority of published studies are onset of uveitis in late childhood, occurrence of oral ulcers as the initial manifestation of the disease in the majority of patients, a high rate of family history, and male predominance [17].

Pregnancy and Behçet's Disease

The influence of pregnancy on the clinical course of Behçet's disease is quite variable between patients and even during different pregnancies in the same patient [57]. In patients with exacerbation of the disease during pregnancy, it most commonly occurs during the first trimester [58]. A study that reviewed 31 Behçet's patients who had 135 pregnancies found that remissions were significantly more frequent during both pregnancy and postpartum periods, while exacerbations were observed only in one-sixth of the patients. However, pregnancy complications, cesarean section, and miscarriage rates were significantly higher in the study group [59].

Differential Diagnosis

The differential diagnosis varies according to the systems involved. In the presence of uveitis, the key to diagnosis is to identify systemic manifestations such as oral and genital ulcers and skin lesions. Recurrent oral aphtha is present in the vast majority of Behçet's patients, and its

Table 12.3 Differential diagnosis of ocular Behçet's disease

Ankylosing spondylitis
Reiter's syndrome
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Whipple's disease
Sarcoidosis
Polyarteritis nodosa
Vogt-Koyanagi-Harada syndrome
Eales' disease
Infectious diseases
Syphilis
Lyme disease
Tuberculosis
Acute retinal necrosis

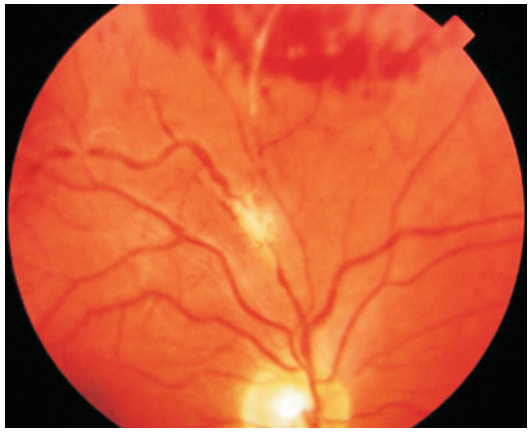

Fig. 12.27 Eales' disease

presence is required according to the International Study Group for Behçet's Disease. However, oral ulcers are very common in the general population and accompany many disorders. Therefore, not everyone who has had oral ulcers should be considered as having Behçet's disease. Sarcoidosis and Reiter's syndrome may also sometimes present with oral ulcers. Table 12.3 summarizes the most possible diseases in the differential diagnosis of ocular Behçet's disease (Fig. 12.27).

Management of Ocular Disease

The aim of the treatment in ocular Behçet's disease is to achieve a rapid resolution of inflammation, reduce frequency and severity of attacks, and to avoid complications. There is not a standard treatment protocol since the extent and severity of the disease and patient response to a certain medication determine the treatment required. A combination therapy is necessary in most cases. The management of patients with Behçet's disease should be in collaboration with other specialties, and systemic administration of drugs should be conducted in consultation with an internist.

For acute, isolated anterior segment inflammation, frequent topical corticosteroids and mydriatics may be adequate. Posterior segment inflammation, however, is severe and progressive in the majority of patients and requires systemic treatment [60]. Mild posterior segment inflammation may be managed by sub-Tenon's capsule corticosteroid injections, particularly if the disease is unilateral. For severe, recurrent, or unremitting posterior segment inflammation, systemic corticosteroids should be given with an extremely slow taper. In the absence of response to systemic corticosteroids within 2–3 months, either another type of medication should be added or treatment should be converted to another medication [60]. In patients with severe findings or aggressive course of the disease, immunosuppressive or immunomodulator therapy could be initiated immediately.

For patients with familial Behçet's disease, poor ocular prognosis in a patient does not indicate aggressive treatment in his/her sibling and that each sibling should be managed on an individual bases [49].

Medical Treatment

Colchicine

There is abnormal leukocyte migration in Behçet's disease, and colchicine—a drug that inhibits such migration by binding tubulin and inhibiting cell division—is effective in controlling skin and joint inflammation. However, it is inadequate in suppressing active ocular inflammation [61] and is used mostly to prevent recurrences of ocular inflammation. The optimum dosage of colchicine is 0.5–1.5 mg/day. The most common side effects of colchicine involve the gastrointestinal system with nausea, vomiting, abdominal pain, and diarrhea. It can cause bone marrow suppression. Therefore, all patients taking long-term colchicine require blood count monitoring. Colchicine can also cause hair loss, weakness, nerve irritation, decreased fertility, and azoospermia.

Corticosteroids

Corticosteroids are still the first choice of treatment in ocular Behçet's patients to treat acute inflammation. Topical preparations are effective only for anterior chamber inflammation, while sub-Tenon's capsule, intravitreal, and/or systemic

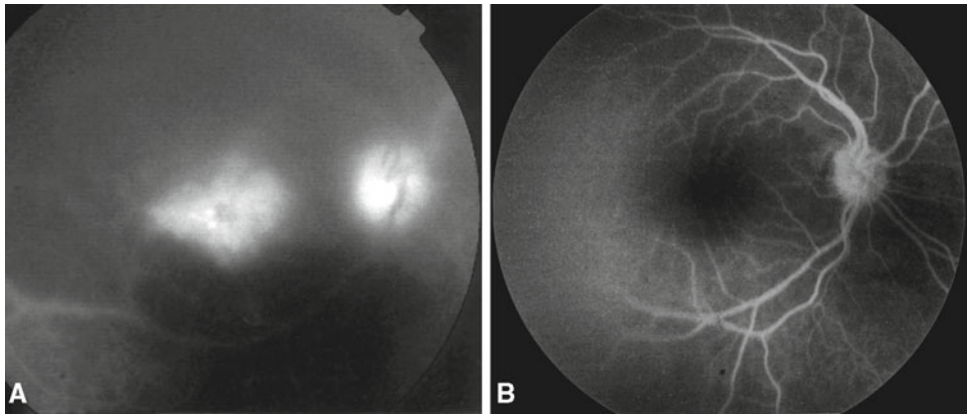

Fig. 12.28 (**a**) Cystoid macular edema and retinal vasculitis before intravitreal triamcinolone (IVTA). (**b**) Cystoid macular edema resolved completely 4 months after IVTA

corticosteroids are commonly used for posterior segment inflammation. Systemic corticosteroids could either be given as oral daily (1 mg/kg/day initial dose) or less preferably as bolus infusion. However, despite being effective in decreasing acute inflammation, systemic corticosteroids alone often fail to prevent recurrences and therefore are frequently used in combination with other medications. The major side effects of corticosteroids are elevated intraocular pressure, cataract, gastrointestinal ulceration, hypertension, diabetes mellitus, electrolyte abnormalities, osteoporosis, and reduced resistance to infections [60].

Intravitreal Triamcinolone

Intravitreal triamcinolone acetonide (IVTA) has become a popular treatment and been reported to be effective in resolving the persistent CME and severe vitritis, as well as in preventing recurrences of resistant uveitis in patients with Behçet's disease (Fig. 12.28) [40, 62–64]. However, the frequent side effects such as intraocular pressure elevation and cataract formation should be balanced with its positive effects.

Cyclosporin A and Tacrolimus (FK506)

Cyclosporin A and tacrolimus (FK506) are the two immunophilin ligands in clinical use today. They act within T cells by binding to cytoplasmic receptors termed immunophilins, thereby inhibiting the action of these cells and inducing a state of immunosuppression via a mechanism entirely separate from corticosteroids [60]. Cyclosporin A is a potent immunoregulator of the cellular immune response and has been found to be effective in controlling the intraocular inflammation in Behçet's disease [65]. It is given as an initial oral dose of 5 mg/kg/day. In patients who respond well, the dosage is gradually reduced over 3 months to a maintenance level of 2 mg/kg/day. For those who respond poorly, the tapering period can be extended. Cyclosporin A has also been found to reduce the number and severity of extraocular symptoms. However, it should be kept in mind that recurrences are very common with the cessation of cyclosporin A.

Tacrolimus, a natural metabolite of the bacterium *Streptomyces tsukubaensis*, is 10–100 times more potent as an immunosuppressive agent than cyclosporine on a weight-for-weight basis [66]. Tacrolimus is not commonly used in the treatment of Behçet's uveitis but has been reported to be effective in patients refractory to cyclosporin A [67]. It is used at doses of 0.03–0.08 mg/kg daily. The use of tacrolimus in the treatment of Behçet's disease is yet to be fully established, but it is currently predominantly indicated for uveitis that is refractory to other medications [68].

Side effects such as hepatotoxicity, nephrotoxicity, hypertension, weakness, paresthesia, gastrointestinal manifestations, anemia, and gingival hyperplasia are seen with cyclosporin A and less with tacrolimus [69]. Combining low-dose corticosteroid and low-dose cyclosporine

may decrease the side effects of both drugs while maintaining their efficacy.

Interferon-α(alpha)

Interferon-α(alpha), a naturally occurring cytokine, was first used in the treatment of Behçet's disease due to its antiviral activity against herpes simplex virus 1. Although the role of herpes simplex virus type 1 in the pathogenesis of Behçet's disease could not be proven, the immunomodulatory properties of interferon-α(alpha) such as decreasing the number of circulating T cells, enhancing HLA-1 expression on peripheral monocytes from Behçet's disease patients, and inhibiting T cell adhesion to endothelial cells in vitro lead to its use in the treatment of Behçet's disease [70].

It is administered as subcutaneous or intramuscular injections of 3 to 18×10^6 units of interferon-alpha-2a or 3 to 5×10^6 units of interferon-alpha-2b daily or 3 times per week. Zouboulis and Orfanos [71] reviewed 22 original reports of 144 patients with Behçet's disease to estimate the efficacy of interferon-alpha on mucocutaneous, ocular, and joint manifestations. Seventy-four percent of patients with mucocutaneous manifestations, 95% of patients with uveitis, and 93% of patients with arthropathy/arthritis exhibited a partial or complete response. Interferon-alpha-2a regimens were more effective than interferon-alpha-2b ones on mucocutaneous and ocular manifestations. Similar effects were also observed in a recent study with 91% partial or complete response with interferon therapy [72]. Recurrences, especially for uveitis is quite common after discontinuation of treatment.

A randomized placebo-controlled and double-blind study also showed the efficacy of interferon-alpha-2a on oral ulcers, genital ulcers, papulopustular lesions, and ocular inflammation in patients with BD [73].

The most common side effects are influenza-like syndrome, increase in serum liver enzymes, and reversible leukopenia. Although lymphocytopenia, thrombocytopenia, ulcerations at the site of injection, alopecia, worsening of psoriasis, epileptic seizures, and autoantibodies or a Behçet-like disease have been reported, interferon appears to be well tolerated and the side effects disappear after dose tapering [72, 74, 75]. A 3-month high-dose regimen (9×10^6 units three times per week) followed by a low maintenance dose (3×10^6 units three times per week) is recommended [71]. However, the optimum dosage and duration of interferon in the treatment of Behçet's disease need to be determined.

Anti-tumor Necrosis Factor Treatment

Tumor necrosis factor-α(alpha) (TNF-α), a proinflammatory cytokine, plays a significant role in the pathogenesis of Behçet's uveitis based on several evidences: increased serum and aqueous levels in Behçet's patients compared to patients without Behçet's uveitis, increased number of TNF-α(alpha)-producing cells during active disease, and its role in experimental models of uveitis [70, 76, 77]. Three TNF-α(alpha) inhibitors are currently used in inflammatory conditions: *infliximab*, a recombinant chimeric monoclonal antibody; *adalimumab*, a humanized monoclonal antibody; and the fusion protein human p75 TNF-α(alpha) receptor IgG1 *etanercept* [70].

Infliximab has been found to be effective in reducing the frequency of uveitis attacks, treating refractory macular edema, and improving the visual acuity especially in cases resistant to combination therapy with azathioprine, cyclosporine, and corticosteroids [72]. In addition, infliximab has a corticosteroid-sparing effect. Intravenous infusions of 5–10 mg/kg at weeks 0, 2, 6, and 10 or 14 have been used [72, 78]. However, controlled masked studies are warranted to determine the optimal dosage and duration in addition to co-medication interaction.

Etanercept has shown some efficacy for the mucocutaneous manifestations of Behçet's disease in a randomized, double-blind, controlled trial using 25 mg subcutaneously twice a week [79]. However, the ocular effects were not evaluated in that study. Two children with BD uveitis were treated with etanercept, one with and one without a good result [80].

Adalimumab has recently been reported to maintain disease remission in three patients with Behçet's uveitis with no recurrence and stable visual acuities during the follow-up after being switched from infliximab to adalimumab [81].

The most common adverse events are upper respiratory tract infection and headache. Hypertension, autoantibody production, infusion reaction, rash, eczema, contact dermatitis, pruritus, and lower back pain are uncommon side effects.

The recommendations for the optimal use of anti-TNF agents are given in an excellent review by Sfikakis et al. [82].

Cytotoxic and Other Immunosuppressive Agents

Antimetabolites such as azathioprine and methotrexate and less frequently alkylating agents such as cyclophosphamide and chlorambucil are being used for the refractory cases of ocular Behçet's disease.

Azathioprine, at 2.5 mg/kg/day, has been shown to be effective in preventing the development of new eye diseases in patients with Behçet's who do not have eye involvement in a randomized, placebo-controlled, double-blind study restricted to male patients [83]. This study also showed that azathioprine was effective in maintaining visual acuity, reducing the number of hypopyon attacks, and reducing the steroid requirement. The patients taking azathioprine also had less frequent oral ulcers, genital ulcers, and arthritis.

A combination of azathioprine and cyclosporine or triple drug therapy combining corticosteroids, cyclosporine, and azathioprine may be more effective than monotherapy with either agent and has been reported to successfully induce remission in some patients [84].

Methotrexate may be used in refractory uveitis especially in children with Behçet's disease or as a steroid sparing treatment and may reduce ocular inflammation.

Cyclophosphamide and *chlorambucil* are used more for the nervous system involvement and much less for ocular involvement in patients who are refractory to other agents at doses of 1 g intravenous pulsed cyclophosphamide and 2–12 mg/day chlorambucil.

The side effects of cytotoxic drugs and other immunosuppressive agents can be serious and include bone marrow suppression, hepatotoxicity, secondary malignancies, and decreased fertility. In the light of these potential side effects, these agents are usually reserved for the most desperate cases that have failed treatment with other medications [60].

Tolerization Therapy

As mentioned in the etiopathogenesis, cross-reactivity between microbial HSP65 and human HSP60 has been hypothesized to trigger the disease in predisposed hosts by stimulating T cells and by inducing TNF-α(alpha) by various cell types [70, 85]. Uveitis, induced by the human HSP60, could be inhibited with the peptide linked to recombinant cholera toxin B subunit in Lewis rats [86]. This strategy was adopted in a phase I/II clinical trial by oral administration of p336-351-CTB, three times weekly, followed by gradual withdrawal of all immunosuppressive drugs used to control the disease in eight patients with Behçet's disease [87]. Although the efficacy of this therapy needs to be confirmed in phase III trials and randomized controlled studies, tolerization therapy seems to be promising in the management of Behçet's disease as well as other autoimmune diseases.

Laser Treatment

The characteristic occlusive retinal vasculitis may result in ischemic changes that may lead to retinal and/or disc neovascularization. Left untreated, retinal and/or disc neovascularization may induce further complications such as vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma. While medical treatment is necessary to suppress inflammation, it has no effect on capillary non-perfusion and neovascularization. Therefore, laser photocoagulation should be performed in areas of capillary non-perfusion and retinal neovascularization (Fig. 12.29) [88]. In the presence of disc

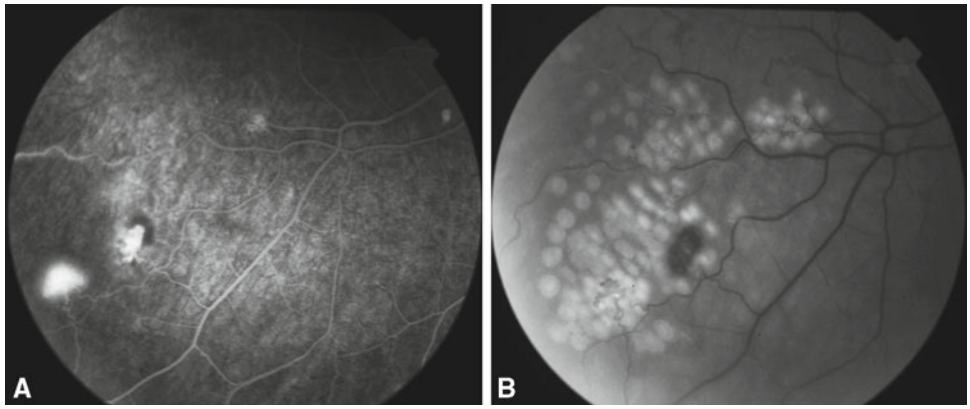

Fig. 12.29 (**a**) Retinal neovascularizations and hypoxic area on fluorescein angiography and (**b**) immediately after laser photocoagulation

neovascularization, panretinal photocoagulation should be performed.

Photocoagulation is well tolerated and does not induce postoperative inflammation. Nevertheless, it is not an alternative to medical treatment and systemic medication must continue. Photocoagulation should not be performed during an inflammatory attack and should not be directed toward edema, and topical steroids should be given after photocoagulation [89].

Plasmapheresis

Studies indicate neutrophil hyperactivity in Behçet's disease. Neutrophils and monocytes produce inflammatory cytokines that promote further neutrophil activity [90, 91]. Therefore, neutrophil apheresis can decrease the severity and frequency of attacks in Behçet's disease as shown by two small open-label trials [91, 92]. However, this procedure does not extensively deplete T cells [91], which are thought to have a significant role in the posterior ocular attacks.

Surgical Management of Ocular Complications

Patients with Behçet's uveitis should receive immunosuppressive therapy prior to any ocular surgery to reduce postoperative inflammation, and surgery should be deferred until the eyes are free of active inflammation for at least 2–3 months.

Cataract Surgery

Cataract formation is very common in Behçet's disease due to multiple factors, including recurrent intraocular inflammation, posterior synechia formation, and corticosteroid therapy. Cataract surgery in uveitic eyes may lead to severe postoperative complications such as recurrent intraocular inflammation, posterior synechia formation, cystoid macular edema, and optic atrophy and requires special attention. However, it is generally a safe procedure with favorable visual results in patients with Behçet's disease [93]. Nevertheless, the visual result after cataract surgery depends on the preoperative status of the posterior segment [94]. The phacoemulsification technique seems to be superior to other techniques due to minimal surgical trauma. It is important to insert the intraocular lens into the capsular bag, which reduces the postoperative inflammation risk by avoiding contact of the intraocular lens with the iris and ciliary body [93, 95]. Foldable acrylic posterior chamber intraocular lenses are recommended for these patients [96, 97].

Trabeculectomy

Trabeculectomy and intraoperative application of mitomycin C appear to provide long-term safety

and effectiveness in uveitic glaucoma associated with Behçet's disease [98, 99].

Vitrectomy

Vitreoretinal surgery is aimed at intense vitreous condensation, non-resolving vitreous hemorrhage, persistent cystoid macular edema, epiretinal membrane, and tractional retinal detachment. Removal of mechanical and humoral factors in vitreous gel by vitrectomy may enable better control of inflammation with a decreased number, severity and duration of uveitis attacks, and better diffusion of drugs to posterior segment, thus better visual acuity [100, 101]. In addition, relieving ciliary traction by vitrectomy may also prevent the development of hypotony and phthisis bulbi [102].

Controversies and Perspectives

The advances in research in the field of immunology and genetics in the last decades enabled a better insight into the etiopathogenesis of Behçet's disease. However, until the exact disease mechanism is found, the management is bound to be symptomatic rather than curative. Until then, new immunomodulatory/immunosuppressant agents with less systemic side effects may aid the prognosis of resistant cases. Most cases with Behçet's disease require more than one medication to suppress inflammation and reduce the frequency of attacks. With the absence of a standard treatment protocol and large randomized, controlled trials, the physician should evaluate each patient on an individual basis and decide the treatment accordingly. Corticosteroids are still the first choice of treatment in ocular Behçet's patients to treat acute inflammation. Cyclosporin A and interferon may be added to the management as the second-line treatment if necessary. Drugs such as infliximab and azathioprine or other immunosuppressants may be preserved for the most severe cases. With the use of such medications, the prognosis of the disease has significantly improved compared to 20 years ago.

Pearls

- The major characteristic of Behçet's disease is a systemic vasculitis with mucosa, skin, and eye being predominantly involved.
- Although Behçet's disease may affect almost any system of the body with exacerbations and remissions of inflammation, the key clinical manifestations are recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions such as erythema nodosum, pseudofolliculitis, papulopustular lesions, and acneiform nodules.
- HLA-B51 has been the most closely associated risk factor for Behçet's disease.
- There are no specific laboratory tests and pathognomonic findings in Behçet's disease. Therefore, the diagnosis remains largely a clinical one. It should be kept in mind, however, that recurrent oral ulcers are reported in almost all patients with Behçet's disease.
- Ocular involvement as anterior, intermediate, posterior, or panuveitis is common. The uveitis is chronic, recurrent, and non-granulomatous.
- Ankylosing spondylitis, Reiter's syndrome, inflammatory bowel diseases, sarcoidosis, Vogt-Koyanagi-Harada syndrome, Eales' disease, and infectious diseases such as syphilis and tuberculosis are among the most common differential diagnosis of ocular Behçet's disease.
- The aim of the treatment in ocular Behçet's disease is to achieve a rapid resolution of inflammation, to reduce frequency and severity of attacks, and to avoid complications. There is not a standard treatment protocol, and the extent and severity of the disease determine the treatment required.
- Corticosteroids, cyclosporin A, interferon-α, anti-tumor necrosis factors (infliximab), and azathioprine are the most commonly used medications for ocular inflammation.
- Laser photocoagulation should be performed in areas of capillary non-perfusion and retinal neovascularization. In the presence of disc neovascularization, panretinal photocoagulation should be performed to prevent complications such as vitreous hemorrhage and neovascular glaucoma.

- Although variable, the prognosis of ocular Behçet's disease is poor in the majority of patients. Nevertheless, increased awareness of the disease, a more aggressive treatment approach, and the availability of several immunosuppressive/modulators seem to have improved the prognosis of Behçet's disease in the last decade.

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Intraocular Lymphoma

13

Lihteh Wu, Narsing A. Rao, Erick Hernandez-Bogantes, Graciela Prado, and J. Fernando Arévalo

Abstract

Primary vitreoretinal lymphoma (PVRL), also known as primary intraocular and central nervous system (CNS) lymphoma, refers to a heterogeneous group of lymphomas that arise intraocularly or multicentrically in the eye and CNS. PVRL is a relatively rare, high-grade non-Hodgkin's lymphoma, usually of B-cell type, that forms part of the spectrum of primary central nervous system lymphoma. A high index of suspicion is essential in diagnosing PVRL. PVRL may present as vitreous infiltration, as a sub-RPE mass, as subretinal deposits, as retinal infiltrates, and as a vasculitic process or retinal necrosis. Combination of chemotherapy and radiation therapy has improved median survival to 40 months, but at the cost of late neurocognitive complications in patients older than 50 years of age. Preliminary trials of intravitreal chemotherapy and biological therapy are encouraging.

Keywords

Central nervous system lymphoma • Interleukin-10 • Intraocular lymphoma • Intravitreal methotrexate • Ocular lymphoma • Ocular masquerade syndrome • Rituximab • Vitreoretinal lymphoma

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Introduction

Lymphomas include tumors of lymphocytes, and traditionally, they have been divided into Hodgkin's disease and non-Hodgkin's lymphomas (NHLs). NHLs constitute the largest group of lymphomas and are further subdivided into B-cell or T-cell lymphomas [1, 2].

Over the years, the classification of NHL has evolved from being based on light microscopy findings to the current World Health Organization (WHO) classification of lymphomas that correlates the clinical characteristics of each lymphoma subtype with its morphological, immunophenotypical, and genotypical features [1]. In the 1960s, Rappaport [2] classified the disease according to its presumed cellular origin: lymphocytic, histiocytic, or undifferentiated. If both lymphocytes and histiocytes were seen, the disease was classified as a mixed cell type. The term reticulum cell sarcoma is a misnomer dating to the days when it was thought that the cell of origin of PVRL was the histiocyte [2]. On routine histological examination, the histiocytes show features indistinguishable from transformed lymphocytes [3]. Immunocytochemical techniques and in vitro lymphocyte function studies have shown that the so-called ocular reticulum cell sarcoma is a large cell lymphoma arising from transformed lymphocytes and not histiocytes [3]. A study of systemic diffuse histiocytic lymphomas showed that 55% were of B-cell origin, 35% had a null cell origin, 5% were of T-cell origin, and only 5% were of true histiocytic origin [4].

In 1978, Lukes and Collins [5] recognized the need to classify the disease in terms of B and T lymphocytes. They based their system on four cell types: the small- to medium-sized cleaved cell, the medium to large noncleaved cell, the large cytoplasmic phagocyte, and the dendritic reticulum cell [5]. Transformed B lymphocytes have immunoglobulins on their cell surface unlike histiocytes [3]. B-cell lymphomas are recognized by the demonstration of monoclonal surface immunoglobulins or, if absent, by immunoglobulin gene rearrangement using specific DNA probes. Characteristic rosetting with sheep red blood cells and T-cell-specific monoclonal antibodies identify T-cell lymphomas [6]. Most cases of primary central nervous system (CNS) lymphoma (PCNSL) and primary intraocular lymphoma (PIOL) when typed were found to be of B-cell origin [7]. Brown et al. [8] reviewed the literature and found that 57 cases of intraocular lymphoma had been reported in which cell marker studies had been done. They found that 53% were of B-cell origin, 21% of T-cell origin, 10% of null cell origin, and 16% were polyclonal or untypable.

Several other classifications were developed in an attempt to classify the lymphomas according to their clinical behavior leading to considerable confusion. In the early 1980s, the National Cancer Institute sponsored a study to resolve the differences between the different classifications. The study found that each of the classifications was useful and none was superior to the other. As a result, the International Working Formulation of NHL for Clinical Usage was born [9]. Ten major cell types were identified, and these were graded according to malignant potential: low-, intermediate-, and high-grade malignant lymphomas. In time, this became the most widely used system. Paradoxically, as treatment protocols became more effective, the prognosis of the different grades changed. Cure rates for intermediate- and high-grade malignancies improved, whereas the death rates of low-grade malignancies increased when most patients relapsed and died from their disease. In addition, a major weakness of the above classification scheme is the lack of immunological typing.

In 1994, the International Lymphoma Study Group proposed the revised European-American lymphoma (REAL) classification where lymphomas were grouped as clinical-pathological entities [1]. Each entity was recognized to have a range of morphological grades and degrees of clinical aggressiveness. Thus, B-cell lymphomas are categorized into low-, intermediate-, or high-grade lymphomas. This is the classification currently adopted by the WHO [1]. Several subtypes of B-cell lymphomas are defined according to the stage of lymphocyte development where they arise [7, 10]. These stages include the pre-germinal,

germinal, or post-germinal stages. These can be differentiated by immunophenotyping and by checking for somatic mutations in the variable region gene of the immunoglobulin. Lymphomas that arise from pre-germinal cells usually do not manifest any somatic mutations. Lymphomas derived from germinal cells are characterized by somatic mutations that are ongoing. Post-germinal derived lymphomas have somatic mutations with only few or no ongoing mutations [7].

PIOL is a rather imprecise term, and Coupland and Damato [7] suggest that the various types of intraocular lymphoma be referred to according to their anatomic location and to whether or not they are primary or secondary at these sites. A distinction should be made between patients with PIOL with or without central nervous system (CNS) disease in which the intraocular involvement is usually vitreoretinal, patients with primary choroidal lymphoma, patients with primary iridal lymphoma, and patients afflicted by a systemic lymphoma with secondary uveal involvement [7]. According to the WHO classification, primary vitreoretinal lymphoma (PVRL) is usually of the diffuse large B-cell lymphoma (DLBCL) type with intermediate- to high-grade malignant potential [1]. Gene expression profiling studies that include both chromosomal and immunohistochemical analyses subdivide DLBCL into three different types: activated B-cell DLBCL (ABC type), germinal center DLBCL (GCB type), and primary mediastinal (thymic large) B-cell DLBCL [7, 10]. Prognosis is dependent on this molecular subtype. Patients with the ABC subtype DLBCL have a much worse prognosis than patients with the GCB DLBCL. Immunophenotyping and somatic mutation analysis suggests that most PVRL is derived from an early post-germinal center B cell. Chromosomal translocation data identifies a subgroup of PVRL that is derived from germinal center B cells [7].

The objective of this chapter is to review the epidemiology, etiology, clinical findings, diagnosis, differential diagnosis, imaging, pathology, and management of intraocular lymphoma.

Historical Background

In 1951, Cooper and Riker [11] made the observation that an intraocular lymphoma could masquerade as an intraocular inflammatory condition. In 1955, Givner [12] reported a case of a woman who suffered from uveitis of an unknown cause and subsequently went on to develop PCNSL. Autopsy revealed intravitreal cells suggestive of PVRL. In 1968, Vogel et al. [13] reported a patient with PVRL who eventually developed neurological symptoms. The patient underwent a craniotomy, and the specimen revealed similar histopathologic findings to the enucleated eye. CNS involvement did not occur from contiguous spread from the eye through the optic nerve. In another autopsy study, the optic nerve was not involved despite involvement of both eye and CNS. However, in some cases, extension through the lamina cribrosa, and involvement of the optic nerve and orbital leptomeninges, has been demonstrated [14]. In 1968, Nevins et al. [15] reported the first isolated intraocular case confirmed by autopsy. Case 3, in the series reported by Barr et al. [16], referred to the autopsy findings in a patient with bilateral PVRL where the rest of the body was completely free of tumor. Investigators proposed that involvement of the eye and CNS was due to a multicentric origin of the tumor [13, 15, 16]. In 1972, Neault et al. [17] reviewed the Mayo Clinic experience with 17 PCNSL patients diagnosed by craniotomy. Of these 17 patients, 7 suffered from posterior uveitis. The uveitis was initially unilateral but eventually became bilateral. They noticed that uveitis was not present in any other type of intracranial tumor. None of the eyes were examined microscopically. Therefore, it was impossible to determine if the ocular findings represented neoplastic involvement, primary inflammation, or an inflammatory process secondary to or coexistent with neoplastic involvement of the uveal tract or retina. On the other hand, of 19 cases of PCNSL seen at the Massachusetts General Hospital, only one had uveitis [18]. Kennerdell et al. [19] reported a fatal case of PCNSL accompanied by uveitis. On histopathology, the

vitreous was clear of neoplastic cells. They suggested that initially the ocular involvement is a benign inflammatory process that over time evolves into a neoplastic one.

In the early days, diagnosis of PVRL or PCNSL was made by craniotomy with debulking of the mass, enucleation of a blind painful eye, or during an autopsy [11–13, 15, 16]. In the 1970s, first vitreous aspiration and then pars plana vitrectomy were employed to obtain cytological material to diagnose PVRL earlier [20, 21]. Rockwood et al. [22] suggested that pars plana vitrectomy and/or lumbar puncture should be employed prior to the consideration of craniotomy. By the late 1980s, it was well established that PVRL forms part of the spectrum of PCNSL. In patients with PCNSL, extracranial involvement, other than the eye, is rare. Both solitary PVRL and that associated with PCNSL usually involve the vitreous, retinal pigment epithelium (RPE), and retina. Very rarely, an association of uveal tract PIOL and PCNSL has been reported.

Epidemiology

NHL usually arises from lymph nodes, but up to 25% of NHLs are of extranodal origin. Approximately 1.6% of NHLs occur intraocularly and 4.5% in the CNS. However, for unknown reasons, the incidence of PCNSL in the USA has been increasing over the years [23]. Eby et al. [24] reported 2.7 cases per 10 million people in 1972–1974 compared to 7.5 cases per 10 million people in 1982–1984. The incidence of PVRL is unknown, but it has been reported that about 20% of patients with PCNSL go on to develop PVRL [23, 25]. A major risk factor for the development of PCNSL and PVRL is immunosuppression [23]. Transplant recipients, acquired immune deficiency syndrome (AIDS) patients, and children with congenital immunodeficiencies are at an increased risk of developing PCNSL. However, the increased number of immunosuppressed patients does not explain the rise in cases of PCNSL [23].

Even though PVRL has been reported in patients as young as 15 years of age, it typically remains a disease of middle age or older people [25]. The average age of affected individuals is 58 years old, which is similar to the average age of 55 years old for PCNSL. With respect to PVRL, women appear to be slightly more commonly affected than men by a ratio of 1.5–1. In contrast, men appear to be slightly more commonly affected than women by a ratio of 1.7–1 in PCNSL. There appears to be no predilection for race [23].

Approximately 80% of cases of PVRL have bilateral involvement. At some point in their disease, 66% of patients with PVRL manifest CNS involvement. Of these, 15–20% presented with CNS disease an average of 18 months prior to the development of ocular symptoms [23, 25]. Forty-five to sixty-six percent had PVRL before the diagnosis of PCNSL. The time of onset from ocular symptoms to the development of CNS symptoms ranged from less than 1 month to 10 years with an average of 21 months. Fifteen percent were diagnosed with concurrent PCNSL and PVRL. About 25% of patients were reported to have solely ocular involvement. Uveal infiltration is the typical ocular manifestation secondary to metastasis from a systemic lymphoid malignancy. Only 5% of patients with PVRL show subsequent systemic involvement. Another 5% of patients show concurrent intraocular, systemic, and CNS involvement [13, 14, 16, 21].

Etiology

Two hypotheses have been proposed for the origin of PVRL and PCNSL [23]. The first states that an infectious or inflammatory process, probably viral, attracts into the CNS or eye a nonneoplastic, reactive population of lymphocytes. The inflammatory cell population undergoes transformation into neoplastic cells by some second event in the local site(s). A second theory proposes that B lymphocytes in a lymph node or extranodal site are activated, caused to proliferate, and transformed to become neoplastic. These neoplastic cells spread hematogenously but aggregate only in sites within the CNS or eye. In the meantime, the true primary site remains obscure and undetected.

The factors involved in cell transformations remain unclear. Low-dose immunosuppressive therapy seems to be harmful, leading to the belief that acquired immune dysfunction plays a role in the disease [21, 23]. Renal transplant patients are at an increased risk for malignancies. NHL was the most common type of tumor in these patients. It is thought that this occurs through depression of the immunological surveillance function. Cases of PVRL and PCNSL in transplant recipients maintained on immunosuppressive therapy have been reported [26]. With the appearance of the AIDS epidemic in the early 1980s, it was noticed that the incidence of NHL in these patients increased. Despite the estimate that 3% of all AIDS patients will develop PCNSL during the course of their disease, there have been only few reports of PVRL cases in AIDS patients [27, 28].

Clinical Findings and Differential Diagnosis

PVRL is a unique disease in its protean manifestations. The clinical findings are quite nonspecific and diverse. These depend on whether the RPE, optic nerve, vitreous, or retina is most extensively involved. It can present as vitreous infiltration, intraretinal, subretinal, or subpigment epithelial masses; as a vasculitic process; or as a localized or diffuse retinal necrosis. Thus, PVRL is a paradigm for the spectrum of the manifestations of disease in the posterior pole: necrosis, vasculitis, multifocal retinochoroiditis, or mass lesions. It is not surprising then that diagnosis is often delayed with fatal consequences since early diagnosis and treatment appear to result in better disease control and survival [29].

Most patients present with a painless loss of vision, floaters, or both [7, 25, 30]. Less common presentations of the disease include a red eye, photophobia, and pain [13, 16, 21].

Pseudohypopyon has been seen in a handful of cases [16]. In one case, it mimicked late postoperative endophthalmitis. In addition, certain cases of secondary glaucoma have been due to PVRL. Rubeosis iridis with neovascular angle closure, accumulation of cellular debris, and synechial closure secondary to inflammation account for the mechanisms of the glaucoma [7].

Vitritis has virtually been reported in every case of PVRL and may vary from infiltration of the vitreous with scattered cells to large aggregates. A posterior vitreous detachment is often present with collections of tumor cells on the detached posterior face [7]. Traditionally, it has been emphasized that PVRL is a common masquerader in the elderly [7, 11, 13, 16, 25, 30]. The typical patient is an older individual with vitritis that is resistant to corticosteroid treatment. However, in a series of newly diagnosed uveitis in 58 patients older than 60 years, 19 patients were suspicious for PVRL. They underwent diagnostic vitrectomy, and only 1 case of PVRL was found (3.4% prevalence). [31]

Initial infiltrations of the lymphoma cells in the sub-RPE space produce small yellow-white placoid lesions that resemble lesions of the multiple evanescent white dot syndrome or punctate inner choroidopathy [7, 32]. As the lesions grow and become elevated, they may resemble multifocal choroiditis, birdshot choroidopathy, or acute multifocal placoid pigment epitheliopathy. Further expansion and solid volume gain leads to multiple, large sub-RPE tumors with sharply circumscribed, yellow-white, dome-shaped masses covered by fine mottled and attenuated pigment epithelium (Fig. 13.1a, b) [32]. Gass et al. [32] consider this clinical picture pathognomonic for PVRL. Nevertheless, these nodular lesions can be mistaken as sarcoidosis, tuberculosis, brucellosis, metastatic lesions, or the Vogt-Koyanagi-Harada disease [6]. The lesions may spontaneously undergo complete necrosis and resolution, leading to atrophic or disciform scars simulating the ocular histoplasmosis syndrome [6, 32].

The lymphomatous process may then infiltrate the overlying retina producing white or grayish-green intraretinal lesions with fluffy outlines that rapidly become confluent obscuring the underlying RPE deposits (see Fig. 13.1) [6, 7, 32]. The retinal capillaries may be disrupted causing focal intraretinal hemorrhages. Arterial and venous sheathing have figured prominently in some cases of PVRL (Fig. 13.2).

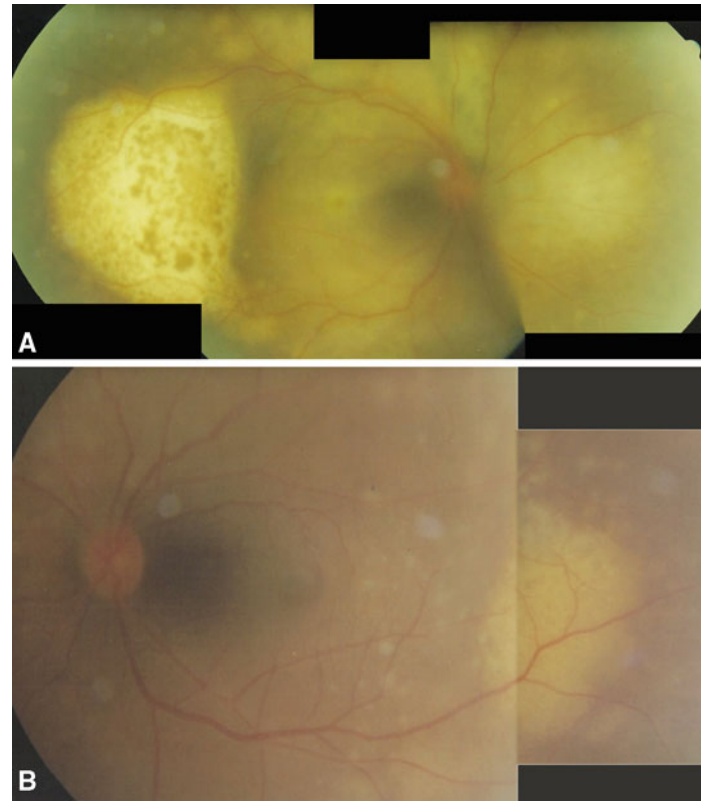

Fig. 13.1 Subretinal pigment epithelium (RPE) elevations with sharply circumscribed, yellow-white, dome-shaped masses covered by fine, mottled, and attenuated pigment epithelium. (**a**) Note two lesions in the right eye, nasal to the optic disc and temporal to the fovea. (**b**) One *yellowish* lesion temporal to the fovea in the left eye (Courtesy of Raul Vianna, M.D.)

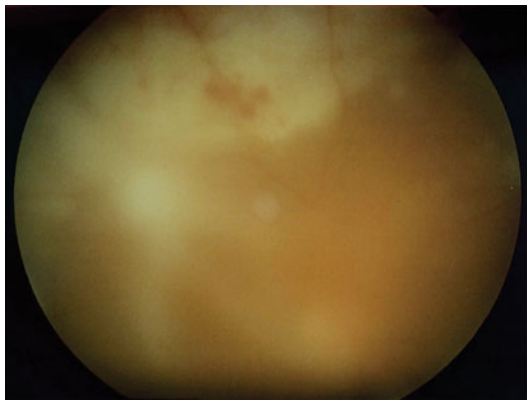

Fig. 13.2 Lymphomatous process infiltrating the overlying retina producing *white* intraretinal lesions with fluffy outlines that rapidly become confluent and obscure the underlying retinal pigment epithelium. Arterial and venous sheathing have figured prominently in some cases of intraocular lymphoma

The resulting clinical picture of a necrotizing retinitis may be confused with toxoplasmosis, acute retinal necrosis secondary to herpetic infection, CMV retinitis, syphilitic retinitis, Whipple's disease, Candida endophthalmitis, sarcoidosis, frosted branch angiitis, Eales disease, Behcet's disease, systemic lupus erythematosus, HTLV-1-associated uveitis, and multiple sclerosis [6, 7]. Extension of the hemorrhage through the internal limiting membrane can lead to vitreous hemorrhage. Plaques of neoplastic cells in a retinal artery wall leading to retinal artery occlusion have been reported [32]. In other cases, the retina is edematous, and if the macula is involved, cystoid macular edema (CME) results [16, 20]. Exudative retinal detachment has also been reported [33].

A difficult situation occurs in AIDS patients with retinal lesions that are being treated with protease inhibitors. As their CD4+ count rises, a syndrome known as immune recovery uveitis may occur. Vitreous inflammation in conjunction with the aforementioned retinal lesions may lead one to the erroneous diagnosis of PVRL [27].

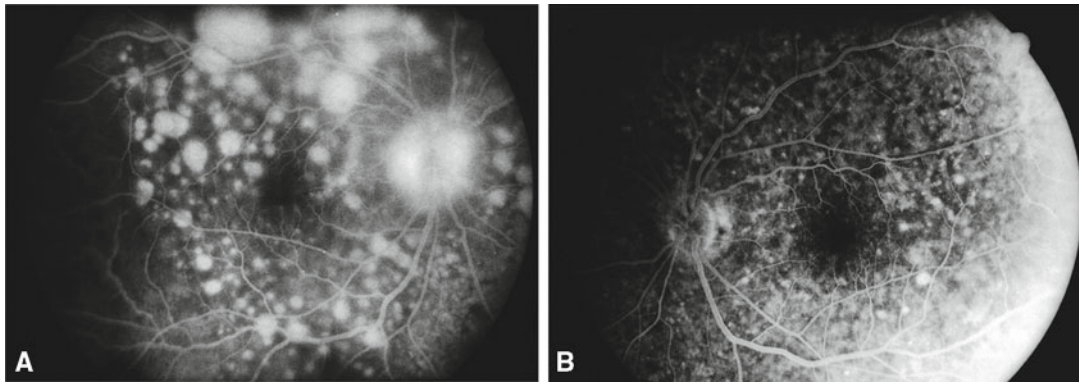

Fig. 13.3 Same patient as in Fig. 13.1. Fluorescein angiogram demonstrated multiple areas of hyperfluorescence in both eyes. (**a**, **b**) Arteriovenous phase demonstrating multiple areas of disturbances at the level of the retinal pigment epithelium (RPE). Deposits of older tumor cells that are either dead or sick absorb fluorescein dye, causing window defects of the RPE. A hot optic disc is seen in Fig. 13.3a (Courtesy of Raul Vianna, M.D.)

Papillitis is sometimes observed (Fig. 13.3a, b) [7]. It may be due to direct invasion of the optic disk by tumor or secondary to increased intracranial pressure related to the cerebral neoplasm [7]. Very rarely the intraocular tumor may invade the orbit [28].

Imaging

Ancillary ocular imaging modalities like fluorescein angiography (FA), optical coherence tomography (OCT), and indocyanine green angiography (ICGA) are useful adjuncts in raising the level of suspicion so that a diagnosis of PVRL is made promptly. A study from the National Eye Institute showed that despite the presence of vitritis in most patients, the FA did not show hallmarks of intraocular inflammation in most eyes [34]. CME was present in 19% and perivascular staining or leakage in 6% of eyes. Furthermore, 83% of eyes with CME had a prior history of intraocular surgery [34]. Since PVRL is often confused with a uveitic process, it is remarkable that the FA is not suggestive of an inflammatory process. The most common FA findings consist of disturbances at the level of the RPE [34]. PVRL cells are often confined to the sub-RPE space, and their viability will determine the FA findings [21, 34]. Deposits of older tumor cells that are either dead or sick absorb fluorescein dye causing window defects of the RPE (see Fig. 13.3).

Alternatively, window defects might represent areas of tumor resolution with secondary RPE atrophic changes. In contrast, healthy tumor cells will not absorb fluorescein and will manifest as focal areas of blocked fluorescence [32, 34]. In some cases, FA detected lesions that were not seen ophthalmoscopically [30, 32, 34]. On the other hand, some eyes with vitritis will have a normal FA study [34].

Fardeau et al. [35] compared the FA, OCT, and ICGA findings among patients with PVRL, infectious uveitis, metastatic tumors, and immune-mediated uveitis. Their most significant findings were clusters of small round hypofluorescent lesions 50–250 μ(mu)m in diameter seen in both the early and late phases of the FA. These were identified in 45% of patients with PVRL and in only 2% of patients without PVRL. These hypofluorescent lesions corresponded to punctate white lesions seen in the fundus. Similarly hypofluorescent lesions that tended to fade in the later phase of the study were seen with ICGA in 26% of PVRL patients and 8% of non-PVRL patients. Nodular hyperreflective lesions at the level of the RPE were observed in the OCT of 42% of patients with PVRL compared to 15% of patients without PVRL. The combination of these

three imaging modalities yielded a positive predictive value of 88.9% and a negative predictive value of 85% for diagnosing PVRL [35].

Some investigators have suggested using ophthalmic echography as an adjunctive study in patients with PIOL [36]. In a series of 13 patients with PVRL, all the patients manifested some ultrasonographic abnormality. The most common findings were vitreous debris (77%) (Fig. 13.4), choroidal scleral thickening (46%) (Fig. 13.5), and widening of the optic nerve (31%). None of these findings are specific for PVRL but in the proper clinical context might provide sufficient evidence to consider it seriously.

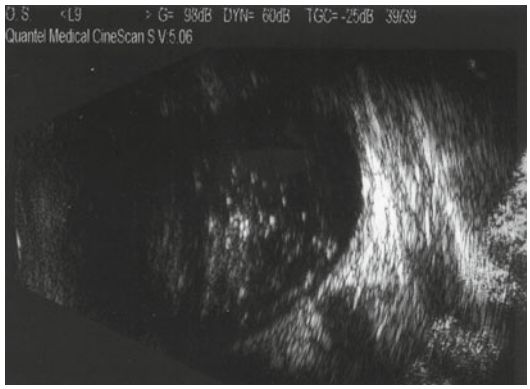

Fig. 13.4 Echographic examination of a patient with primary vitreoretinal lymphoma (PVRL) demonstrating vitreous debris

Fundus autofluorescence (FAF) is a relatively new ophthalmic imaging modality that utilizes the fluorescent properties of lipofuscin to study the health of the RPE and photoreceptor complex. There has been recent interest in studying the FAF of several chorioretinal diseases such as central serous chorioretinopathy, non-exudative age-related macular degeneration, and Stargardt's disease, among others [37]. Ishida and colleagues [38] have recently published their FAF findings in five eyes with PVRL. They reported that the FAF patterns were diverse but distinctive according to the individual funduscopic findings. Sub-RPE tumors were generally

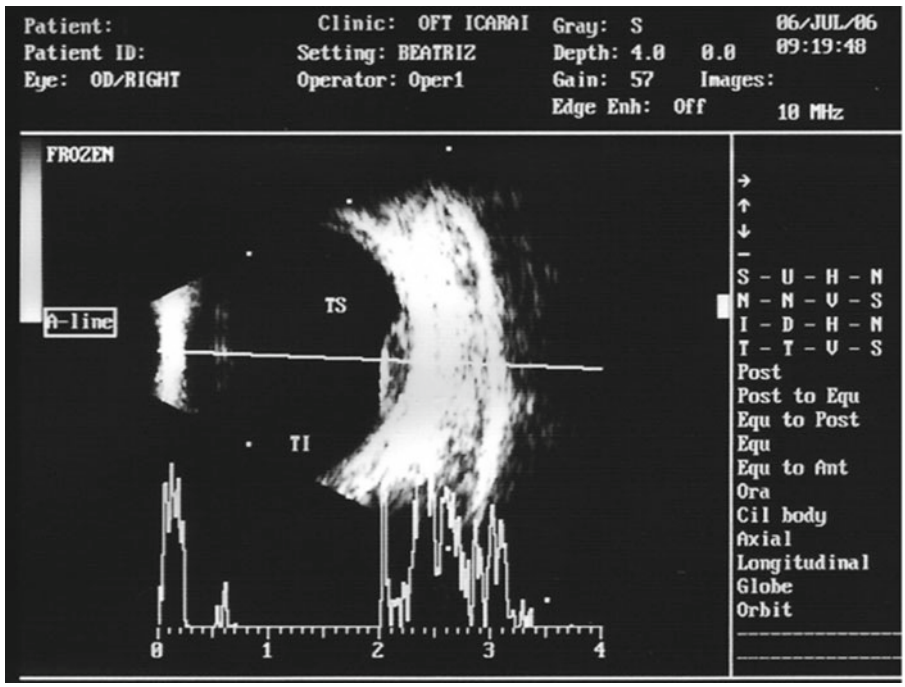

Fig. 13.5 Same patient as in Figs. 13.1 and 13.3. A- and B-scan ultrasound shows an irregular internal reflectivity and no internal vascularity. No extensive serous retinal detachment is usually seen with this type of tumor (Courtesy of Raul Vianna, M.D.)

weakly hyperfluorescent on FAF. The hyperpigmented mottling of the RPE overlying the sub-RPE tumors was very hyperfluorescent on FAF. In eyes with tumor infiltration into the retina causing whitening of the retina, the FAF pattern was that of hypofluorescence. Spontaneous resolution of the sub-RPE tumors usually leaves an atrophic area of RPE that appears hypofluorescent on FAF [38].

Novel ophthalmic imaging techniques including magnetic resonance spectroscopy, magnetic resonance imaging, and novel positron emission tomography agents with the ability to detect lymphoma cells between the RPE and Bruch's membrane may be in the horizon [39]. Malignant B lymphoma cells can be differentiated from normal and activated T-cell populations from as few as 8 cells by their intrinsic autofluorescence when excited with wavelengths of 351, 458, and 488 nm.

Diagnosis and Pathology

In patients over 50 years of age with posterior or pan-uveitis unresponsive to corticosteroid treatment, the possibility of the lymphoma must be considered [6, 7, 11, 15, 16, 20, 40]. Some cases have been reported where PVRL responds briskly to steroids, thus delaying the diagnosis [6, 25, 30]. If PVRL is suspected, fluorescein angiography, OCT, and a complete medical history and physical examination are conducted. Neurological work-up including neuroimaging and lumbar puncture is then performed. If lymphoma cells are isolated from the CSF, it is not necessary to pursue further diagnostic procedures. Some have clinically defined PVRL by the presence of ocular symptoms and signs in patients with known PCNSL [25]. However, as mentioned previously, during the autopsy of a patient with PCNSL and uveitis, the vitreous was clear of neoplastic cells [19]. Conversely, Zimmerman [41] pointed out that whenever a patient with PVRL showed neurological manifestations, it was implied that PCNSL was present. However, in his experience, that was not always the case. In 18 patients with histopathologically proven PVRL, biopsies of the brain did not always confirm the presence of PCNSL. In nine cases of PVRL with neurological symptoms, PCNSL was confirmed; however, in six cases, CNS manifestations were secondary to other causes such as nocardiosis, hemorrhage, and Behcet's disease [41]. If PCNSL is not evident, then one should proceed with a diagnostic vitrectomy. Just like in any type of malignancy, tissue diagnosis is a prerequisite for the initiation of therapy in PVRL.

Currently, diagnosis of PVRL is based primarily on cytological evaluation, immunohistochemistry, and molecular techniques on the tumor. The CSF and the vitreous are examined and processed in the same fashion [6].

A single vitreous biopsy may not always be diagnostic of PVRL [6, 25, 30, 33]. Steroids can hinder the diagnosis by clearing some malignant cells [6, 30]. They are known to shrink CNS lymphoma lesions [42]. Some have advocated discontinuing the steroids for a period of time before the specimens are obtained [6, 30]. In certain selected cases when vitreous cytological findings are equivocal and the suspicion for PVRL remains high, retinal biopsy, chorioretinal biopsy, full thickness eye wall biopsy, and aspiration of subretinal lesions may be considered [6, 40].

In patients with bilateral involvement, the eye with the worse visual acuity or the most prominent cellular infiltration in the vitritis is selected to undergo diagnostic vitrectomy. A very experienced cytopathologist is often needed to make the diagnosis since the yield from vitrectomy samples is often small [6, 30, 33]. Cytological analysis should be given precedence. An undiluted sample of vitreous (1–2 mL) is first obtained and immediately placed into 2–3 mL of cell culture medium such as RPMI (Associated Biomedic Systems, Inc., Buffalo, NY, USA) and then immediately transported to the cytology lab [6]. Rapid processing of the vitrectomy specimen is critical in maintaining the morphology and integrity of the cells [33]. The ocular pathologist then proceeds to isolate the cells by cytocentrifugation. Staining of the PVRL cells with Diff-Quick or Giemsa is superior to hematoxylin-eosin and Papanicolaou stains [6]. The supernatant is used for cytokine analysis and possibly viral polymerase

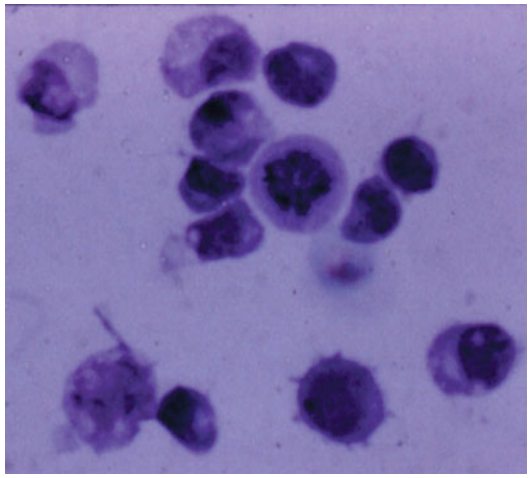

Fig. 13.6 Cytological examination of a vitrectomy specimen showing lymphoma cells with large round nuclei with indistinct cytoplasm

chain reaction (PCR) [6]. In cases where shipment of the vitrectomy specimen to different institutes is required, the material can be fixed in equal volume of 90% ethanol. Such fixed tissue is processed for cell block preparations followed by hematoxylin-eosin stain, immunophenotyping to determine clonality, and special stains for infectious agents. A core vitrectomy is completed, and the resulting diluted sample and cassette washings may be used for additional studies such as flow cytometry, immunohistochemistry, and molecular analysis [6].

Under light microscopy, tumor cells typically display large round, oval, or indented hyperchromatic nuclei with prominent eccentric eosinophilic nucleoli, mitotic figures, a coarse chromatin pattern, indistinct cytoplasm, pleomorphism, and occasionally finger-like projections from the nuclei (Fig. 13.6) [6, 13, 15, 16, 30, 33]. Reactive T lymphocytes, fibrin, cellular debris, and apoptotic and necrotic cells are often found in conjunction with the lymphoma cells, underscoring the importance of having an experienced cytopathologist [6]. Electron microscopic studies reveal that intranuclear inclusions, cytoplasmic crystalloids, pseudopodal cytoplasmic extensions, cytosomes with autophagic vacuoles, and electron-dense bundles may be seen in the intercellular space [43]. Cytological examination can detect lymphoma cells, but it cannot differentiate between a B-cell and T-cell origin [6].

Histopathologic examination reveals that neoplastic cells are primarily seen in the vitreous, in the sub-RPE and subretinal spaces, and in the retina, optic nerve head, and rarely choroid [17, 19]. Involvement of the vitreous by neoplastic cells can produce effects similar to inflammation [7]. The vitreous can become condensed, liquefied, cloudy, and detached. A vitreous cellular infiltrate might be the only ocular manifestation of the disease. They form fluffy nondiscrete opacities. Occasionally, the anterior segment of the eye is involved. A chronic inflammatory infiltrate in the uveal tract has been described [16]. The choroid can be diffusely thickened and sometimes infiltrated with inflammatory cells primarily made up of reactive T cells, macrophages, and B lymphocytes [15, 21]. The RPE detachments from sub-RPE tumor cell deposits can evolve to RPE atrophy, photoreceptor layer atrophy, and disciform scars [32]. Tumor cells are typically arranged around blood vessels in the retina and/or brain. Extensive infiltration of the retina and optic nerve head may lead to coagulative necrosis [14, 16].

Most PVRLs are monoclonal B-cell lymphomas [3, 6–8]. A minority of cases are of T-cell origin and can simulate a reactive inflammatory process. Immunohistochemical stained sections or immunophenotyping by flow cytometry showing a monoclonal response of B-cell markers such as CD19, CD20, and CD22 with either a kappa or lambda light chain restricted expression help make the diagnosis in cases where cytopathology is equivocal [6, 30]. Flow cytometry can analyze multiple markers simultaneously. The number of cells required to perform cell typing was the limiting factor in studying immune characterization of PVRL by flow cytometry [6]. Furthermore, some B-cell lymphomas do not express surface markers, thus preventing its recognition by flow cytometry [6]. Immunohistochemistry for T-cell markers such as CD3 and/or PCR for T-cell receptor gene rearrangements can help identify PVRL of T-cell origin [6].

PCR analysis can demonstrate the monoclonal proliferation of B lymphocytes in the vitreous [6, 7].

It can also demonstrate the bcl-2 oncogene indicating the presence of a t(14;18) translocation, an immunoglobulin heavy chain gene rearrangement indicating a B-cell lymphoma, and rearrangements of the T-cell receptor gamma gene indicating the presence of a T-cell lymphoma. The presence of multiple inflammatory cells found in conjunction with the lymphoma cells renders conventional PCR techniques less specific and sensitive. A novel way of obtaining material of higher purity for PCR has been described [6]. The histological slides are prepared in the usual manner. Under direct visualization from the light microscope, the cells of interest are identified and scraped from the slide with a 30-gauge needle or with laser capture. These are then placed in a single-step extraction buffer, which happens to be the starting point for PCR. PCR is then performed as usual. Demonstration of rearrangement of the IgG heavy chain confirms monoclonality [6].

Intravitreal interleukin-10 (IL-10) levels may help in the diagnosis of PVRL [6, 7, 44]. IL-10 is a growth and differentiation factor for B lymphocytes and plays a role in the growth of lymphocytic leukemia, AIDS, lymphoma, Burkitt's lymphoma, and other NHL. Intravitreal IL-10 levels that correlated with the severity of the vitritis were detected in 3 patients with PVRL by enzyme-linked immunosorbent assay (ELISA) [44]. In this same study, intravitreal IL-10 was not detected in any other uveitic conditions such as sarcoid, acute retinal necrosis, and endophthalmitis. Cerebrospinal fluid (CSF) levels of IL-10 were suggestive of the presence of malignant cells. Intravitreal IL-6 levels were shown to be elevated in patients with intraocular inflammation unrelated to malignancies. Others have suggested using the ratio of IL-10 to IL-6 to control for the dilution factor involved in obtaining the vitreous sample from the vitrectomy cassette. An intravitreal IL-10/IL-6 >1 provides a 75% specificity and sensitive to distinguish PVRL from other conditions. Aqueous levels of IL-10 are also significantly high in PVRL [44]. Aqueous levels of IL-10 greater than 50 pg/mL give a sensitivity of 89% and a specificity of 93% for detecting PVRL. Similarly, intravitreal levels of IL-10 greater than 400 pg/mL yield a sensitivity of 80% and a specificity of 99%. Since T cells do not secrete IL-10, low IL-10 levels may suggest a T-cell lymphoma [6]. However, cytopathologic findings combined with immunophenotyping are considered gold standard for the diagnosis of the lymphoma and subsequent treatment.

Treatment

Effective treatment of PVRL has been difficult to determine because of its rarity. Furthermore, the small number of patients receiving each therapy makes comparisons between studies difficult. The natural history of PVRL seems to be death from progression of CNS disease [14, 25]. In patients with PVRL, the interval between diagnosis of PCNSL and death was of 12 months [25]. Therefore, the goal of treatment should be the eradication of CNS and intraocular disease. The treatment protocol will depend on whether or not the patient has isolated PVRL or has concurrent CNS disease. Treating the ocular disease prior to CNS involvement probably improves survival [29]. However, the results of an international multicenter retrospective study were not able to confirm the benefits on survival of treating ocular lymphoma [45].

In order to better understand treatment of PVRL, an understanding of the unique characteristics of PCNSL is required. Unlike other brain tumors, complete resection of PCNSL has not been shown to improve survival over supportive care and therefore has no therapeutic role [42]. Likewise, removal of an eye involved by PVRL in an otherwise healthy person does not constitute a cure either [22]. The existence of the blood-brain barrier has been a limiting factor in the penetration of systemic chemotherapeutic agents into the CNS and eye. Although PCNSL disrupts the blood-brain barrier, disruption may be limited to areas of bulky tumor, whereas areas of microscopic disease may have a relatively well-preserved blood-brain barrier. Thus, chemotherapy protocols such as CHOP (cyclophosphamide, hydroxydaunomycin, oncovin, and prednisone) that are generally effective in systemic lymphoma are ineffective in PCNSL and PVRL [46, 47].

Untreated patients with PCNSL survive an average of 1.5 months. Whole brain radiation therapy was once the treatment of choice for PCNSL [42, 48]. In one prospective study, 41 patients with PCNSL underwent whole brain radiation therapy consisting of 40 Gy with a 20-Gy tumor boost. Despite the high response rate of 90%, 68% of patients relapsed and the median survival was only 11.6 months. Similarly, the mainstay of therapy for PVRL used to be irradiation to the CNS and/or eye [46, 49, 50]. The initial response was dramatic, but recurrences were typical. Shrinkage of the retinal and/or intracranial lesions was observed following radiation therapy. The radiation dose varied between 30 and 50 Gy in fractions of 1.5–2.0 Gy. Some had proposed to irradiate the fellow eye even if not currently involved [50]. Prophylactic radiation treatment of 45 Gy to the whole brain was recommended even if no CNS involvement was documented [50]. However, Isobe et al. [49] reported that 2 of 9 patients who received prophylactic cranial irradiation developed CNS disease compared to 1 of 4 patients that did not receive prophylactic cranial irradiation. This suggests that cranial irradiation is ineffective as a prophylactic measure to prevent CNS disease. In one series despite adequate radiation therapy, 7 of 9 patients eventually died of CNS disease progression. In another study, recurrent CNS disease was the cause of death in 12 of 13 patients.

Prognosis is poor with ocular irradiation with a median survival of 20 months [46, 50]. This is slightly better than PCNSL treated with steroids and radiation where the median survival is only 10–18 months [42]. In general, radiation therapy offers satisfactory local control for patients with isolated PVRL; however, it has fallen out of favor since it does not treat or prevent PCNSL [46]. If no additional treatment is given to treat or prevent PCNSL, 90% of the patients will develop or have a relapse of PCNSL [25]. Visual acuity rarely returns to normal due to complications secondary to ocular radiation therapy such as conjunctivitis, cataract, vitreous hemorrhage, radiation retinopathy, and retinal atrophy [46, 50]. Finally, ocular radiation therapy cannot be repeated if a relapse occurs [46]. However, Berenbom et al. [51] challenged the notion that radiotherapy should be abandoned as first-line therapy for ocular disease without CNS involvement. They claimed that PVRL is more radiosensitive than PCNSL and thus can be treated with lower radiation doses of 35–40 Gy given in 15 fractions to both globes rather than the typical 50 Gy used in the treatment of CNS disease. Furthermore, they mentioned that customized blocks made following computed tomographic simulation may minimize normal tissue toxicity [51].

B-cell neoplasms are responsive to chemotherapy [42, 47, 48]. Chemotherapy may be administered by intrathecal, intravenous, or intravitreal routes. The blood-brain barrier and the blood ocular barrier limit the penetration of systemic chemotherapeutic agents into the CNS and eye. There is not enough information to determine if one drug or drug regimen is superior over the others, but intraocular penetration as well as CNS drug penetration are essential characteristics [46]. Methotrexate (MTX) and cytosine arabinoside (ARA-C) are favored by most investigators in the field because they appear to reach therapeutic levels in the vitreous after intravenous administration [46]. Fifty to eighty percent of patients with PCNSL show a complete response to high-dose MTX [47, 48]. ARA-C also reaches cytotoxic levels in the CSF. Chemotherapy has been employed for PCNSL and PVRL at relapse causing remission but not a cure [47, 48]. Several investigators felt that chemotherapy should not be reserved for recurrent disease and recommended combined radiotherapy and chemotherapy as initial therapy for PVRL and PCNSL [42]. The response to ARA-C has not been uniform. Three patients treated with a combination of radiation therapy to the brain and orbits, intrathecal ARA-C, and intravenous MTX treatment were still alive after 36 months [50]. In another study, three patients with PVRL, two of whom also had PCNSL, were treated with intravenous MTX, intravenous high-dose ARA-C, intrathecal MTX, and radiation therapy to the brain and orbits. All patients had a complete response including the CNS and have remained disease free for at least 2 years following completion of treatment [46].

In one study, a patient with PCNSL developed bilateral vitreoretinal involvement while on high-dose ARA-C [42]. In another study, 5 out of 7 patients treated with ARA-C had a relapse after treatment. They reported a 81% complete response rate and a median survival of 44.5 months [25]. Conjunctivitis, keratitis, and ocular irritation are common in patients receiving high-dose IV ARA-C. Periorbital edema, blepharitis, conjunctival hyperemia, and photophobia have been reported with intravenous MTX [46]. Despite the lack of a uniform response, chemotherapy in combination with radiation therapy improves median survival to 40 months with 25% of patients surviving 5 years or more. However, ocular relapse is common occurring in up to 50% of patients; the mean interval between diagnosis and death was almost 16 months [42, 46].

As patients survive longer with combination therapy, late neurological sequelae of radiation therapy that affect quality of life such as neurocognitive disorders and irreversible visual loss have been observed, especially in patients older than 50 years of age [42, 46–48]. Protocols utilizing chemotherapy alone without radiation therapy as primary therapy have been investigated [47, 48]. In one trial, the median survival was 30.5 months, while in another, the median survival had not been attained after a mean follow-up of 3.3 years. High doses of intravenous MTX (8 g/m2) achieve therapeutic levels in both the aqueous and vitreous [46]. Nine patients with either PCNSL and PVRL or isolated PVRL were treated with only intravenous MTX at high doses. This protocol consisted of an induction phase of 8 g/m [2] MTX every 14 days until a complete response, a consolidation phase of 8 g/m [2] MTX twice a month for a month, and a maintenance phase of 8 g/m [2] MTX every 28 days for 11 doses. Four of the nine patients had a sustained response to the intravenous MTX. The remaining five patients required ocular radiation therapy. The lack of a sustained response of these 5 patients is probably a reflection of the fact that intravitreal levels of MTX are much lower than the aqueous levels. In a retrospective study of eight patients with PVRL that were treated solely with systemic chemotherapy, 100% relapsed. The chemotherapeutic regimen consisted of either ARA-C or MTX in all patients. Some patients also received procarbazine and vincristine. The relapse occurred in the eyes in 75% and in the CNS in 25% [46]. Others have favored hyperosmolar blood-brain barrier disruption (HBBBD) chemotherapy to treat PCNSL [52]. Intra-arterial mannitol is used to disrupt the blood-brain barrier. The chemotherapeutic agents used included cyclophosphamide, MTX, leucovorin, procarbazine, and dexamethasone. Patients treated with this protocol experienced a greater mean survival from diagnosis in addition to preservation of cognitive function as compared to patients treated with conventional radiotherapy [52]. Fifty-four to sixty-five percent of patients treated with HBBBD may develop a pigmentary maculopathy [46]. This maculopathy is bilateral but asymmetric. It is characterized by fine clumps of RPE hyperpigmentation in the foveal region associated with a variable loss of the RPE. Permanent and progressive visual loss may result from this maculopathy.

The alkylating cytostatic agent, trofosfamide, that has been used as maintenance therapy in hematologic malignancies, and its main metabolite ifosfamide, which can reach cytostatic levels in the CNS, have both been investigated in PVRL [53]. Trofosfamide has an excellent bioavailability of almost 100%. It has been used successfully in the treatment of PCNSL. Its side effects include a dose-related hematotoxicity, nausea, and vomiting. The response rate was high but so was the relapse rate. Thus, the authors concluded that both ifosfamide and trofosfamide were promising candidates for combination therapy [53]. Clearly systemic chemotherapy without local therapy does not appear to be sufficient in the treatment of PVRL.

The addition of high-dose MTX to the treatment protocol of PVRL and PCNSL has greatly improved the prognosis for these patients [47, 48]. Nevertheless, anywhere from 35% to 60% of patients do not respond to treatment. Furthermore, up to 60% of patients that initially have a complete clinical remission develop a relapse. If no treatment is given, the overall survival of recurrent PCNSL is only 5 months. Less than 50% of

these patients have a second complete remission. Salvage radiotherapy, which can only be given to those patients who did not receive it, previously increases the overall survival to 11 months. Intensive chemotherapy followed by hematopoietic stem cell rescue (IC + HCR) appears to be promising [47]. In a small prospective trial of 11 patients with PVRL, 11 patients were prospectively treated with ESHAP (cisplatin, VP-16, ARA-C, methylprednisolone) plus intrathecal steroids, MTX, and ARA-C, and whole brain and ocular radiation therapy in some cases; or alternating ESHAP and high-dose MTX; or just high-dose MTX as primary treatment. All the patients experienced either treatment failure or relapse. Second-line therapy was given to nine patients and included ocular and whole brain radiotherapy, high-dose MTX, or a combination of holoxan, natulan, and thiotepa. Disease progression was documented in all the nine patients that underwent second-line treatment. Of these nine patients, five were treated with doses of busulfan, thiotepa, and cyclophosphamide, followed by autologous bone marrow transplant. They achieved complete remission. None of the patients experienced CNS progression. Of these patients, two relapsed after 6 months but the other three were disease free after 15 months. A more recent study from the same group expands on their initial experience. Selection criteria for IC + HCR included patients with refractory or recurrent PCNSL that responded to two salvage cycles of ARA-C and etoposide (VP-16) or patients with PVRL that failed treatment with high-dose MTX and ARA-C. Nine out of 12 patients achieved clinical remission with a median survival greater than 53 months. However, 5 of 7 patients older than 60 years old died during therapy. A larger multicenter trial of 43 patients validated the value of IC + HCR as salvage treatment for PCNSL and PVRL. After a median follow-up of 36 months, the median overall survival and the median progression-free survival were 18.3 and 11.6 months in the whole cohort compared to 58.6 and 41.1 months in patients that completed IC + HCR, respectively. Patients who responded to the salvage cycles of ARA-C and VP-16 and went on to IC + HCR had the best prognosis. In this subgroup, the median overall survival and median progression-free survival had not been reached at 36 months. Of concern was the development of late neurotoxicity in 5 (11%) patients, including 3 with severe cognitive impairment, which proved to be fatal in one patient. Since neuropsychometric testing was not performed at baseline, it remains unclear if IC + HCR was responsible for this adverse event as many patients had received radiation therapy as part of their primary or secondary treatment [47].

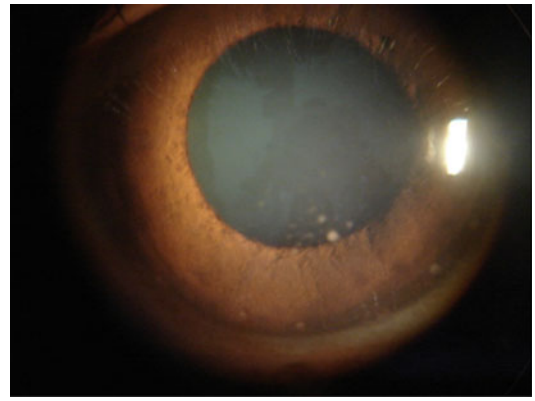

Fig. 13.7 Same patient as in Figs. 13.1, 13.3, and 13.5. Slit lamp examination of a patient with intraocular lymphoma. The right eye demonstrates the presence of keratic precipitates more prominent in the right eye (shown) and 1+ cells in the anterior chamber (Courtesy of Raul Vianna, M.D.)

Intravitreal chemotherapy for PVRL has been advocated given the disadvantages of ocular radiation therapy and the poor ocular penetration of systemic chemotherapy [46]. Several chemotherapeutic agents, including MTX, have been tested intravitreally in rabbits. No evidence of retinal toxicity was found for MTX using electroretinography and light microscopy. A single intravitreal injection of 400 μg of MTX can lead to a prolonged intravitreal tumoricidal concentration (>0.5 μM for 48–72 h in the rabbit eye) lasting longer than that achieved by systemic administration. Several investigators have reported that serial injections of 400 μg of intravitreal MTX clear the eye of lymphoma cells (Figs. 13.7, 13.8, and 13.9a, b). Another group reported their success with intravitreal MTX in achieving remission in a patient with an aggressive recurrent

PVRL. Based on their good experience of 10 years, Frenkel et al. [54] proposed intravitreal MTX as first-line treatment for PVRL. Their protocol consisted of an induction phase of two injections of 400 μg of intravitreal MTX per week for a month, followed by a consolidation phase consisting of a weekly injection for 2 months, and finally a maintenance phase of a monthly injection for a year. In their series of 44 eyes that were followed for a median of 21 months (range, 3–120 months), clinical remission was obtained after a mean of 6.4 injections (range, 2–16 injections). Fourteen patients died from their CNS or systemic lymphoma after a median of 17 months (range, 3–84 months). None of the patients had an ocular relapse. Interestingly, in those patients with bilateral disease, there was no difference in the response to intravitreal MTX between the eye that underwent the diagnostic vitrectomy and the fellow eye. The visual acuity in most patients remained stable or improved [54].

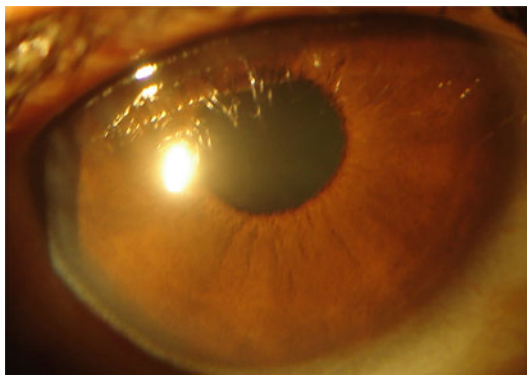

Fig. 13.8 Same patient as in Figs. 13.1, 13.3, 13.5, and 13.7. Slit lamp examination of the patient with intraocular lymphoma (right eye) in Fig. 13.1 after 2 months of intravitreal methotrexate (Courtesy of Raul Vianna, M.D.)

Local recurrences and MTX resistance following intravitreal MTX monotherapy have been reported by others [39]. A patient with PVRL and PCNSL that had a complete resolution of her disease with systemic chemotherapy developed a relapse in her right eye and was treated with multiple injections of intravitreal MTX. Complete resolution of her disease was documented, but recurrences were noted over the next 18 months. It was noted that the PVRL became less and less responsive to intravitreal MTX. Examination of the intraocular lymphoma cells revealed that there was an aberrant expression of multidrug resistance protein (MRP) and decreased expression of both reduced folate carrier (RFC) and folate binding protein (FBP). This suggests that this patient's PVRL cells acquired the ability to reduce the intracellular accumulation and metabolism of MTX [55]. To decrease the chances of resistance, cases of recurrent PVRL have been treated with a combination of MTX and dexamethasone in one case and MTX and thiotepa in the other case. Another patient with recurrent bilateral PVRL was treated with several treatment

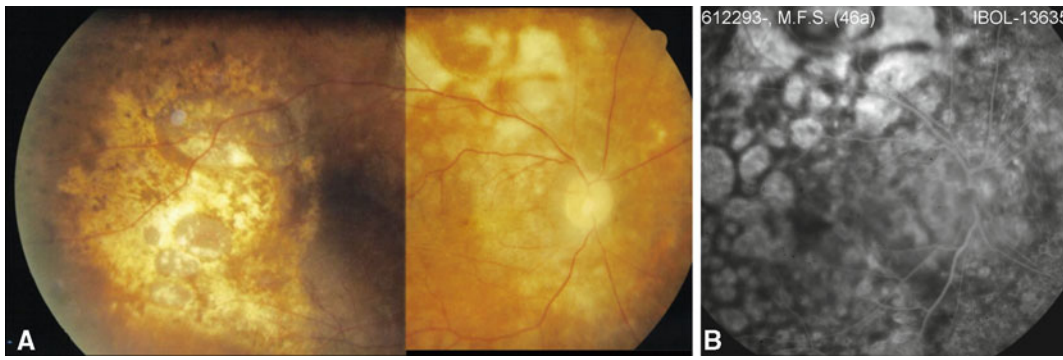

Fig. 13.9 Same patient as in Figs. 13.1, 13.3, 13.5, 13.7, and 13.8. (**a**) Fundus examination of a patient with intraocular lymphoma (right eye) in Figs. 13.2 and 13.3 after 2 months of intravitreal methotrexate. (**b**) Arteriovenous phase fluorescein angiogram demonstrating multiple areas of disturbances at the level of the retinal pigment epithelium (RPE). Window defects might represent areas of tumor resolution with secondary RPE atrophic changes (Courtesy of Raul Vianna, M.D.)

cycles of 200 μg of intravitreal MTX (given on days 1, 5, and 8) and 7.5 mg of periocular dexamethasone phosphate (injected on day 9) over a course of 5 months. Complete regression of the PVRL was sustained over a period of 24 months [46]. Based on pharmacokinetic data obtained in the rabbit eye, Velez and associates [56] devised an intravitreal chemotherapy treatment cycle consisting of 400 μg of intravitreal MTX (given on days 1, 4, and 6), fluorouracil 500 μg (injected on day 2), and 500 μg of dexamethasone sodium phosphate on day 7. They reasoned that using this protocol would provide intravitreal antitumor activity for 8 days. This would allow most cells that are active in the cell cycle to pass through the S phase and be exposed to the drug. MTX exhibits a maximal antineoplastic cytotoxic synergistic response with fluorouracil when fluorouracil is given 24 h after MTX exposure. Since steroids are cell cycle nonspecific and are cytotoxic to lymphoma cells at all stages of the cell cycle, dexamethasone is given at the end of the cycle to treat those cells that do not progress through the S phase. In addition, steroids can treat a potential inflammatory reaction that may result from the necrosis of tumor cells [56]. Adverse reactions to intravitreal MTX have been reported and include filamentary keratitis that resolved with topical folinic acid, corticosteroid responsive sterile endophthalmitis, and vitreous hemorrhage [46, 54]. Other complications that could not be directly attributed to the intravitreal MTX included irreversible loss of visual acuity, neovascular glaucoma, optic atrophy, maculopathy, and progression of cataract. In order to avoid the repetitive intravitreal injections of MTX and its potential complications, researchers have studied alternative drug delivery methods in rabbits such as subconjunctival injections and trans-scleral hydrogel iontophoresis. Unfortunately, therapeutic levels of MTX were achieved in the aqueous but not in the vitreous with both methods [46].

Most PVRL and PCNSL are B-cell neoplasms that express the cell surface molecule CD20 [45, 46, 57]. Rituximab (Rituxan, Genentech, Inc., South San Francisco, CA, USA) is a humanized mouse monoclonal antibody directed against the CD20 B-cell antigen [46, 57]. It has been approved for systemic use in patients with B-cell lymphomas. Its efficacy in PCNSL has been limited by its poor penetration of the blood-brain barrier when given as a systemic infusion. To enhance CSF levels, intraventricular injection of rituximab through an Ommaya reservoir has been reported. In an animal model, intravitreal and intracerebral rituximab eradicated lymphoma in more than 50% of animals and significantly inhibited tumor progression in the remainder. Light microscopic histopathologic studies in rabbits have shown a lack of retinal toxicity following a single intravitreal injection of 1 mg/0.1 mL of rituximab. Rituximab has been shown to be able to penetrate full thickness retina in rabbit eyes, which is an important property given that subretinal infiltrates are often found in PVRL. Clinical studies in rabbits showed mild vitritis in all four eyes examined with inflammatory cells infiltrating the optic nerve and ciliary body. Serial intravitreal injections of rituximab appear to be well tolerated in human eyes. Pharmacokinetic studies in rabbits demonstrate a half-life of 4.7 days, implying that injections should be given every 2 weeks. Preliminary results regarding the use of intravitreal rituximab in the treatment of PVRL are encouraging and promising. However, further research is needed in particular to determine the most appropriate dose, dosing sequence, and length of treatment. Validation of its efficacy against PVRL also is needed [46, 57].

Several novel experimental immunotherapies are currently under investigation [39, 46]. Target-specific killing using recombinant immunotoxin HA22 therapy has been successfully tested in a mouse model of PVRL. Ocular immune privilege promotes tumor growth by interfering with the development of innate and adaptive immunity. The membrane only form of Fas ligand (FasL) terminates immune privilege inducing systemic protective immunity. Co-inoculation of the anterior chamber of several mice with lymphoma cells and microvesicles expressing either membrane FasL or no FasL showed that membrane FasL eliminated the lymphoma cells and prevented metastatic spread in most of the treated mice [46].

Controversies and Perspectives

It has been nearly 60 years since the first description of an intraocular masquerade syndrome secondary to lymphoma [11]. Much has been learned in these six decades yet there is still plenty to learn. Perhaps one of the main unanswered remaining quests is the elusive cellular origin of PVRL [10]. Some evidence points to a germinal center origin, whereas other evidence points to an early post-germinal center origin [10]. The cellular origin has important implications since in systemic DLBCL, the prognosis depends on the molecular subtypes. There is conflicting evidence as to whether the treatment of PVRL influences the prognosis for survival [29, 45]. There is no general consensus with regard to the best treatment in patients with isolated PVRL. The initial excitement with systemic chemotherapy has been dampened by the high rates of ocular relapse and progression to CNS disease [46]. It is possible that precise genetic profiling of each individual patient with PVRL may allow to individualize treatment to improve the outcomes in this devastating disease [39].

Focal Points

- PVRL forms part of the spectrum of PCNSL.
- PVRL is a high-grade NHL, usually of B-cell type, with a poor prognosis due to CNS disease.
- A high index of suspicion, in particular of any patient with a uveitis that is unresponsive to steroids, is essential in diagnosing PVRL.
- A single vitreous biopsy may not always be diagnostic of PVRL.
- Cytological analysis remains the gold standard for diagnosing PVRL.
- Cytokine analysis, flow cytometry, and molecular analysis are useful adjuncts in the diagnosis of PVRL.
- Methotrexate is the cornerstone of any chemotherapeutic regimen for PCNSL/PVRL.
- Systemic chemotherapy alone may not be sufficient treatment for PVRL, even with drugs that penetrate the eye such as ARA-C and MTX.
- Ocular relapse is common both in patients treated for CNS disease and those successfully treated for ocular disease.

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Choroidal and Retinal Metastasis

14

Carol L. Shields and Jerry A. Shields

Abstract

Metastasis to the eye involves the choroid (88%), iris (9%), or ciliary body (2%), and rarely the retina (<1%). Intraocular metastases most commonly originate from primary cancers in the breast (47%), lung (21%), gastrointestinal tract (4%), kidney (2%), skin (melanoma) (2%), prostate gland (2%), and other sites (4%). Metastases are unilateral in 76% of cases and bilateral in 24%. Patient prognosis is poor, and those with metastatic skin melanoma or lung carcinoma typically show survival less than 1 year. Those with metastases from breast cancer show survival of 65% at 1 year, 34% at 3 years, and 24% at 5 years.

Keywords

Breast cancer • Choroid • Ciliary body • Eye • Iris • Lung cancer • Metastasis • Retina • Uvea

Introduction

In the 2008 annual report to the nation on the status of cancer in America from the collaborative work of the National Cancer Institute (NCI), American Cancer Society, Centers for Disease Control and Prevention (CDC), and the North American Association of Central Cancer Registries (NAACR), it was documented that the incidence and death rates from all cancers combined decreased significantly [1]. These decreases were driven by declines in incidence and death rate for the three most common cancers in men including lung, colorectum, and prostate cancers. Additionally, two of the three leading cancers in women declined including breast and colorectum cancers. The lung cancer death rate in women leveled off. They emphasized that even though the overall lung cancer death rate had stabilized, this finding varied by region as in areas of high cigarette smoking prevalence, such as the southern and midwestern states, the death rate actually increased. They advised improvement in state tobacco control programs.

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Systemic cancers can metastasize to the eye. The most common cancers to spread to the ocular structures include breast and lung cancer [2]. The decreasing incidence of these cancers could impact the frequency of ocular metastasis.

Historically, metastatic tumors to the eye were believed to be rare. A classic ophthalmic textbook in 1966 stated that few surgeons had observed more than one case of ocular metastasis [3]. Later, it was realized that ocular metastases were more common, and over the past 50 years, there have been several reports on the incidence and prognosis of patients with metastatic tumors to the eye [4–12]. Albert and associates found that 2% of 213 patients with known systemic cancer and metastases had choroidal metastases [5]. Bloch and Gartner reported that 8% of eyes in 230 patients with autopsy-proven carcinomas had histologically confirmed uveal metastatic foci [7]. Nelson and coworkers found in an autopsy study that 4% of patients dying of carcinoma had ocular metastases [10]. They estimated that in the year 1983, 22,000 patients who died of cancer had ocular metastatic disease [10].

Most reports on ocular metastases come from pathology laboratories or from general cancer centers where patients have had known primary cancers and/or metastatic disease and the eyes were subsequently examined. These studies have focused on the source of the primary tumor, as well as on general clinical and histopathologic features of the tumor (derived from autopsy or pathology reports in some instances) [4–8, 10]. Ocular metastases on file at the Armed Forces Institute of Pathology were reviewed by Hart in 1962 [4] and Ferry and Font in 1974 [8].

There are only a few comprehensive reports on the clinical features of ocular metastases from an ophthalmologic point of view. In 1979, Stephens and Shields reviewed 70 cases of uveal metastases and provided general details on the clinical findings of these tumors [9]. In 1997, Shields and coworkers reported extensive detail on the clinical features and management of uveal metastases in a large group of 420 consecutive patients [2]. Later, findings on the features of metastasis to the optic disk were reported [13]. Others have focused on the features of uveal metastases from specific primary sites such as breast [14–20], prostate [21], skin [22–25], and carcinoid tumors [26]. In 1987, Freedman and Folk reported on the clinical aspects of metastatic tumors to the choroid in 61 patients, and they addressed specifically the factors affecting the median survival time after ocular diagnosis [11]. Later, Shields and Shields summarized their experience with clinical features, diagnostic techniques, and management of intraocular metastases in a textbook and comprehensive atlas on ocular tumors [27, 28].

Primary Cancer Sites Leading to Intraocular Metastasis

Metastatic tumors generally spread to the ocular region via hematogenous dissemination. Metastases can occur in the intraocular structures such as the uvea, retina, optic disk, or vitreous cavity, and they can manifest in the adnexal structures like the eyelid, conjunctiva, or orbit [1, 2]. The great majority of ocular metastases are detected in the uvea. In an analysis of 950 individual uveal metastases, metastatic tumors most often occurred in the choroid (88%) and less frequently in the iris (9%) or ciliary body (2%) [2, 29] (Fig. 14.1). Rarely, ocular metastases are found in the retina, optic disk, or vitreous [13, 27, 28].

Uveal metastases most commonly originate from primary cancers in the breast (47%), lung (21%), gastrointestinal tract (4%), kidney (2%), skin (melanoma) (2%), prostate gland (2%), and other sites (4%) [2] (Table 14.1) (Fig. 14.2). In approximately 17% of all patients, the primary tumor site remains unknown. At the time of presentation with a uveal metastasis, approximately 30% of patients have no known history of primary cancer [2]. Subsequent evaluation of these patients reveals a primary tumor most commonly in the lung (35%) and less frequently in the breast (7%) and others sites (6%) (Fig. 14.3). Despite repeated evaluation, the primary site in these select patients who present without a history of cancer remains unknown in 51% of patients.

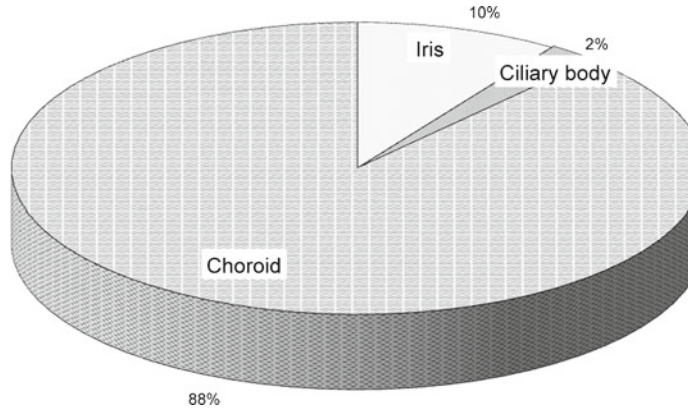

Fig. 14.1 Anatomic location of 950 consecutive uveal metastases [2]

Table 14.1 Uveal metastases related to site of primary cancer in 520 eyes of 420 patients [2]

Primary site of tumor								
	Breast	Lung	Kidney	GI	Skin	Prostate	Others	Unknown
Eyes [n=520]	260	108	19	10	11	11	20	81
Patients [n=420]	196	90	18	9	9	9	16	73
Age[a](years) [n=420]	56	57	60	65	50	67	57	64
Race [n=420]								
Caucasian	175	80	17	9	9	8	15	67
African-American	17	10	1	0	0	0	1	5
Others	4	0	0	0	0	1	0	1
Sex [n=420]								
Male	2	55	13	8	5	9	5	40
Female	194	35	5	1	4	0	11	33
Laterality [n=420]								
Unilateral	132	72	17	8	7	7	12	65
Bilateral	64	18	1	1	2	2	4	8
Symptoms [n=520]								
None	28	12	4	1	1	3	2	8
Blurred vision	192	68	14	5	4	7	12	59
Flashes, floaters	35	14	0	2	2	0	6	6
Pain	5	14	1	2	4	1	0	8
Other ocular metastases								
Eyelid	1	0	0	0	1	0	1	0
Orbit	2	1	0	1	0	1	0	2
Conjunctiva	2	1	0	0	2	0	1	2
Retina	2	1	0	0	0	0	0	2
Optic disk	10	1	1	0	0	0	2	10
Location uveal metastases								
Iris [n=43]	17	8	2	1	4	1	2	8
Ciliary body [n=21]	4	2	2	1	3	1	1	7
Choroid [n=479]	252	98	18	8	5	10	17	71

(continued)

Table 14.1 (continued)

Primary site of tumor	Breast	Lung	Kidney	GI	Skin	Prostate	Others	Unknown
Number[a] uveal metastases/location								
If iris	2	1	1	2	1	1	7	1
If ciliary body	1	1	1	1	1	1	1	1
If choroid	2	1	1	1	2	1	1	2
Choroidal metastasis (largest tumor)								
Base[a]	8	9	9	8	7	9	10	8
Thickness[a]	2	3	4	4	1	3	2	3
Color [n=479]								
Yellow	249	90	17	5	0	9	12	66
Brown/gray	2	1	1	0	5	0	5	3
Orange	1	7	0	3	0	1	0	2
Shape [n=479]								
Plateau	197	55	7	1	3	5	12	45
Dome	55	43	11	7	2	5	5	24
Mushroom	0	0	0	0	0	0	0	2

GI gastrointestinal
[a]mean

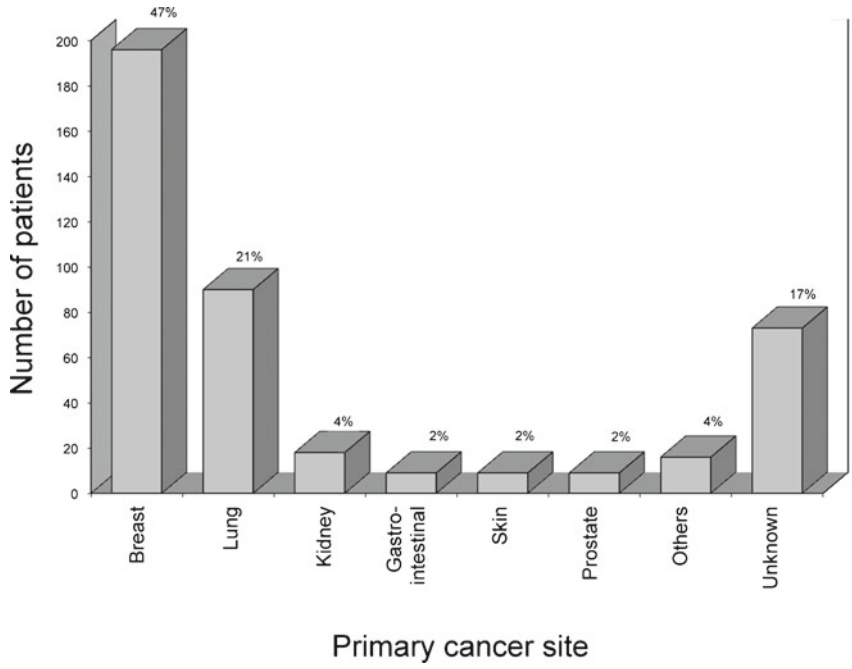

Fig. 14.2 Location of primary cancer in 420 patients with uveal metastases [2]

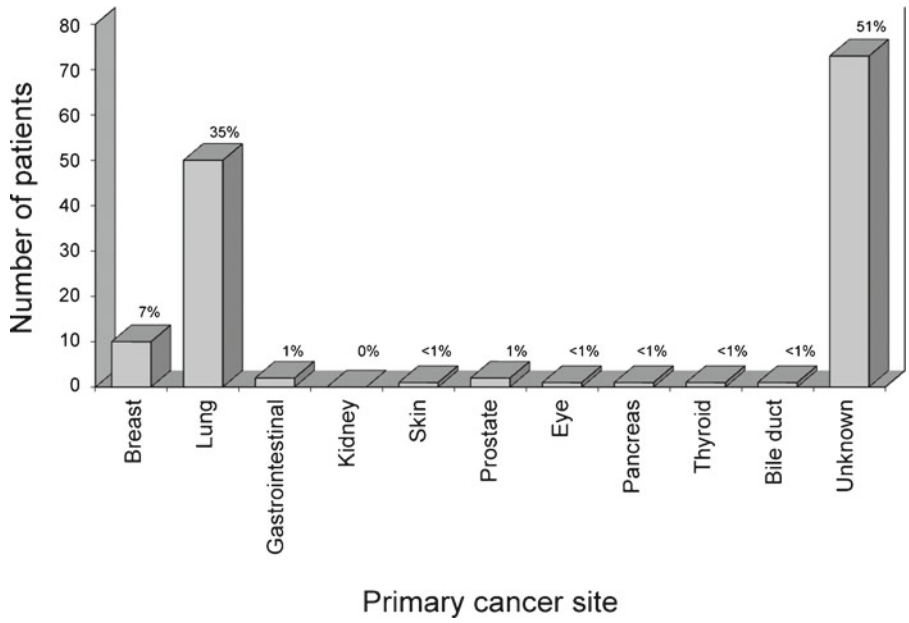

Fig. 14.3 Eventual primary cancer site in 142 patients who presented with a uveal metastasis and no prior history of cancer [2]

Nearly one-half of such patients with no detectable primary site die of diffuse metastatic disease shortly after the ocular diagnosis [2].

Patient Profile

Breast cancer is by far the most common malignancy to metastasize to the uvea, accounting for 39–49% of all uveal metastasis [2, 5–12]. In a review of 3,802 breast cancer patients, Kamby and coworkers reported the five most common sites of metastasis from breast cancer were the lung (71%), bone (71%), lymph nodes (67%), liver (62%), and pleura (50%) [30]. Ocular metastasis from breast cancer occurs in 9–37% of patients depending on the source of the study [7, 10, 16]. Uveal metastases represent the smallest detectable lesions of systemic dissemination of breast cancer and occur at a median of 3 years following diagnosis of the primary tumor [16].

Uveal metastases are more commonly found in women, primarily due to the high frequency of breast cancer metastatic to the eye. In an analysis of 450 patients with uveal metastases from all primary cancer sites, the tumor was found in men in 33% and women in 67% [2]. Uveal metastases in men originated from cancer of the lung (40%), gastrointestinal tract (9%), kidney (6%), skin (melanoma) (4%), prostate gland (6%), breast (1%), others (4%), and unknown primary site (29%) [2]. Single cases of breast cancer metastatic to the eye in men have been published (see Table 14.1) [31, 32]. Uveal metastases in women were from cancer of the breast (68%), lung (12%), gastrointestinal tract (2%), kidney (<1%), skin (melanoma) (1%), others (4%), and unknown (12%) [2]. In an analysis of 264 patients with uveal metastases from breast cancer, the primary tumor was found in women in 99% and men in 1% [17].

Intraocular Metastasis Onset

Ocular metastases from any primary site typically occur in the sixth to seventh decade of life at a mean age at 58 years (median 58 years, range 10–85 years) [2]. For breast cancer metastasis, the mean age at diagnosis of the ocular metastasis was 56 years (median 57 years, range 23 years to 84 years) [17].

Most patients with ocular metastases from breast cancer have a known history of breast cancer and previous nonocular metastases. Of 264 patients with uveal metastasis from breast cancer, the eye finding was the first manifestation of breast cancer in 3% [17]. In 14% of patients, the ocular metastasis was the first metastatic site. The locations of systemic nonocular metastases prior to and following the detection of ocular metastasis are listed in Table 14.2.

Of those patients who develop ocular metastases, the mean age at diagnosis of the primary breast cancer was 56 years (median 57 years, range 23–84 years) [17]. The initial treatment of breast cancer was radical or modified mastectomy (83%), systemic chemotherapy (42%), external beam radiotherapy (27%), lumpectomy with or without lymph node dissection (14%), and hormone therapy (4%). The axillary lymph nodes were involved in 46% of patients who developed eventual uveal metastases. At the time of diagnosis of the ocular metastases, 52% of patients were on systemic therapy, including chemotherapeutic agents (36%), hormone therapy (20%), and immunotherapeutic agents (2%). Uveal metastases developed a mean of 65 months following the diagnosis of the primary breast cancer (median 48 months, range 0–300 months) [17].

Table 14.2 Locations of systemic nonocular metastasis before and after the uveal metastasis was established in 264 consecutive patients with uveal metastasis from breast cancer [17]

	Number of patients (%)
Location of systemic metastases diagnosed before the ocular metastasis was established	
Lung	71 (27%)
Long bone	68 (26%)
Chest wall	19 (7%)
Spine	17 (6%)
Liver	14 (5%)
Other breast	16 (6%)
Brain	15 (6%)
Skin	10 (4%)
Skull	8 (3%)
Others	6 (2%)
None	116 (44%)
Location of systemic metastases diagnosed after the ocular metastasis was established	
Brain	73 (28%)
Lung	64 (24%)
Long bone	64 (24%)
Liver	37 (14%)
Spine	22 (8%)
Chest wall	18 (6%)
Skull	10 (4%)
Skin	5 (2%)
Others	14 (5%)

Location and Multiplicity of Intraocular Metastasis

Intraocular metastases show a strong tendency to involve the posterior uvea (choroid). Less commonly, the tumor affects the iris or ciliary body. Rarely do metastases involve the optic disk or retina. Of 361 eyes with uveal metastases, the tumor was located in the choroid in 349 eyes, iris in 23 eyes, and ciliary body in 2 eyes (see Fig. 14.1) [17]. Some patients had metastatic tumors in more than one intraocular location.

In general, intraocular metastases commonly show multifocality and/or bilaterality. In an analysis of 520 eyes with uveal metastases from all primary sites, the median number of metastatic tumors per eye was 1 and the mean was 1.6 [2]. Furthermore, 370 (71%) eyes had 1 focus, 63 (12%) had 2 foci, 87 (17%) had 3 or more foci, up to a maximum number of 13 metastatic foci in one eye [2]. The tumor was unilateral in 76% and bilateral in 24% of patients. With regard to ocular metastases from breast

cancer, the tumor was unilateral in 62% and bilateral in 38% [17]. Of 99 patients (38%) with bilateral uveal metastases from breast cancer, 85 (32%) had bilateral involvement at the time of diagnosis and 14 (5%) developed the second eye involvement after a mean follow-up of 10 months (median 7 months, range 2–33 months). The mean number of the uveal metastatic tumors (from breast cancer) per eye was two (median 1, range 1–19) and more than one metastatic focus was detected in 48% [17].

Clinical Features of Intraocular Metastasis

Choroidal Metastases

The patient with a metastatic tumor to the choroid may be asymptomatic or may experience painless blurred vision. In rare instances, pain caused by secondary glaucoma can be the initial manifestation. Ophthalmoscopic examination of a choroidal metastasis characteristically reveals a homogeneous, creamy yellow placoid lesion in the posterior choroid (Fig. 14.4) [2, 27, 28, 33]. Tumors that are slightly more elevated can produce a serous detachment of the retina and alterations in the retinal pigment epithelium (RPE). The RPE changes can be marked, appearing as well-delineated clumps of golden brown pigment on the surface of the tumor. In some instances, the tumor may appear multinodular.

In some cases, a choroidal metastasis can be highly elevated and have a dome shape, similar to a primary amelanotic melanoma [34]. The finding of multiple choroidal tumors in such a case, however, is strong evidence for a metastatic tumor rather than a primary melanoma, which is usually solitary (Figs. 14.5 and 14.6).

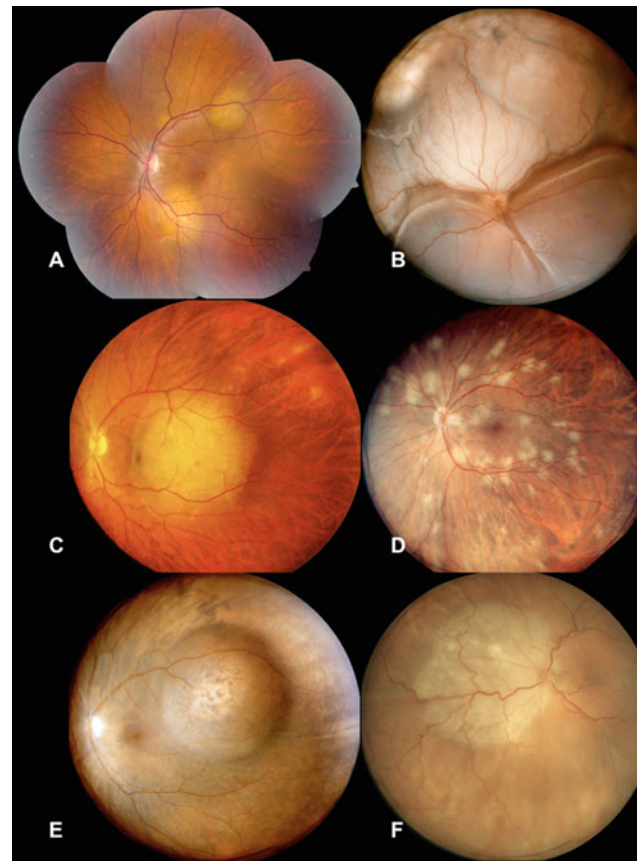

Fig. 14.4 Metastatic tumors to the choroid. (**a**) Multifocal metastases from breast carcinoma. (**b**) Ill-defined peripheral choroidal metastasis with total nonrhegmatogenous retinal detachment from underlying breast carcinoma. (**c**) Solitary choroidal metastasis from lung carcinoma. (**d**) Multifocal choroidal metastases from lung carcinoma. (**e**) Solitary choroidal metastasis from carcinoid tumor of the lung. (**f**) Solitary juxtapapillary choroidal metastasis from renal cell carcinoma

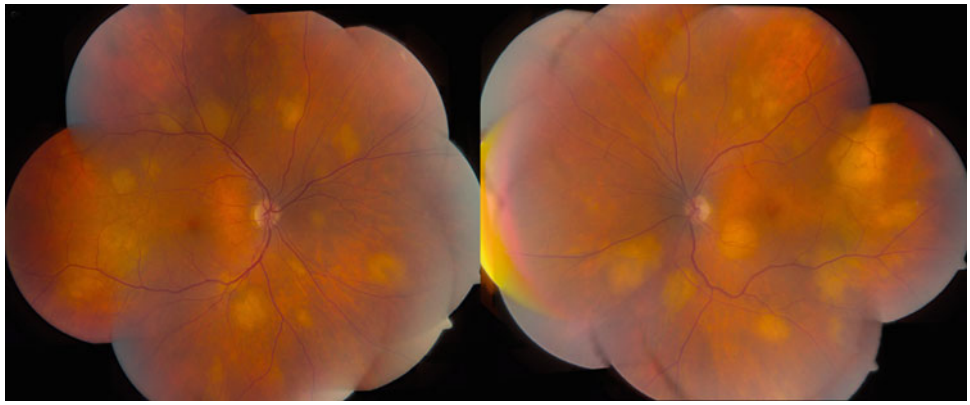

Fig. 14.5 Bilateral, minimally symptomatic multifocal choroidal metastasis in a woman with known breast cancer and spinal metastasis

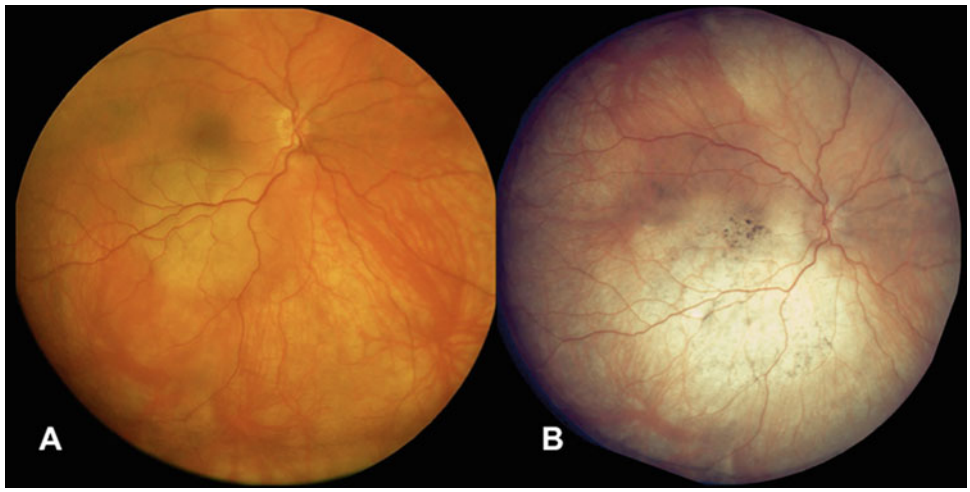

Fig. 14.6 Choroidal metastasis from breast cancer before (**a**) and after (**b**) treatment with plaque radiotherapy

Serous detachment of the sensory retina is associated with choroidal metastases from breast cancer in 64% of cases [17]. In some instances, the detachment only involves the fovea adjacent to the tumor, whereas in other cases, it may be bullous. When the detachment is extensive, dramatic shifting of the subretinal fluid can be demonstrated with movements of the patient's head.

Several conditions can clinically simulate a metastatic cancer to the choroid and should be considered in the differential diagnosis [35]. These include amelanotic nevus, amelanotic melanoma, hemangioma, osteoma, posterior scleritis, retinitis and choroiditis, rhegmatogenous retinal detachment, Harada's disease, uveal effusion syndrome, and central serous chorioretinopathy [27, 28, 35–37]. A detailed history is often helpful in making the differentiation, but the ophthalmoscopic differences are also very important. The specific clinical features of the various tumors and pseudotumors are illustrated in textbooks [27, 28]. With some experience, the clinician can differentiate simulating lesions from metastatic tumors by their typical ophthalmoscopic features and by using ancillary diagnostic procedures, to be discussed subsequently.

A choroidal melanoma is the most important lesion to differentiate from a metastatic tumor [34]. The melanoma is characteristically

pigmented but can be completely amelanotic and closely resemble the color of a metastasis. The melanoma is typically unilateral, solitary, and more elevated. An amelanotic melanoma frequently has large visible intrinsic blood vessels and often assumes a mushroom shape from herniation through Bruch's membrane; these findings rarely occur with a metastatic tumor.

A choroidal hemangioma can also resemble a metastatic tumor in size, shape, and location [36]. The distinct red-orange color of most hemangiomas differentiates them from the yellow color of a metastatic tumor. A choroidal hemangioma is classically unilateral and unifocal.

A choroidal osteoma characteristically appears as an amelanotic choroidal mass [37]. Like a metastatic tumor, it is more common in women. In contrast to a metastatic tumor, it has an irregular but well-defined border and can show subretinal neovascularization on the surface. We have seen one patient who underwent three breast biopsies elsewhere because a choroidal osteoma was suspected to be a metastatic cancer before the correct diagnosis was eventually established. Ultrasonography and computed tomography of a choroidal osteoma reveal echoes characteristic of a calcified plaque.

A number of inflammatory processes of the fundus can simulate a choroidal metastasis. Certain viral and mycotic infections are more commonly seen in patients with systemic cancer, thus making the differentiation even more difficult. Patients with cytomegalovirus (CMV) retinitis often have a history of cancer and are on chemotherapy. The yellow-white areas of retinal necrosis may be bilateral and multiple. In contrast to metastatic tumors, they involve the retina rather than the choroid, have an irregular border, and frequently show surrounding and overlying retinal hemorrhages. Mycotic retinitis or choroiditis also can resemble a choroidal metastasis, but it is more likely to be associated with inflammatory signs.

Ciliary Body Metastases

Ciliary body metastases are often difficult to detect clinically. They can masquerade as a chronic uveitis or secondary glaucoma, and the affected patient may be treated with topical or systemic corticosteroids or glaucoma medications, while the tumor remains undetected. Like primary ciliary body melanoma, a ciliary body metastasis can produce a shallow anterior chamber, subluxated lens, or cataract. Prominent episcleral blood vessels can occur in the quadrant of the lesion. In some cases, the ciliary body may be involved because of anterior extension of a diffuse tumor from the choroid. With time, some ciliary body metastases can extend through the iris root into the anterior chamber. The differential diagnosis of a ciliary body metastasis includes many of the same conditions that fall under the differential diagnosis of choroidal metastasis, except for those that affect only the posterior pole, such as central serous chorioretinopathy, choroidal hemangioma, and osteoma.

Iris Metastases

The clinical presentation of iris metastases can be vary greatly [2, 29]. Some patients with iris metastases are visually asymptomatic or with only mild symptoms. In some instances, however, pain caused by inflammation or secondary glaucoma can be the presenting manifestation in some instances. Occasionally, iris metastases are multiple and bilateral. Slit lamp biomicroscopy reveals an iris mass that is usually pink or white, depending on the intrinsic vascularity (Fig. 14.7). In some cases, iris metastases are friable, and loosely cohesive cells settle in the inferior portion of the anterior chamber angle, producing a pseudohypopyon, simulating endophthalmitis. The differential diagnosis of metastatic tumors to the iris includes amelanotic melanoma, leiomyoma, granulomatous iritis, and endophthalmitis.

Retinal Metastases

Metastatic tumors to the retina are extremely rare. In contrast to choroidal metastases, retinal metastases are less cohesive and may seed tumor cells into the vitreous. They sometimes resemble a retinitis and can have associated exudation or hemorrhage (Fig. 14.8).

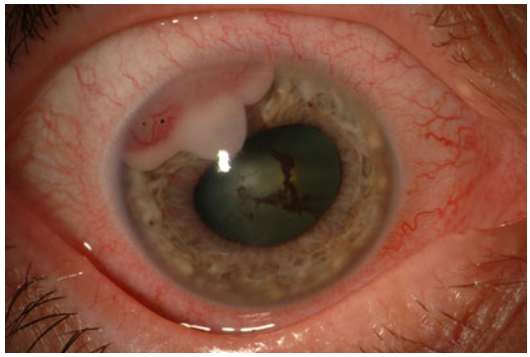

Fig. 14.7 Iris metastasis from lung carcinoma

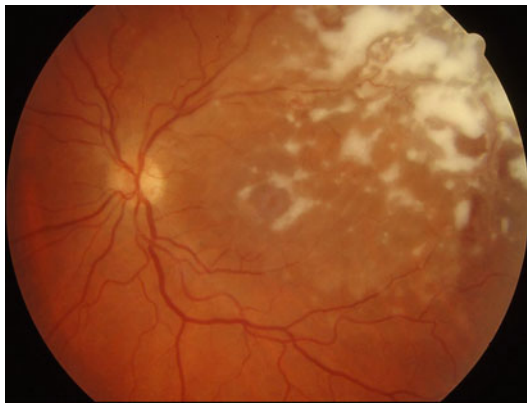

Fig. 14.8 Retinal metastasis from esophageal carcinoma

Optic Disk Metastases

Metastatic tumors can develop in the optic disk, and both optic nerves can be simultaneously involved [13]. Optic disk metastases can clinically resemble papilledema, papillitis, or various types of pseudopapilledema (Fig. 14.9).

Vitreous Metastases

Metastatic tumors to the vitreous are extremely rare and generally occur in patients who have retinal or ciliary body metastasis. Affected patients develop floaters, and vitreous examination reveals clumps of tumor cells. There have been reports of metastatic melanoma to the vitreous appearing as brown clumps in the hyaloid (Fig. 14.10) [38]. The differential diagnosis includes inflammatory vitritis, senile vitritis, endophthalmitis, vitreous hemorrhage, synchisis scintillans, asteroid hyalosis, and large cell lymphoma.

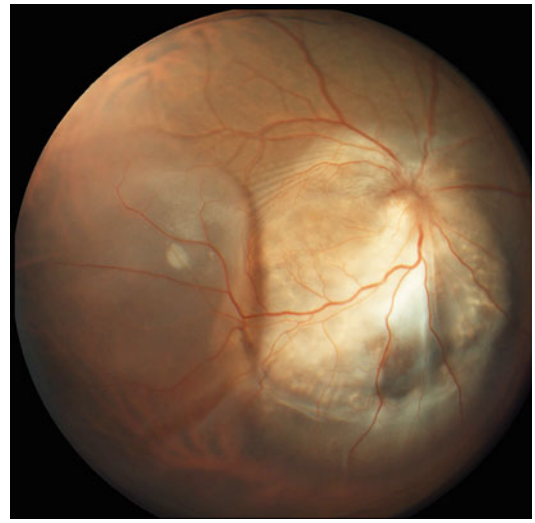

Fig. 14.9 Optic disk and choroidal metastasis from lung carcinoma

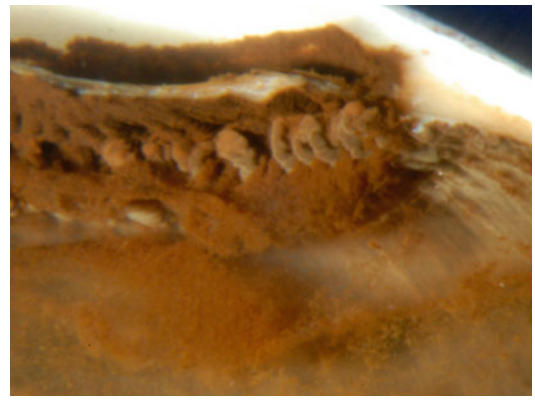

Fig. 14.10 Vitreous metastasis from cutaneous melanoma in an enucleated eye

Ocular Paraneoplastic Syndromes

A paraneoplastic syndrome is defined as the malfunction of an organ system from cancer in a remote site of the body without the presence of metastases in that end organ. Neurologic paraneoplastic syndromes include peripheral neuropathy, cerebellar degeneration, myasthenia

gravis, and motor neuron degeneration. Ocular paraneoplastic syndromes include optic neuritis, external ophthalmoplegia, and retinal disease [39]. Retinal paraneoplastic syndromes consist of carcinoma-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), acquired cone dysfunction, bilateral diffuse uveal melanocytic proliferation (BDUMP), and paraneoplastic polymorphic vitelliform maculopathy (previously termed Vogt-Koyanagi-Harada (VKH)-like syndrome). Breast cancer can produce CAR and BDUMP. In CAR, the patient notes night blindness, photopsia, transient obscuration of vision, ring scotoma, and photophobia. In BDUMP, multiple pigmented and nonpigmented uveal tumors develop along with dilated episcleral vessels, rapid-onset cataract, anterior uveitis, and serous retinal detachment. Treatment for paraneoplastic syndromes with corticosteroids or immune globulin is occasionally helpful.

Diagnostic Evaluation for Ocular Metastasis

A number of ancillary ophthalmic procedures may aid in the diagnosis of metastatic tumors. These include a systemic evaluation, intravenous fluorescein angiography (IVFA), indocyanine green angiography (ICG), ultrasonography (US), optical coherence tomography (OCT), computed tomography (CT), magnetic resonance imaging (MRI), fine-needle aspiration biopsy (FNAB), and surgical biopsy.

Systemic Evaluation

Once a metastatic tumor to the intraocular structures is suspected on the basis of ophthalmic examination, a detailed systemic evaluation is mandatory. The patient's history may reveal a previous malignancy, which can be helpful in the diagnosis. As mentioned earlier, however, many patients seen by the ophthalmologist have no history of cancer. Initially, if a female patient has a suspected metastatic tumor, breast and lung examination with appropriate ancillary studies are indicated. In men, the evaluation should be directed initially toward a primary tumor in the lung. If the lung is normal, then gastrointestinal tract, kidney, thyroid, pancreas, and other organs are evaluated.

Fluorescein Angiography

Fluorescein angiography is a method of imaging the vascularity within a choroidal tumor and is sometimes helpful in the diagnosis of a choroidal metastasis [2, 27, 28]. In contrast to choroidal hemangioma and melanoma, most metastatic carcinomas are hypofluorescent in the arterial and early venous phases and show progressive hyperfluorescence in the subsequent phases. Pinpoint foci of hyperfluorescence appear over the tumor in the venous phase and persist into the late angiograms. There may be moderate late hyperfluorescence of serous subretinal fluid related to the metastatic tumor.

Indocyanine Green Angiography

Indocyanine green angiography provides detail of the choroidal vascular pattern. Imaging of choroidal metastases with this technique generally reveals mild hypofluorescence throughout the angiogram, whereas choroidal melanoma shows gradual hyperfluorescence over 5–10 min, and choroidal hemangioma shows bright hyperfluorescence within 1 min [40].

Ultrasonography

Ocular ultrasonography provides resolution within 1 mm and is useful in the diagnosis of intraocular metastasis. A-scan ultrasonography demonstrates a sharp initial spike and moderate internal reflectivity. This is in contrast to malignant melanoma, which usually shows relatively low internal reflectivity. B-scan ultrasonography typically shows a choroidal mass pattern with moderate to high acoustic solidity, overlying subretinal fluid,

and no choroidal excavation. In contrast, melanoma shows relative acoustic hollowness.

Optical Coherence Tomography

Optical coherence tomography is a method of imaging the retina with high resolution of 5–8 μm. This technique allows for subclinical analysis of minor subretinal fluid, retinal edema, and retinal pigment epithelial changes associated with choroidal metastases [41]. This can assist in deciphering the exact cause of visual loss.

Computed Tomography

Computed tomography is used most frequently in the evaluation of metastatic orbital tumors and less often for intraocular tumors. This technique can demonstrate the anatomic location and configuration of orbital metastases as well as surrounding periorbital changes. It is important to evaluate the brain in all patients with ocular metastasis from breast cancer as brain involvement occurs in nearly 30% of patients (see Table 14.2).

Magnetic Resonance Imaging

Magnetic resonance imaging is useful in delineating the anatomic location, configuration, and internal tissue qualities of choroidal and orbital metastases. It is superior to computed tomography for soft tissue resolution, especially when using fat suppression technique, orbital surface coil, and gadolinium enhancement. In general, uveal metastases are slightly hyperintense to vitreous on T1-weighted images and hypointense to vitreous on T2-weighted images [42]. The associated retinal detachment is hyperintense to vitreous on T1 and isointense to vitreous on T2-weighted images. Metastatic carcinomas show mild enhancement with gadolinium. Orbital metastases show hyperintense signal to the suppressed orbital fat on T1- and T2-weighted images and moderate gadolinium enhancement.

Fine-Needle Aspiration Biopsy

When the diagnosis of an ocular lesion is particularly difficult to establish, fine-needle aspiration biopsy (FNAB) is appropriate [28, 43, 44]. This technique requires exceptional skill for lesions within the eye, using indirect ophthalmoscopy to guide the needle through the pars plana of the ciliary body into the solid mass. For orbital lesions, ultrasound or computed tomography is employed for localization of deep lesions. In 90–99% of cases, an adequate cytologic sample is obtained [43, 44]. This is especially useful for patients who present with no previous cancer and systemic evaluation is nonrevealing.

Surgical Biopsy

Open surgical biopsy is commonly employed to diagnose orbital, conjunctival, and eyelid metastases and less commonly for intraocular metastases. In such instances, complete resection is performed if the tumor is circumscribed. For ill-defined lesions, incisional biopsy is performed. For intraocular metastases, the biopsy is performed microscopically via a scleral flap. Surgical biopsy obtains more tissue for the pathologist, but radiotherapy or chemotherapy is generally indicated in order to eliminate tumor seeding at the biopsy site.

Pathology of Ocular Metastasis

Since the intraocular structures have no lymphatic channels, metastatic tumors reach these sites by hematogenous routes. Probably because of its marked vascularity, the uvea is the location of most ocular metastases, especially the posterior portion of the choroid. Gross examination of an eye with metastatic carcinoma usually reveals one or more diffuse or nodular amelanotic tumors in the uvea. In rare instances, the mass is highly elevated with a dome shape, similar to that of choroidal melanoma, but melanoma is generally pigmented.

Low-power magnification of a metastatic carcinoma reveals a placoid or diffuse mass, often with an overlying serous detachment of the sensory retina. Well-differentiated tumors may retain certain histologic or histochemical features of the primary tumor. Breast metastases typically appear histologically as solid epithelial nests or glandular structures. It is important to differentiate a primary adenocarcinoma of the retinal pigment epithelium, ciliary body epithelium, and iris pigment epithelium from a metastatic adenocarcinoma.

Treatment Options for Ocular Metastasis

The preferred treatment for an ocular metastasis from breast cancer depends on the location, extent, activity, and symptoms related to the ocular tumor, as well as the patient's systemic status [27, 28, 45]. Management may involve observation alone, chemotherapy, hormone therapy, anti-vascular endothelial growth factor (VEGF), laser photocoagulation, thermotherapy, photodynamic therapy, irradiation, or surgical resection.

Observation

Some metastatic tumors to the eye are inactive and require no treatment. They may have regressed spontaneously or they may have regressed following systemic treatment of the primary breast cancer months or years previously. With some experience, the ocular oncologist can recognize such inactive metastasis. When located in the choroid, they are generally flat tumors with pigment epithelial clumping on the tumor surface and without retinal detachment.

Chemotherapy, Hormone Therapy, Anti-VEGF Therapy

Active tumors, characterized by a homogeneous mass with a secondary retinal detachment, usually require treatment. In general, if the patient is asymptomatic and the eye tumor appears to be controlled with chemotherapy or hormone therapy that is being used to treat the systemic disease, then no specific ocular treatment is indicated. The patient should be followed at 2–4-month intervals for documentation of tumor and visual status. In some cases, intravitreal injection of anti-VEGF medications can resolve the choroidal tumor [46].

Laser Photocoagulation, Thermotherapy, Photodynamic Therapy

Rarely, choroidal metastases are treated with laser photocoagulation or thermotherapy. This is only employed for small tumors located outside the macular region. Methods of laser treatment using diode red, diode green, or argon laser can be applied to small choroidal metastases measuring less than 5 or 6 mm in base dimension [47–49]. Thermotherapy using a large spot diode laser to heat the tumor to a subphotocoagulation level is gaining some interest. These methods, however, are damaging to the normal retina and induce a dense scotoma. For this reason, most clinicians prefer focal treatment with radiotherapy rather than methods of laser or thermotherapy.

Radiotherapy

If the patient has an active choroidal metastasis, external beam irradiation is generally effective in controlling the tumor [50, 51]. The entire uvea or orbit is irradiated, with approximately 3,000–4,000 cGy delivered in divided doses over 3 weeks [50, 51]. Plaque brachytherapy is a method of focal radiotherapy using an implant with radioactive sources (see Fig. 14.6). The implant is surgically applied to the eye to deliver a radiation dose to a select region. This minimizes radiotherapy to surrounding normal structures. Plaque brachytherapy is employed for circumscribed

tumors measuring less than 18 mm in base and less than 10 mm in thickness [52]. The benefit of plaque brachytherapy is the speed of treatment, as it only takes 2–4 days to deliver the dose. This is important for patients whose life expectancy is limited because it occupies less time of their remaining days than other methods of radiotherapy [52].

Following radiotherapy, choroidal metastases decrease in tumor thickness on ultrasonography, and secondary retinal detachment resolves, often with improved visual acuity. Rudoler and associates found that external beam radiotherapy provides globe preservation in 98% of patients, with visual improvement or vision better than 20/200 in 57% of patients [50, 51]. Ocular radiation complications were found in 12% of patients. Newer methods of radiotherapy such as gamma knife and cyberknife radiotherapy have been employed to successfully treat metastasis over a short time period.

Surgical Excision, Enucleation

In some instances, enucleation or local surgical excision of an intraocular metastasis may be justified. Uncontrollable, large tumors occasionally require enucleation for intractable pain caused by secondary glaucoma. However, chemotherapy or radiotherapy, rather than enucleation, should generally be considered first. Local excision of a tumor that has metastasized to the eyelid, conjunctiva, orbit, and occasionally the intraocular structures is justified in certain instances [53, 54]. This technique is useful for both diagnostic and therapeutic reasons.

Patient Prognosis

In general, the life prognosis is poor for patients with metastatic tumors to the ocular structures [11, 25]. Patients with breast carcinoma metastatic to the uvea have a mean survival of 18 months, which is better survival compared to patients with metastases from lung cancer (mean, 6 months) or cutaneous melanoma (mean, 1 month) [11]. Data collected from our department showed Kaplan-Meier survival estimates for patients with uveal metastasis from breast cancer to be 65% at 1 year, 34% at 3 years, and 24% at 5 years [25].

Controversies and Perspective

The main controversies regarding intraocular metastasis center around establishing the diagnosis and providing the best therapy to the patient with quality of life in mind. If a patient has known primary malignancy with multifocal metastasis systemically, then the diagnosis of a choroidal metastasis can be presumed by the history without the need for further intraocular biopsy. If the patient has known primary malignancy with no metastatic disease, then it is advisable to establish the diagnosis with systemic evaluation to look for other involved sites. If negative, then fine-needle aspiration biopsy of the mass should be performed. If the patient has no known primary cancer, then the ocular diagnosis should be established with fine-needle aspiration biopsy as simulating conditions like amelanotic melanoma and nevus, scleritis, and others can cloud the picture.

Regarding therapy, the clinician should choose the most effective method with the understanding that quality of life is perhaps the most important issue. The therapy should cure the ocular malignancy and provide the best visual acuity to allow good quality of life. Minimizing physician monitoring is also important. Our preference is to first treat the ocular metastasis with systemic therapy if the general oncologist agrees as there could be subclinical disease elsewhere. If, on the other hand, there is no need for systemic therapy, then we would use localized ocular therapy with external or plaque radiotherapy or even photodynamic therapy to the eye to control the cancer and regain visual acuity. We usually prefer plaque over external radiotherapy as plaque is faster and controls the disease over a 4-day period compared to external radiotherapy that takes 4 weeks. This is important when considering the guarded life prognosis.

Pearls

- Intraocular metastasis develops most commonly in the posterior choroid.
- Less commonly, intraocular metastasis is found in the retina, optic disk, and vitreous.
- The most important primary cancer sites include breast, lung, kidney, and gastrointestinal tract.
- The malignancy appears classically as a yellow choroidal mass producing serous retinal detachment.
- Diagnostic confirmation can be made with trans-pars plana fine-needle aspiration biopsy.
- Therapy generally involves systemic chemotherapy or local radiotherapy, and the globe is usually retained, often with intermediate or good visual acuity.
- Life prognosis is guarded with mean survival for some malignancies like lung cancer and skin melanoma at less than 1 year and breast cancer mean survival at 4 years or more.

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Autoimmune Retinopathy and Paraneoplastic Syndromes

15

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Abstract

Autoimmune retinopathies and paraneoplastic retinopathies are rare ocular syndromes that can signal the presence of an underlying autoimmune condition or systemic malignancy. This chapter will present the pathogenesis, diagnostic features, and management strategies for cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and autoimmune-related retinopathy and optic neuropathy (ARRON).

Keywords

Autoimmune-related retinopathy and optic neuropathy • Cancer-associated retinopathy • Melanoma-associated retinopathy • Paraneoplastic syndromes • Optic neuropathy • Vision loss

Introduction

Autoimmune retinopathy includes three main forms: cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), and nonneoplastic autoimmune-related retinopathy and optic neuropathy (ARRON). Autoimmune retinopathies encompass ophthalmic disorders in which autoantibodies are directed at various retinal components and lead to progressive vision loss. If evaluation reveals an underlying malignancy, it is considered a paraneoplastic syndrome. Although paraneoplastic syndromes occur in 10–15% of cancer patients [1], the incidence of paraneoplasia-induced antiretinal antibodies is considered rare. Without confirmed malignancy, patients with retinal dysfunction related to antiretinal antibodies are considered to have ARRON or nonneoplastic autoimmune retinopathy (npAIR). The differential for nonneoplastic cases of antiretinal autoantibodies usually includes inherited retinal degenerations [2, 3], as well as occult malignancies. This chapter will review and provide illustrative cases of CAR, MAR, and ARRON.

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Paraneoplastic Retinopathy: Cancer-Associated Retinopathy (CAR)

Cancer-associated retinopathy (CAR) is a paraneoplastic retinopathy in which autoantibodies are directed against retinal antigens causing retinal dysfunction and retinal cell death. CAR is believed to be the most common form of paraneoplastic retinopathy, although the exact prevalence has not been reported in the literature. Typically, older adults are affected, and the incidence is equal among men and women [4]. The malignancy most commonly associated with CAR is small cell lung cancer, followed by gynecologic and breast cancers [4]. Less commonly, cases have also been associated with non-small lung cancer, Hodgkin's lymphoma, bladder, prostate, pancreatic, laryngeal, and colon cancers [4].

Malignancies associated with CAR:

- Small cell lung cancer
- Gynecologic malignancies: endometrial, uterine, and cervical
- Breast
- Lymphoma
- Colon
- Prostate
- Bladder
- Laryngeal
- Pancreatic
- Metastases of unknown primary

CAR was first described in 1976 by Sawyer et al. in three patients with small cell lung cancer with progressive vision loss and has since become an increasingly recognized clinical disorder [5].

A humoral immune reaction leading to photoreceptor destruction is the most likely underlying etiology for CAR. McGinnis et al. in 1995 proposed that CAR may be initiated with a p53 tumor suppressor gene mutation in the tumor cells [6]. This mutation subsequently turns on production of the recoverin protein with the cell line becoming cancerous due to loss of the tumor suppressor activity. The human gene for recoverin protein and the p53 gene have both been localized to chromosome 17 in proximity of one another [6]. Recoverin is a calcium-binding protein located within retinal photoreceptor cells and bipolar cells and is highly immunogenic and leads to anti-recoverin antibody production [4, 7]. The anti-recoverin antibodies bind to recoverin molecules in the photoreceptor cells by penetrating the blood–retina barrier [1]. The inactivated form of retinal recoverin then causes closure of ion channels, depolarization of cells, and photoreceptor death. Specifically, anti-recoverin antibody is likely incorporated into photoreceptor cells and modulates increased phosphorylation of rhodopsin, which increases the intracellular level of calcium and the activation of caspase-dependent apoptosis, ultimately leading to photoreceptor death [1, 4, 6]. Adamus et al. in 1998 demonstrated this concept with the injection of anti-recoverin antibodies intravitreally in rats, which caused flattening of both the a and b wave on ERG and triggered photoreceptor cell death [7].

In 1987, Thirkill et al. elucidated the autoimmune etiology of CAR by identifying antiretinal antibodies via immunofluorescence [1, 8]. These autoantibodies were demonstrated to be reactive with photoreceptor outer segments as well as retinal ganglion cells [1, 8]. The 23-kDa protein recoverin, which is a calcium-binding protein found in both rods and cones, is the most frequently identified antigen in CAR [1, 8]. The second most common autoimmune retinal antibody is a 46-kDa (anti-enolase) protein, followed by 45 and 60 kDa [4]. Antibodies against 65-kDa heat shock protein 70, 44, 43, and 63 kDa have also been identified [1]. Antibodies to TULP-1 (tubby-like protein 1) protein are directed against the inner segment of photoreceptor cells, which is in contrast to anti-recoverin antibodies that are directed against the outer segments of these cells [4]. The anti-TULP-1 protein has been identified in a CAR patient with endometrial cancer [4]. Antibodies against the photoreceptor cell–specific nuclear receptor (PNR) gene product have also been reported in a case of CAR secondary to lung cancer [4]. In addition, combined paraneoplastic retinopathy with vitreous cells and optic neuritis has been associated with CRMP-5-IgG antibody, which has a 77% association with small cell lung cancer [9].

Histopathologically, CAR demonstrates diffuse photoreceptor degeneration of both rods and cones with loss of nuclei from the outer nuclear layer [1, 4]. The retinal pigment epithelium and choriocapillaris are well preserved, and ganglion cells in the inner retina, optic nerve, and geniculocalcarine pathway are all spared [1, 4, 10]. In addition, there may also be a secondary cellular response with inflammatory infiltrates being sporadically reported in CAR [1, 4].

In terms of clinical symptoms, patients may present with progressive bilateral visual loss over weeks to months. Entoptic symptoms such as flashing or flickering lights, swirling vision, or other positive visual phenomenon are often prominent [1, 4]. Patients may also report transient dimming of vision [4]. CAR affects both rods and cones. Clinical problems associated with rod dysfunction include nyctalopia, prolonged dark adaptation, midperipheral ring scotomas, and peripheral visual field deficits [4]. Cone dysfunction can present with photosensitivity, reduced visual acuity, prolonged glare after light exposure, decreased color perception, and central scotomas [4]. Visual symptoms may precede diagnosis of a systemic malignancy in 50% of patients [1]. Early in the disease, fundus examination may appear normal [1]. However, characteristic changes may occur over time with disease progression and include attenuation of arterioles, thinning and mottling of the retinal pigment epithelium, and optic disk pallor [1, 4, 5, 11]. Anterior chamber and vitreous cells, periphlebitis, and arteriolar sheathing may also be present particularly late in the course of disease [1, 4, 5, 11].

Early diagnosis of CAR may be complicated due to subtle clinical findings, and maintaining a high index of clinical suspicion is warranted. Ancillary testing can include a Goldmann visual field test, which may indicate peripheral field or central deficits [1]. Optical coherence tomography (OCT) may demonstrate extensive photoreceptor loss, and fluorescein angiography can help exclude other clinical entities as potential causes of vision loss. Fluorescein findings are usually normal, but may demonstrate mild peripheral vascular leakage consistent with vasculitis in occasional cases [12]. The most sensitive test in detecting retinal dysfunction associated with CAR is often electroretinography (ERG), in which findings are usually abnormal in the majority of cases [1]. Patients with a predominant rod or cone dysfunction show abnormal scotopic or photopic patterns, respectively [1]. In both scotopic and photopic conditions, a and b waves are depressed [1, 5, 13]. Along with ERG findings, a diagnosis of CAR can also be made by the demonstration of antiretinal antibodies using western blot analysis, immunofluorescent antibody assays, and enzyme-linked immunosorbent assay (ELISA) [1].

Results of ERG and antibody testing are not always definitive, and in patients suspected of CAR, an extensive evaluation for a malignancy should be initiated. A complete physical examination, including pelvic and breast examination for women, is recommended. A chest radiograph should initially be obtained. If normal, a chest CT scan should be performed for further evaluation [12]. Additional imaging studies for a possible malignancy include CT of the abdomen and pelvis, mammography, and total-body positron emission tomography (PET) [12]. Further evaluation for metastatic disease as the source of vision loss should also include contrast-enhanced MRI of the head and orbits and lumbar puncture for cytologic examination. Cerebrospinal fluid analysis in CAR often reveals a nonspecific finding of a mild lymphocytic pleocytosis and an increased concentration of protein [4].

The differential diagnosis in the setting of subacute unilateral or bilateral vision loss and the presence of retinal dysfunction includes paraneoplastic syndromes (CAR and MAR), npAIR (hereditary retinal degenerations and ARRON), and toxic retinopathy [12]. Etiologies for toxins include mellaril, chloroquine, and plaquenil. The time course of progression of visual symptoms is usually over years with hereditary retinopathies and weeks to months with acquired disease. Furthermore, the presence of antiretinal antibodies will also facilitate the diagnosis of autoimmune retinopathy, and evaluation for malignancy will distinguish between paraneoplastic conditions and npAIR. Specifically, npAIR can include

hereditary retinal diseases such as retinitis pigmentosa (RP), which may also have antiretinal antibodies. In a study of 116 RP patients, 43 (37%) of patients demonstrated antibodies reacting with donor eye retinal antigens on indirect immunofluorescence [2, 3, 14]. A prospective study also demonstrated that 90% of patients with RP and cystoid macular edema have antiretinal antibodies compared with 13% of RP patients without CME and 6% of controls [2, 14, 15]. However, the pathogenic role of these antiretinal antibodies in hereditary disorders remains unclear. Overall, antiretinal antibodies may be useful in helping to identify a broad spectrum of autoimmune retinopathies.

Additional diagnostic considerations for clinical symptoms similar to CAR include a retrobulbar optic neuropathy in which patients present with vision loss and a normal fundus examination. Etiologies can include ischemia, demyelinating disease, compressive lesions, toxicity, and hereditary disorders [12]. Cancer-associated cone dysfunction and toxic nutritional and hereditary optic neuropathy can also present with findings similar to CAR, such as bilateral central vision loss, central scotomas, and reduced color vision. In order to evaluate for these etiologies, additional history regarding possible alcohol, tobacco, toxic medication use, dietary patterns, and a family history of similar problems is warranted [12].

In the majority of CAR cases, the visual prognosis is often guarded, and various immunotherapies have resulted in mild to moderate visual recovery. Treatment of the underlying systemic malignancy with chemotherapy, radiation therapy, and surgery has not been shown to alter the visual prognosis [4, 16, 17]. Initial treatment for CAR usually involves modulation of the immune system with steroids. The most widely reported therapy consists of 250 mg of intravenous methylprednisolone four times daily or 60–80 mg of oral prednisone daily, followed by a slow taper to a low maintenance dose [18, 19]. Several case reports have described mild to moderate transient improvement in visual acuity and visual fields in CAR patients with high-dose intravenous methylprednisolone treatment [4, 19–21]. Keltner et al. in 1992 described a patient with improvement and stabilization of visual function and reduced antibody levels during 7 months of corticosteroid therapy; this patient died 7 months after the diagnosis of CAR [19, 22]. However, the beneficial effect of oral steroids has been limited in other reports [23–25]. Treatment with plasmapheresis alone did not prevent progression of visual loss in a patient with CAR [22, 26]. Murphy et al. reported that plasmapheresis in conjunction with oral corticosteroid therapy resulted in vision improvement, but the recovery lasted only 4 months [22, 24]. In another report, Guy and Aptsiauri reported the results of three patients with CAR treated with intravenous immunoglobulin therapy [16]. One patient had improvement in both visual acuity and visual fields; one had improvement in only visual field defects; and the other only had stabilization of vision [4, 16]. In 2007, a report of the treatment with alemtuzumab for CAR and paraneoplastic optic neuropathy described maintenance of visual acuity and visual fields during an 8-year follow-up period [22]. Currently, it remains unclear whether initiating immunomodulatory therapy prior to diffuse degeneration of photoreceptors may improve or stabilize visual acuity. Overall, due to the high mortality rate of CAR patients, observation of any definitive long-term effects of treatment on both retinal structure and visual function remains limited.

CAR Cases

CAR can present with heterogeneous clinical and diagnostic findings. Although the most common reported antigen associated with CAR is recoverin [27], three CAR cases are described with several unique clinical features and without the presence of anti-recoverin antibodies. In case 1, CAR signaled the presence of metastatic esthesioneuroblastoma, an uncommon association with paraneoplastic retinopathy. Antiretinal antibodies were not detected in this case. Cases 2 and 3 present more frequently reported malignant associations, breast cancer and small cell lung cancer. Anti-enolase antibody was positive in association with breast cancer, and CRMP-5-IgG

was detected in the small cell lung cancer case. These cases highlight that CAR facilitated the diagnosis of a systemic malignancy, clinical symptoms may be variable and subtle, and patients may have a variety of antiretinal antibody activity (see Figs. 15.1, 15.2, 15.3, 15.4, and 15.5).

CAR Case 1: CAR Secondary to Esthesioneuroblastoma (Olfactory Neuroblastoma)

A 58-year-old white female with a history of esthesioneuroblastoma treated with prior surgical resection and radiation therapy 6 months earlier

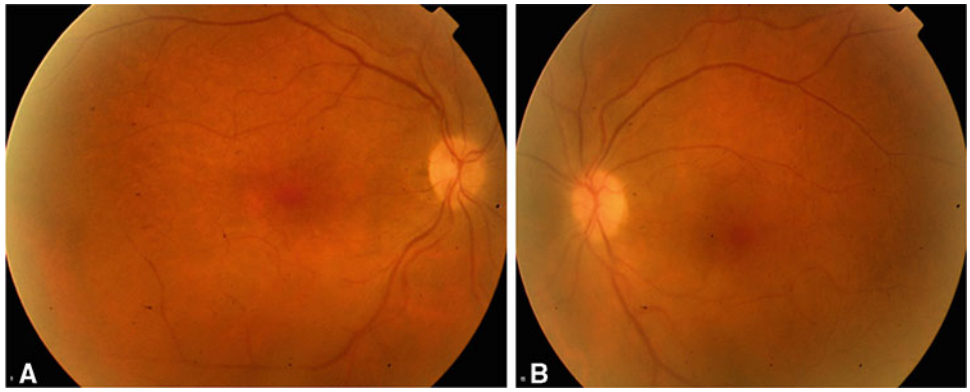


Fig. 15.1 CAR case 1: fundus photos (**a**) OD and (**b**) OS demonstrate trace disk edema OU, mild narrowing of the arterioles and venules, and a hazy media secondary to vitritis

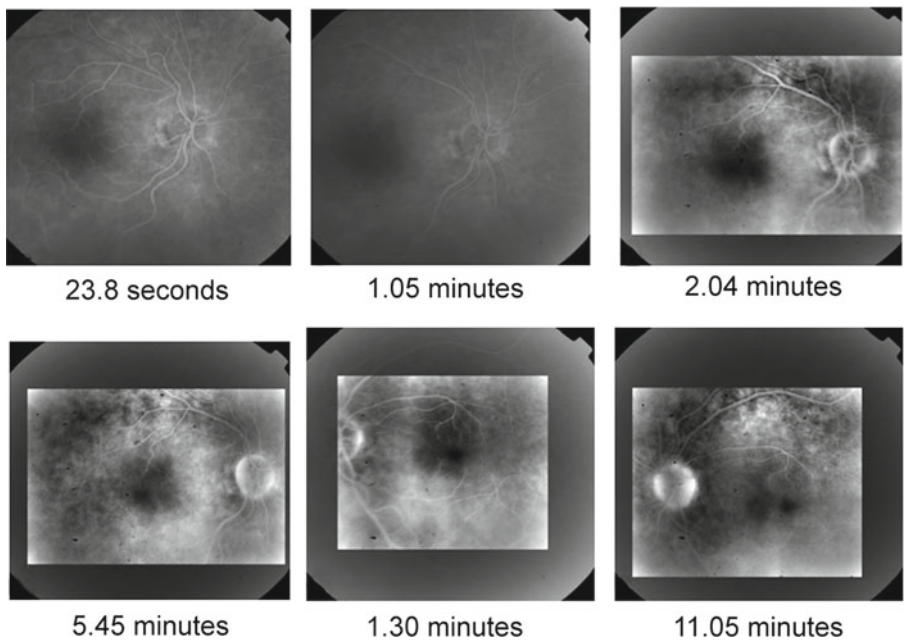


Fig. 15.2 CAR case 1: fluorescein angiography demonstrates mild perivascular leakage in both eyes with increased optic nerve fluorescein. Atypical for dense vitreous cellular reaction on an immunologic basis, there is no appreciable macular edema

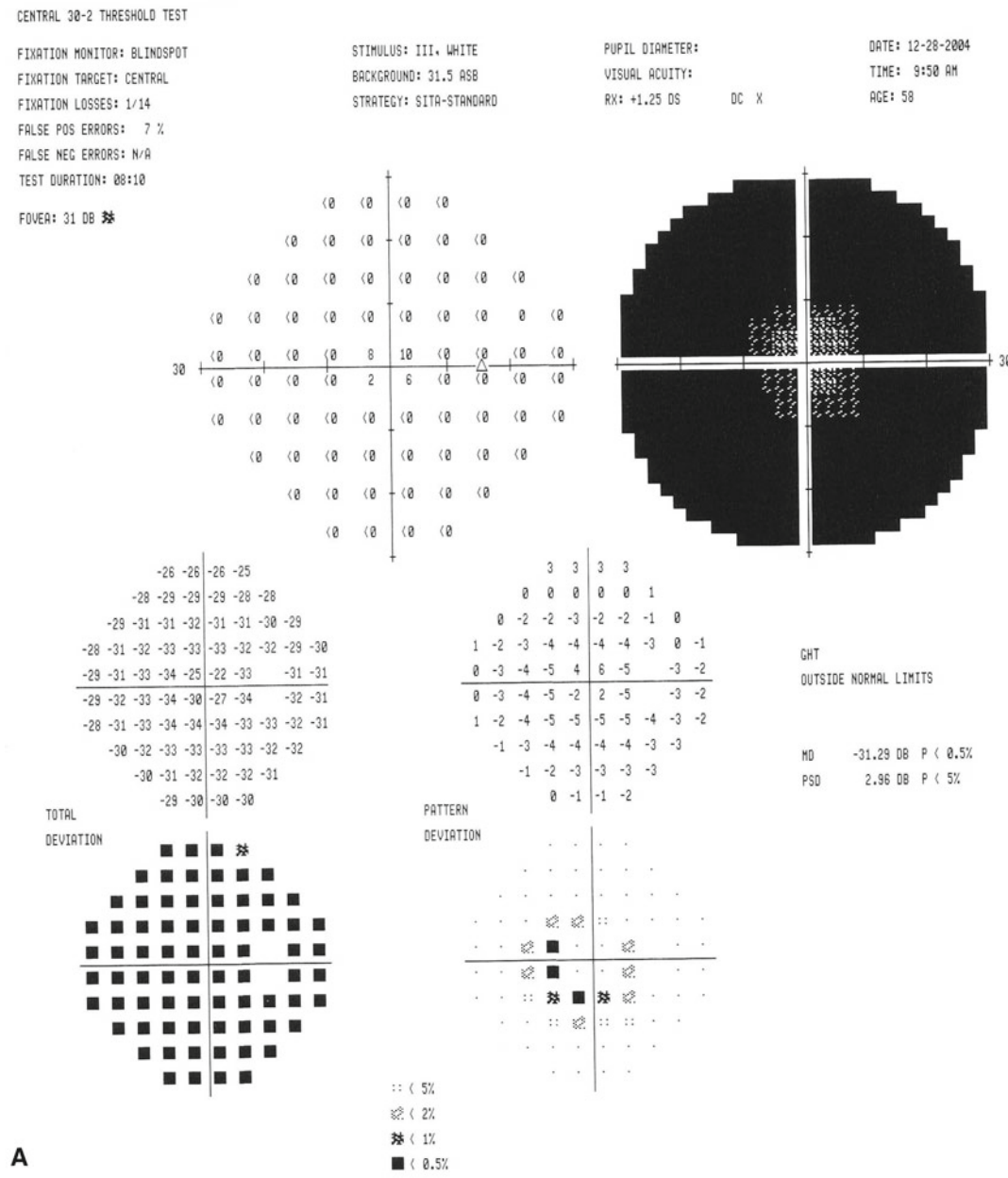


Fig. 15.3 CAR case 1: Humphrey visual fields (**a**) 30–2 OD and (**b**) OS demonstrate global depression of retinal sensitivity

presented with a 2-week history of gradually decreasing vision greater in the right than left eye. Best corrected visual acuity was 20/25 OD and 20/30 OS. Clinical examination demonstrated no afferent pupillary defect, +3 vitreous cells OU with +1 disk edema in both eyes (Figs. 15.1a, b and 15.2a–e). ERG and visual fields were markedly abnormal in each eye (Figs. 15.3a, b, 15.4a, b,

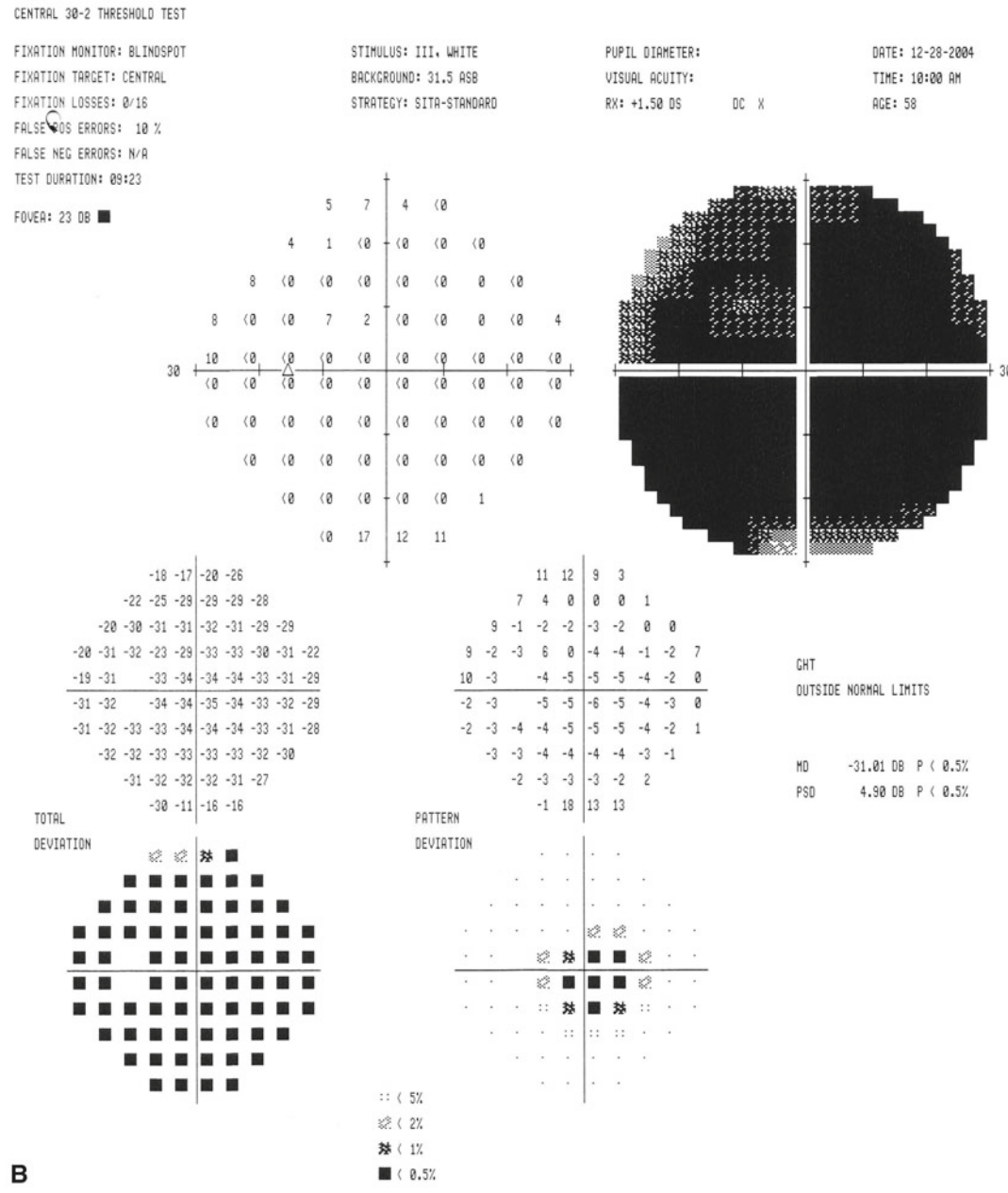
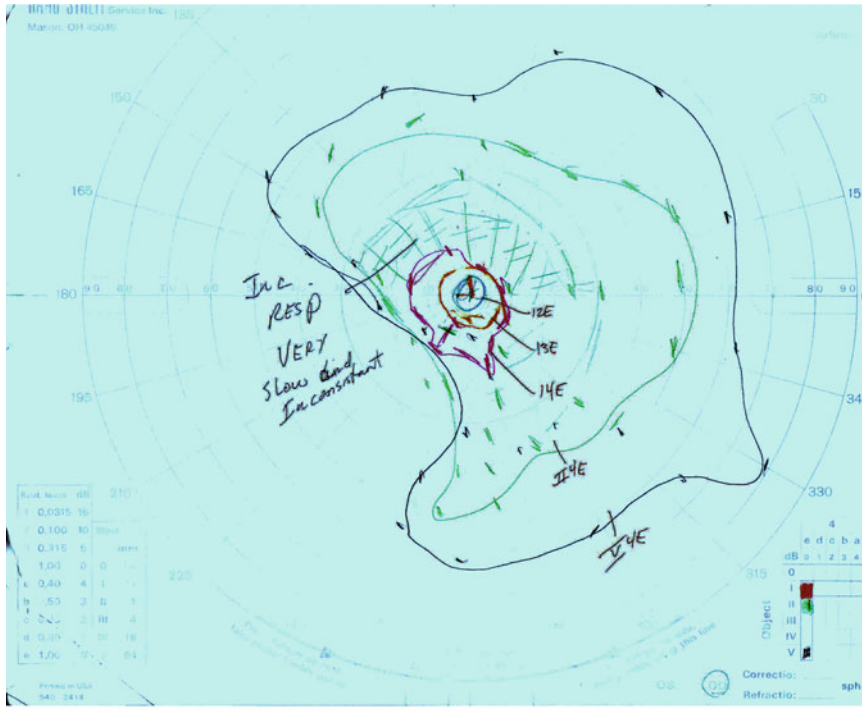
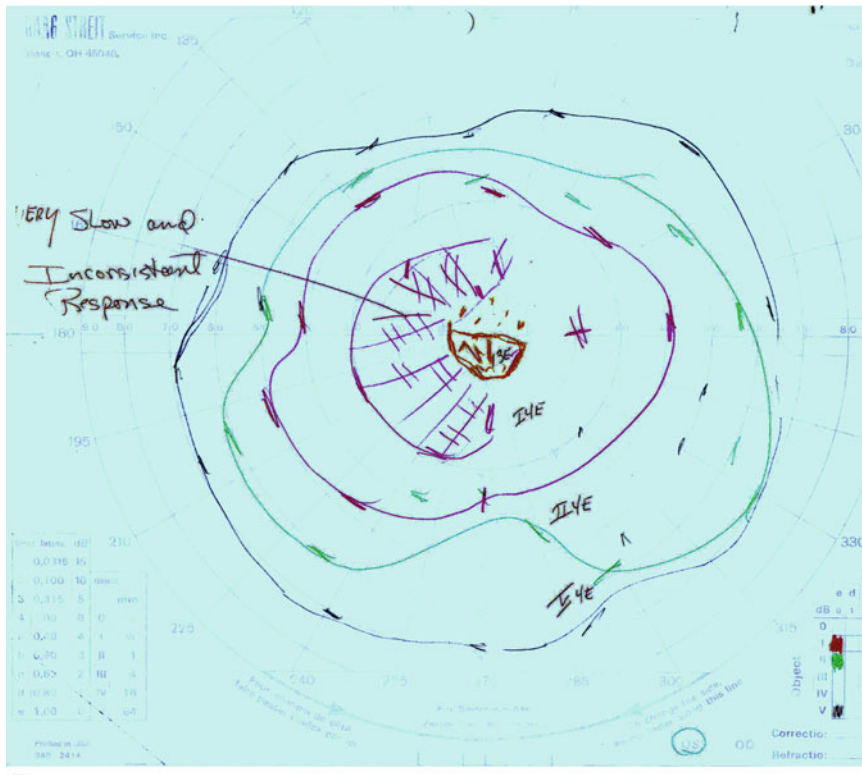


Fig. 15.3 (continued)

and 15.5). MRI brain/orbits with gadolinium demonstrated multiple hyperintense lesions throughout the brain with no evidence of optic nerve enhancement. Laboratory evaluation was negative for CAR antibody, FTA, and RPR. The patient was treated with prednisone 100 mg daily and a subsequent taper as the inflammation improved. Two months after initial presentation,

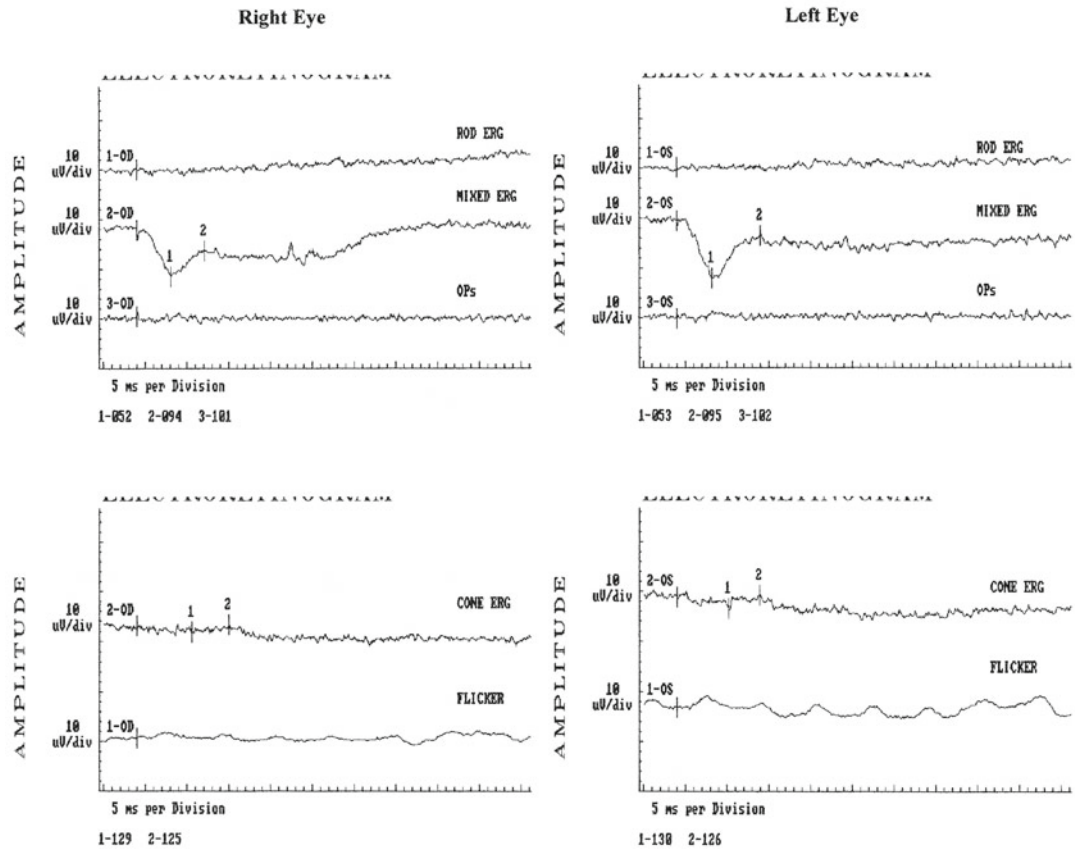


A



B

Fig. 15.4 CAR case 1: Goldmann visual fields (**a**) OD and (**b**) OS demonstrate field constriction and depression in both eyes, right eye greater than left eye



		Amplitude (uV)		Timing (ms)	
		Right eye	Left eye	Right eye	Left eye
ROD ERG:	b-wave	--	--	--	--
MIXED ERG:	b-wave	25.5	42.4	40.5	50.0
	a-wave	47.7	59.5	20.5	21.0
OSCILLATORY POTENTIALS:					
CONE ERG:	b-wave	3.7	9.3	51.0	51.0
	a-wave	17.9	18.9	22.5	18.0
	30 Hz flicker	4.9	11.5	38.6	37.8

Fig. 15.5 CAR case 1: full-field ERG demonstrates that rod ERG was not detectable; mixed cone and rod ERG was reduced in amplitude and b/a <1; and cone ERG was severely reduced in amplitude and prolonged. Overall, the full-field ERG and VEP responses were markedly impaired

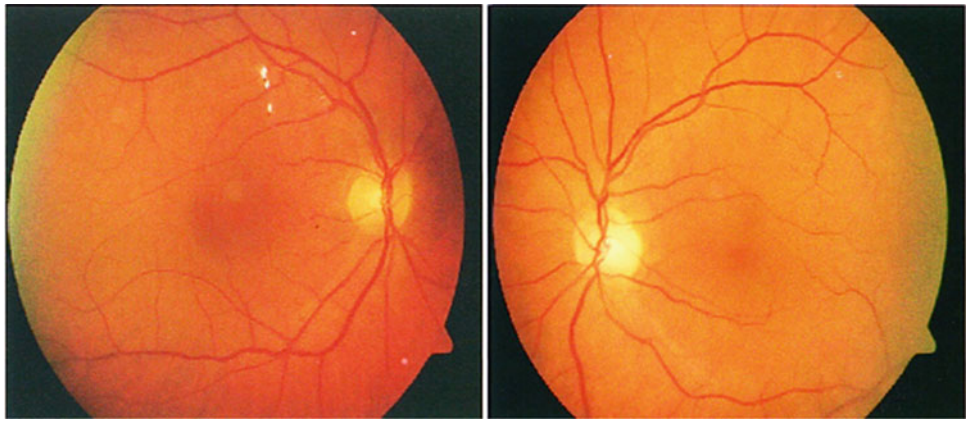


Fig. 15.6 CAR case 2: fundus photos of OD and OS demonstrate clear media, C/D 0.3 OU with no evidence of disk edema, and a blunted foveal reflex OU

the patient was symptomatic with a neck mass. Biopsy results and a subsequent total body scan demonstrated metastatic esthesioneuroblastoma. Antibody determinations were not available, but it was concluded that the ocular inflammation was a paraneoplastic retinopathy.

CAR Case 2: CAR Associated with Metastatic Breast Cancer

A 66-year-old female with a history of metastatic breast cancer treated with prior chemotherapy complained of progressively decreasing vision in both eyes for 6–8 months. Best corrected visual acuity is 20/60 OD and 20/70 OS. Clinical examination demonstrated no evidence of afferent pupillary defect, and there were full extraocular movements and confrontational field testing. There was no evidence of anterior chamber or vitreous cell, and no disk edema. Cystoid macular edema was present in both eyes (Fig. 15.6), and there were peripheral reticular pigmentary changes in the retina (not shown). Goldmann visual field testing revealed constriction of the I-4e and II-4e isopters that was asymmetric (Fig. 15.7a, b). Fluorescein angiography did not reveal retinovascular leakage although the optic nerves were mildly hyperfluorescent (Fig. 15.8). There were mild ERG changes (Fig. 15.9). MRI brain/orbits with contrast demonstrated no evidence of cerebral metastasis or orbital involvement. Laboratory testing demonstrated positive anti-enolase antibody and a negative CAR antibody. The patient was started on Taxol chemotherapy by her oncologist.

CAR Case 3: Paraneoplastic Optic Neuritis and Retinitis Associated with Small Cell Lung Cancer

A 72-year-old male with a history of testicular and epididymal mesenchymoma and abdominal sarcoma treated with surgical resection presented with progressively decreasing vision in both eyes for 4 months [9]. Best corrected visual acuity was 20/200 OD and 20/400 OS. Evaluation indicated no afferent pupillary defect, and color plates were 5/15 OD and 8/15 OS. Goldmann visual fields had central depression as well as constriction in both eyes, OS greater than OD. Clinical examination demonstrated no anterior chamber inflammation, +1 vitreous cells OU, and marked disk edema in both eyes with bullous fluid extending to the macula (Fig. 15.10). Fluorescein angiography showed optic nerve leakage (Fig. 15.11). ERG was markedly abnormal

(Fig. 15.12). The patient was evaluated for malignancy, including CNS lymphoma. Lumbar punctures revealed increased protein, and negative cryptococcal antigen and VDRL. Cytology from the diagnostic vitrectomy OD showed that the majority of cells were T cells with a predominance of CD4-positive T cells, a minor heterogeneous B cell population with a normal kappa to lambda ratio. Chest CT demonstrated mediastinal adenopathy with a left hilar mass, which upon biopsy was consistent with small cell lung cancer. Antibody testing showed a positive CRMP-5-IgG and negative CAR antibody. The patient was treated with systemic chemotherapy, radiation, and oral prednisone with improvement in his ocular condition (Figs. 15.13a, b and 15.14a, b).

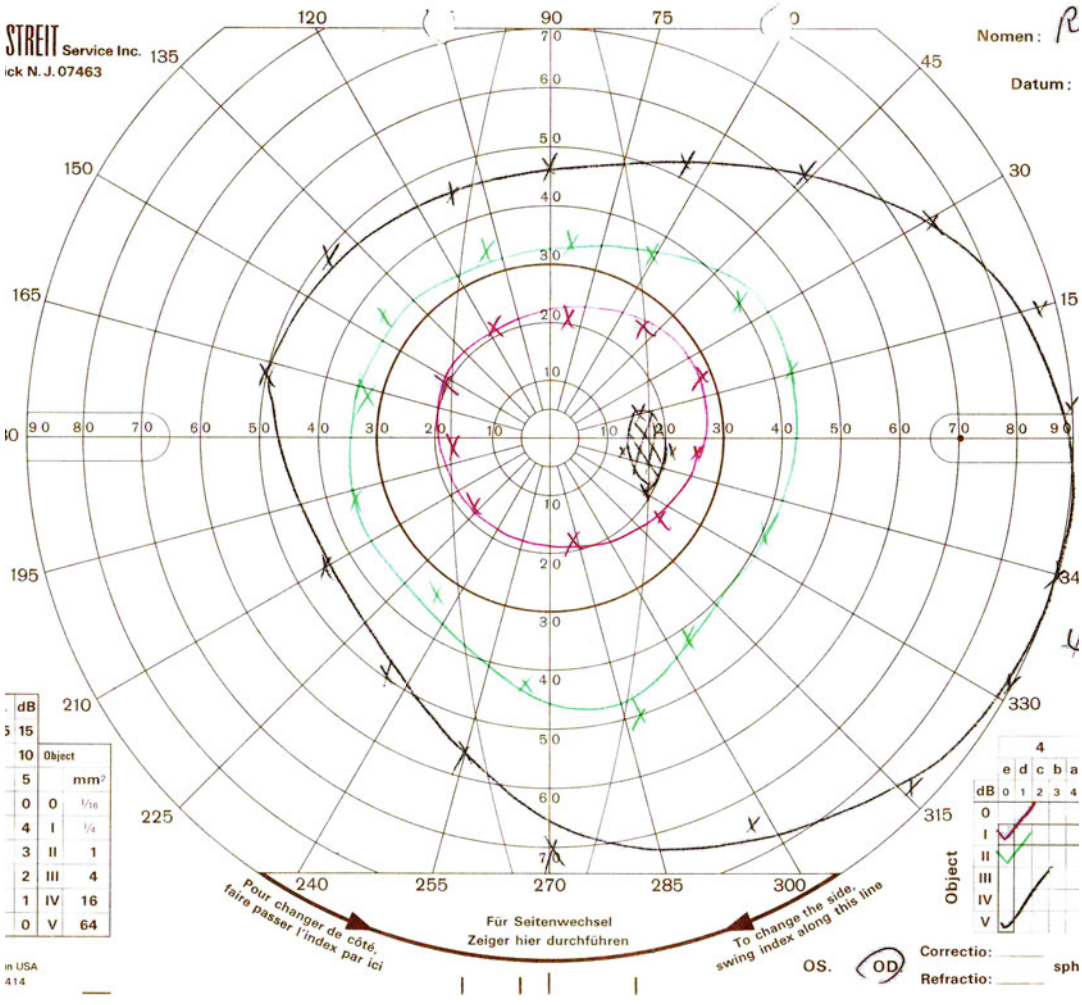
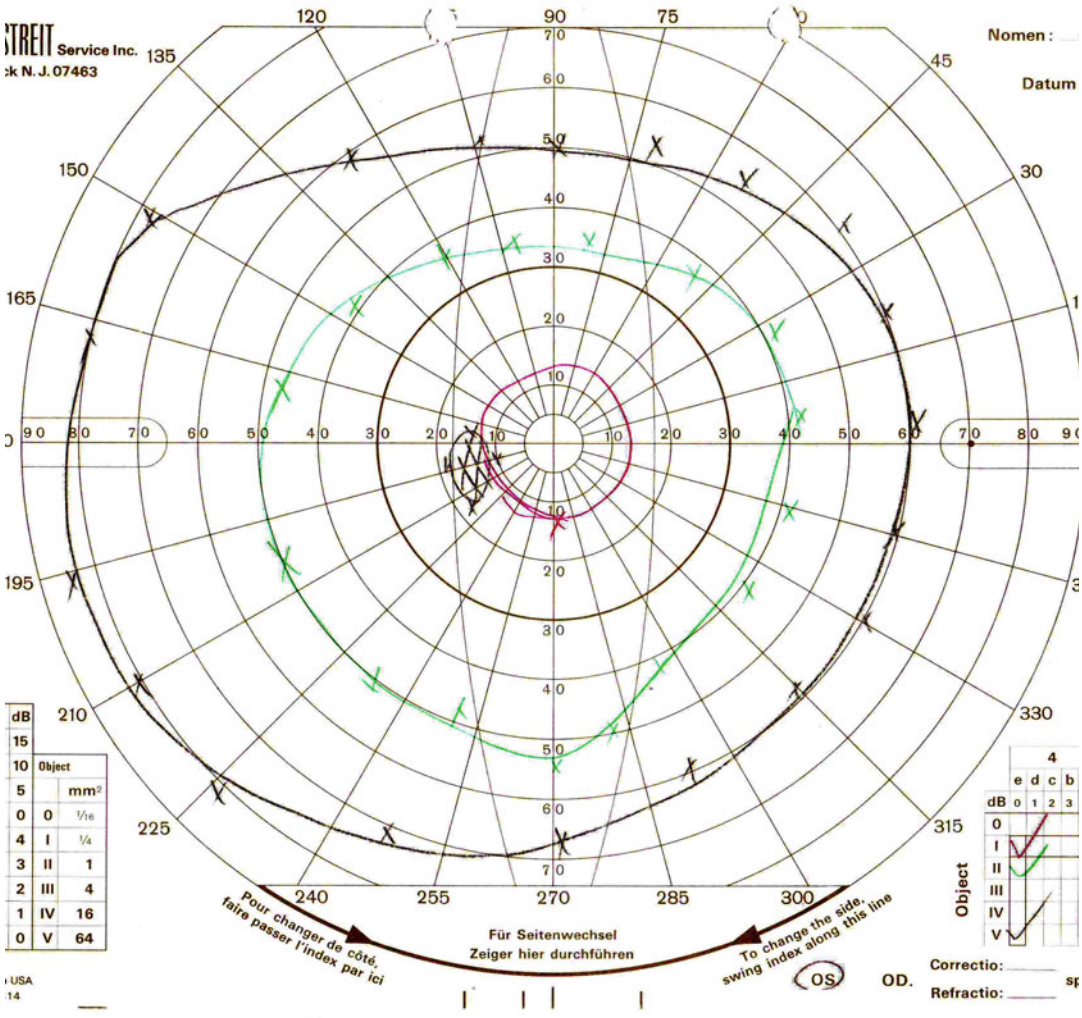


Fig. 15.7 CAR case 2: Goldmann visual fields (**a**) OD and (**b**) OS demonstrate a full field to the largest isopter with symmetric constriction of the smaller isopters. There was no evidence of peripheral field constriction or ring scotomas



B

Fig. 15.7 (continued)

Paraneoplastic Retinopathy: Melanoma-Associated Retinopathy (MAR)

Melanoma-associated retinopathy (MAR) is a form of paraneoplastic retinopathy that has been described in patients with cutaneous malignant melanoma. MAR commonly presents after the melanoma is diagnosed, often at the stage of metastases. MAR has been reported to occur in higher frequency in men than women [4]. Berson et al. in 1988 initially classified MAR as a paraneoplastic retinopathy in a patient with both visual loss and the diagnosis of metastatic melanoma [28].

The pathogenesis theory of MAR is based on molecular mimicry: tumor cells and retinal bipolar cells share epitopes [29, 30]. The tumor's retina-like antigens sensitize the immune system. The immune system, in turn, recognizes certain portions of the retina as foreign. The specific antigen responsible for MAR has not been determined, but analysis of previous cases has shown autoantibodies to bipolar cells, Muller cells, and membrane-associated proteins within the retina

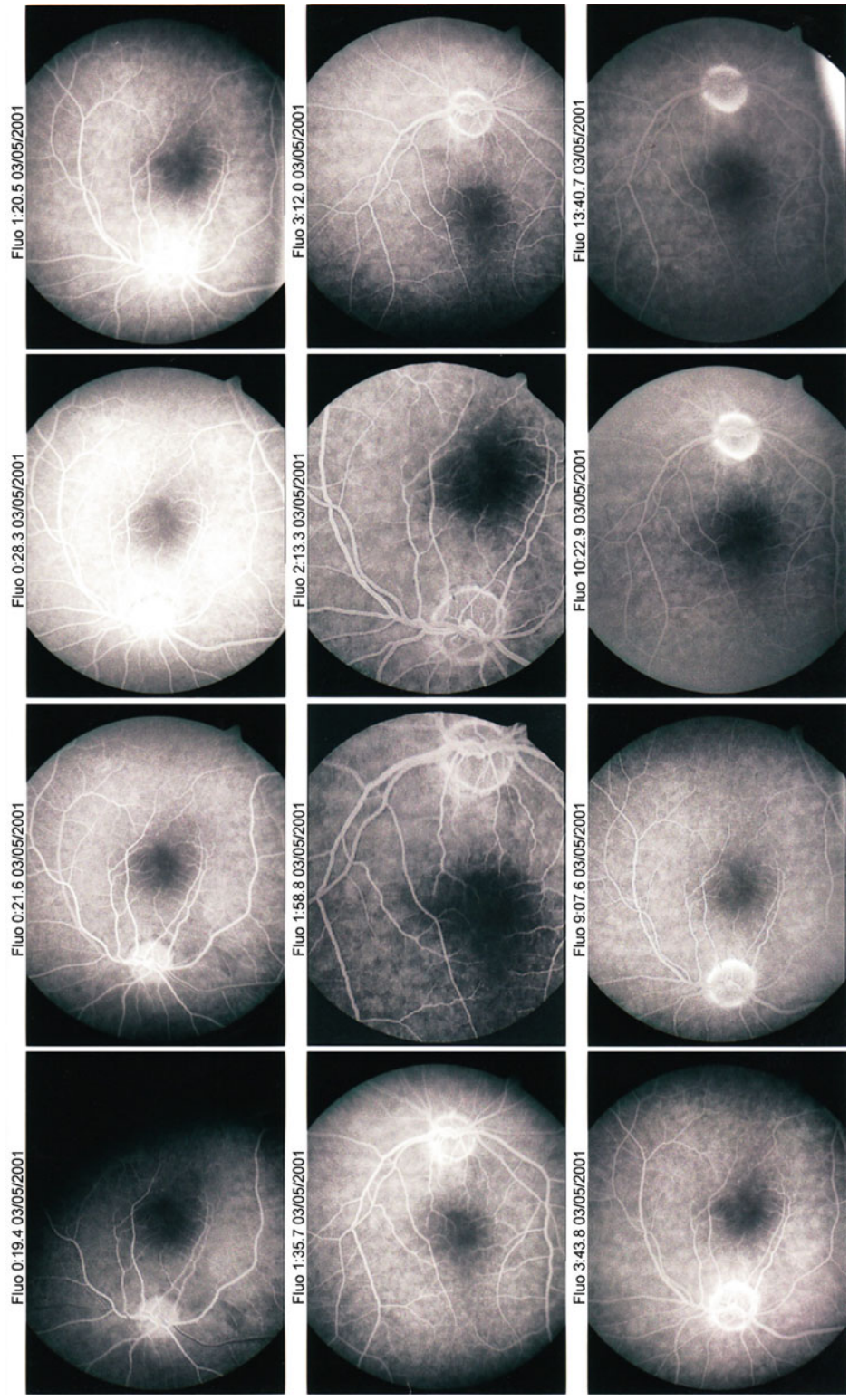
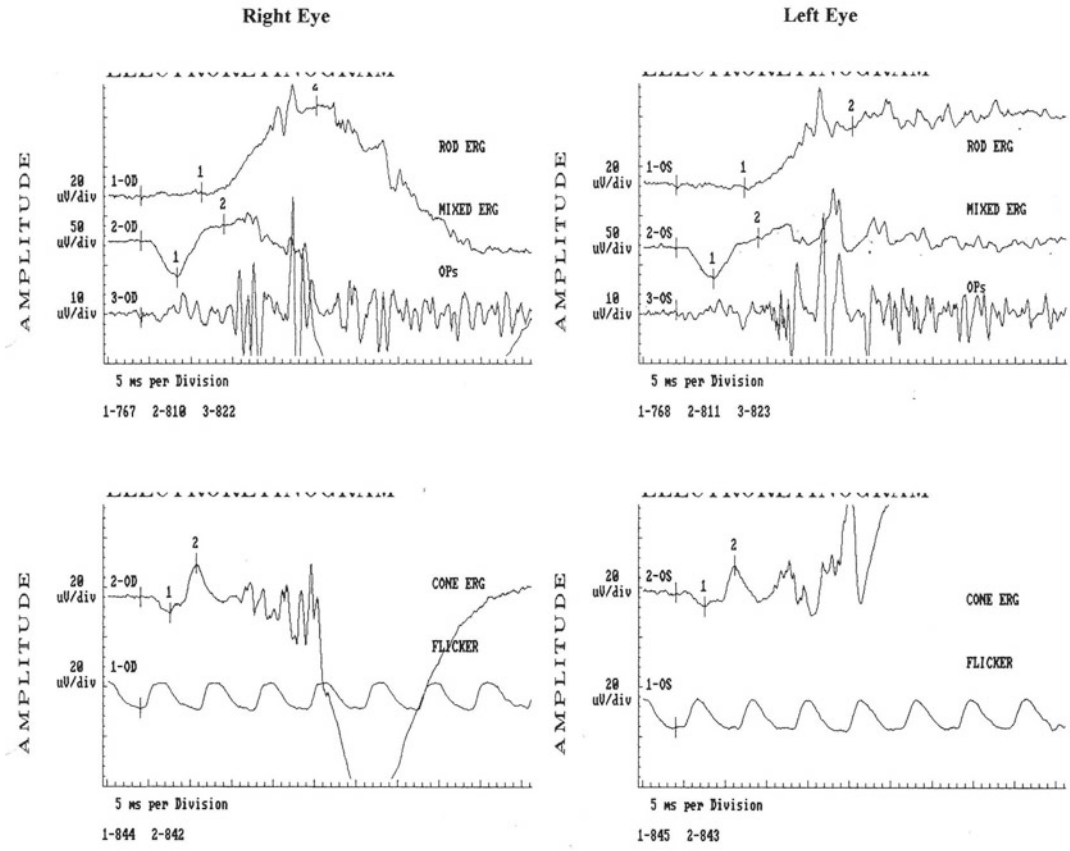


Fig. 15.8 CAR case 2: fluorescein angiography demonstrates no leakage of dye at the macula, optic nerves, or vasculature, despite clinical cystoid macular edema. Cystoid macular edema is an infrequent finding in CAR



		Amplitude (uV)		Timing (ms)	
		Right eye	Left eye	Right eye	Left eye
ROD ERG:	b-wave	175.3	124	106.0	106.5
MIXED ERG:	b-wave	274	212.4	50.0	49.5
	a-wave	183.9	158.3	22.0	22.5
OSCILLARY POTENTIALS:					
CONE ERG:	b-wave	102.5	85.4	33.5	35.5
	a-wave	34.7	32.2	18.0	17.5
	30 Hz flicker	54.4	59.4	33.3	35.2

Fig. 15.9 CAR case 3: rod ERG is slightly below the lower end of normal in amplitude and prolonged; mixed cone and rod ERG shows a-reduced and b-waves normal in amplitude; and the cone ERG is normal in amplitude and implicit time. Overall, the ERG was abnormal in each eye with relatively mild reduced rod dysfunction compared to cone responses

[30–35]. The most common hypothesis is that autoantibodies react with rod bipolar cells and their dendrites in the outer plexiform layer of the retina and cause failure of neural transmission from rods to the inner retina [4].

In the setting of clinical features, patients may present with photopsias including shimmering or flickering lights, night blindness, and peripheral visual field loss [4]. MAR patients will often have near normal visual acuity, color

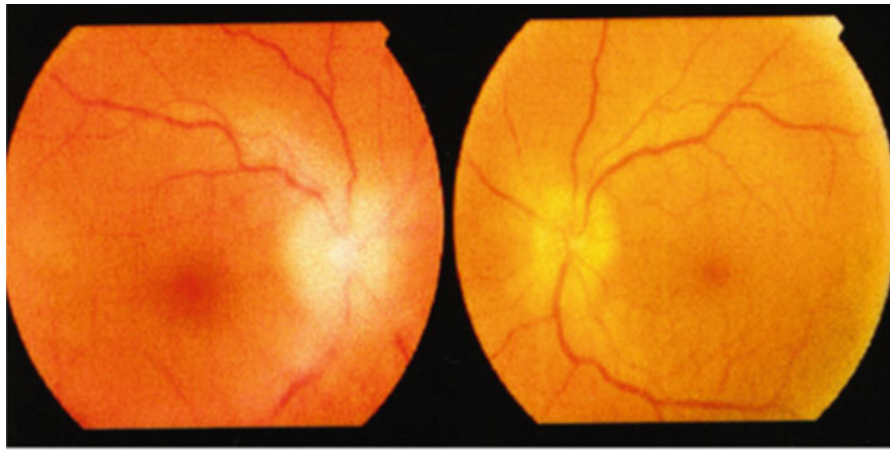


Fig. 15.10 CAR case 3: Fundus photos OD and OS demonstrate hazy media secondary to vitritis, disk edema OU, and a blunted foveal reflex secondary to macular edema

vision, and central visual field [4]. In contrast to CAR, only rods are affected and cones are spared. The most common fundus finding is that of a normal retina. Approximately 25–35% of patients will have vitreous cell, vessel attenuation, retinal pigment epithelium (RPE) changes, or optic nerve pallor [30].

The histopathologic result may be the destruction of normal retinal architecture, especially the inner retinal layers [36, 37]. Specifically, there may be reduction of bipolar neurons in the inner nuclear layer with normal photoreceptor cells in the outer nuclear layer and possible evidence of ganglion cell transsynaptic atrophy [4].

The diagnosis of MAR is based upon a positive history of malignant melanoma and the demonstration of patient IgG autoantibodies reacting with human donor rod bipolar cells on immunofluorescent stains. However, anti-bipolar cell antibodies are not specific to MAR. Typical ERG findings include a negative scotopic waveform with a markedly reduced or absent dark adapted b wave, indicating bipolar and Muller cell dysfunction, and sparing of the a wave [4].

Recently, treatment has been reported to involve reduction of tumor load by surgery or radiation to allow adjuvant immunotherapy (intravenous immunoglobulin [IVIg], plasmapheresis, or systemic corticosteroids) to be more effective [30]. Unfortunately, the vast majority of patients have metastatic disease at diagnosis [30]. Keltner et al. in 2001 described therapeutic outcomes in 11 MAR patients. Cytoreductive surgery was reported to improve visual acuity and visual field in one patient and the color vision and visual field in another [4, 30]. Also, IVIg alone improved the visual acuity in one patient, and both IV methylprednisolone and plasmapheresis improved the visual acuity and visual field in another patient [4, 30]. In other reports, IVIg and cytoreductive surgery were effective in improving visual symptoms, visual field, and color vision in one patient [38] and visual field in another patient [4, 39]. The reported cases of MAR in the literature indicate that steroids alone may not likely improve vision. In only 3 out of 64 MAR patients, steroids decreased vitreous haze and improve retinal phlebitis [4, 29, 40]. However, combination therapy with plasmapheresis, oral prednisone, azathioprine, and gabapentin together improved the visual fields and ERG in one patient [4]. Similar to CAR, ineffective treatments may also be the result of irreversible damage to retinal cells and raise the question of whether visual loss can be prevented with treatment prior to structural damage. Overall, the long-term stabilization of visual outcome and prognosis for MAR is unknown at this time and will require longer follow-up data in the reported literature.

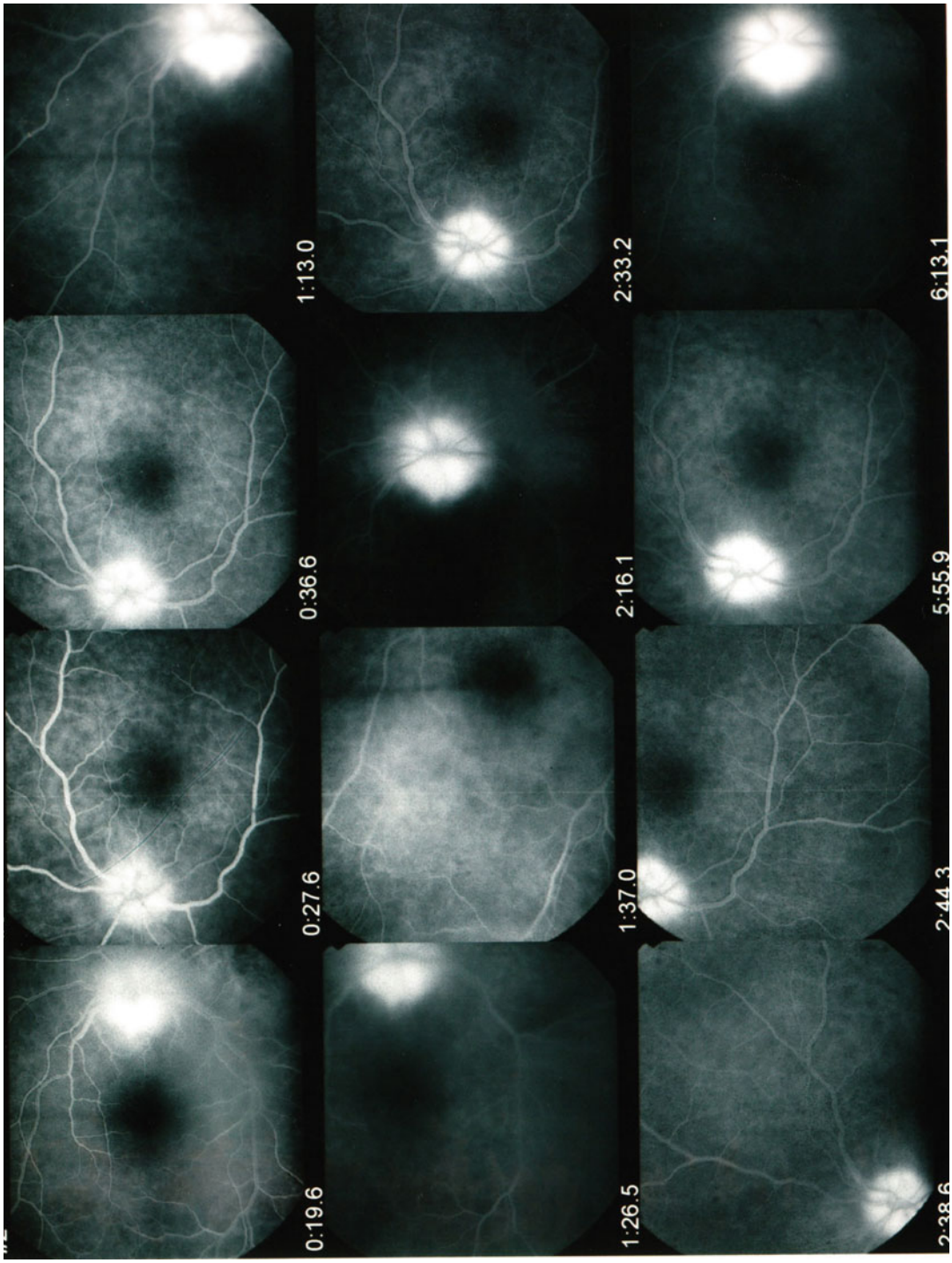
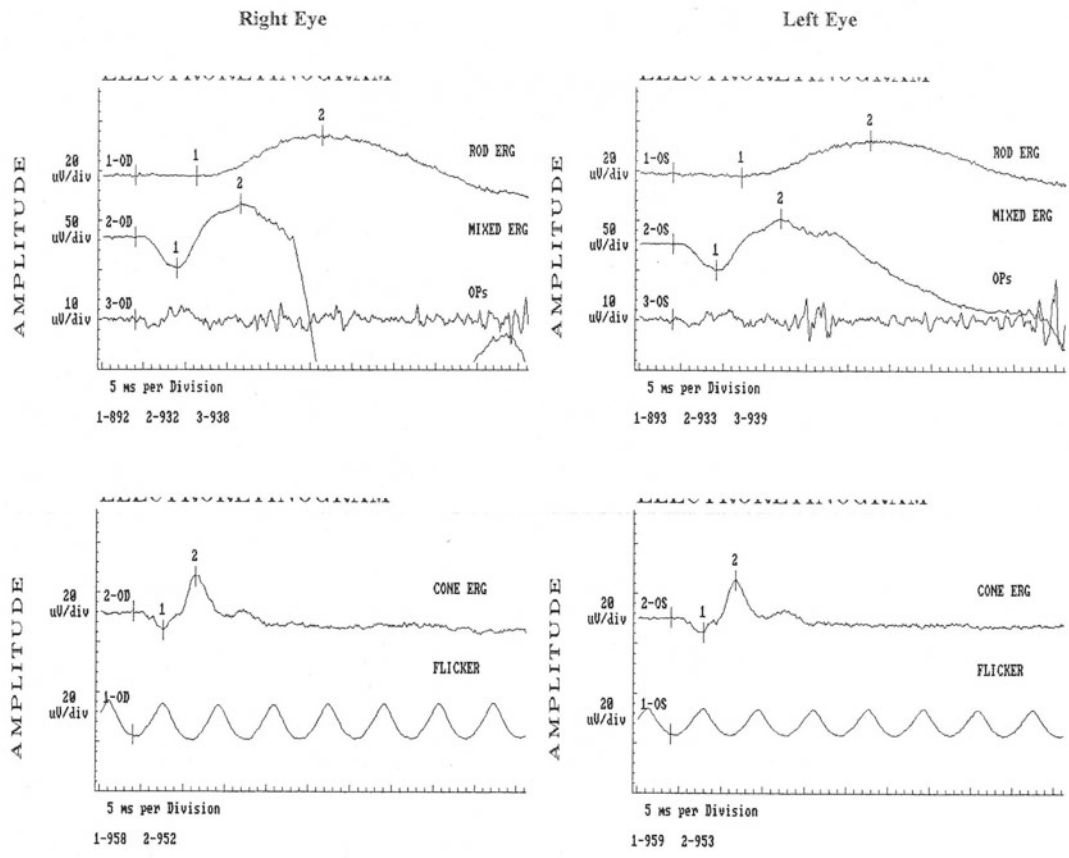


Fig. 15.11 CAR case 3: Fluorescein angiography at the initial visit demonstrates leakage from the optic nerves, OD greater than OS



		Amplitude (uV)		Timing (ms)	
		Right eye	Left eye	Right eye	Left eye
ROD ERG:	b-wave	81.5	77.9	112.0	118
MIXED ERG:	b-wave	327.1	263	63.0	64.5
	a-wave	159.1	133.6	25.0	26.0
OSCILLATORY POTENTIALS:		41.2	53		
CONE ERG:	b-wave	110.1	107.4	37.0	38.5
	a-wave	35.7	29.4	18.0	19.5
	30 Hz flicker	73.6	56.0	37.9	38.8

Fig. 15.12 CAR case 3: Rod ERG is reduced in amplitude with prolonged implicit time; mixed cone and rod ERG shows that a and b waves are at lower end of normal in amplitude but prolonged; and cone ERG is normal in amplitude but markedly prolonged. Overall, full-field ERGs showed rod and cone dysfunction–based amplitudes with prolonged response for both rods and cones

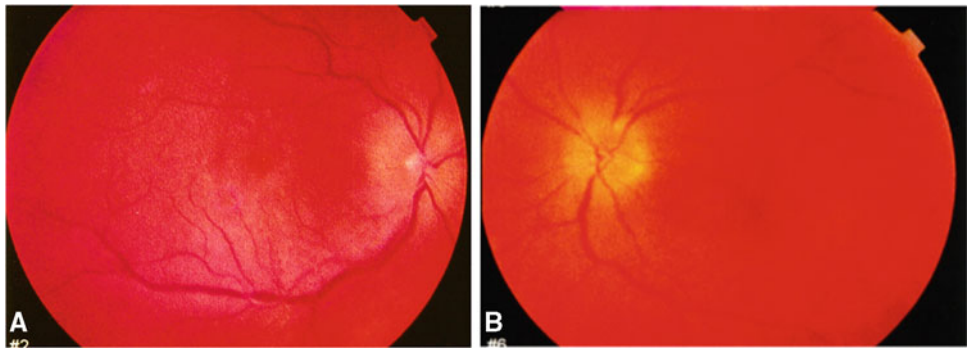


Fig. 15.13 CAR case 3: Fundus photos (**a**) OD and (**b**) OS 1 month after initiating systemic chemotherapy and radiation for small cell lung cancer, which demonstrated improved disk edema OU. Visual acuity improved to 20/50 OD and 20/80 OS

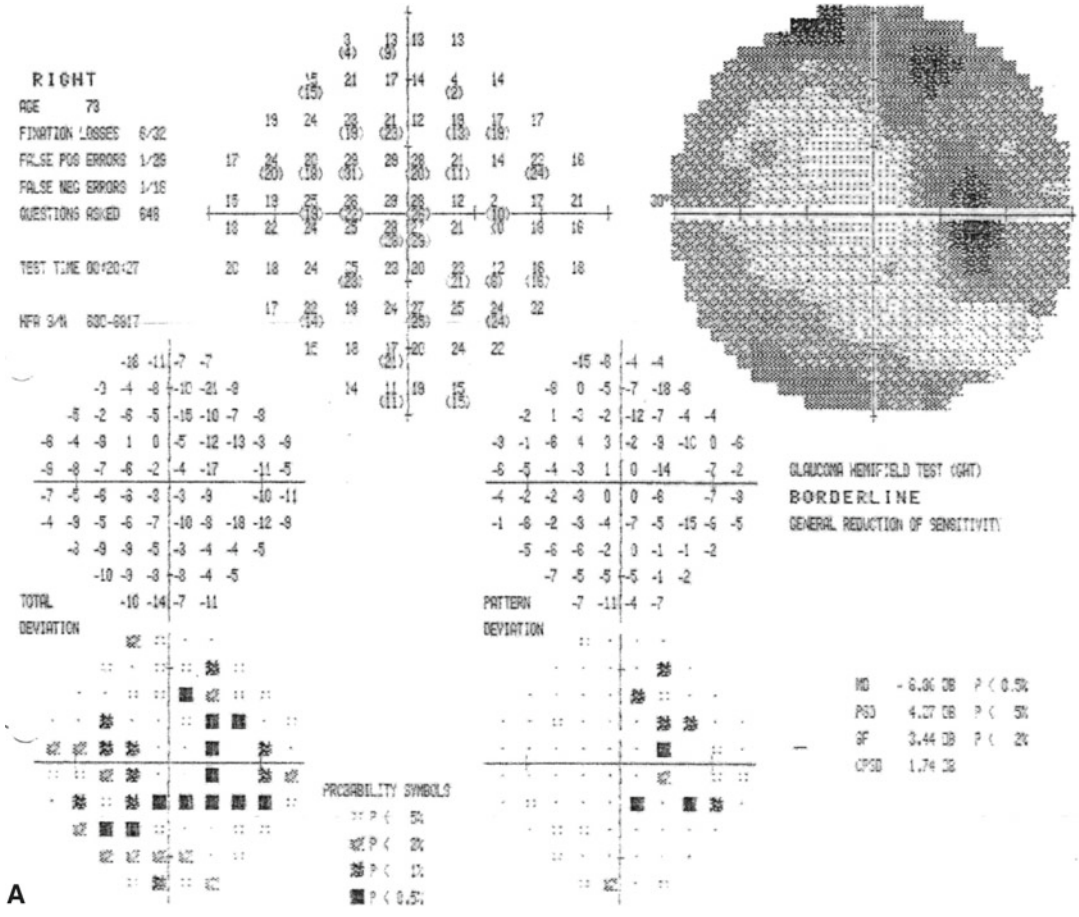


Fig. 15.14 CAR case 3: (**a**) HVF 30–2 OD and (**b**) OS 1 month after initiating systemic chemotherapy and radiation demonstrate improved constriction OU. Visual acuity improved to 20/50 OD and 20/80 OS

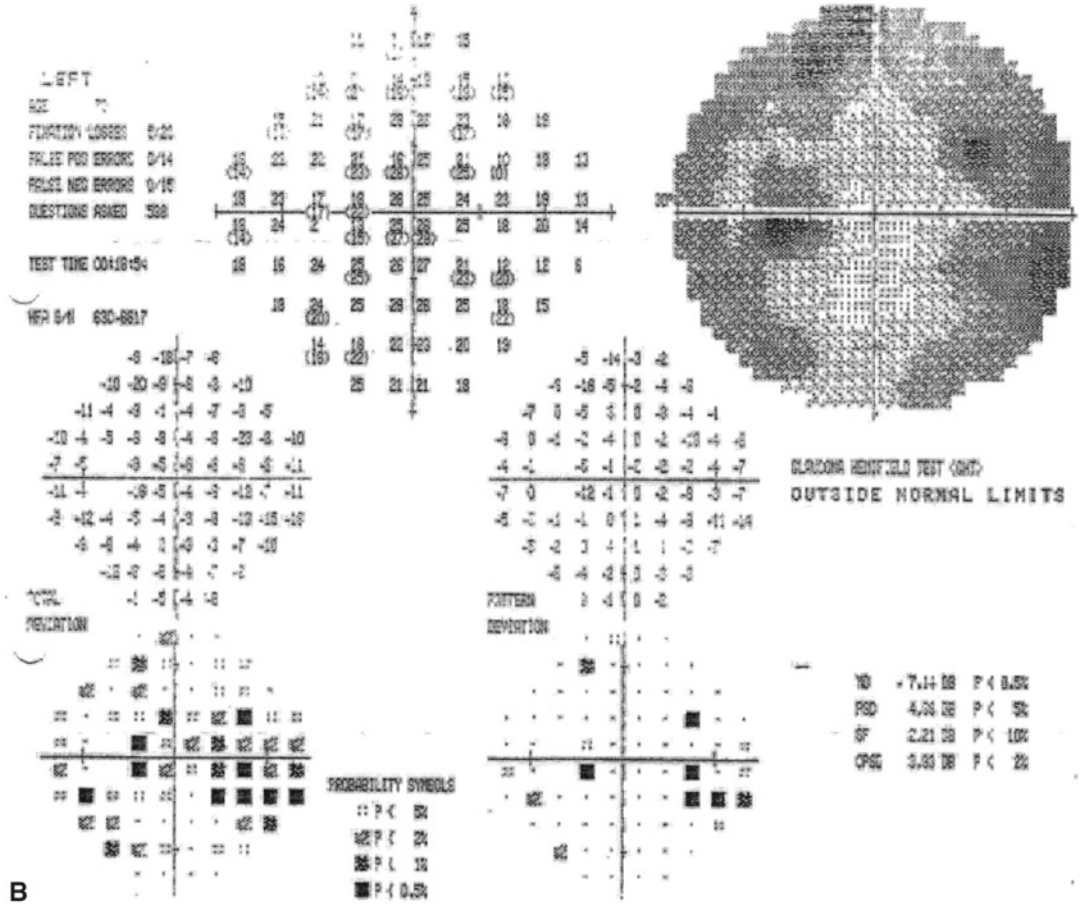


Fig. 15.14 (continued)

MAR Case

A 57-year-old Hispanic male presented with bilateral nyctalopia, blurred vision, and occasional flashes for the past month. His history was significant for excision of a small melanoma from his right heel approximately 3 years previously. He received a brief course of interferon therapy following the melanoma excisional biopsy, which was completed approximately 2½ years prior to presentation. Initial and all subsequent metastatic workups (most recently 2 years prior to presentation) were negative. The patient's family members had no heritable ocular diseases. He gave no history of tobacco, alcohol, or street drug use.

On examination, best corrected visual acuity was 20/40 OD and 20/25 OS. The anterior chambers were quiet, and intraocular pressure was 16 OU. There were trace vitreous cells. A retinal pigment epithelial detachment (RPED) was present superior to the fovea in the right macula, and there were some minor pigmentary changes in the left macula (Fig. 15.15a, b). There were myelinated nerve fibers OD and an area of retinal whitening in the inferonasal periphery (Fig. 15.15c, d)

On fluorescein angiography, the most striking aspect of the angiogram was the late staining of the optic disk and vasculature, right eye greater than left eye (Fig. 15.16a–d). Pigment epithelial

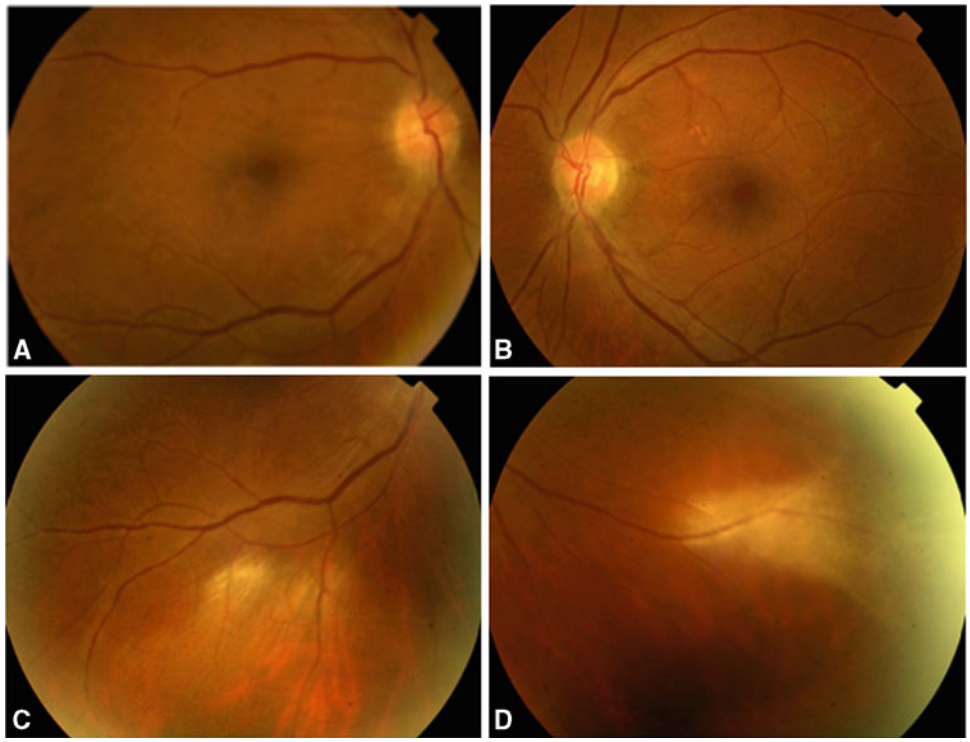


Fig. 15.15 MAR case. (**a**) Fundus photo OD shows elevated lesion superior to fixation in the right macula suggestive of a pigment epithelial detachment. (**b**) Fundus photo OS shows flat pigmentary alterations in the left macula. (**c**) Myelinated nerve fibers are present below the inferior arcade OD. (**d**) There is an area of superficial retinal whitening OD approximately one disk area in size inferonasally. This *whitening* appeared more intense around the arterioles and venules

defects and an RPED were confirmed. Humphrey and Goldmann visual fields showed generalized severe reduction of sensitivity to the size III stimulus and constriction of the peripheral fields (Fig. 15.17). An ERG showed loss of the scotopic B wave consistent with his complaints of nyctalopia and as previously reported in MAR [41]. Testing for autoantibodies directed against retina was performed at the University of California at Davis.

The differential diagnosis of low-grade retinal vasculitis of indolent course associated with nyctalopia and mild decreased visual acuity with constricted fields was quite broad and included infectious, inflammatory, pharmacologic, neoplastic, and idiopathic causes. The history of interferon treatment raised the possibility of interferon retinopathy with retinal ischemia, but these findings usually resolve within 9–12 months after cessation of interferon. This patient had no cotton wool spots, which are seen in almost all cases, and his last interferon dose was more than 2 years ago making interferon retinopathy highly unlikely.

Given the patient's history of cutaneous melanoma, the leading diagnostic consideration was melanoma-associated retinopathy. This paraneoplastic syndrome commonly presents with nyctalopia. However, there is only one previously reported case of melanoma-associated retinopathy presenting with vasculitis [40].

Laboratory studies were performed and demonstrated normal values for the complete blood count, basic metabolic panel, ANA, ANCA, ACE, ESR and RPR. A chest radiograph revealed mild flattening of the diaphragms but no hilar lymphadenopathy or masses.

Dr. Charles Thirkill at the University of California, Davis, performed serologic and immunologic testing on blood samples from this

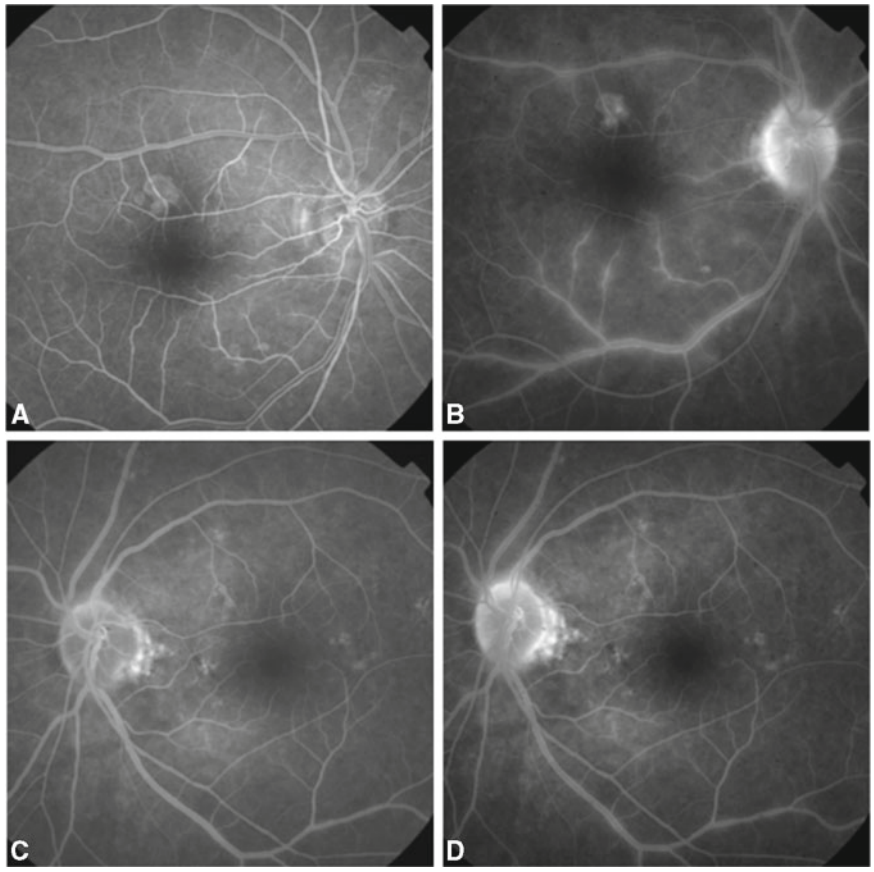


Fig. 15.16 MAR case. (**a**, **b**) Fluorescein angiography OD. (**a**) At 0:23 s, there is early hyperfluorescence in the pigment epithelial detachment, which has an atypical, irregular border and a small satellite lesion temporally. At 7:47 min, diffuse staining of the retinal veins and optic nerve is seen. (**b**) The RPED stains inhomogeneously with an irregular border. (**c**, **d**) Fluorescein angiography OS. (**c**) At 2:10 min, there are scattered areas of hyperfluorescence consistent with pigment epithelial window defects in the left peripapillary and perifoveal areas. The nerve and venules show early staining. (**d**) At 7:30 min, there is an increase in the mild staining of the proximal venules and the optic nerve

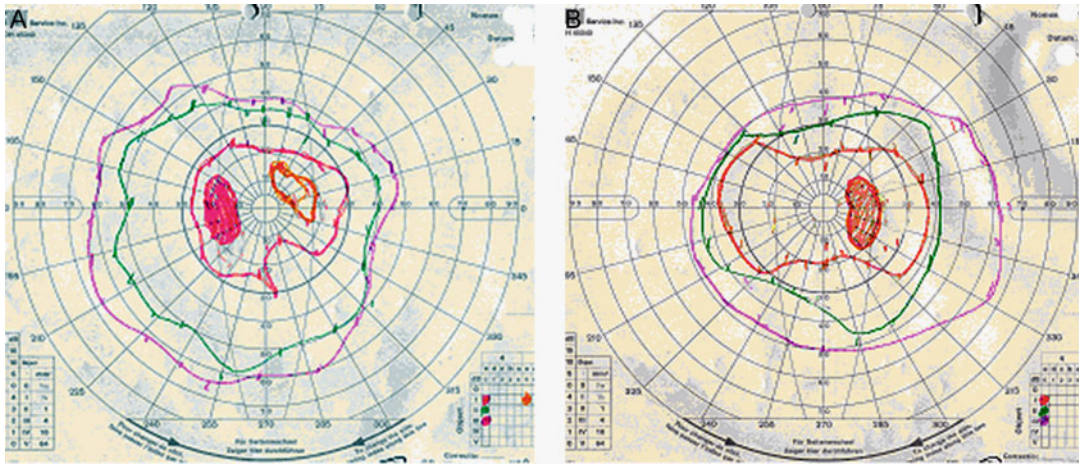


Fig. 15.17 MAR case. (**a**) Goldmann visual fields OD and (**b**) OS revealed generalized constriction

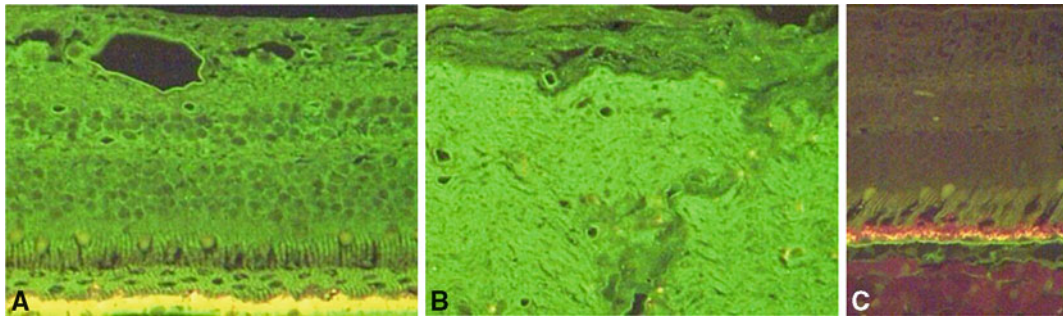


Fig. 15.18 MAR case. (**a**) The patient's serum diffusely stained all layers of rhesus monkey retina and vasculature. (**b**) The patient's serum also diffusely stained optic nerve stroma. In other reported cases of MAR, staining has been confined to bipolar cells. (**c**) Control human serum demonstrates a lack of staining of monkey retina (Courtesy of Dr. Charles Thirkill, University of California at Davis)

patient. Western blot with bovine retina extract revealed diffuse abnormal activity. Indirect immunohistochemistry revealed abnormal antibody activity upon rhesus monkey retina and optic nerve. FITC-conjugated rabbit anti-human gamma globulins indicated that human antibody had bound all layers of the neurosensory retina, vasculature, and optic nerve stroma (Fig. 15.18a, b). No human antibody from control patient serum bound the rhesus monkey retina (Fig. 15.18c).

Based on a presumptive diagnosis of MAR, the patient was treated with systemic corticosteroids. A metastatic workup revealed liver metastases related to melanoma. He survived for another 2 years before succumbing to his disease.

Autoimmune-Related Retinopathy and Optic Neuropathy (ARRON)

The disease spectrum of autoimmune-related retinopathy and optic neuropathy (ARRON) encompasses cases of retinal and/or optic nerve involvement and was classified by Keltner et al. in 2002 [30, 42]. ARRON is characterized by visual loss and often the presence of antibodies that are reactive with the optic nerve and/or retina. ARRON has been reported to be more common in women than men (2:1), and the average age is 50 years (range 37–75 years) [42–44]. The majority of ARRON patients have associated systemic immunologic diseases such as systemic lupus erythematosus, rheumatoid arthritis, thyroid disease, celiac sprue, Sjogren's disease, psoriatic arthritis, and idiopathic thrombocytopenic purpura [30, 42, 45].

The pathophysiology of ARRON syndrome has not been fully established. Autoantibodies against a 22-kDa antigen, a 23-kDa antigen (recoverin), Muller cells, a 35-kDa antigen, and a 47-kDa antigen have all been reported in the literature [43, 44]. Specifically, anti-recoverin antibody has been described to stain photoreceptors, and anti-47-kDa antibodies stain ganglion cells, bipolar cells, and Muller cells [43, 46]. Western blot analysis can be utilized to identify patients with ARRON syndrome, and most commonly demonstrate autoantibodies reactive with the 22-kDa neuronal antigen present in the retina and/or optic nerve [42]. In ARRON, it remains unclear whether antibodies directed against optic nerve and retina play a direct role in loss of visual function or whether antibodies are possibly the result of an epiphenomenon and are produced secondary to nonspecific breakdown of retinal and optic nerve proteins [45, 46].

ARRON syndrome may present in a similar clinical manner to CAR and MAR in the absence of an underlying malignancy. In the setting of visual function, ARRON patients will often present asymmetrically in terms of visual acuity and visual deficits [43]. The majority of ARRON cases will present with ERG abnormalities, which

are often detectable prior to the onset of visual loss and are similar to findings in CAR [45]. Mizener et al. in 1997 described autoimmune retinopathy in the absence of an underlying cancer [47]. They reported two patients that presented with severe monocular vision loss with photopsias, ring scotomas, abnormal ERGs, and a normal-appearing fundus [45, 47]. The sera from both patients also demonstrated antiretinal antibodies that specifically labeled the inner plexiform layer by indirect immunoperoxidase staining [45, 47]. Keltner and Thirkill in 1999 described eight patients with unexplained visual loss [46]. Seven of these cases were determined to have ARRON syndrome, and one of the eight had MAR [46]. Autoantibody reactions to the retina and optic nerve were detected in each case, including a common antibody reaction with the 22-kDa neuronal antigen [45, 46]. In 2002, Keltner and Thirkill evaluated 12 ARRON patients [42]. The described clinical findings included 11 of 12 who had optic nerve atrophy and 8 of 12 who had nonspecific retinal changes except for blood vessel attenuation in three patients [42, 45]. ERG abnormalities were present in ten patients [42]. Furthermore, there was no underlying malignancy in any of these patients, and systemic immunologic disease was present in 8 out of 12 patients [42]. Additional clinical findings included the presence of fine vitreous cells, and the visual fields displayed diffuse loss or constriction [42].

Suggestive diagnostic criteria for ARRON syndrome were described by Oyama et al. in 2009 and include four of the following features: visual loss as demonstrated either by visual acuity or by visual field examination, evidence of optic nerve or retinal abnormalities, no evidence of malignancy after extensive evaluation, and no identifiable cause for optic neuropathy and/or retinopathy [43]. Also, additional diagnostic evidence can include the presence of serum antibodies against retina and or optic nerve [43]. Screening recommendations for evaluation for an underlying malignancy can include dermatologic skin survey, colonoscopy, standard prostate screening, gynecologic examination, mammography, lumbar puncture, whole body imaging, and serum testing for recoverin and 62-kDa neuronal antigen called collapsin response mediator protein-5 (CRMP-5) [43]. The differential diagnosis for ARRON, therefore, includes similar clinical entities discussed earlier with the paraneoplastic retinopathies.

Several treatments for ARRON have been reported in the literature with variable success. The primary approach is often based upon treatment of any underlying systemic disorders. The goal of treatment for ARRON syndrome consists of suppressing the immune response [45]. Oral or intravenous corticosteroids are typically used as first-line therapy [45]. Depending on the response to corticosteroid treatment, cyclophosphamide, methotrexate, IVIg, and plasma exchange (PE) have been used singly or in combination as the next line of therapy [45]. Specifically, 70% of ARRON patients have been reported to require combination therapy [42]. In 2008, Barret et al. described a case of an ARRON patient with declining visual acuity, visual field, and color vision despite multiple treatment modalities including prednisone, methylprednisolone, IVIg, azathioprine, and methotrexate [45]. In this case, there was a successful response to plasma exchange (PE) followed by intravenous immunoglobulin (IVIg) and later PE maintenance therapy alone [45]. More recently, Oyama et al. in 2009 reported stabilization of clinical manifestations in a patient with ARRON treated with autologous hematopoietic stem cell transplantation (HSCT) [43]. In this case, the progressive hearing and visual loss was slowed by IVIG treatment; however, the peripheral symptoms continued to worsen [43]. The non-myeloablative HSCT regimen was utilized to treat this patient since an identical regimen had been used safely and with encouraging outcomes in systemic lupus erythematosus (SLE) and type I diabetes mellitus [43]. In this case, the HSCT was well tolerated, and there was an improvement in symptoms and reversal of declining visual fields and acuity [43]. There was also a reduction in the total number of antibodies after HSCT against both the retina and optic nerve [43]. As ARRON syndrome is newly described and often underdiagnosed, no treatment regimen has been proven optimal due to the

Table 15.1 Summary characteristics for autoimmune retinopathy and paraneoplastic syndromes

Conditions	Systemic associations	Clinical presentation	ERG findings	Antibody detection
CAR	Small cell lung, gynecologic, breast cancer (most common) [4]	Subacute, bilateral visual loss; entoptic symptoms; manifestations of rod and cone dysfunction; normal fundus early in disease course [1]	Abnormal scotopic and photopic response; a and b waves may both be flat	23, 46 (most common), 45, 60, 65, 44, 43, 63 kDa, TULP-1, PNR, CRMP-5-IgG [4]
MAR	Cutaneous malignant melanoma	Photopsias, near normal visual acuity, normal fundus (most common) [4]; symptoms usually present when melanoma is already diagnosed	Abnormal scotopic response with markedly reduced or absent dark adapted b wave	Autoantibodies to rod bipolar cells and dendrites in the outer plexiform layer [4]
ARRON	Systemic immunologic diseases (SLE, RA, ITP, psoriatic arthritis, thyroid disease, celiac sprue, Sjogren's syndrome) [30, 42, 45]	Similar to CAR and MAR in absence of malignancy; asymmetric visual acuity and visual field deficits [43]	Abnormal scotopic and photopic patterns (similar to CAR)	22 (most common), 23, 35, and 47 kDa [43, 44]

limited number of cases. Further studies will be needed to determine and evaluate for an effective long-term treatment approach.

Pearls

See Table 15.1.

- Autoimmune retinopathies and paraneoplastic retinopathies are rare ocular conditions with diverse and often subtle clinical and immunological features that require a high index of clinical suspicion.
- CAR is most frequently associated with small cell carcinoma of the lung, and antibodies are directed against both rods and cones resulting in ERG abnormalities in the majority of cases. Antibodies directed toward recoverin, a 23-kDa retinal protein, and 46-kDa retinal enolase are most commonly identified.
- The key diagnostic features with MAR are a history of cutaneous malignant melanoma, and a negative ERG pattern with antibodies being directed most commonly against rod bipolar cells. In both CAR and MAR syndromes, the fundus can appear normal in the early stage of the disease.
- ARRON typically presents with asymmetric visual loss, and antibodies are directed against the retina and/or optic nerve without the presence of an underlying malignancy. ERG findings may be similar to CAR. Autoantibodies reactive with the 22-kDa neuronal antigen are most commonly demonstrated.
- Many retinal antibodies involved in these autoimmune retinopathies likely remain to be identified.
- Future considerations are for standardization of assays to measure the presence and titers of antiretinal antibodies in order to enhance the clinical value of antibody testing for these conditions [48].

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Retinal and Choroidal Manifestations of Gastrointestinal Diseases

16

Francisco J. Rodriguez, Mariana Cabrera, and Alexander J. Brucker

Abstract

This chapter describes some of the gastrointestinal diseases that have ocular manifestations, especially in the retina and choroid. They include inflammatory bowel disease (IBD), Whipple's disease, pancreatitis, avitaminosis A, familial adenomatous polyposis, and zinc and copper deficiency. Their etiologies are diverse: IBD is thought to arise from an alteration in the immune response, Whipple's disease is caused by the bacteria *Tropheryma whipplei*, pancreatitis causes a vaso-occlusive retinopathy possibly arising from fibrin aggregates, and familial adenomatous polyposis is a genetic disorder. It is important to keep these diseases in mind, as they require specific treatments and in some cases may be the initial manifestation of a potentially fatal disease.

Keywords

Avitaminosis A • Congenital hypertrophy of the retinal pigment epithelium • Familial adenomatous polyposis • Inflammatory bowel disease • Nyctalopia • Pancreatitis • Posterior uveitis • Purtscher-like retinopathy • Vasculitis • Whipple's disease

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Introduction

Many gastrointestinal diseases have manifestations in the retina and choroid. Their physiopathology is related to the type of disease. Most present with nonspecific manifestations such as posterior uveitis, intraretinal hemorrhages, vasculitis, choroiditis, optic neuropathy, and vaso-occlusive phenomena. Most importantly, many patients exhibit ophthalmologic manifestations and symptoms before the systemic compromise is evident, and the ophthalmologic findings may be

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the key for obtaining a diagnosis. This is especially important as some of these diseases such as inflammatory bowel disease, pancreatitis, and Whipple's disease may be fatal if not treated.

Another important entity in this chapter is the retinal and choroidal manifestations of malabsorption syndromes, such as vitamin A deficiency, which is accompanied by nyctalopia. These manifestations are reversible with the supplementation of the specific vitamin or minerals, but an appropriate diagnosis needs to be made. These vitamin deficiency syndromes have become more prevalent in recent years in developed countries with the increase in bariatric surgery procedures, which are very often followed by malabsorption syndromes.

Many posterior segment inflammatory findings are often left as idiopathic, but it is important to keep in mind that they may be manifestations of gastrointestinal diseases. Because they are frequently nonspecific and variable, the clinician must have a high degree of suspicion regarding the possibility of any gastrointestinal disease, as different tests can be performed and specific treatment needs to be prescribed.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an immune-mediated chronic intestinal condition. It has been divided into two different types: ulcerative colitis (UC) and Crohn's disease (CD).

It is thought that the disease is brought about by an abnormal immune response to certain microorganisms in a person with a genetic predisposition. Both diseases consist of chronic inflammation of the colon but they have different characteristics. Ulcerative colitis involves the large intestine and the colon and is often most severe in the rectal area, which can cause frequent diarrhea. By definition, ulcerative colitis only involves the mucosa of the intestinal wall. Crohn's disease generally involves both the ileum and colon, usually in a discontinuous pattern. The inflammation in CD is transmural and can be associated with granuloma formation, severe scarring, and fistulas (not generally found in UC) [1].

Epidemiology

The incidence of IBD varies depending on the location and type of population. It is found more frequently in Europe and North America. In North America, the incidence is estimated at 1.3–2.2 cases per 100,000 persons/year for ulcerative colitis and 3.1–14.6 cases per 100,000 persons/year for Crohn's disease. Prevalence rates for UC in North America are estimated at 37–246 cases per 100,000 persons/year and at 26–199 cases for CD [2]. Incidence and prevalence rates in Europe are similar. IBD was thought to be rare in other locations, but its incidence is increasing in areas such as Japan, South Korea, Singapore, India, and Latin America, especially referring to cases of UC. The mortality ratio for UC and CD has been estimated to be 1.37 and 1.51, respectively based on a Swedish population [2]. Mortality generally occurs from complications in the first years of the disease or as a result of late-stage colon cancer.

The peak age of onset is 15–30 years, although there is a second peak from ages 60 to 80. In Crohn's disease, men and women are equally affected, whereas in UC, men are slightly more affected (1.2–1.8 men per woman). Prevalence of the disease is also related to population type: Jewish populations have a higher prevalence, especially Ashkenazi Jews. It is also more frequently found in urban areas as opposed to rural populations, especially in people of higher economic status. Smoking has a different effect on the risk of developing IBD: nonsmokers have a greater risk for developing UC, whereas smokers have a twofold risk of developing CD. Oral contraceptives also seem to increase the risk of CD (odds ratio: 1.4). Appendectomy increases the chance of having CD but is protective against UC. IBD is frequently associated to immune diseases such as psoriasis, ankylosing spondylitis, and primary sclerosing cholangitis.

IBD is most likely related to certain genetic susceptibilities and therefore runs in families. A first-degree relative of a patient has a 10% chance of developing the disease, and this figure rises to 36% if the subject is the child of two parents with IBD.

A hereditary pattern seems to be more present in CD than UC [3].

Pathophysiology

The normal intestine has a specific immune state in which the mucosa is usually unresponsive to luminal contents because of oral tolerance, as opposed to exposure to the same antigens subcutaneously or intramuscularly. This is regulated by anergic T cells or suppressor CD4 lymphocytes. In IBD, the key pathologic finding is infiltration into the lamina propia of immune cells, both related to the cellular response (macrophages, neutrophils, natural killer T cells) and the humoral response (T and B cells). Additionally, there is a high concentration of proinflammatory substances, such as tumor necrosis factor α (alpha) (TNF-α), cytokines, and interleukins. It appears that both in UC and CD, a genetic predisposition results in activation of the immune response by CD4 T lymphocytes, as a response to normal intraluminal content. Once initiated, this immune response is perpetuated by T cell activation. In a normal immune response, as the infection subsides, anti-inflammatory substances are secreted to regulate the reaction and avoid excessive tissue damage. In IBD, there is an imbalance between pro- and anti-inflammatory agents, and abnormal reaction continues uncontrolled [1].

Some authors suspect an infectious etiology for IBD. There have been several agents implicated in the abnormal activation of the immune system. These include pathologic organisms such as *Salmonella sp.*, *Shigella sp.*, *Campylobacter sp.*, *Clostridium difficile*, *Mycobacterium paratuberculosis*, and *Escherichia* among others. This idea is supported by the improvement of symptoms by different nutritional plans and with agents that modify the normal intestinal flora (antibiotics, antihelminths). Psychosocial factors, such as stress, are also related to exacerbation of the symptoms.

Various genes have been implicated in the development of IBD. The gene NOD2 is a sensor of peptidoglycans present in bacterial cell walls and has been associated especially with Crohn's disease. *ATG16L1* and immunity-related GTPase M protein (*IRGM*) have also been associated with CD. Alterations in the interleukin-10 (IL-10) receptor have been related to CD, whereas mutations in the IL-23 receptor and signaling pathway have been related to both UC and CD.

Clinical Presentation

Ulcerative Colitis

Patients usually present with diarrhea, rectal bleeding, tenesmus, passage of mucus or pus, and abdominal pain. The severity is very variable, and the symptoms usually last from weeks to months. Complications range from massive hemorrhages (1% of patients) to an acute dilation of the transverse colon, referred to as "toxic megacolon," which may end up in a perforated bowel and the need for urgent surgery. About 5–10% of patients develop strictures and rarely present anal fissures or abscesses.

Crohn's Disease

This form starts with similar symptoms of chronic bowel inflammation. However, as opposed to ulcerative colitis, CD progresses to one of two patterns of disease: a fibrostenotic-obstructing pattern or a penetrating-fistulous pattern. Complications include a small number of free perforations (1–2%) but very frequent fistula formation. Additionally, 10–30% of patients will develop pelvic or intra-abdominal abscesses, usually needing resection of the compromised bowel portion. They can also present with severe hemorrhage, malabsorption, and severe perianal disease.

Between 25% and 36% of patients have extraintestinal complications, which include cutaneous, articular, hepatobiliar, and ocular manifestations [4]. Sacroiliitis (14%) and peripheral arthritis (10.7%) were found to be the most frequent in a case study [5].

Ocular Manifestations

Ocular manifestations occur in approximately 6% of patients [6] with CD and 8% of patients with UC [7]. The patient with ocular involvement usually either has a diagnosis of IBD or has gastrointestinal symptoms. However, it is important to know that ocular manifestations may be the presenting feature of the disease [8]. Ocular involvement can be independent of the severity of the disease at the time [9] and usually presents within the first years of diagnosis [6].

Most of the ocular symptoms in IBD relate to the anterior segment and ocular surface: mainly anterior

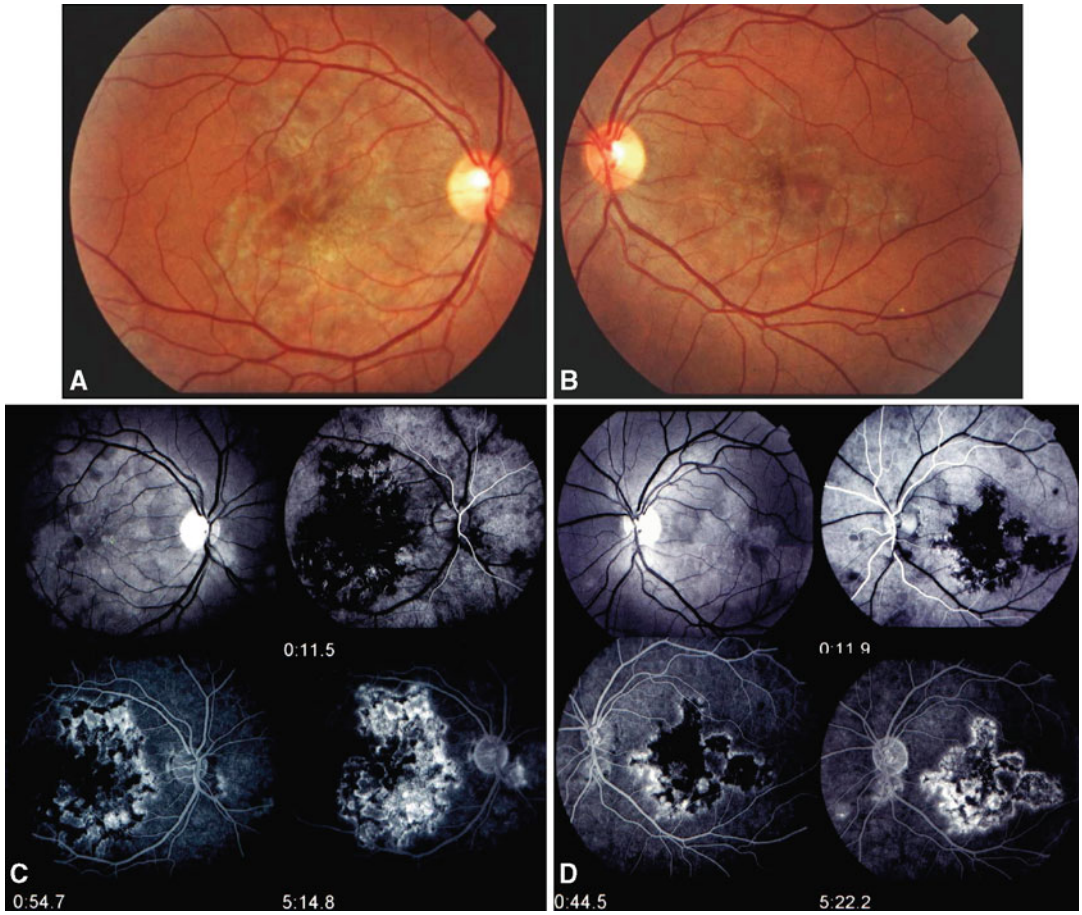

Fig. 16.1 (**a**, **b**) A 25-year-old female complains of decreased visual acuity in both eyes. Past ophthalmological history was positive for anterior uveitis in both eyes, which resolved with topical steroids. At examination, visual acuity was 20/50 in both eyes. Fundus examination disclosed nonactive, confluent, plaque-like lesions involving the macula in both eyes. The patient was lost for follow-up. (**c**, **d**) Fluorescein angiography shows early hypofluorescent lesions with late hyperfluorescence and staining in both eyes. (**e**, **f**) Five years later, the patient returned with a diagnosis of Crohn's disease. Visual acuity was 20/25 in both eyes. Fundus examination showed nonactive lesions in both maculas. (**g**, **h**) Fluorescein angiography confirmed nonactive lesions in the macula in both eyes

uveitis, conjunctivitis, corneal ulcers, and episcleritis [6]. The most frequent ocular manifestation is anterior uveitis, often coinciding with acute gastrointestinal symptoms. It usually presents as a mild anterior nongranulomatous uveitis (60% of the cases), but it can present as panuveitis or retinal vasculitis in up to 30% of the time [10]. In patients with IBD, the presence of uveitis is closely related to HLA-B27 and the appearance of erythema nodosum and seronegative arthritis [11]. Women are at much higher risk of developing uveitis in IBD [9]. Episcleritis has been reported in up to 29% of patients, often related to the severity of the disease, resolving when the underlying cause is treated [12]. Scleritis has been reported in up to 18% of the cases with much more serious consequences [10, 12].

Posterior Segment Lesions

There have been several reports of IBD associated with vitritis and retinitis, often with papillitis [13, 14]. Posterior uveitis was as frequent as 10% in one case series [15]. Features of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) (Fig. 16.1a–h) have been described, mainly consisting of choroidal infiltrates responsive to steroids and patches of choroidal inflammation associated

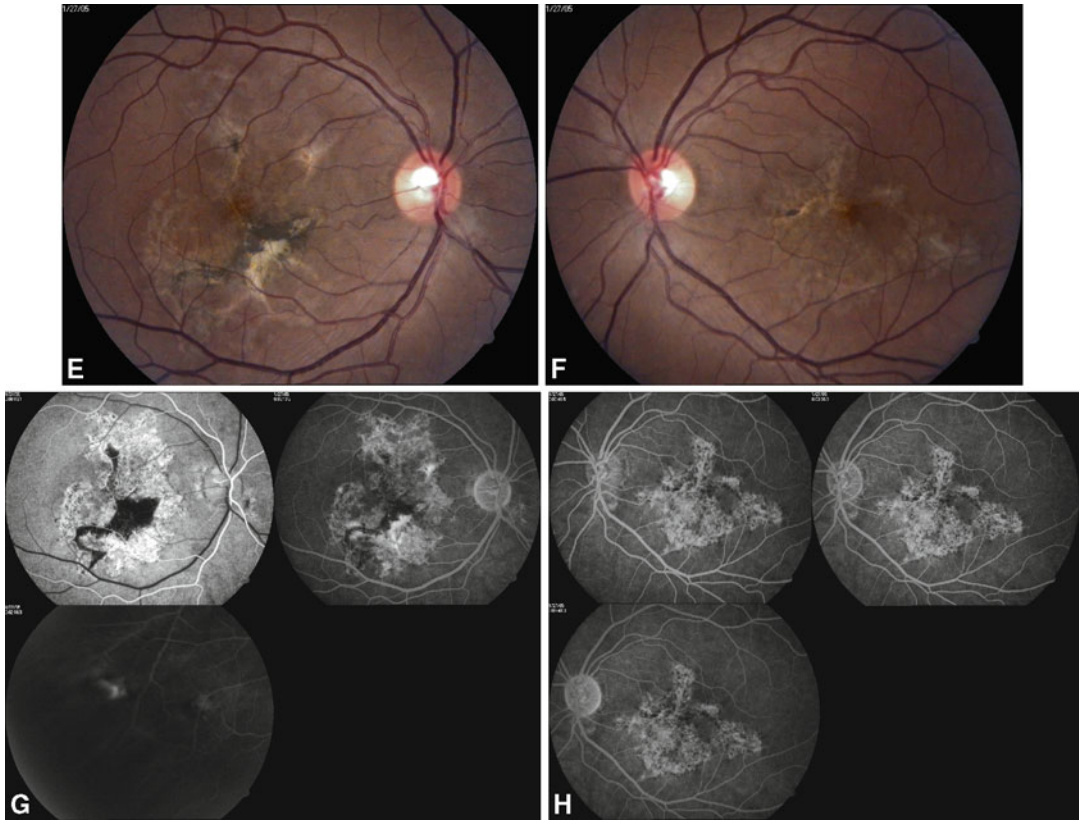

Fig. 16.1 (continued)

with serous retinal detachments [16]. Posterior scleritis has also been described associated with choroidal infiltrates and retinal detachment [12]. Other manifestations include central serous chorioretinopathy, multifocal choroiditis [17], serpiginous choroidopathy [18], retinitis, macular edema, and retinal telangiectasias.

Retinal vascular disease has also been described, mainly branch retinal artery occlusion [19], central retinal artery occlusion, retinal vasculitis [20] (Fig. 16.2a, b, c), and ischemic optic neuropathy [21]. These events have been attributed to a likely prothrombotic state caused by activation of the coagulation cascade. Secondary retinal neovascularization has also been described [22].

Treatment of Ocular Manifestations

Patients with uveitis, scleritis, and other anterior segment inflammation usually respond to steroids—either topical, periocular, or systemic. In some cases, the inflammation is resistant to steroids, in which case other immunosuppressive medications should be used. Patients with uveitis and HLA-B27 usually have a more severe disease, less responsive to steroids [23].

For posterior segment inflammation, systemic steroids are the initial therapy and may require use of long-term immunosuppressant "steroid-sparing agents." Inflammation may subside with resection of the affected bowel segment, although ocular inflammation is not an indication for surgery.

Steroid-sparing agents such as azathioprine, mycophenolate, and methotrexate may need to be used chronically, although special attention needs to be paid to their multiple serious side effects (bone marrow depression, pancreatitis, hepatitis, hepatic fibrosis, opportunistic infections). Cyclosporine and tacrolimus are T cell inhibitors that have been used in cases of both uveitis and scleritis [24, 25].

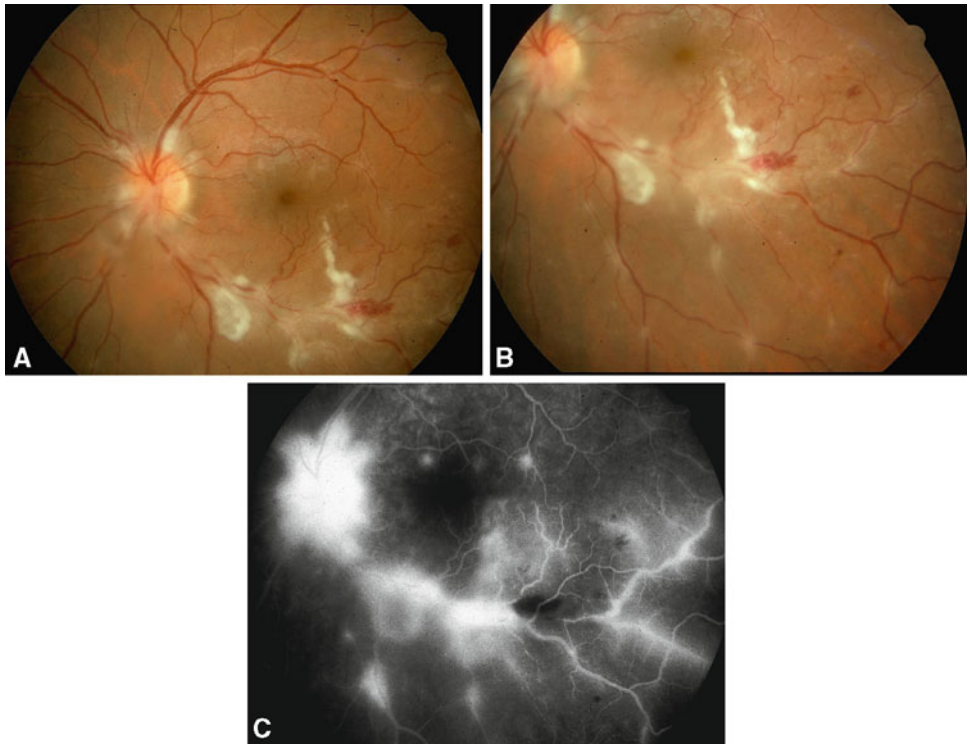

Fig. 16.2 (**a**, **b**) Retinal vasculitis and ischemia in a patient with Crohn's disease. Observe cotton-wool spots and intraretinal hemorrhages. (**c**) Late phase of fluorescein angiography shows staining of the retina vessels, areas of ischemia also observed in the color photographs and optic disk staining

Anti-tumor necrosis factor (TNF) monoclonal antibodies (infliximab, etanercept, adalimumab) have been proven effective to regulate the immune response in IBD and reestablish the anti-inflammatory effects of T cells. They are particularly useful in patients with uveitis or scleritis that have been refractory to other types of treatment. Unfortunately, their use is limited by the high cost and high rate of reactions upon infusion (up to 20%), serious infections (particularly tuberculosis), and hypersensitivity reactions after multiple doses.

Other strategies include use of antibiotics for active infections, or agents such as metronidazole or ciprofloxacin, which have been shown to alter the intestinal flora and reduce inflammation. Nutritional therapies have also been shown to alter the immune response. They have been proven more useful for CD than UC.

Finally, nearly half the patients with extensive chronic UC undergo surgery within the first 10 years of their illness. Many different surgical techniques are used dependent upon the extent and location of the inflammation, but this information is beyond the scope of this chapter.

Whipple's Disease

Whipple's disease is a rare, multisystemic chronic infectious disease that primarily involves the gastrointestinal tract and usually manifests as malabsorption, weight loss, diarrhea, and nondeforming seronegative polyarthralgias. It can manifest with extraintestinal involvement, compromising the central nervous system, lungs, heart, and eyes.

Whipple's disease was first described by George Hoyt Whipple in 1907, but it was not until almost a century later that the causative organism and the pathogenesis of the disease

were discovered. Whipple's disease is quite rare, and its incidence is estimated at less than one case per million persons/year [26]. A postmortem study revealed a prevalence of 0.1%. A previous study reported 18–30 systemic cases per year/100,000 people. Most of those affected are Caucasian middle-aged men.

The classic, previously described symptoms present in approximately 85% of patients, with 15% of patients having atypical manifestations. Without treatment, Whipple's disease is ultimately fatal. Even with antibiotic treatment, 2–33% [27] of cases relapse, usually with neurologic involvement and a poor prognosis.

Whipple's disease is caused by infection by the gram-positive bacillus *Tropheryma whipplei* [28]. However, there appears to be a certain genetic susceptibility for the actual disease given the very specific type of population that is affected (middle-aged Caucasian men) and the finding of healthy subjects with *T. whipplei* in their saliva and stools. Data regarding the prevalence of *T. whipplei* in healthy subjects is controversial as the results are very variable, although the latest data seems to indicate a prevalence of *T. whipplei* in 0.6% of saliva samples and 1.5% in stool samples. HLA-B27 has been related to this susceptibility, but no causative relationship has been established.

Pathologic studies of Whipple's disease patients usually show tissue with a massive infiltration by macrophages. In healthy subjects, the bacillus multiplies in macrophages but not monocytes, whereas in affected individuals, it appears to replicate in both types of cells. Additionally, it is believed that patients with Whipple's disease may have antigen-presenting cells that do not process *T. whipplei* properly and therefore cannot contain it. Various interleukins and cytokines have been implicated in this abnormal reaction. An increase in interleukins 10 and 16 and a decrease in γ (gamma) interferon and interleukin-12 have been associated with an abnormal performance of antigen-presenting cells [29]. Additionally, *T. whipplei* has been found to replicate within macrophages and monocytes that have been deactivated with interleukin-16.

Diagnosis

Up until a few years ago, the diagnosis was made with pathologic studies of biopsy samples, mainly staining with periodic acid-Schiff (PAS). The diagnosis is made by demonstrating intracellular PAS-positive rod-shaped bacillary bodies within macrophages. At least five different samples are needed from different parts of the duodenum. PAS staining can also be performed in any of the suspected tissues (synovial fluid or tissue, cerebrospinal fluid, hepatic biopsy, aqueous humor). Polymerase chain reaction (PCR) is beginning to be used more frequently for the diagnosis and especially for the follow-up and response to treatment. However, PCR alone does not make a definitive diagnosis due to the large number of false positives. Both PCR and PAS staining need to be positive to confirm the diagnosis.

Extraintestinal Manifestations

Central Nervous System

Neurologic manifestations are found in 6–63% of patients [30]. They are very diverse, although most (71%) present with some kind of cognitive change. Patients can also present with depression and personality changes. Neuro-ophthalmologic findings such as supranuclear ophthalmoplegia are frequently seen, as well as ptosis, nystagmus, and other alteration of the extraocular muscles. Patients also present with generalized motility alterations, such as myoclonus. Hypothalamic dysfunction has also been described. The prognosis is poor with a mortality rate of 25% in 4 years.

Others

Joint involvement is seen in 65–90% of cases. It usually manifests as intermittent polyarthralgia and/or polyarthritis.

Cardiac involvement, most frequently pericarditis, is seen in over 50% of patients. Importantly, *T. whipplei* has been associated with blood culture–negative endocarditis, a difficult diagnosis to make.

Pulmonary involvement occurs in an estimated 30–40% of patients, manifested as pleural effusion,

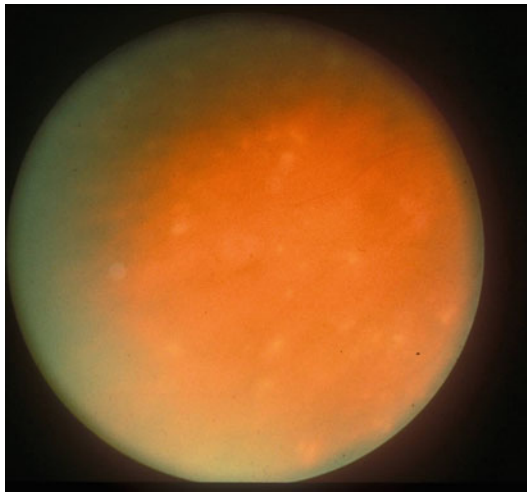

Fig. 16.3 Patient with Whipple's disease. Photograph shows multiple faint, white choroidal lesions (Courtesy of Lawrence A. Yanuzzi, M.D.)

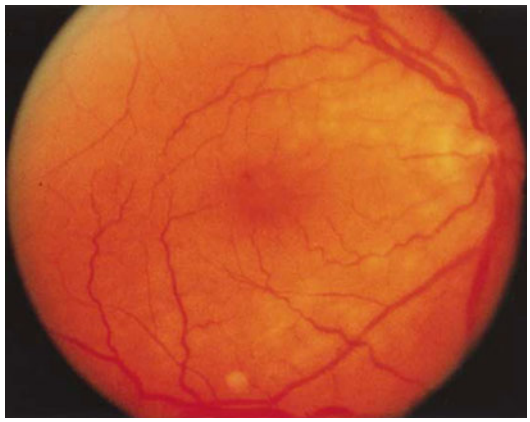

Fig. 16.4 Patient with Whipple's disease. Photograph shows multiple faint, white choroidal lesions (Reprinted with permission from Chan RY, Yannuzzi LA, Foster CS. Ocular Whipple's disease: earlier definitive diagnosis. Ophthalmology. 2001;108:2225–2231)

pulmonary infiltration, or granulomatous mediastinal adenopathies [26]. Occasionally, it presents with cutaneous and renal manifestations, among others.

Ocular Manifestations of Whipple's Disease

The first case of ocular compromise in Whipple's disease was published in 1949 by Jones and Paulley. Ocular involvement usually occurs late in the disease in patients with both gastrointestinal and neurologic symptoms. It presents in approximately 10% of patients with classic Whipple's disease [31, 32]. Patients complain of blurred vision or visual loss. The ophthalmologic exam may reveal any of the following: keratitis, uveitis, vitritis, retinal hemorrhages, retinitis (Fig. 16.3), choroiditis (Fig. 16.4), and even optic atrophy.

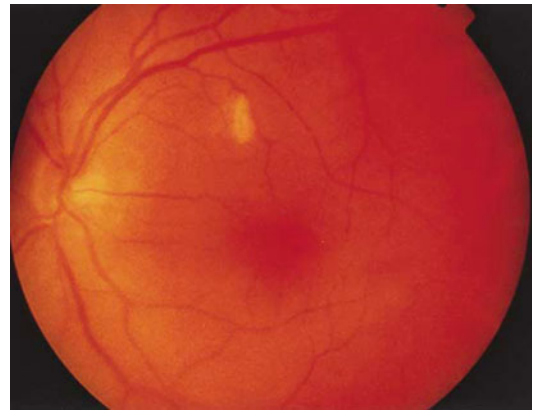

Fig. 16.5 Patient with Whipple's disease. Cotton-wool spot in superior macula (Reprinted with permission from Chan RY, Yannuzzi LA, Foster CS. Ocular Whipple's disease: earlier definitive diagnosis. Ophthalmology. 2001;108:2225–2231)

Anterior or posterior uveitis is the most frequent finding and is usually bilateral and chronic in nature [31, 32]. Retinal involvement can also include retinitis, exudates, retinal capillary occlusion (Fig. 16.5), and choroidal folds [33].

Vitreous or aqueous humor samples may make the definitive diagnosis in patients with few systemic manifestations [34].

Treatment

Death was certain from Whipple's disease before the use of antibiotics. Tetracycline was the mainstay of therapy initially, but a high recurrence rate has been documented (28%), especially since it does not penetrate the blood-brain barrier.

Historically, the most frequently used treatment was oral administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole

twice per day for 1–2 years, usually preceded by parenteral administration of ceftriaxone (2 g daily) for 2 weeks. However, this regime is not always effective and recurrence has been documented. Additionally, trimethoprim has been proven ineffective against *T. whipplei* in in vitro studies.

Therefore, new evidence recommends the use of a different scheme: doxycycline (200 mg per day) and an alkalinizing agent, hydroxychloroquine (200 mg three times per day), which has been the only combination to prove bactericidal against *T. whipplei*.

In patients with neurologic involvement, the use of sulfamethoxazole or sulfasalazine has been recommended. Treatment duration is not standard, but at least 12–18 months of treatment is recommended. Follow-up should be performed with PCR as it quickly becomes negative if the regime is effective.

Avitaminosis A

Vitamin A is a fat-soluble vitamin that exists in three forms: retinoic acid, retinol, and retinaldehyde. It is not synthesized in the body, which is why it has to be obtained from different types of foods. It is essential for the formation of rhodopsin, the visual pigment of photoreceptors. Several conditions cause vitamin A deficiency: malabsorption, malnutrition, and conditions that impair vitamin A metabolism, such as alcoholism and liver diseases. Bariatric surgery is quickly becoming an important cause of vitamin A deficiency because of the alteration in nutrient absorption. Vitamin A deficiency has a prevalence of 52% in 1 year and 69% 4 years after bariatric surgery [35].

In the presence of early vitamin A deficiency, its demand can be met by the liver and blood, which contain significant amounts of the vitamin. With prolonged deficiency, the outer segments of photoreceptors start to shrink and are lost. At this point, there is a loss of visual sensitivity, and patients complain of night blindness (nyctalopia) as the first symptom [36]. Up to 2.8% of all patients who undergo bariatric surgery complain of nyctalopia. Other ocular symptoms include bilateral conjunctival and corneal xerosis, with scarring and the presence of Bitot's spots, which are the buildup of keratin debris located superficially in the conjunctiva and are oval, triangular, or irregular in shape [37].

The fundus examination of these patients will reveal multiple white or gray-white spots scattered in the peripheral retina that will resolve with supplementation. The diagnosis is made based on an electroretinogram (ERG) and dark adaptometry. Dark adaptometry will demonstrate elevated rod and cone thresholds, especially for rods. The ERG will reveal a reduced or undetectable rod ERG and a cone ERG with reduced amplitude and prolonged latency periods. S-cone function is also undetectable and is the last to recover [38].

Symptom improvement and changes in the ERG are generally seen within 1–3 days after supplementation. Peripheral rods and cones recover first, followed by macular photoreceptors, and S-cone function is the last to recover. Macular function may not recover until the 12th day and may remain abnormal for more than 6 months.

The reason why rods are more affected is not well known, but some authors suggest that because cones synthesize their pigment at a faster rate, they do so at the expense of the rods. Another theory states that there might be an alternative pathway for opsin photopigment regeneration involving Müller cells that could make cones less susceptible to vitamin A deficiency [38].

Other Deficiencies: Zinc and Copper

A case report described bilateral whitening of retinal layers simulating a cherry-red spot that returned to normal after supplementation of zinc and copper. Nyctalopia has also been reported in patients with chronic pancreatitis, alcoholic cirrhosis [39], and hemodialysis, which improved upon supplementation with zinc. This manifestation may be due to an alteration in the zinc-dependent enzyme alcohol dehydrogenase which catalyzes an important step in the rhodopsin pathway [40]. Patients with zinc deficiency also exhibit a depressed ERG, especially in scotopic conditions, suggesting rods may be more susceptible to zinc deficiency than cones.

Pancreatitis

In 1912, Othmar Purtscher described an entity consisting of multiple white retinal patches and peripapillary retinal hemorrhages in five patients with visual loss after head trauma. A similar picture has been observed as a rare complication of acute pancreatitis and has thus been referred to as "Purtscher-like retinopathy." The incidence of the disease is unknown, but fewer than 60 cases have been published. It has been reported secondary to both acute alcoholic and nonalcoholic pancreatitis [41], systemic lupus erythematosus, thrombocytopenic purpura, renal failure, amniotic fluid or fat embolism. It usually presents as a sudden unilateral or bilateral decrease in vision, and a relative afferent pupil defect is often found. The episode is usually associated with symptoms such as epigastric pain, vomiting, fever, and elevated amylase and lipase levels. The retinopathy may precede the diagnosis of pancreatitis by as much as 6 months [42].

Fundus examination reveals numerous white retinal patches, superficial retinal hemorrhages, and cotton-wool spots around an apparently normal optic disk. Other findings include dilated and tortuous vessels, disk edema, and serous retinal detachment [7]. It usually spares the periphery. Fluorescein angiography can reveal focal areas of arteriolar obstruction, patchy capillary nonperfusion, disk edema, and dye leakage from retinal arterioles, capillaries, and venules [43].

The pathogenesis of this condition is unknown. Current evidence suggests that thrombi consisting of leukocytes form when proteolytic enzymes are released into the circulation as a result of pancreatic injury. This causes activation of the complement cascade and the formation of leukocyte, platelet, and fibrin aggregates. An experimental clinicopathologic study revealed occluded retinal arterioles and choroidal vessels with damage to the photoreceptors [44].

The severity of the retinopathy appears not to be related to the severity of the pancreatitis. Management consists in treatment of the underlying pathology. Clinically, the retinal lesions resolve over a period of weeks to a few months. After resolution, the fundus may appear normal, but pigment migration and optic atrophy can occur. Although visual acuity may remain reduced, it will likely return to normal or near normal. Systemic steroids have been proposed for the treatment of traumatic Purtscher's retinopathy, with positive results in one case report. The proposed mechanism of action is to block C5a-induced granulocyte aggregation and prevent the formation of thrombi, but the evidence is lacking to recommend this type of therapy.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease in which adenomatous polyps form in the colon and rectum. To make the diagnosis, more than 100 polyps have to be found. These usually appear in adolescence and almost invariably become malignant by age 50. It affects one in 7,500–10,000 people and accounts for approximately 1% of all colorectal cancers. The disease is due to an alteration in the adenomatous polyposis coli (APC) gene, a tumor suppressor gene on the long arm of chromosome 5 (5 q21-q22) [45].

FAP can manifest with extracolonic involvement (Gardner's syndrome). The most frequent is congenital hypertrophy of the retinal pigment epithelium (CHRPE). Other manifestations include gastroduodenal polyps, osteomas, dental abnormalities, and intra-abdominal desmoid tumors.

Congenital hypertrophy of the RPE was first described by Blair and Trempe in 1980 [46]. The lesions are congenital and are variable in number: from 1 to 40 in both eyes, with an average of 6 in each eye. This type of congenital hypertrophy of the retinal pigment epithelium is better known as "bear tracks." They are bilateral in 86% of cases [47]. Most lesions are round, small, and pigmented (Fig. 16.6), although they can present with a depigmented halo and have a variable size and variable degree of pigmentation. They can be present in normal individuals but are always less than 3 in number. They do not affect visual acuity but do create a scotoma in the area of the lesion as a result of photoreceptor atrophy. Histopathologic studies

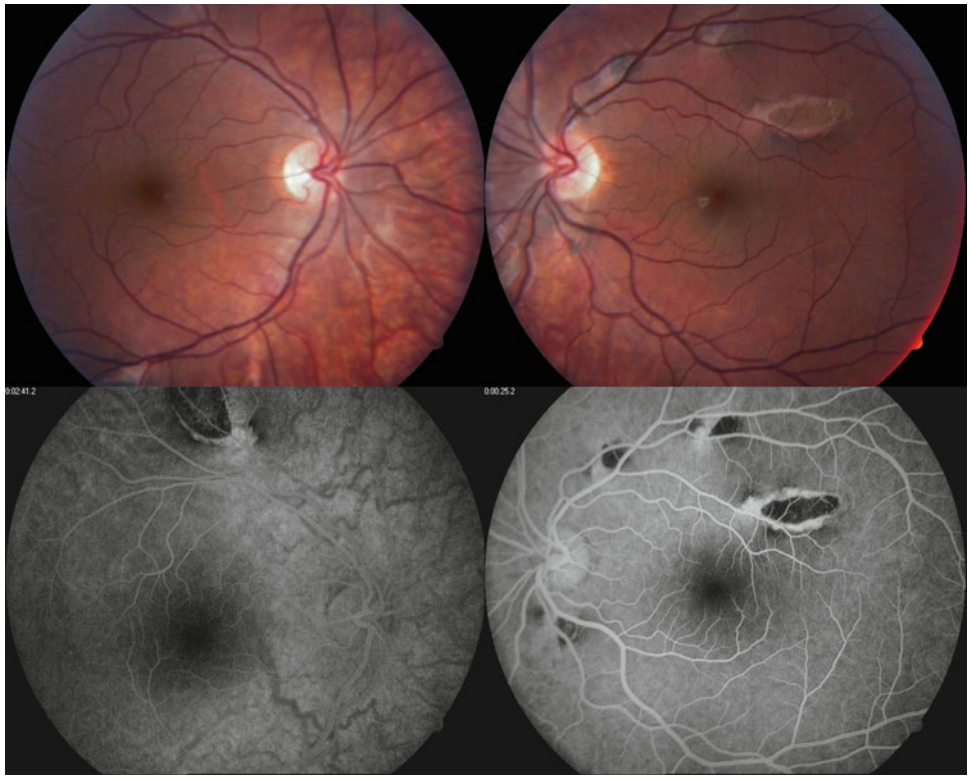

Fig. 16.6 Multiple lesions of congenital hypertrophy of the RPE associated with familial adenomatous polyposis and Gardner's syndrome in a 19-year-old male (Courtesy of Ricardo Infante, M.D.)

have shown these lesions to correspond to benign hamartomatous malformations of the RPE.

CHRPE in familial adenomatous polyposis has been extensively studied because of the high degree of genotype-phenotype correlation that it exhibits. More than two-third of patients with FAP exhibit CHRPE, and the characteristics of the lesions are very similar within a family. Because they are congenital, they provide a useful tool for diagnosis and genetic counseling. For example, in fundus-positive families, the finding of retinal lesions will have a positive predictive value of 100%, whereas no retinal lesions will mean that the gene has not been inherited. Additionally, depending on the characteristics of the lesions, each type is being traced to a different location on the APC gene and correlated with a specific severity/prognosis for the disease [48]. This means that in the future, a prediction of the presence and characteristics of the disease may be made based mainly on the characteristics of the fundus lesions.

Controversies and Perspectives

Gastrointestinal diseases with choroidal and retinal manifestations form a very diverse group of diseases, from autoimmune, to infectious, to related to malabsorption. Because they are relatively rare, their pathogenesis and treatment are not fully understood.

Inflammatory bowel disease still remains a mystery regarding its pathogenesis. Various theories have been proposed, including abnormal antigen-presenting cells, specific microorganisms, and genetic mutations. Various factors have also been implicated and include smoking or not smoking, HLA-B27 positivity, and stress. Until this is fully known, treatment will not be completely effective as it is not necessarily targeting the mechanism of disease. Actual treatments include sulfasalazine, systemic steroids, steroid-sparing immunomodulators, anti-TNF monoclonal antibodies, nutritional

modifications, and even some antibiotics and antihelminths. Despite the many treatments available, IBD patients often require extensive surgeries and many still die from the disease. Future research is directed towards a larger understanding of the pathogenesis and finding a more effective treatment.

Our knowledge of Whipple's disease has increased greatly in the last decade, but despite treatment, recurrences are still frequent. Future directions are directed towards a more effective antibacterial treatment and more reliable tests for follow-up, such as PCR. Additionally, prospective lines of research include determining and understanding why some subjects are susceptible to the bacillus, and some never develop the disease.

Vitamin and mineral deficiencies are still quite prevalent in some developing countries, but bariatric surgery has created a whole new group of subjects with malabsorption syndromes, especially in developed countries. Future directions with this condition include better management of postoperative nutrition in these patients, and possibly the implementation of ophthalmic evaluation in these patients, as their risk of avitaminosis (specifically for vitamin A) is over 50%. Functional studies in these patients have also provided more information into the physiology of photoreceptors and their metabolic pathways.

Regarding familial adenomatous polyposis, the finding of congenital hypertrophy of the RPE is becoming very important for genetic counseling. Future research is directed towards linking specific lesion characteristics with specific mutations. In the future, a fundus exam could provide information not only regarding the diagnosis but also regarding the course and prognosis of the disease.

Research regarding immunologic susceptibilities will also be very useful in the diagnosis and treatment of these diseases. As stated in this chapter, patients with specific markers in human leukocyte antigens (HLA) such as HLA-B27 may have a worse prognosis or be more at risk for a specific manifestation. Therefore, more knowledge regarding the role of HLA in these diseases may help the physician give a more accurate diagnosis and prognosis, and in the future, a more specific treatment may be indicated in subjects with these findings.

Focal Points

Choroidal and retinal manifestations of gastrointestinal diseases may precede other systemic symptoms and are usually very nonspecific. Most present as anterior or posterior uveitis. It is very important to determine the etiology as their treatments are very different (antibiotics, vitamin supplementation, steroids). Additionally, some of these diseases can be fatal (inflammatory bowel disease, pancreatitis, Whipple's disease) and a more prompt diagnosis and treatment can lead to a better prognosis.

The most common ocular manifestation of inflammatory bowel disease is anterior nongranulomatous uveitis. In the posterior segment, it can present as vitritis, retinitis, papillitis, and posterior uveitis. Retinal vascular occlusion and vasculitis may also be present, among many other nonspecific findings. They may be present in as much as 10% of patients.

Whipple's disease is caused by the bacillus *Tropheryma whipplei* and consists of gastrointestinal symptoms associated with seronegative polyarthralgias. Approximately 10% of patients with Whipple's disease have ocular manifestations. These include keratitis, uveitis, vitritis, choroiditis, and retinitis.

Patients with avitaminosis A may present with corneal and conjunctival xerosis and nyctalopia. Multiple white spots may be seen in the fundus, and the ERG will show a decrease in rod and cone function. The condition is reversible with vitamin supplementation.

Pancreatitis may be accompanied by a Purtscher-like retinopathy, showing large areas of hemorrhages and ischemia, probably caused by vascular thrombosis by fibrin and leukocyte aggregates. The retinopathy may precede the gastrointestinal manifestations and could be important in providing either preventive or very early treatment.

Familial adenomatous polyposis is often associated with congenital hypertrophy of the RPE,

"bear tracks." If the retinal lesions are present, the diagnosis is made even before the appearance of polyps in a patient with family history. The lesions have become very useful for genetic counseling.

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Fundus Manifestations of the Oculoneurocutaneous Syndromes (Phakomatoses)

17

Jerry A. Shields and Carol L. Shields

Abstract

The oculoneurocutaneous syndromes have fundus findings that are fairly consistent, and the ophthalmic clinician should be able to recognize them and be aware of their ocular complications and system associations. The syndromes described herein include tuberous sclerosis complex (TSC), neurofibromatosis (NF), von Hippel-Lindau (VHL) syndrome, Sturge-Weber (SW) syndrome, Wyburn-Mason (WM) syndrome, and oculoneurocutaneous cavernous hemangiomatosis.

Keywords

Neurofibromatosis • Oculoneurocutaneous cavernous hemangiomatosis • Oculoneurocutaneous syndromes • Phakomatoses • Retinal racemose hemangioma • Sturge-Weber syndrome • Tuberous sclerosis complex • von Hippel-Lindau syndrome • Wyburn-Mason syndrome

Introduction

The oculoneurocutaneous syndromes (ONCS) are a group of disorders characterized by systemic hamartomas of the eye, brain, skin, and sometimes the viscera [1–38]. The term "phakomatoses," previously used to designate these entities, is nonspecific and is used less often in the literature. As a result, we have chosen to group these entities under the rubric oculoneurocutaneous syndromes (ONCS), which more accurately reflects their true nature. However, we realize that better terminology may be adopted in the future when the genetics of these conditions are better understood. The syndromes described herein include tuberous sclerosis complex (TSC), neurofibromatosis (NF), von Hippel-Lindau (VHL) syndrome, Sturge-Weber (SW) syndrome, Wyburn-Mason (WM) syndrome, and oculoneurocutaneous cavernous hemangiomatosis. This chapter discusses these syndromes with emphasis on their fundus manifestations, in keeping with the goals of this textbook. Although the genetics, central nervous system (CNS), dermatological,

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and systemic features of these syndromes are mentioned briefly, they are discussed in more detail in recent textbooks [1–3].

Tuberous Sclerosis Complex (Bourneville's Syndrome)

Definition

Tuberous sclerosis complex (TSC) is characterized by retinal astrocytic hamartomas, cutaneous abnormalities, CNS astrocytomas, and internal tumors such as cardiac rhabdomyoma, renal angiomyolipoma, and other tumors [1–9]. It is best known to produce a triad of adenoma sebaceum (cutaneous angiofibromas), seizures, and mental deficiency.

Demographics

The incidence of TSC is about 1 in 10,000 [5]. Although TSC usually is diagnosed during the first few years of life, it has occasionally been recognized in patients as young as 1 month of age or as old as 50 years. This syndrome has been identified in all races, and there is no predilection for gender.

Genetics

Most evidence suggests that TSC is transmitted by an autosomal dominant mode with incomplete penetrance. In many cases, the family history is unremarkable and examination of family members is normal. Such patients are considered to be sporadic mutations. About half of the families show linkage to chromosome 9q34 and about half to chromosome 16p13 [1].

Fundus Manifestations

The retinal astrocytic hamartoma is the characteristic fundus lesion of TSC (Figs. 17.1 and 17.2) [1–3]. However, an identical lesion occasionally is found in patients who have no other clinical or genetic evidence of TSC. In either case, a small noncalcified tumor can be extremely subtle and appear only as ill-defined translucent thickening of the retinal nerve fiber layer. A slightly larger tumor is more opaque and appears as a sessile white lesion at the level of the nerve fiber layer of the retina (see Fig. 17.1). The calcified variant contains characteristic dense yellow, refractile, structures that resemble fish eggs or tapioca (see Fig. 17.2). Although it is generally stable and does not usually cause serious complications, it can occasionally produce retinal traction or vitreous hemorrhage. Retinal astrocytic hamartoma generally is a small asymptomatic lesion that does not show enlargement. However,

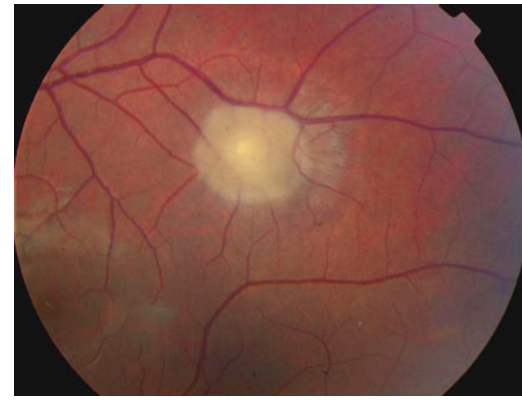

Fig. 17.1 Tuberous sclerosis complex. Noncalcified retinal astrocytic hamartoma

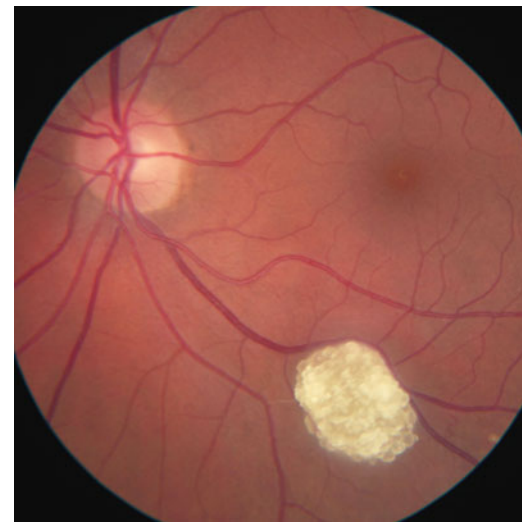

Fig. 17.2 Tuberous sclerosis complex. Calcified retinal astrocytic hamartoma

an aggressive variant has recently been identified in which the lesions show marked progression, with total exudative retinal detachment and neovascular glaucoma, sometimes necessitating enucleation of the eye [9].

Occasionally, ancillary studies such as fluorescein angiography and ultrasonography assist in the diagnosis of retinal astrocytic hamartoma. With fluorescein angiography, the tumor is relatively hypofluorescent in the arterial phase. A network of fine blood vessels is apparent in the venous phase. Typically, these vessels leak in the recirculation phase and stain the mass in the late angiograms. Ultrasonography is most important for the larger retinal astrocytic hamartoma. With A- and B-scan ultrasonography, the mass appears as a sessile or dome-shaped retinal mass with acoustic solidity and orbital shadowing if there is calcification in the lesion [1].

Management

With exception of the rare aggressive variant mentioned previously, retinal astrocytic hamartomas are generally asymptomatic and nonprogressive and do not require treatment. Ocular examination should be performed yearly and the patient followed for other manifestations of TSC. If there should be associated subretinal fluid that extends into the foveal area, then laser photocoagulation or photodynamic therapy can be employed in order to bring about resolution of the subretinal fluid [1–3]. The astrocytic hamartoma of the retina has an extremely low tendency to undergo malignant change and has no recognized tendency to metastasize. The visual prognosis is also excellent, except in the rare instances in which exudation, subretinal fluid, or vitreous hemorrhage occur.

Neurofibromatosis (von Recklinghausen's Syndrome)

Definition

Neurofibromatosis (NF) is an oculoneurocutaneous syndrome characterized by multisystem involvement that can lead to a wide variety of clinical symptoms and signs [10–17]. von Recklinghausen [11] published a classic monograph on this disease in 1882, and the condition is now known as von Recklinghausen's syndrome. More recently, NF has been subcategorized into type 1 (NF-1) and type 2 (NF-2) [12]. Since there is some overlap in the two types, they are discussed together in this chapter.

Demographics

The frequency of a new mutation for NF is estimated to be about 1 in 2,500–3,000 births. There appears to be no appreciable predilection for gender [13].

Genetics

NF is transmitted by an autosomal dominant mode of inheritance with about 80% penetrance. NF-1 is also known as peripheral neurofibromatosis or von Recklinghausen's syndrome. It is recognized to occur from an abnormality of chromosome 17. NF-2 is called central or bilateral acoustic neurofibromatosis. It is characterized by CNS tumors and early onset of posterior subcapsular cataract and is recognized to be related to an abnormality in chromosome 22 [12, 13].

Ophthalmologic Features

NF has the most diverse systemic and ocular findings among the ONCS [1–3, 12, 13]. Ocular changes include abnormalities in the uveal tract (80%), eyelid (25%), optic nerve (12%), retina (9%), and conjunctiva (4%) [11]. These are described in detail elsewhere [1].

Fundus Manifestations

Uveal tract involvement is present in about 80% of patients with NF [13]. Multiple iris hamartomas, known as Lisch nodules, are the most

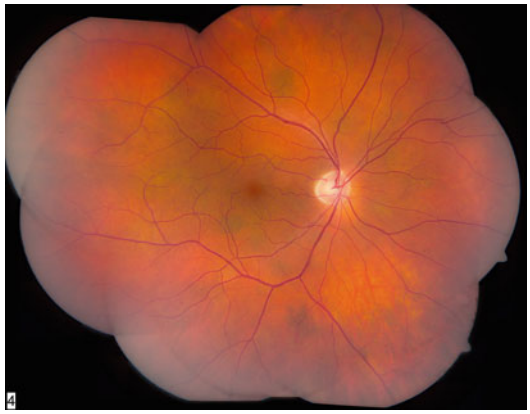

Fig. 17.3 Neurofibromatosis type 1. Multiple choroidal nevi. There are several subtle lesions, with the two most prominent ones near the superotemporal vascular arcade and inferotemporal to the fovea

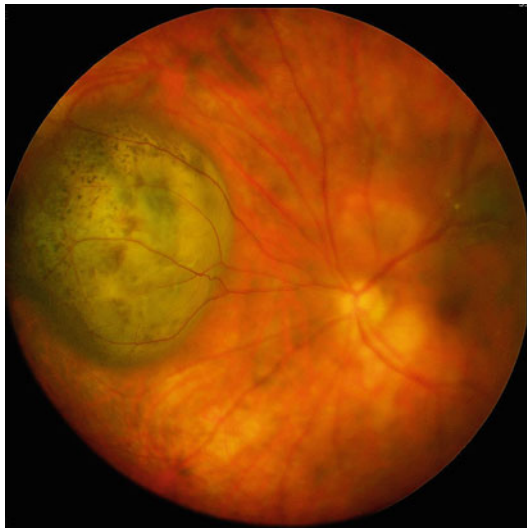

Fig. 17.4 Neurofibromatosis type 1. Choroidal melanoma located near equator superonasally

common uveal abnormality in NF-1 [13]. They first appear in childhood around age 5 years or later as discrete, multiple, lightly pigmented elevations of the anterior border layer. Relatively flat pigmented choroidal lesions, presumably melanocytic hamartomas identical to choroidal nevi, are often seen in NF-1 (Fig. 17.3). Other choroidal tumors that rarely associated with NF are choroidal melanoma (Fig. 17.4) and schwannoma. Most cases of choroidal schwannoma,

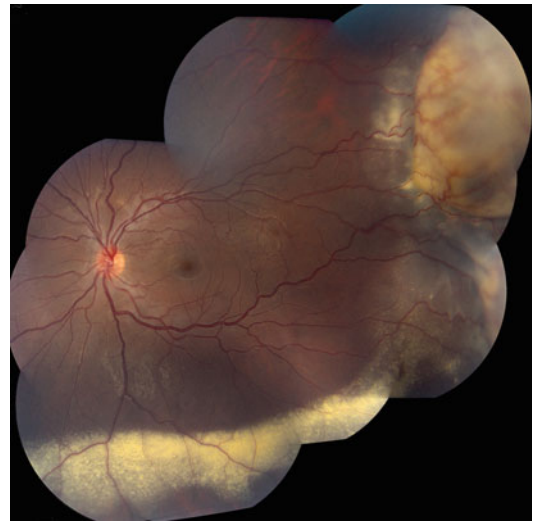

Fig. 17.5 Neurofibromatosis type 1. Retinal vasoproliferative tumor. The tumor is located superotemporally, but there is massive exudation inferiorly

however, are isolated and not associated with NF-1 or NF-2 [1, 15]. The retinal findings of NF are less common and include retinal astrocytic hamartoma, retinal vasoproliferative tumor (Fig. 17.5), myelinated retinal nerve fibers, multifocal congenital hypertrophy of the retinal pigment epithelium ("bear tracks"), and a lesion similar to combined hamartoma of the retina and retinal pigment epithelium [12]. The latter typically occurs in patients with neurofibromatosis type 2 but can be seen with NF-1. The astrocytic hamartoma is relatively rare in NF but is very common in TSC.

Management

The management of the fundus lesions of NF varies with the location and the extent of the disease. Treatment can be very complex. In general, the fundus tumors including retinal astrocytic hamartoma, myelinated nerve fibers, and combined hamartoma of the retina and RPE require no treatment. Choroidal neurilemoma, choroidal melanoma, and vasoproliferative tumor are managed with any of several methods depending on many factors [1].

Retinocerebellar Hemangioblastomatosis (von Hippel-Lindau Syndrome)

Definition

In 1895, von Hippel reported the clinical findings of so-called retinal angiomatosis [18], and in 1926, Lindau made a study of cerebellar lesions and pointed out their relationship to the retinal tumors previously described by von Hippel [19]. Consequently, the combination of retinal and cerebellar involvement has been called the von Hippel-Lindau (VHL) syndrome. Subsequently, VHL syndrome was recognized to have several other components in addition to the eye and CNS findings, including renal cell carcinoma, pheochromocytoma, endolymphatic sac tumors, and other less common cystic lesions [20–24].

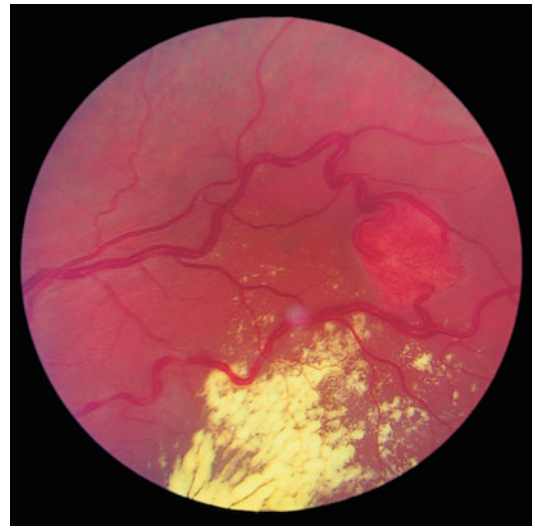

Fig. 17.6 von Hippel-Lindau syndrome. Typical retinal hemangioblastoma, showing *red* tumor with dilated afferent and efferent retinal blood vessels and lipoproteinaceous exudation

Demographics

The incidence of VHL syndrome is about 1 in 40,000 live births.

There is no clear-cut predilection for race or gender, although most of our patients have been Caucasians [3, 26, 27].

Genetics

The VHL syndrome is recognized to be a hereditary disorder, with an autosomal dominant mode of inheritance and incomplete penetrance. Many cases that are seen by the ophthalmologist, however, occur as spontaneous mutations with no apparent family history of the disease. Probably about 20% of cases have a positive family history. The condition is related to a partial deletion of the short arm of chromosome 3 [3, 24].

Fundus Manifestations

The ocular manifestations of VHL syndrome are not so diversified as they are in the other systemic hamartomatoses. Hemangioblastomas ("retinal capillary hemangioma") of the retina and/or optic disk are the only intraocular hamartomas that are known to occur. When associated with the VHL syndrome, the retinal and optic disk tumors are often multiple and bilateral [1, 3, 24]. The diagnosis of the ocular lesions is usually made in the second or third decade of life.

Retinal hemangioblastoma can occur in the peripheral retina or adjacent to the optic disk. Peripheral retinal hemangioblastoma appears as a variably sized distinct red nodule with a typical dilated tortuous afferent artery and an efferent vein that comes from the optic disk to the tumor, often associated with yellow lipoproteinaceous exudation (Fig. 17.6). Juxtapapillary retinal hemangioblastoma appears as a reddish mass overlying or immediately adjacent to the optic disk (Fig. 17.7). Either type can be associated with extensive intraretinal or subretinal exudation and variable degrees of vitreoretinal traction.

Fluorescein angiography is the most helpful ancillary study in confirming the diagnosis of a hemangioblastoma [1]. In the early arterial phase, the dilated retinal feeder arteriole appears prominent. Within 2–3 s, the retinal tumor is fluorescent as the fine capillaries that comprise the tumor fill

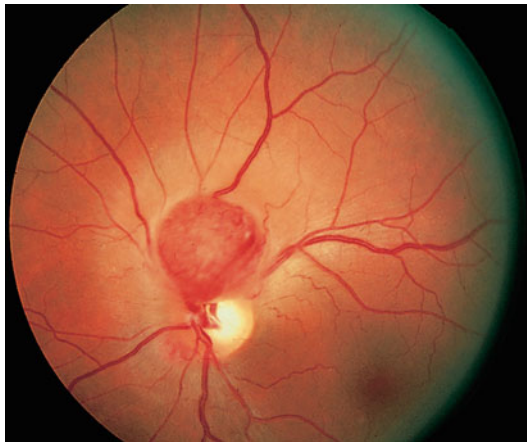

Fig. 17.7 von Hippel-Lindau syndrome: hemangioblastoma adjacent to optic disk, with mild surrounding exudation

with fluorescein. In the venous phase, the dilated draining vein fills with dye and the tumor maintains its bright fluorescence. In the late phase, the tumor generally remains fluorescent and leaks dye into the vitreous. The intrinsic rapid fluorescence of the optic disk hemangioma assists in differentiating this tumor from other optic disk lesions.

Management

The management of retinal hemangioblastoma is difficult and controversial. No active treatment may be necessary for small asymptomatic retinal tumors because some of them remain stable for many years and some even regress spontaneously. The patient should be examined periodically and treatment instituted if the tumor grows or if there is accumulation of exudation or subretinal fluid. In such instances, several methods of treatment have been advocated, including argon laser, cryotherapy, photodynamic therapy, and intravitreal injection of angiostatic agents. No single treatment has emerged as the treatment of choice. If a hemangioblastoma has caused an extensive retinal detachment with subretinal exudation, a vitrectomy and/or a scleral buckling procedure may be necessary to reattach the retina. We have used plaque radiotherapy for selected tumors with extensive retinal detachment.

Analysis of the DNA of the patient and all family members can be performed in an attempt to identify markers indicating VHL disease. The gene for VHL syndrome has been mapped to the short arm of chromosome 3. All patients with VHL syndrome should be followed carefully with yearly testing for systemic tumors. Furthermore, relatives of patients with VHL disease may benefit from a screening protocol depending on the results of DNA testing. The retinal hemangioblastoma is often the initial sign of VHL disease, and the various other systemic tumors found in this disease are best treated at an early stage. Therefore it is important to routinely evaluate these patients systemically.

Encephalofacial Hemangiomatosis (SW Syndrome)

Definition

In 1879, Sturge described a syndrome composed of a facial hemangioma with ipsilateral buphthalmos and contralateral seizures [26]. Later, Weber studied the clinical manifestations in greater detail, and the fully expressed entity became known as the Sturge-Weber (SW) syndrome [27]. The SW syndrome is now recognized to consist of a facial hemangioma, buphthalmos, seizures, and radiographic evidence of intracranial calcification [28–30]. Most patients, however, have a forme fruste rather than the entire syndrome.

Genetics

In contrast to most of the other ONCS, there is no recognizable hereditary pattern associated with SW syndrome.

Ophthalmologic Features

The ocular findings associated with SW syndrome include eyelid involvement with the nevus flammeus, prominent epibulbar blood vessels, glaucoma, retinal vascular tortuosity, and diffuse choroidal hemangioma.

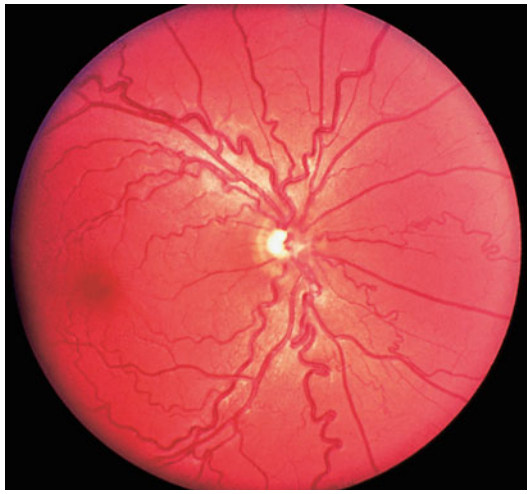

Fig. 17.8 Sturge-Weber syndrome: diffuse choroidal hemangioma producing an exaggerated red reflex to the fundus ("tomato catsup fundus")

The facial hemangioma can frequently involve the eyelids. Although it is usually unilateral, bilateral involvement occasionally occurs. Involvement of the upper eyelid has a high association with ipsilateral glaucoma. Prominent tortuous epibulbar blood vessels, in both the conjunctiva and episclera, are common findings. Glaucoma is more common in patients with SW syndrome than in the other ONCS. If the facial hemangioma involves both the first and second divisions of the trigeminal nerve, the incidence is 15% [28]. The glaucoma occurs unilaterally on the side of the facial hemangioma.

Fundus Manifestations

The only important abnormality of the uveal tract in patients with SW syndrome is the diffuse choroidal hemangioma. Patients with this tumor usually have a bright red pupillary reflex in the involved eye compared to the normal contralateral eye ("tomato catsup" fundus) (Fig. 17.8). The diffuse choroidal hemangioma is usually diagnosed when the affected patient is young (median age 8 years), either because the associated facial hemangioma prompts a fundus examination or because visual impairment occurs from hyperopic amblyopia or from a secondary retinal detachment. The diffuse choroidal hemangioma appears as a red-orange thickening of the choroid, often with overlying subretinal fluid. The tumor is usually a few millimeters thicker than normal choroid. The details of fluorescein angiography, indocyanine green angiography, and ultrasonography, which can be helpful in the diagnosis, are discussed elsewhere [1, 3]. Other fundus manifestations of SW syndrome include retinal vascular tortuosity (see Fig. 17.8) and cupping of the optic disk if glaucoma is present.

Management

The management of the diffuse choroidal hemangioma can be difficult, and it varies with the extent of the tumor. It may range from observation only if it is asymptomatic to laser photocoagulation or retinal detachment surgery or irradiation, depending on the clinical circumstances [3].

Racemose Hemangiomatosis (Wyburn-Mason Syndrome)

Definition

Racemose hemangioma of the midbrain and ipsilateral retina is called the Wyburn-Mason (WM) syndrome. Wyburn-Mason described this relationship in 1943 [31]. It consists of an abnormal congenital arteriovenous communication that can involve any combination of lesions in the retina, midbrain, and sometimes other areas including the orbit, mandible, maxilla, and pterygoid fossa [1, 3].

Genetics

This congenital condition does not appear to be familial and does not exhibit a hereditary pattern.

Fundus Manifestations

The classic ocular finding is the racemose (cirsoid) hemangioma of the retina [31, 32]. It is

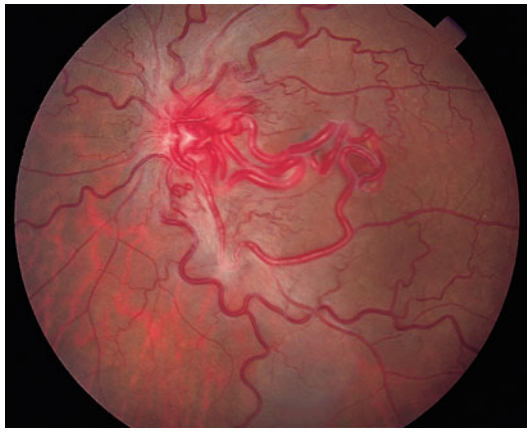

Fig. 17.9 Wyburn-Mason syndrome: retinal racemose hemangioma

actually a retinal arteriovenous communication ranging from a very subtle asymptomatic lesion to a more extensive one that consists of intertwining blood vessels, sometimes forming a tumor-like vascular mass (Fig. 17.9). The lesion has been divided into three groups that are detailed in the literature [32].

The diagnosis of the retinal racemose hemangioma is made ophthalmoscopically, but fluorescein angiography can be of assistance. The affected artery fills rapidly with fluorescein, and the transit to the venous side is rapid due to the lack of intervening capillary network.

Management

In general, no ophthalmic treatment is necessary for patients with racemose hemangiomatosis. If the retinal lesion produces persistent vitreous hemorrhage that does not resolve, then the blood can be removed by vitrectomy.

Oculoneurocutaneous Cavernous Hemangiomatosis

Definition

There are several systemic syndromes that are characterized by multiple cavernous hemangiomas or other vascular malformations. This chapter includes only those with a combination of cavernous hemangiomas that involve the retina, skin, and CNS, called oculoneurocutaneous cavernous hemangiomatosis (ONCCH) [1, 33–37]. The retinal and skin tumors are frequently asymptomatic, but the CNS hamartomas can sometimes produce clinical symptoms.

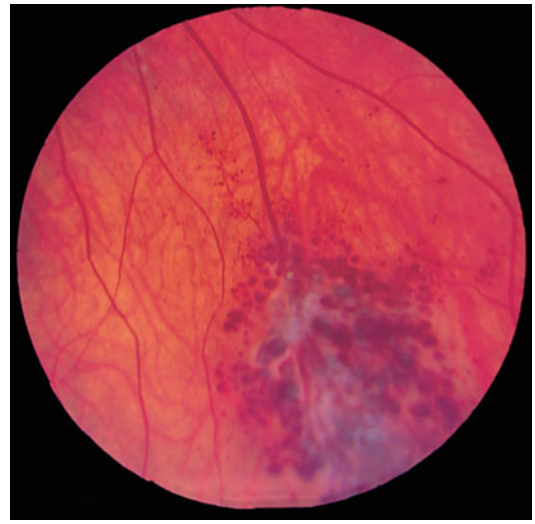

Fig. 17.10 Retinal cavernous hemangiomatosis. Cavernous hemangioma of the retina, showing characteristic "cluster of grapes" appearance

Genetics

This syndrome appears to have an autosomal dominant mode of inheritance [33–37]. A 7q locus has also been implicated in a large family with retinal cavernous hemangioma, choroidal cavernous hemangioma, and widespread CNS and cutaneous lesions [35]. Although the genetics are poorly understood, a mutation in the KRIT1 gene has been recognized in a family with retinal and CNS cavernous hemangiomas [37].

Fundus Manifestations

The only fundus manifestation of ONCCH is the retinal cavernous hemangioma. Ophthalmoscopically, the retinal lesion appears as a cluster of dark venous intraretinal aneurysms (Fig. 17.10).

There is no feeder artery and usually no yellow exudation, but white fibroglial tissue, possibly due to prior hemorrhage, is characteristically present on the surface of the tumor. The main complication of retinal cavernous hemangioma is vitreous hemorrhage. Severe fibrogliosis and dragging of the retina can occur. During fluorescein angiography, the vascular channels comprising the lesion remain hypofluorescent until the late venous phase when fluorescein begins to slowly enter the vascular spaces and produces the characteristic fluorescein-blood interface.

Controversies and Perspectives

This chapter has described the fundus manifestations of a diverse group of syndromes called the oculoneurocutaneous syndromes. There is some controversy regarding the terminology of these entities, and newer terminology may develop as their genetics are better understood. The fundus findings are fairly consistent in these entities, and the ophthalmic clinician should be able to recognize them and be aware of their ocular complications and system associations.

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18 Retinal and Choroidal Manifestations of Systemic Lupus Erythematosus (SLE)

J. Fernando Arévalo, Careen Yen Lowder, and Reinaldo A. Garcia

Abstract

Systemic lupus erythematosus (SLE) is a chronic, immunological disorder that may affect multiple organ systems. Keratoconjunctivitis sicca (KCS) is the most common ocular manifestation, but visual morbidity is usually due to retinal and neuro-ophthalmic manifestations of the disease. Ocular manifestations of lupus are a reflection of systemic disease. The presence of ocular manifestations should alert the clinician to the likely presence of disease activity elsewhere. Therefore, all patients with ocular lupus should be carefully evaluated for systemic involvement to detect potentially treatable and preventable complications of the disease. In addition, the ophthalmologist should include SLE in the differential diagnosis of many retinal vascular and neuro-ophthalmic disorders. The ophthalmologist may play an important role in the care of patients with SLE since ocular inflammatory lesions may precede potentially serious extraocular disease.

Keywords

Chronic immunological disorder • Lupus choroidopathy • Ocular manifestations • Systemic lupus erythematosus (SLE)

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Initial Considerations and Epidemiology

Systemic lupus erythematosus (SLE) is a chronic, idiopathic, multisystem inflammatory disease characterized by hyperactivity of the immune system and prominent autoantibody production. Acute exacerbations of disease activity are followed by periods of remission, and its course and spectrum of clinical manifestations are variable. The disease can present in a variety of forms ranging from mild cutaneous and joint involvement to lethal renal, cardiac, and cerebral involvement.

According to a population-based study in a geographically defined population over a 42-year period, the incidence of SLE has nearly tripled over the past four decades. [1] The average incidence rate (age and sex adjusted to the 1970 US white population) was 5.56 per 100,000 (95% CI = 3.93–7.19) during the period from 1980 to 1992, as compared with an incidence of 1.51 (95% CI = 0.85–2.17) during the period from 1950 to 1979. In general, studies reporting higher incidence rates utilize more comprehensive case retrieval methods. Later, two studies of self-reported diagnoses of SLE indicated that the prevalence of SLE in the United States might be much higher than previously reported. One of these studies validated the self-reported diagnoses of SLE by reviewing available medical records revealing a prevalence of 124 cases per 100,000 [2].

The average age of onset is 30 years, with a range from infancy to old age. In general, seven women are stricken with the disease for every man, and women of childbearing age are 11 times as likely to be affected as men, compared with a 2:1 female-to-male ratio in prepubertal girls and postmenopausal women. This raises the question of a potential role for hormones as either a causative or exacerbating factor in SLE.

The survival rates for individuals with this condition has significantly improved due to earlier diagnosis, recognition of mild disease, increased utilization of antinuclear antibody testing, and better approaches to therapy [3]. According to Krishnan and Hubert [4], the overall, unadjusted, lupus mortality in the National Center for Health Statistics data was 4.6 per million, whereas the proportion of in-hospital mortality from the nationwide inpatient sample in the USA was 2.9%. African-Americans with lupus have two- to threefold higher lupus mortality risk than Caucasians. The magnitude of the risk disparity is disproportionately higher than the disparity in all-cause mortality, so a lupus-specific biological factor, as opposed to socioeconomic and access-to-care factors, may be responsible for this phenomenon [4].

Systemic Lupus Erythematosus: General Diagnosis

The diagnosis can be definitively established if 4 of the 11 American College of Rheumatology criteria are met (Table 18.1 and "Controversies and Perspectives" section). Although ocular disease is associated with SLE (it may even be the first clinical manifestation of SLE), ocular lesions are not included among the 11 diagnostic criteria. Foster believes that this is an oversight, and that inclusion of ocular manifestations among the diagnostic criteria for SLE would lead to earlier diagnosis and therapeutic intervention in those instances. Nowadays, ocular manifestations have been included as one of the clinical parameters used to assess disease activity in the British Isles Lupus Assessment Group 2004 index (BILAG-2004); furthermore, some studies suggest that ocular manifestations themselves are associated with disease activity in lupus and others have shown ocular problems to be associated with particular clinical manifestations of SLE such as neurologic involvement and the presence of anticardiolipin antibodies [5].

Pathogenesis and Laboratory Findings

Systemic lupus erythematosus may derive from a dysfunction in immunoregulation in a genetically predisposed individual and may be triggered by environmental agents such as microbes or chemicals. Over the past decade, several studies have helped uncover genetic associations and susceptibility loci in human lupus. More recently,

Table 18.1 American Rheumatism Association (ARA) criteria for diagnosis of SLE (need four or more over any span of time for diagnosis)

Criteria for diagnosis of SLE	
Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR*
	Pericarditis—documented by EKG, rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria greater than 0.5 g per day or greater than 3+ if quantitation not performed *OR*
	Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures *OR* psychosis—in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia—with reticulocytosis *OR*
	Leukopenia—less than 4,000/mm^3 total on two or more occasions *OR*
	Lymphopenia—less than 1,500/mm^3 on two or more occasions *OR*
	Thrombocytopenia—less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorders	Positive antiphospholipid antibody *OR*
	Anti-DNA—antibody to native DNA in abnormal titer *OR*
	Anti-Sm—presence of antibody to Sm nuclear antigen *OR*
	False-positive serologic test for syphilis known to be positive for at least six months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

SLE systemic lupus erythematosus, *EKG* electrocardiogram

genome-wide association studies (GWAS) in SLE supported by government agencies, foundations, industry, and academic centers have uncovered a large number of associated genes in human SLE including several regions of the major histocompatibility complex (MHC) with independent contributions to SLE risk [6]. Given this plethora of candidate genes, the next challenge for lupus biologists is to fathom how these different genes operate to engender lupus.

According to Crow [7], lupus-associated genes contribute to one or more essential mechanisms that must be implemented to generate lupus susceptibility (Fig. 18.1). Some genetic variants (IRF5, PTPN22, STAT4, SPP1, FCGR2A, IRAK1, TNFAIP3) will facilitate innate immune system activation, particularly type I IFN (interferon) productions; other genetic variants (C2, C4, C1q, TREX1) will result in increased availability of self-antigen; and other genetic variants (HLA-DR, PTPN22, BLK, BANK1, FCGR2A, PXK, LYN, OX40L, SPP1) will alter the threshold for activation or regulation of cells of the adaptive immune response, resulting in production of autoantibodies. Additional genetic variants (ITGAM, KLK1, KLK3) might promote inflammation and damage to target organs or fail to protect those organs from proinflammatory mediators. The lupus-associated

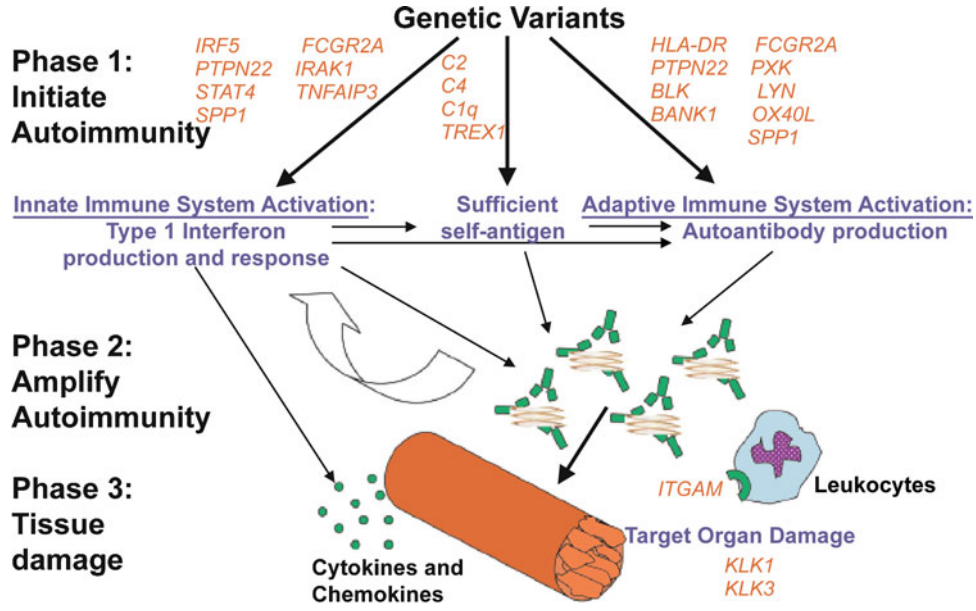

Fig. 18.1 Genetic determinants of lupus pathogenesis (Reproduced with permission from Crow MK. Developments in the clinical understanding of lupus. Arthritis Res Ther. 2009;11:245)

genetic variants prepare the immune system and target organs to be responsive to exogenous and endogenous triggers.

Innate Immune System Activation

Activation of the IFN pathway has been associated with the presence of autoantibodies specific for RNA-associated proteins, and the current literature supports RNA-mediated activation of TLR (Toll-like receptor) as an important mechanism contributing to production of IFN-alpha and other proinflammatory cytokines. Activation of the IFN pathway is associated with renal disease and many measures of disease activity [7].

Increased Availability of Self-antigen and Apoptosis

Recent data has supported the hypothesis that components of the classical complement pathway are required for phagocytic clearance of apoptotic cells, providing a possible explanation for the high frequency of SLE among the rare individuals with genetic deficiencies of those components, particularly C1q. Mutations have been identified in a DNase encoded by TREX1 in a SLE patient. Rare mutations in that gene are associated with a lupus-like syndrome characterized by anti-DNA antibodies, high levels of IFN-alpha, and neurologic disease. It appears that altered structure or function of the TREX1-encoded DNase results in inefficient clearance of intracellular DNA rich in endogenous genomic repeat element sequences and induction of type I IFN [7].

Adaptive Immune Response

Activated T and B cells are features of SLE, and many of the genetic variants that are being studied in association with SLE are likely to contribute to immune activation and clinical disease by altering the threshold for lymphocyte activation or modifying the capacity of inhibitors of signaling pathways to appropriately function. The autoantibodies produced as a result of these T and B cells interactions may directly contribute to inflammation and tissue damage in target organs but also amplify immune system activation and autoimmunity through their delivery of stimulatory nucleic acids to TLRs [7].

Autoantibodies to a number of nuclear and cytoplasmic constituents may be present and may be the result of a generalized polyclonal B cell hyperactivity [8]. Antinuclear antibodies (ANAs) are elevated in about 95% of patients with SLE.

However, their absence does not rule out the diagnosis. In addition, ANA can be seen in other systemic diseases. Antinuclear antibodies include anti-native double-stranded DNA (anti-ds DNA) that is very specific for SLE, anti-single-stranded DNA (anti-ss DNA) that is commonly found but nonspecific, and the anti-ribonucleoproteins (RNP), the anti-Ro/SSA, and the anti-La/SSB antibodies. Ro/SSA and La/SSB are antigens detectable in the nuclei and cytoplasm of cells. Antibodies against these RNP are highly associated with certain subsets of lupus including ANA-negative lupus, subacute cutaneous lupus erythematosus (SCLE), neonatal lupus, and lupus associated with inherited disorders of complement [8, 9]. These heterogeneous autoantibodies are known to affect the clinical features of SLE. A concept that has been developed in recent years considers the kinetics of the disease, with lupus autoantibodies present in serum of lupus patients up to 5 years prior to the development of clinical manifestations of disease. It is notable that autoimmunity, when considered in a population of lupus patients, develops in a stereotypical manner, with anti-Ro and anti-La antibodies, common to several systemic autoimmune diseases, developing early in the preclinical stage of disease, while anti-Sm and anti-RNP antibodies, those that are more specific for SLE, developing very close to the time that disease becomes clinically apparent [7].

Autoantibodies to cytoplasmic antigens include a group reactive against phospholipids. These antibodies, including the "lupus anticoagulant" (LA) and anticardiolipin (ACA), are a heterogeneous group of immunoglobulins and appear to have major clinical significance. These autoantibodies are thrombogenic in the coagulation cascade and can also react directly with phospholipid antigens present on the surfaces of platelets and endothelial cells. Lupus anticoagulant and ACA have been associated with recurrent arterial and venous thromboses, recurrent abortions, thrombocytopenia, and most of the neurological complications of lupus [10, 11]. The antiphospholipid antibodies cross-react with the cardiolipin used in standard screening tests for syphilis leading to the "biologic false-positive" test for syphilis that has long been associated with lupus and related disorders.

Damage to Target Organs

Antibodies, immune complexes, cytokines, and product generated by Fc receptor ligation and complement activation likely represent important mediators of tissue damage in SLE including placental inflammation and fetal loss, atherosclerosis, and central nervous system manifestations, particularly cognitive dysfunction. The strong association of a polymorphism in the ITGAM genes raises the possibility that leukocytes expressing the lupus-associated ITGAM variant might demonstrate a propensity to adhere more avidly to the local renal vasculature. In addition to augmented inflammatory mechanisms, target organ damage, particularly in the kidney, might be amplified by impaired protective mechanism [7].

In addition, sex hormones are known to affect the disease. Estrogen enhances SLE and testosterone suppresses it. Drugs such as chlorpromazine, hydralazine, methyldopa, isoniazid, and procainamide can produce a systemic inflammatory disorder that usually fulfills all of the diagnostic criteria for SLE. The pathophysiological mechanism by which this induction occurs remains unknown, and the associated systemic complications are typically mild.

General Clinical Findings

Constitutional symptoms include fever, malaise, arthralgias, myalgias, headache, loss of appetite and weight, and fatigue. Systemic lupus erythematosus may be triggered by sunlight, infection, and other stresses. Recurrences are common and tend to occur during active phases of disease. The most common systemic manifestations of SLE involve the skin and musculoskeletal systems [12, 13]. Mucocutaneous complications include the classic butterfly malar rash (Fig. 18.2), photosensitivity eruptions, mucosal ulcers, and discoid skin lesions. The term "discoid" refers to a specific type of skin lesion, not to a subtype of lupus. Musculoskeletal changes may be due to the disease process itself or may be secondary to the drugs that are used to treat it. Inflammatory arthralgias and arthritis are frequent. Aseptic bone necrosis may result from either lupus or corticosteroids. Lupus myopathy may result from steroids or antimalarial drugs.

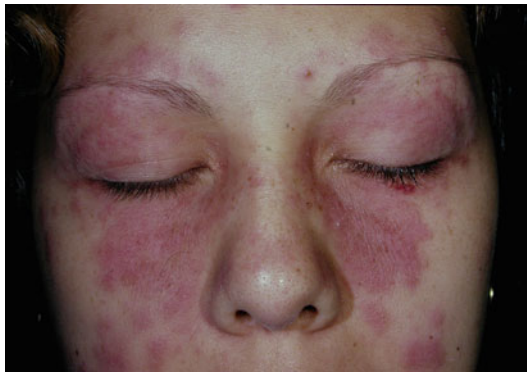

Fig. 18.2 Classic butterfly malar rash (Courtesy of Rafael Muci-Mendoza, M.D.)

Lupus serositis includes pleurisy, pericarditis, and peritonitis. Renal disease accounts for a significant portion of the mortality from lupus. Circulating immune complexes localize in the kidney, resulting in lupus nephritis, the nephrotic syndrome, and renal failure [13]. Central nervous system manifestations include organic brain syndrome, generalized seizures, and psychosis. Focal seizures, strokes, movement disorders, and cranial and peripheral neuropathies are also seen. Headaches, including classic migraines with scotomas, occur frequently. These neurological complications result from small vessel occlusive disease as well as direct autoantibody damage to neuronal tissue [14]. Lupus vasculitis, Raynaud's phenomenon, myocarditis, endocarditis (Libman-Sacks), pneumonitis, and diffuse interstitial fibrosis are other major complications of SLE.

Ocular Symptoms

In general terms, pain (often accompanied by visible inflammation or redness) usually indicates significant external/anterior segment disease, whereas problems with vision (blurring, distortion, double vision) usually indicates posterior segment/neuro-ophthalmic disease. Visual impairment is usually secondary to ischemic retinopathy, and higher incidences are reported in association with antiphospholipid syndrome (APS) [15, 16]. Mild retinopathy may be asymptomatic, but more severe disease may cause permanent or transitory loss of vision, field defects, distortion, or floaters.

Sometimes a SLE patient could present with ocular symptoms without any identifiable ocular manifestations, and the etiology of the problem could not be elucidated unless the doctor activates a systemic workup. In that sense, transient visual symptoms are usually not properly evaluated until they turn into a more serious condition. According to Giorgi et al. [16], unilateral vision loss is the most common transient visual symptom (TVS) with a frequency of 53%, followed by blurring of vision in 20.6%, with the least common being bilateral visual loss at a frequency of 5.9%. The pathophysiology of TVS in that review has been attributed to ischemia secondary to thromboembolism induced by cardiac valve abnormalities, hence the recommendation for anticoagulation along with immunosuppressive therapy.

Binocular acute onset reversible visual loss in association with APS is well known; however, more recently, a visual phenomenon has been described in association with a rare and recently described neurologic condition called posterior reversible encephalopathy syndrome (PRES). PRES is associated with renal insufficiency, hypertension, and rheumatologic diseases. Patients present with headache, seizures (usually generalized), loss of vision (ranging from blurred vision and hemianopia to cortical blindness) and altered mental function. The diagnosis is supported by predominantly transient hyperintensities on T2-weighted MRI images of the parieto-occipital white matter. Diffusion-weighted imaging (DWI) scans show increased diffusion in PRES, consistent with vasogenic edema. The etiology of PRES is believed to be dysregulation of brain perfusion by sympathetic innervations in the setting of severe hypertension. The causes may be diverse, but the most common precipitants are acute elevations in blood pressure, renal decompensation, and treatment with immunomodulatory drugs. It is usually treated with immunosuppression (methylprednisolone and cyclophosphamide), rapid control of seizures, and management of hypertension [15].

In SLE, acute or chronic permanent or reversible loss of vision can also be secondary to corneal, scleral, uveal, retinal, choroidal, and neuro-ophthalmological involvement.

Table 18.2 Systemic lupus erythematosus posterior ocular manifestations

Involvement	Posterior manifestation	FA and ICG	Systemic associations
Mild retinopathy	Cotton-wool spots	*FA*: capillary non-perfusion	Hypertension
	Retinal hemorrhages	Vascular incompetence	
	Retinal edema		
	Hard exudates	Fluorescein leakage	Steroid use
	Microaneurysms		
	Arterial narrowing		Dyslipidemia
	Venous engorgement		Anticardiolipin antibodies or lupus anticoagulant
	Vascular tortuosity		
Vaso-occlussive retinopathy	Arteriole occlusions	*FA*: arterial and capillary non-perfusion, leakage from neovascular fronds, and staining of the walls of involved vessels	Antiphospholipid antibodies (thrombogenic)
	Central or branch retinal artery or vein occlusions		
	Neovascularization		
	Vitreous hemorrhage		
	Retinal traction		
	Retinal detachment		CNS manifestations
	Pseudoretinitis pigmentosa		
Choroidopathy	Retinal/RPE multifocal serous detachments	*FA*: focal or multiple sites of ischemia, choroid leakage into subretinal/RPE spaces	Hypertension resulting from lupus nephritis, corticosteroid therapy, and/or vasculitis
	Exudative retinal detachments	*ICG*: early focal hypofluorescence, fuzziness, abnormal diffusion, focal pinpoint spots	
	CSCR		
	Choroidal effusions		
	Choroidal infarction		
	Choroidal neovascular membranes		
	Rare choroid infections		
CNS anterior pathway	AION	*FA*: optic nerve hyperfluorescence	Antiphospholipid syndrome (APS)
	Optic neuritis		
	Devic's syndrome		
	Chiasmal involvement		
CNS posterior pathway	Pupillary abnormalities		Cardiac valvular disease, APS, vasculitis
	Visual disturbance		
	Stroke		
CNS oculomotor complications	Cranial nerve palsies		Antiphospholipid antibodies
	INO		
	Miller Fisher syndrome, intracranial hypertension syndrome		

FA fluorescein angiogram, *ICG* indocyanine green, *CNV* central nervous system, *RPR* retinal pigment epithelium, *AION* anterior ischemic optic neuropathy, *CSCR* central serous chorioretinopathy, *INO* internuclear ophthalmoplegia

Posterior Ocular Manifestations

Systemic lupus erythematosus can affect many ocular and adnexal structures. Ocular manifestations tend to occur in patients who have active systemic disease (Table 18.2) [17, 18]. Retinal involvement is the second most common (after keratoconjunctivitis sicca) ophthalmological manifestation in SLE, [19] the incidence varies between 3.3% and 28.1%, and the appearance

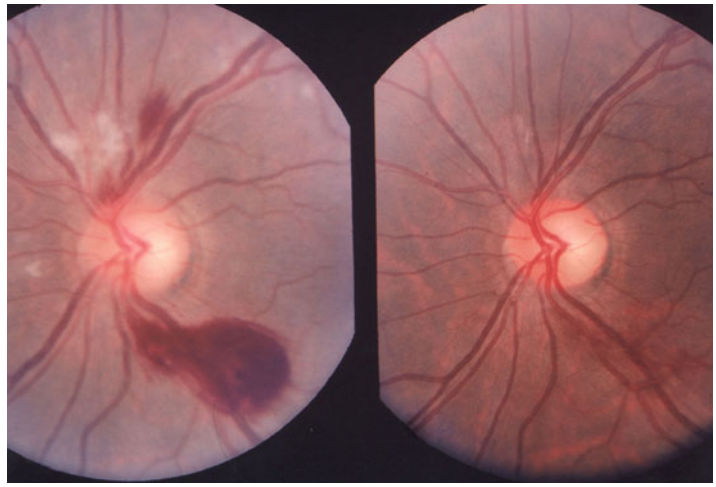

Fig. 18.3 Cotton-wool spots and retinal hemorrhages are the most frequently reported ophthalmic findings in systemic lupus erythematosus (*left*). Disappearance of retinal lesions after systemic disease improvement (*right*) (Reprinted with permission from Arévalo JF, Lowder CY, Muci-Mendoza R. Ocular manifestations of systemic lupus erythematosus. Curr Opin Ophthalmol 2002, 13:404–410.)

and disappearance of some of the retinal lesions parallel the course of systemic disease [17–20].

Mild Retinopathy

Most patients with mild retinopathy are at low risk of vision loss [19, 21]. Cotton-wool spots and retinal hemorrhages (Fig. 18.3) are the most frequently reported findings, but retinal edema, hard exudates, microaneurysms, arterial narrowing, venous engorgement, and vascular tortuosity have also been noted [17, 18]. Although many of these changes are part of the clinical picture of hypertensive retinopathy and hypertension is often present secondary to lupus renal disease, lupus retinopathy can occur as an independent manifestation of the underlying disease process in the absence of hypertension [17, 18]. Fluorescein angiography demonstrates capillary non-perfusion, vascular incompetence and fluorescein leakage even in eyes that appear clinically normal in patients with both active and mildly active disease [18].

The retinal microangiopathy associated with SLE is thought to be due to widespread immune complex deposition with resultant vasculitis, endothelial damage, and vessel leakage or microvascular thrombosis [21–23]. Although anticardiolipin antibodies or lupus anticoagulant may play a critical role in some patients, their precise role in this process is uncertain [22, 24]. It is felt that accelerated atherosclerosis as a result of hypertension, steroid use, and dyslipidemia in SLE may have a role in the development of this form of retinopathy [19, 25, 26]. Due to the fact that appearance and disappearance of retinal lesions parallel the course of systemic disease, the effective treatment of SLE and any associated systemic hypertension results in concurrent decrease in some of the retinal lesions, specially the disappearance of cotton-wool spots (see Fig. 18.3) [17, 19].

Vaso-occlusive Retinopathy

Severe vaso-occlusive retinopathy is a rare form of retinopathy in SLE often associated with poor visual prognosis and neovascularization. It is associated with antiphospholipid antibodies, which are thrombogenic and are associated with both central nervous system (CNS) and vaso-occlusive phenomena [27]. According to Montehermoso et al. [28], antiphospholipid antibodies were found in 77% of patients with lupus-related retinal or optic nerve disease, compared with only 29% of SLE patients without such ocular involvement. There is a strong association between this severe form of retinopathy and central nervous system manifestations of SLE [27, 28].

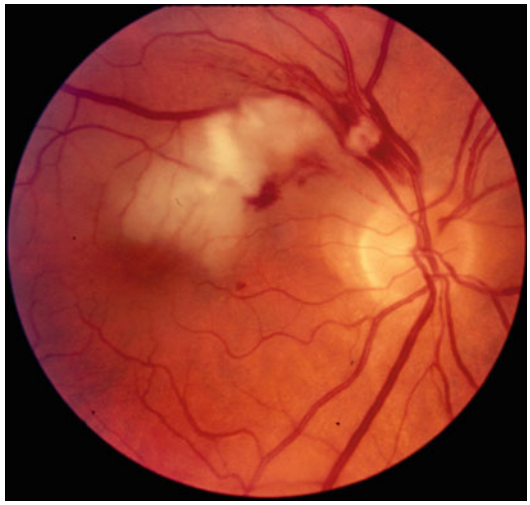

Fig. 18.4 Branch retinal arteriole occlusion and consequent retinal infarction

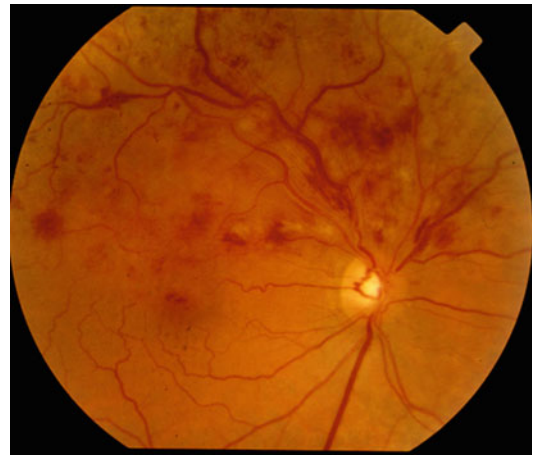

Fig. 18.5 Upper branch retinal vein occlusion with superficial retinal hemorrhages in resolution. See the difference between the upper tortuous and dilated veins against the normal inferior retinal veins

This form of retinopathy is typically characterized by occlusion of retinal arterioles and consequent retinal infarction (Fig. 18.4). Proliferative retinopathy with severe vaso-occlusive disease can occur in up to 40% of patients; poor visual outcomes with visual loss have been reported in 80% of these cases [26] and are often related with vitreous hemorrhage, retinal traction, and retinal detachment. Fluorescein angiography demonstrates arterial and capillary non-perfusion, leakage from neovascular fronds, and staining of the walls of involved vessels. Other retinal presentations include large vessel occlusions (central and branch retinal vein occlusions (Fig. 18.5) and central and branch retinal arteriole occlusions) (see Fig. 18.4). Central retinal vein occlusion appears to be less common than arterial occlusive disease [17, 18]. Some patient's retinopathy may resemble that seen in patients with retinitis pigmentosa because previous vascular occlusive disease resulted in retinal mottling and large clumps of pigment. In the immunosuppressed state, rare retinal infections may occur: retinal necrosis due to herpes simplex, varicella zoster, and cytomegalovirus are all reported [27, 29].

The histopathological findings include perivascular lymphocytic infiltrates, endothelial swelling, and thrombus formation, with occlusion of retinal and choroidal vessels, including the choriocapillaries [29]. Complete agreement has not been reached concerning the medical treatment of ocular thrombotic disease in SLE. Anticoagulant therapy is generally recommended (particularly when APAs are present), and the addition of an antiplatelet drug such as low dose of acetylsalicylic acid may be beneficial. The role of immunosuppressive agents in preventing the thrombotic complications remains unclear. These drugs should probably be given to patients with severe and progressive lesions that compromise the visual prognosis. Initial treatment is usually with oral corticosteroids (e.g., prednisolone 1 mg/kg/day), but may be preceded by intravenous methylprednisolone (e.g., 500 mg/1 g daily for 3 days). This is then supplemented with, or replaced by, other immunosuppressive agents as part of a steroid-sparing strategy or for resistance disease [27]. Proliferative retinopathy usually requires treatment with laser (panretinal photocoagulation) similar to the treatment for proliferative diabetic retinopathy [25, 27].

Lupus Choroidopathy

Although lupus choroidopathy is less common than retinopathy, its presence is well recognized and usually suggests active systemic vascular disease [27]. It typically manifests as multifocal serous detachments of the retina and underlying retinal pigment epithelium (RPE) (Fig. 18.6),

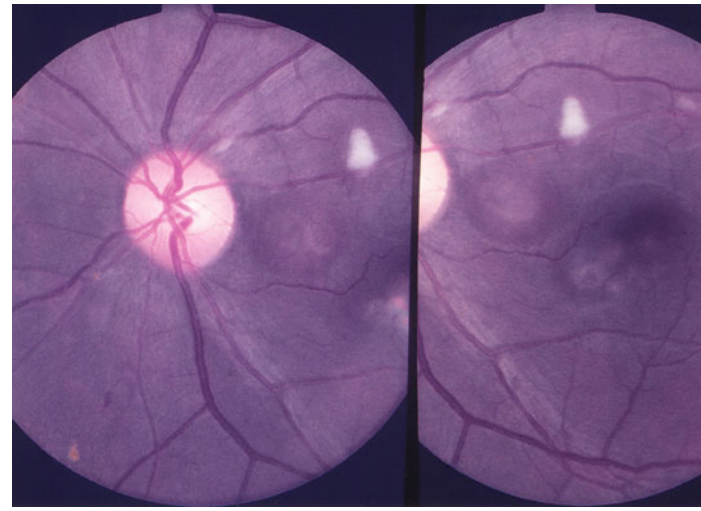

Fig. 18.6 Lupus choroidopathy characterized by multifocal retinal pigment epithelium detachments. Note the cotton wool spot (Reprinted with permission from Arévalo JF, Lowder CY, Muci-Mendoza R. Ocular manifestations of systemic lupus erythematosus. Curr Opin Ophthalmol. 2002, 13:404–410)

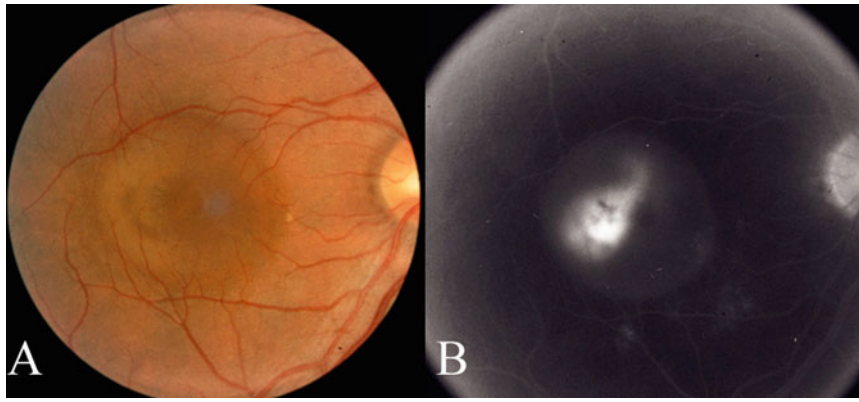

Fig. 18.7 Central serous chorioretinopathy. (**a**) Color picture showing an area of round subretinal fluid involving the fovea. (**b**) Fluorescein angiography showing a focal site or leakage from the choroid into the subretinal space with fluorescein pooling

sometimes progressing to large, exudative retinal detachments [30, 31]. Typical central serous chorioretinopathy has been described (Fig. 18.7) [31]. Other complications include choroidal effusions (which have been reported to cause secondary angle closure) [32], choroidal infarction or ischemia, choroidal neovascular membranes [33], and choroidal infections [34, 35]. Fluorescein angiography demonstrates focal or multiple sites of ischemia or leakage from the choroid into the sub-RPE and subretinal spaces (Fig. 18.8) [23]. Indocyanine green angiography (ICG) can provide information that is not detectable by clinical or fluorescein angiographic examination in patients with systemic lupus choroidopathy. ICG may reveal early focal areas of transient choroidal indocyanine green hypofluorescence suggesting choroidal filling delay, fuzziness of large choroidal vessels probably caused by choroidal vessel wall damage, with abnormal diffusion and retention of the indocyanine green molecule in the choroidal stroma and poorly defined areas of indocyanine green hypofluorescence suggesting vascular obstruction of the fenestrated choriocapillaris or choroidal stromal atrophy [36]. According to Gharbiya, [36] these three features are all nonspecific and are seen in other inflammatory or noninflammatory ocular and systemic diseases involving the choroid,

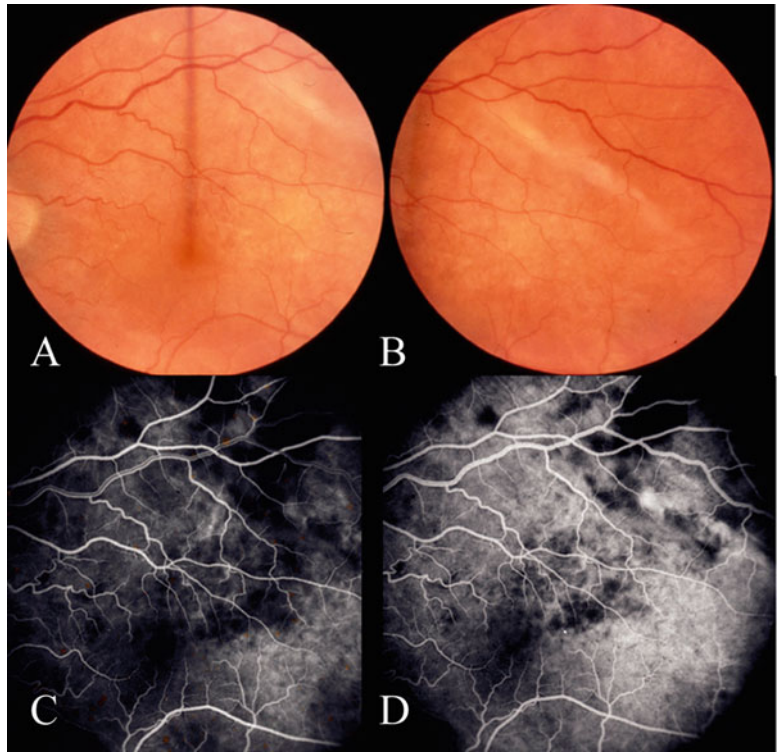

Fig. 18.8 (**a**) Central and (**b**) peripheral ocular fundus color pictures with a whitish superotemporal streak of choroidal infarction. (**c**) Early venous phase of the fluorescein angiogram showing multiple sites of choroidal ischemia. (**d**) Focal leakage from the choroid into the subretinal space in the late frames of the angiogram

including central serous chorioretinopathy. However, the presence of a focal cluster of pinpoint spots of ICG choroidal hyperfluorescence, appearing from the intermediate to late phases, may represent immune deposits at the level of the choroidal stroma, Bruch's membrane, or RPE's basement membrane, containing immunoglobulins and leukocytes, which have been shown to bind the indocyanine green molecule.

The pathogenesis of lupus choroidopathy remains still unclear. Choroidal vascular damage and/or occlusion can produce multifocal serous retinal and RPE detachments; immune complex deposition in the choriocapillaris or autoantibody directed against the RPE has been hypothesized [30, 36]. An associated hypertension, resulting from lupus nephritis and corticosteroid therapy, can contribute to vessel wall damage due to increased hydrostatic pressure which forces fluid and blood cells out of the intravascular compartment into surrounding tissues [30]. Thus, choroidal vasculopathy associated with systemic lupus erythematosus may be secondary to vasculitis, systemic hypertension, and corticosteroid therapy or probably to a variable combination of these processes [36]. Histopathology of SLE choroidopathy reveals massive mononuclear infiltration, diffuse thickening of medium-sized choroidal vessels, and extensive deposition of immune complexes in the basement membrane of choroidal vessels and basement membranes of the RPE, which is facilitated from the high-volume choroidal flow [19, 23, 36, 37].

Systemic lupus erythematosus choroidopathy can be resolved in up to 82% of patients once systemic control of the disease is achieved [38]. Initial treatment is usually with immunosuppression. However, in some patients, corticosteroids may themselves induce central serous chorioretinopathy, in which case alternative agents should be

used [39]. Pulsed methylprednisolone and cyclophosphamide have been reported to be effective in treating bilateral exudative retinal detachment secondary to ischemic choroidopathy [27, 40].

Central Nervous System and Neuro-ophthalmological Involvement

Involvement of the CNS occurs in approximately 39–57% of patients with SLE [19, 41]. However, antiphospholipid syndrome increases the risk of nervous system involvement in up to 78% of patients [41].

Anterior Visual Pathway

While not common, the prevalence of optic nerve disease in a referral rheumatology population can be estimated at approximately 1% of patients with SLE. In general, signs of optic nerve disease include reduced visual acuity, impairment of color vision (dyschromatopsia), diminished light brightness sensitivity, decreased contrast sensitivity, afferent pupillary defect, and visual field defects [19]. The patient may present with acute painless visual loss, an altitudinal or arcuate field defect, and optic disk swelling, the typical picture of anterior ischemic optic neuropathy. The patient may also present with similar symptoms but with a normal-appearing optic disk, i.e., a retrobulbar ischemic optic neuropathy. In some cases, there may be associated orbital pain, and the visual field defect may be a central scotoma; thus, the patient may be believed to have an optic neuritis, a papillitis (Fig. 18.9), or a retrobulbar neuritis depending on whether or not the optic disk is swollen. Both optic neuropathy/neuritis and retinal occlusive disease can result in optic atrophy. The histopathologic appearance of SLE cranial neuropathies is thought to be caused by vaso-occlusive disease in small vessels, with only nerve demyelination in milder forms of ischemic disease and axonal damage and necrosis in more severe cases [42]. Visual prognosis following optic neuropathy is generally poor, although good outcomes have been reported.

Treatment options of SLE optic neuropathy include systemic corticosteroids and immunosuppressive agents such as cyclophosphamide and methotrexate [22, 43]. Some patients may need anticoagulation in addition to immunosuppression [27]. Devic's syndrome (neuromyelitis optica or NMO) often presented with blindness and paraplegia is characterized by severe episodes of optic nerve and spinal cord inflammation. NMO-IgG (anti-aquaporin-4) has been recently described as a sensitive and specific marker for NMO. Testing for the NMO-IgG in cases of isolated or recurrent transverse myelitis attributed to current SLE and APLS may help clarify the diagnosis of a distinct disease process likely to cause recurrent and severe disability, warranting more aggressive immunotherapy [44]. Inflammation and/or thrombosis of medium to small vessels in the central nervous system are thought to underlie the nerve damage in this syndrome. Chiasmal involvement (chiasmopathy or chiasmitis) in SLE may occur in patients with positive antinuclear antibody and elevated anti-double-stranded DNA titers or in absence of any other evidence of systemic activity [45, 46].

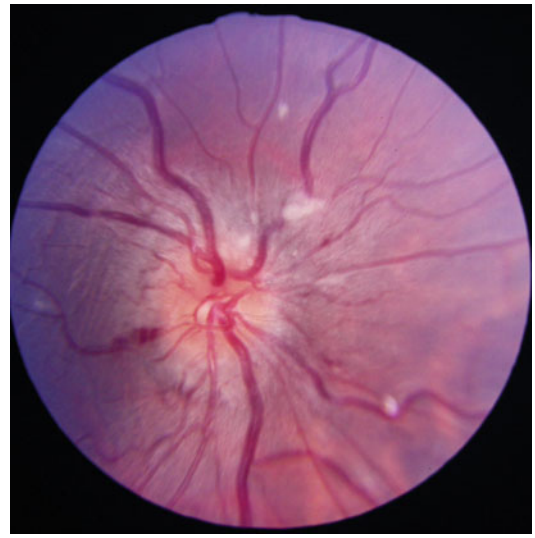

Fig. 18.9 Swollen optic disk (papillitis) in a systemic lupus erythematosus patient. Note the associated cotton-wool spots and retinal hemorrhages (Courtesy of Rafael Muci-Mendoza, M.D.)

Posterior Visual Pathway

Lesions of the posterior visual pathways include pupillary abnormalities such as light near dissociation (reduced pupillary light reflex but preserved

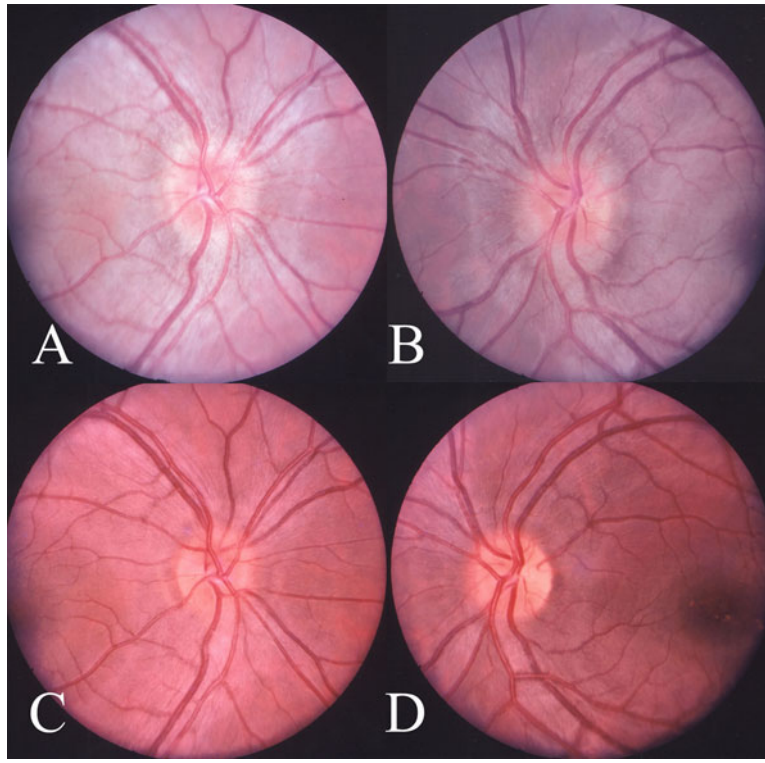

Fig. 18.10 (**a**) Right and (**b**) left color pictures of ocular fundus showing optic nerve engorgement due to papilledema in a systemic lupus erythematosus patient. (**c**) Right and (**d**) left optic nerves after intracranial hypertension syndrome resolution

near reflex), Horner's syndrome, Adie's pupil, visual disturbance ranging from transient amaurosis fugax to cortical blindness, visual hallucinations unformed (e.g., bright lights, straight lines) or highly formed (e.g., faces), as well as visual field defects and scotomas [19, 47]. These features indicate disease in the posterior cerebral artery circulation [19]. Strokes occur in up to half of the patients and most likely result from cardiac valvular disease, coagulopathy, or antiphospholipid antibody syndrome. Immune complex–mediated cerebral vasculitis is associated with SLE but is uncommon [47].

Oculomotor System

Cranial nerve palsies may result in ophthalmoplegias accompanied by diplopia, ptosis, and/or pupillary abnormalities. The incidence of cranial neuropathy is reported to range from 5% to 42% and is often associated with multiple cranial nerve involvement [19]. Disorders of conjugate gaze such as internuclear ophthalmoplegia (INO), uni- or bilateral, and one and a half syndrome (INO with ipsilateral horizontal gaze palsy) are seen [48–50]. INO in SLE is uncommon, affecting <5% of hospitalized SLE patients [48]. Other reported oculomotor complications include nystagmus [51] and Miller Fisher syndrome (ataxia, areflexia, and ophthalmoplegia) [52]. A possible cause of oculomotor palsy in SLE patients is microthrombosis associated with presence of antiphospholipid antibodies [53]. Intracranial hypertension syndrome (characterized by an elevated intracranial pressure, papilledema [Fig. 18.10], and headache with occasional abducens nerve paresis, absence of a space-occupying lesion or ventricular enlargement, and normal cerebrospinal fluid chemical and hematological constituents) has been reported [19, 54, 55]. Deschler et al. [54] reported a SLE intracranial hypertension syndrome that did not improve

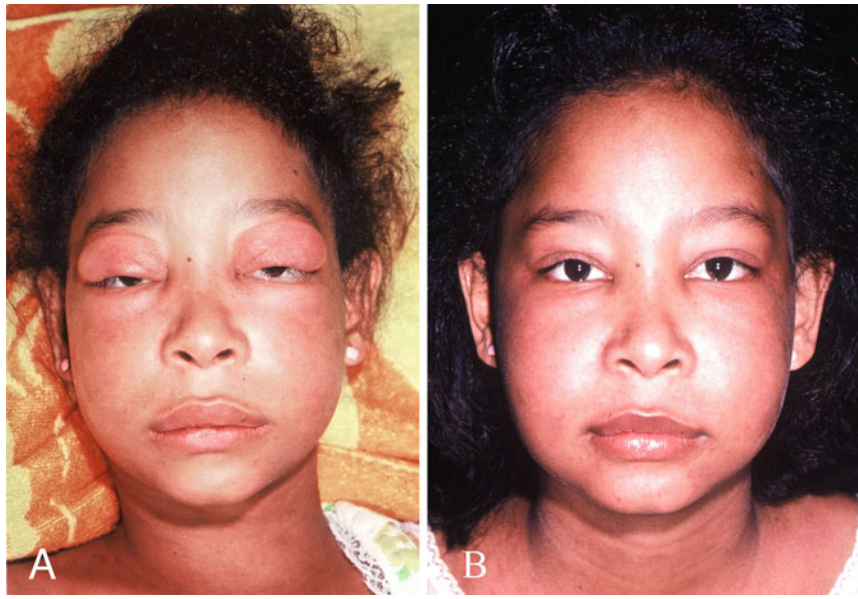

Fig. 18.11 (**a**) Bilateral periorbital and eyelid edema as an initial manifestation of systemic lupus erythematosus. (**b**) Complete resolution of bilateral periorbital and eyelid edema after high-dose systemic steroids (Reprinted with permission from Arévalo JF, Lowder CY, Muci-Mendoza R. Ocular manifestations of systemic lupus erythematosus. Curr Opin Ophthalmol. 2002, 13:404–410)

despite medical therapy with leflunomide, methotrexate, prednisone, rituximab, and intravenous and oral corticosteroids, but after monthly cyclophosphamide, the visual fields dramatically improved and the papilledema resolved.

Anterior Ocular Manifestations

The pathologic appearance of secondary Sjogren's syndrome is a frequent finding in SLE. It may produce clinical ocular manifestations such as keratoconjunctivitis sicca and is strongly associated with the presence of HLA-DRW52 antigen and anti-Ro (SSA) and anti-La (SSB) antibodies [9, 12]. Corneal manifestations of SLE are confined primarily to ocular surface epitheliopathy secondary to keratoconjunctivitis sicca. Stromal keratitis is rare. Superficial punctate keratitis and recurrent epithelial erosions have been reported in patients with discoid lupus erythematosus.

Orbital inflammation in SLE may result in episodes of acute proptosis, lid edema (Fig. 18.11), conjunctival chemosis and hyperemia, and limited ocular motility. Elevated intraocular pressure and myositis with enlargement of the extraocular muscles on CT scanning have also been reported. The eyelid may be involved in the cutaneous facial changes of lupus (Fig. 18.12). Discoid lesions of the eyelids can mimic chronic blepharitis.

Episcleritis or scleritis may also occur as a consequence of SLE, and scleritis is a reasonably accurate indicator of the presence of significant systemic activity in the SLE patient; scleritis will only resolve with adequate control of disease activity and usually does not respond to local therapy. Other, less common, ocular complications of lupus include conjunctivitis, keratitis, corneal staining, uveitis, and anterior segment neovascularization [17].

Drug-Related Ocular Manifestations

In addition to lupus-induced eye problems, the drugs used to treat the systemic disease have potential ocular side effects. Corticosteroids may

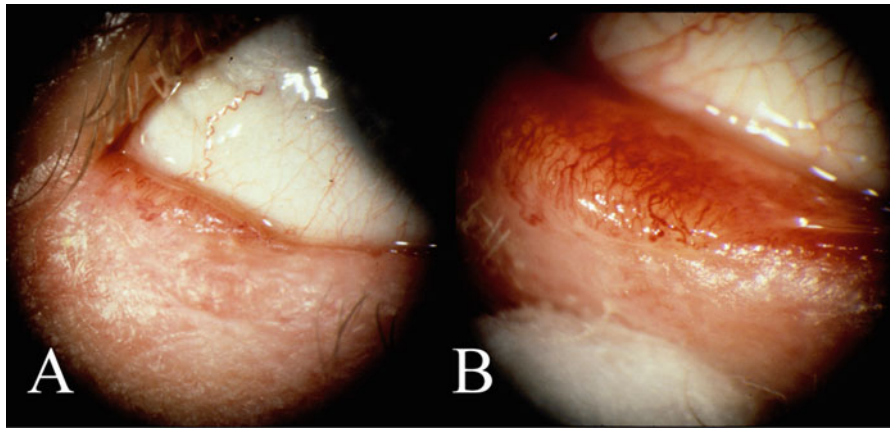

Fig. 18.12 The eyelid may be involved in the cutaneous facial changes of lupus. (**a**) Eyelid lesion simulating chronic blepharitis. (**b**) Tarsal aspect of the lesion

induce cataracts and glaucoma, and antimalarials can cause ocular toxicity including keratopathy, ciliary body involvement, lens opacities, and retinopathy. Chloroquine or hydroxychloroquine retinopathy is the major concern because others are more common but benign. The retinopathy of chloroquine or hydroxychloroquine may cause subtle, asymptomatic, reversible macular pigment mottling in its early phases and profound irreversible visual loss with a bull's-eye pattern of pigmentary maculopathy in its later phases (Fig. 18.13a–d).

The incidence varies between studies and ranges from 0% to 4%, such variation being mainly due to the different definitions of retinopathy and use of different drug doses [56]. Early retinopathy is defined as an acquired paracentral scotoma on threshold visual field testing without any observable fundus changes. Advance chloroquine or hydroxychloroquine retinopathy is defined as an acquired paracentral scotoma on threshold visual field testing with associated parafoveal retinal pigment epithelial retinopathy. Although pathogenesis of retinopathy due to hydroxychloroquine is not well established, the similarity of its chemical structure to chloroquine and the characteristics of the retinopathy suggest that the mechanism may be analogous [56, 57]. Chloroquine is highly concentrated in the pigmented ocular tissues such as retinal pigment epithelium (RPE), binds to melanin, and remains there for prolonged periods of time even after cessation of therapy [56, 58]. Histopathological studies of advance chloroquine retinopathy in humans revealed destruction of rods and cones with sparing of the foveal cones. This explains the fundoscopic appearance of the bull's-eye maculopathy. It is suggested that the metabolism of the RPE is first affected, with disturbance of its function of phagocyting the physiologically shed outer segments of the photoreceptor cells [59, 60]. Animal studies have shown that the earliest reversible histopathological changes are membranous cytoplasmic bodies that accumulate in ganglion cells and degenerative changes in photoreceptor outer segments. Thus initially the drug may destroy ganglion cells and photoreceptors, with later involvement of the RPE [58].

Although the risk of developing maculopathy has been thought to depend on the total cumulative dose of the drugs, the size of the daily dose rather than the total dosage or duration of treatment may be the most important factor. Dosages of 400 mg/day or 6.5 mg/kg body weight/day of hydroxychloroquine, whichever is less, may permit very high intake without inducing clinical retinal toxicity. Chloroquine has a less clear safety profile and should be avoided where possible. Authors have stated that no patient should receive more than 250 mg/day of chloroquine. The dose of oral chloroquine 250 mg may be too small to achieve a rheumatologic therapeutic effect, but

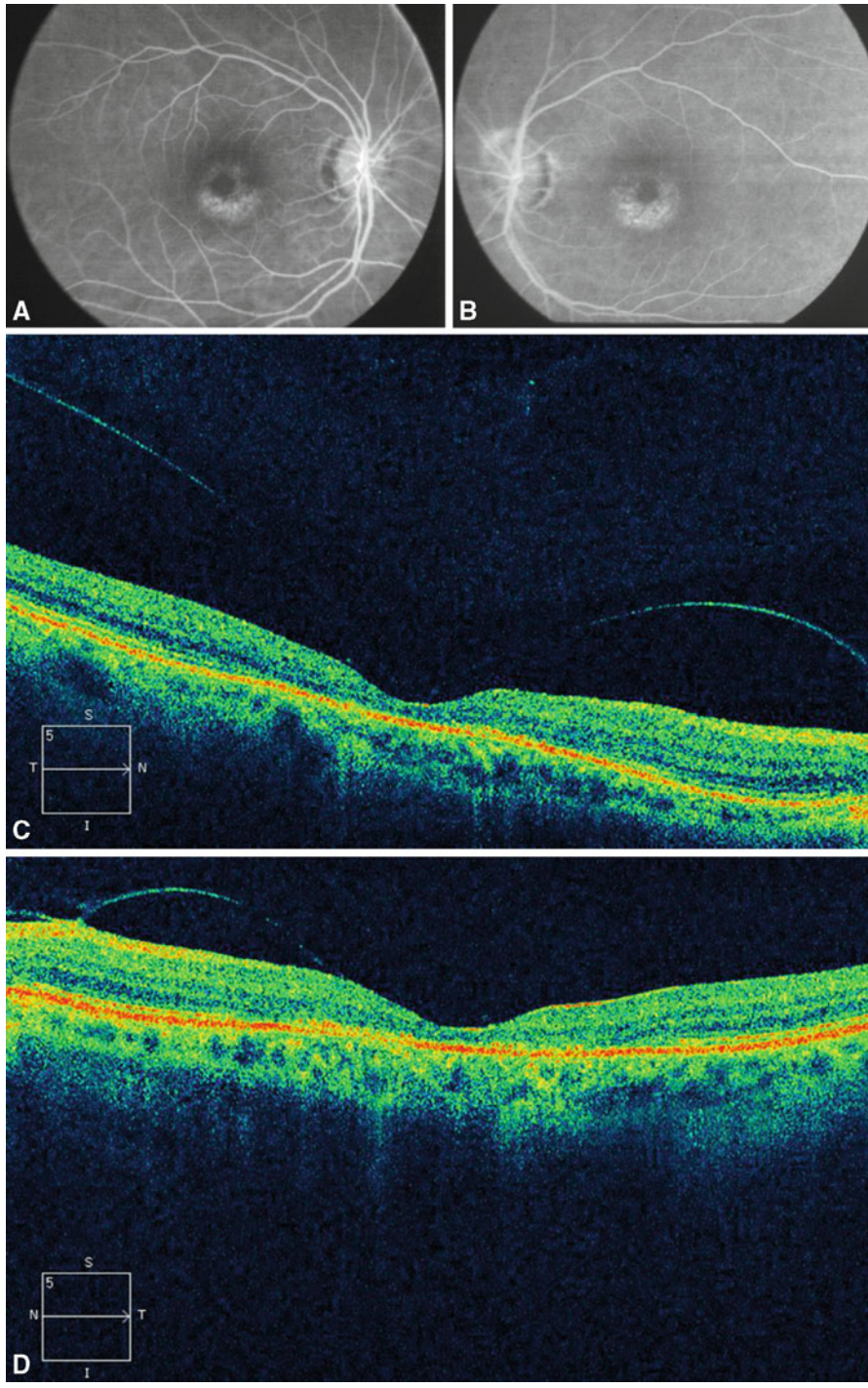

Fig. 18.13 (**a**) Fluorescein angiogram (FA) shows a transmission defect corresponding to the area of central retinal pigment atrophy in a complete bull's-eye lesion in a patient on chloroquine, who had lost central vision. (**b**) Left eye's FA of same patient. (**c**) Spectral-domain optical coherence tomography (SD-OCT) demonstrating an increase in choroidal reflectivity corresponding to the area of central retinal pigment atrophy in the same patient's right eye. (**d**) Left eye's OCT of same patient

the next incremental dosage available orally, 500 mg/day, puts dosing into the toxic range for patients weighing less than 125 kg. [61]

General Management

The three major classes of drugs used in treating SLE are nonsteroidal anti-inflammatory agents, corticosteroids, and nonsteroidal immunosuppressive agents [62]. Nonsteroidal anti-inflammatory agents (including aspirin) and antimalarials (usually hydroxychloroquine, Plaquenil 200–800 mg/day) are useful for nonspecific manifestations of disease such as fever, arthralgias, arthritis, and serositis. Systemic corticosteroids are used orally (prednisone 1–2 mg/kg/day) and intravenously (methylprednisolone 1–2 g/day for 3–6 days) for major organ involvement and for hematological complications such as hemolytic anemia and thrombocytopenia. Immunosuppressive drugs, especially azathioprine, are used when life-threatening complications of lupus are unresponsive to corticosteroids. Cyclophosphamide, chlorambucil, nitrogen mustard, methotrexate, and cyclosporine A have also been employed in the treatment of SLE.

The development of new drugs for systemic SLE such as mycophenolate mofetil, abatacept, rituximab, abetimus, and belimumab, among others, has also been tested, and there seem to be new therapeutic approaches that appear rational and likely to target important mechanisms of autoimmunity and inflammation. Plasmapheresis can reduce levels of circulating immune complexes and antibodies [62]. Hemodialysis and renal transplantation are used in lupus patients who have renal failure. Thrombotic events associated with antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) are often treated with oral anticoagulants, though no treatment exists that is consistently effective for this major lupus-associated complication. Anticoagulation may prevent recurrent thrombosis, and there is a recognized tendency for rebound thrombosis if anticoagulation therapy is stopped. Cutaneous lesions may respond to topical or intralesional steroids, antimalarials, systemic steroids, immunosuppressives, topical or systemic steroids, topical or systemic retinoids, or oral gold. Sunscreens are useful in preventing photosensivity skin eruptions.

Appropriate therapy for specific complications of SLE is also important and may include antihypertensive agents for lupus-induced hypertension and antibiotics for infections in these immune-compromised patients. Varying combinations of drugs and other modes of therapeutic intervention have dramatically improved the prognosis for SLE patients.

Since the ocular complications of SLE are generally associated with active disease elsewhere in the body, control of the systemic disease may lead to resolution of ocular manifestations. Systemic steroids with or without immunosuppressive agents have been used in the treatment of lupus optic neuropathy, choroidopathy, orbital inflammation, and pseudotumor cerebri [30, 42]. Simultaneous control of any associated systemic hypertension is also important. Treatment of the sequelae of retinal vascular occlusive disease has generally been limited to local ocular measures. Retinal neovascularization responds to scatter laser photocoagulation in a manner similar to that observed in diabetic retinopathy, retinal vein occlusion, and other retinal neovascular disorders [63–65]. Anterior segment ischemia has been observed as a complication following laser treatment in a patient with SLE [65]. Vitrectomy and scleral buckling may be required for cases involving vitreous hemorrhage or retinal detachment.

Controversies and Perspectives

Systemic lupus erythematosus is a chronic, immunological disorder that may affect multiple organ systems. The etiology of this disease continues to be unclear. In recent years, new therapeutic modalities have led to some improvement in morbidity and mortality.

Ocular manifestations are not included among the 11 diagnostic criteria of lupus, and the inclusion of ocular lesions among these criteria would lead to earlier diagnosis and therapeutic intervention in those instances. Their presence should alert the clinician to the likely presence of extraocular disease activity [17, 30, 63–65].

Severe retinal arterial occlusive disease [63–65] and lupus optic neuropathy [42, 66] have been particularly associated with CNS lupus. Lupus choroidopathy [30] (or other ocular complications) may coexist with widespread systemic vascular disease. All patients with ocular lupus should be carefully evaluated by a rheumatologist for potentially treatable and preventable complications of the disease.

Focal Points

General diagnosis of SLE (see Table 18.1), using the analogy of the American Rheumatism Association (ARA) criteria for the diagnosis of rheumatoid arthritis, suggests that patients be classified as follows:

1. Classical SLE—many criteria
2. Definite SLE—4 or more criteria
3. Probable SLE—3 criteria
4. Possible SLE—2 criteria (of the patients with probable or possible SLE, some experience resolution of symptoms, some evolve into another illness, and a few develop SLE)
    - When you get a positive ANA, order an ANA profile, which should include anti-double-stranded DNA, anti-Smith, anti-SSA and anti-SSB, and anti-RNP.
    - Anti-dsDNA and anti-Sm are virtually 100% (96–100%) specific for SLE (they are ONLY positive in patients with SLE). However, their sensitivity is not as good—52% for Crithidia anti-dsDNA and 73% for Farr anti-dsDNA, and 18–31% for anti-Smith.
    - If ANA is negative and clinical signs strongly suggest SLE, check for anti-SSA(Ro) antibodies. If this is positive, the patient probably has "ANA-negative" SLE (rare). As many as 62% of patients with "ANA-negative" SLE have anti-SSA antibodies.
    - Complement levels can also be helpful diagnostically—total serum hemolytic complement (CH50) and individual complement components (C3 and C4) may be low in patients with active SLE due to the presence of immune complexes: low sensitivity (40%) but high specificity (90%).

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Vogt–Koyanagi–Harada Disease

19

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Abstract

Vogt–Koyanagi–Harada disease is a bilateral granulomatous panuveitis, generally symmetrical, associated to extraocular manifestations such as poliosis, vitiligo, alopecia, central nervous system, and auditory signs. It is considered an autoimmune disease, mediated by T cells, against melanocytes of uveal tract, skin, central nervous system, and inner ear. A genetic predisposition has been suggested. Patients have no history of ocular trauma and no clinical or laboratory evidence of other ocular or systemic disease. Therapy includes early, high doses of systemic steroids. Immunomodulatory therapy has also been used with good results.

Keywords

Immune disorders • Immunosuppressors • Inflammation • Major histocompatibility complex • Sunset glow fundus • Vogt–Koyanagi–Harada disease

Introduction

Vogt–Koyanagi–Harada syndrome (VKH) is an inflammatory disease that affects different organs including eye, inner ear, skin, and meninges. Typical ocular manifestations are severe bilateral iridocyclitis, serous retinal detachment, diffuse choroidal edema, and optic disk hyperemia.

Central nervous system involvement manifests as headache, meningismus, and occasionally focal neurologic signs. Dermatologic alterations include alopecia, skin and scalp hypersensibility, poliosis, and vitiligo. Auditory manifestations are tinnitus, hearing loss, and vertigo. In most cases, diagnosis is made clinically, although some ancillary testing may be useful to confirm it.

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Vogt–Koyanagi–Harada syndrome is more common in certain ethnic groups such as Japanese, Chinese, Indian-Americans, and Mexican-Mestizo, among others. Prognosis depends on age at onset, initial visual acuity (VA), ethnicity, duration of disease, initial treatment, number of recurrences, and associated complications.

History

An Arab physician Ali-Ibn-Isa (940–1010 C.E.) was the first to describe a patient with poliosis and ocular inflammation. In the nineteenth century, Jacobi et al. described patients with poliosis, neuralgia, and hearing disorders [1]. This clinical description was also reported by Schenkl in 1873, by Hutchison in 1882 [2], and by Vogt in 1906 [3]. In 1926, Harada [4] reported a patient with serous retinal detachment associated with cerebrospinal fluid pleocytosis. In 1929, Koyanagi described six patients with bilateral chronic iridocyclitis associated with vitiligo, alopecia, poliosis, deafness, and tinnitus [5].

Babel in 1939 [6] and, 10 years later, Bruno and McPherson [7] proposed that these manifestations corresponded to a spectrum of the same disease. Since then, this group of signs and symptoms receives the name of VKH syndrome [1].

Epidemiology

VKH disease has been reported around the world; however, some ethnic and racial groups are more frequently affected. It is common in people with dark skin pigmentation such as Asians [8, 9], Native Americans [10], Hispanics [11], Asian-Indians [12], and Middle East population. It is uncommon in Caucasians [12].

Most of the studies report that women are more commonly affected than men. In North America, female patients represent 55–78% of the cases, and in Mexico 69.5% [13]. In Japan, it has been reported that only 38% of their VKH patients are women [10].

Age of presentation has a wide range, from 3 to 63 years. The highest frequency is reported between the third and fourth decades of life. Small children may be affected; however, VKH is a rare cause of pediatric uveitis [14–17].

Recently we reviewed the clinical files of 156 VKH patients, seen in a 15-year period at a referral Inflammatory Eye Disease Clinic; only nine of them were 16 years old or younger at admittance (unpublished data).

Prevalence of VKH syndrome depends on the studied population. In Japan it represents 10% of referral uveitis patients [18, 19]. It is also one of the most common uveitis in China [9, 19], Brazil [20], and Saudi Arabia. In the Middle East, 13.4% of uveitis diagnosis corresponds to VKH, 14.4% in Argentina, and 6.4% in a referral center of Mexico City [21]. In the United States, prevalence is lower, between 1% and 4% of all uveitis diagnosis [22].

Immunopathogenesis

The exact immunopathogenic mechanisms of VKH syndrome are still unknown, but there are clinical and experimental evidences that indicate an autoimmune process involving melanocytes.

In VKH patients, it has been demonstrated that melanin-laden cells of the epidermis are partially lost, and the presence of infiltrates composed mainly by T cells suggests that a cell-mediated immune response plays a central role in the pathogenesis of dermal lesions [23]. Vitiligo lesions show an increase in helper/inducer $CD4^+$ lymphocytes and an altered ratio of $CD4^+/CD8^+$ (3:1) cells.

In 1991, Sakamoto demonstrated that eyes affected with VKH had an increased $CD4^+/CD8^+$ ratio and that activated lymphocytes expressed costimulatory molecules such as CD2 and CD26 in the choroidal inflammatory foci. In active VKH patients, choroidal infiltrates show predominantly activated $CD4^+$ T cells that express CD25, a transmembrane protein; this molecule is an interleukin-2 (IL-2) alpha-chain receptor for lymphocytes, and it is involved in the proliferation

process of T cells. In the choroidal inflammatory foci, T cells also express CD26, which is considered a T cell activation antigen; CD26 costimulation potentiates T cell receptor-mediated response leading to an effector function. CD26 is considered a marker of lymphocytic late activation [11, 24–26]. Other authors have shown an increased expression of $CD1a^+$ in lymphocytes of peripheral blood in patients with active VKH, suggesting an activation of the immune system that is increased by the T cells lymphokines released as product of activated signaling cascades [27].

Choroidal melanocytes and endothelial cells from choriocapillaris do not express molecules of the major histocompatibility complex (MHC) class II (HLA-DR and HLA-DQ) in physiological conditions. These molecules require for antigen presentation $CD4^+$ cells; these are expressed abnormally in choroid tissue of VKH patients. Innomata and Sakamoto demonstrated the absence of choroidal melanocytes in chronic VKH patients. These findings suggest a retarded hypersensibility against melanocytes with aberrant expression of class II molecules that can play a role in the inflammatory process in patients with VKH [28].

Norose et al. have demonstrated cytotoxic activity of leukocytes against a human melanoma cellular lineage in patients with VKH [29]. Specific cytotoxic T cells against an antigen expressed on melanocytes and the retina were demonstrated using $CD8^+$ T cell clones from intraocular fluid from HLA-A2-positive VKH patients. These cell lyses the eye melanocytes, suggesting a cellular basis of the HLA-restricted autoimmune process [30]. Tyrosinase or tyrosinase-related proteins have been implicated as target antigens on the melanocytes [31]. Several studies have shown that tyrosinase family protein in a rat model can induce an autoimmune disease strongly resembling human VKH and that lymphocytes of VKH patients are reactive to tyrosinase family proteins [32]. Chan detected serum antibodies against the external segments of the photoreceptors and Müller cells, as well as antibodies against anti-ganglioside in 71% of their VKH patients [33]; however, it is not known if these changes are secondary to retinal damage produced during inflammatory response. Chan also observed that lymphocytes of patients with active disease, without treatment, proliferated when they were exposed to a union of interphotoreceptor protein and retinal antigen.

Damico and coworkers [34] demonstrated that in patients with VKH, T cells recognize peptides derived from melanocytes with greater affinity and proliferative response when compared to controls. They also found that peripheral blood mononuclear cells (PBMC) produce a cytokine response with a specific Th1 profile. Other authors suggest that an external factor may bind to Toll-like receptors (TLRs), a receptor family that recognizes molecular patterns usually found in pathogens, and produce an intracellular signaling cascade; the stimulation of TLR [35] induces changes in chemokine and cytokine secretion and costimulatory molecule expression. Chan et al. proposed [36] that meningeal and auditory system involvement was a response against melanocytes that express altered antigens on their surface. It is not known if these changes are due to a spontaneous alteration or if they are secondary to exogenous factors such as Epstein-Barr virus (EBV). Bassili and coworkers believe that EBV could be related to the stimulus that starts a specific immune response against melanocytes [37]. Sugita et al. [31] studied the cross-reaction between tyrosinase peptides and cytomegalovirus (CMV) antigen by T cells in VKH patients. Cytomegalovirus (CMV) infection could stimulate production of T cells that cross-react with tyrosinase by a mechanism of molecular mimicry and could be responsible of the onset of VKH. Also VKH-like disease has been reported in patients treated with interferon (IFN)-a2a for chronic viral hepatitis [38–40].

MHC class I molecules can interact with other immune cells and can play a role in the pathogenesis of VKH. Killer cell immunoglobulin-like receptors (KIR) are members of a group of regulatory molecules found on subsets of lymphoid cells, which either activate or inhibit natural killer (NK) cells and certain subsets of T lymphocytes [41, 42]. Levinson et al. reported that VKH

patients had a higher frequency of KIR gene-associated B haplogroup. Signals transduced by the activated KIRs upon their binding to putative class I ligands may overcome HLA class-I-dependent inhibition and trigger natural killer (NK) reactivity, leading to the autoimmune condition in VKH [43].

Recently, an increased expression of IL-23 (interleukin-23) and elevated production of IL-17 (interleukin-17) have been reported in PBMC of VKH patients [44]. This finding led to the hypothesis that IL-23 stimulated production of IL-17 by $CD4^{+}$T cells and these may be involved in the development of VKH syndrome [45].

Histopathology

VKH has been described as a bilateral granulomatous uveitis, similar to sympathetic ophthalmia. The main feature of VKH is a diffuse thickening of the uveal tract caused by a nonnecrotizing granulomatous inflammation that predominates in the juxtapapillary choroid, with less involvement at equatorial and peripheral areas [46].

In 1977, Perry and Font reported nine eyes with chronic VKH, with a granulomatous response in only four of them. In these cases, a diffuse inflammation of the uvea consisting of epithelioid cells, lymphocytes, some plasma cells, and multinucleated giant cells was observed; epithelioid cells and multinucleated giant cells contained melanin pigment. There was a relative sparing of the choriocapillaris from inflammation; in long-standing cases, inflammation may extend into the choriocapillaris and retina, resulting in chorioretinal adhesions.

In the uveitic stage, the neurosensory retina is detached by an eosinophilic exudate with proteinaceous material. In immunohistochemical studies, the presence of T suppressor/cytotoxic cells and macrophages [46, 47] and T lymphocytes close to uveal melanocytes, which express class II MHC, has been reported [29, 48]. These inflammatory cells do not reach the choriocapillaris or retina, but do involve the ciliary body and iris.

In the chronic stage, the melanocytes tend to disappear from the choroid; focal collections of lymphocytes, pigment-laden macrophages, epithelioid cells, and proliferative retinal pigment epithelium (RPE) cells with altered histologic appearance are noted. They are virtually identical to Dalen-Fuchs nodules, described in sympathetic ophthalmia, and become more evident in the convalescent stage [49].

In the convalescent stage, a mild to moderate nongranulomatous inflammatory cell infiltration occurs, mainly with lymphocytes and macrophages. Choroid is depigmented, exhibiting spindle cells without melanin granules; these changes are observed clinically as the "sunset glow" fundus image [50]. Histopathologic analysis shows focal RPE loss with chorioretinal adhesions [46].

RPE proliferation has the clinical appearance of hyperpigmented changes on ophthalmoscopic examination. Subretinal neovascular channels and mound-like pigmented lesions may also be observed. In other cases, hyperplasic RPE can be reorganized as subretinal fibrosis [50]. There is also a combination of photoreceptor degeneration and gliosis of the overlying neural retina. The choriocapillaris has a degenerative process, and chorioretinal adhesions are apparent at these sites [50]. In this phase, Dalen-Fuchs-like nodules may be observed. They are constituted by proliferated RPE with few inflammatory cells and sometimes are calcified.

Friedman and Deutsch-Sokol made a clinic-pathologic correlation of Sugiura sign; absence of pigment in the basal epithelial layer at the limbus was found. Extraocular changes have also been studied. Vitiligo shows aggregates of lymphocytes, mostly around sweat glands, hair follicles, and small blood vessels of the dermis; melanin-laden cells are disrupted [51]. Dermal inflammatory infiltrate with melanin-containing macrophages is observed. Alopecia areas have a mononuclear cell infiltration with discharge of melanin pigment from the matrix into the dermal papillae and surrounding perifollicular sheaths of hair follicles [46].

These previous reports confirmed what Rao and coworkers proposed: "… at tissue level, there is a role of autoimmunity in the pathogenesis of

VKH. Choroidal melanocytes are the target of an inflammatory response and immune reaction mediated by cells, amplifies the inflammatory response with final tissular destruction" [46].

Immunogenetics

It is well known that VKH concentrates in certain ethnic groups, leading to the assumption of an important genetic basis. The most important immunogenetic association in VKH patients is with the major histocompatibility complex (MHC) class II, mostly with HLA-DR4 in Japanese, Chinese, American Indians, and patients with Mexican and Central American background [52–57]. In Japanese patients, HLA-DR4 has been found more frequently in VKH patients compared to normal subjects. Zhang and coworkers [54] found that 75% of Chinese patients with VKH are HLA-DR positive, compared to 23.1% of the control group. Martínez and coworkers [55] studied eight VKH patients with Indian-Cherokee ancestry. They found HLA-DR52, DR6, DR3, DR13, or DR8 haplotypes, which were associated to DR52 in seven patients. In Hispanic patients [56], an association to DR4 and/or DR1 was found in 85% of VKH patients, compared to 35% of the control group, which suggests a common epitope in gene DRβ1 as a pathogenic mechanism.

Our group reported a strong association with HLA-DR4 (RR = 5.3) in 48 Mexican-Mestizo VKH patients [13, 22]. A similar study in Japanese patients demonstrated an association with HLA-DQ4 with an RR = 9.9 to develop the disease. Ishikawa, Ito, and Rutzen reported VKH in homocygotic twins, HLA-DR4 positive, which emphasizes the role of immunogenetics in the pathogenesis of the disease [58].

Shindo et al. used polymerase chain reaction (PCR) to limit the length of the fragments of polymorphism (PCR-RFLP) and to analyze type II alleles of the MHC and found that DRB1*4 alleles codify specifically for DR4 in 100% of patients with DRB1*0405 or DRB1*0410. Only DRB1*0405 and DQB1*0401 had increased levels when compared to the control group. Reports of studies conducted on Brazilians of different ethnic origins and Japanese demonstrated that MHC class II genes were clearly involved, with DRB1*0405 allele being the major susceptibility factor [52, 59].

In a study of 46 Mexican-Mestizo VKH patients compared with 170 controls, no association with any particular DRB1*04 subtype was found; however, a strong positive association of VKH with DRB1*0101 was found ($p = 0.009$, OR = 4.2). When looking for DRB1*04 and/or DRB1*0101 in the same individual, 89.1% (41/46) of the patients carried either one [13]. Another allele with predisposition for developing disease is DQA1*0301 [60]. In Chinese patients, Yang reported association with HLA DRw53 in 63.6% of 223 VKH patients compared with 150 controls [20].

Clinical Features

In 1978, the American Uveitis Society (AUS) established the diagnostic criteria for VKH which were later revised by an International Committee in 2001 (Table 19.1) [61]. These criteria serve as a basis in the diagnosis and subsequent management of VKH patients.

The clinical course of the VKH syndrome has four stages or phases:

- *Prodromal Stage*. It can mimic a viral illness; fever, nausea, vertigo, orbital pain, and neurologic signs such as meningismus can be observed, and rarely cranial nerve palsies, transverse myelitis, and optic neuritis may be present. These symptoms are present for 3–5 days [10, 62, 63]. Photophobia and tearing may follow 1–2 days later [64]. Cerebrospinal fluid pleocytosis may be present at this stage [65].
- *Acute Uveitic Stage*. It follows the previous phase and lasts for several weeks. It is characterized by bilateral posterior uveitis. It begins with bilateral blurry vision in up to 70% of patients [64]. One eye is affected first in 30% of patients; the second eye is involved

Table 19.1 Diagnostic criteria for Vogt–Koyanagi–Harada disease [61]

Complete Vogt–Koyanagi–Harada disease (criteria 1–5 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
2. No clinical or laboratory evidence suggestive of other ocular disease entities
3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined)
a. Early manifestations of disease
(1) There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disk hyperemia), which may manifest as one of the following:
(a) Focal areas of subretinal fluid
(b) Bullous serous retinal detachments
(2) With equivocal fundus findings, both of the following must be present as well:
(a) Focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, subretinal fluid pooling, and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography
(b) Diffuse choroidal thickening, without evidence of posterior scleritis by ultrasonography
b. Late manifestations of disease
(1) History suggestive of prior presence of findings from 3a, and either both (2) and (3) below or multiple signs from (3)
(2) Ocular depigmentation (either of the following manifestations is sufficient)
(a) Sunset glow fundus
(b) Sugiura sign
(3) Other ocular signs
(a) Nummular chorioretinal depigmented scars
(b) Retinal pigment epithelium clumping and/or migration
(c) Recurrent or chronic anterior uveitis
4. Neurological/auditory findings (may have resolved by time of examination)
a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors; headache alone is not sufficient to meet definition of meningismus, however)
b. Tinnitus
c. Cerebrospinal fluid pleocytosis
5. Integumentary findings (not preceding onset of central nervous system or ocular disease)
a. Alopecia
b. Poliosis
c. Vitiligo
Incomplete Vogt–Koyanagi–Harada disease
Criteria 1–3 and either 4 or 5 must be present
Probable Vogt–Koyanagi–Harada disease
Isolated ocular disease
Criteria 1–3 must be present

1–10 days later [66]. Signs of posterior uveitis start with thickening of the posterior choroid, hyperemia and edema of the optic disk, and retinal edema [62]. Later, choroidal inflammation becomes multifocal and is associated with alterations of the overlying pigment epithelium. The retinal pigment epithelial barrier breaks down, and multiple serous retinal detachments develop. This is the characteristic clinical image of Harada's form of the disease (Fig. 19.1).

- Some days later, intraocular inflammation becomes diffuse and anterior segment is affected; cells, flare, mutton fat keratic precipitates, and Koeppe and Busacca iris nodules are observed (Fig. 19.2). In most patients, intraocular pressure is low; however, in some cases, edema and ciliary body inflammatory cell infiltration can cause a forward displacement of the lens–iris diaphragm with narrowing of the anterior chamber angle and elevate intraocular pressure [67]. These cases may mimic angle-closure glaucoma in the uveitic stage of VKH syndrome. Few reports describe an annular choroidal detachment sometimes associated with prominent serous retinal detachment [68].
- *Convalescent/Chronic Phase*. There is a gradual integumentary and uveal depigmentation several weeks after the acute phase. It can last for several months to years; severity is related to time to diagnose and type of treatment. Perilimbal vitiligo, also known as "Sugiura sign," has been described as the first

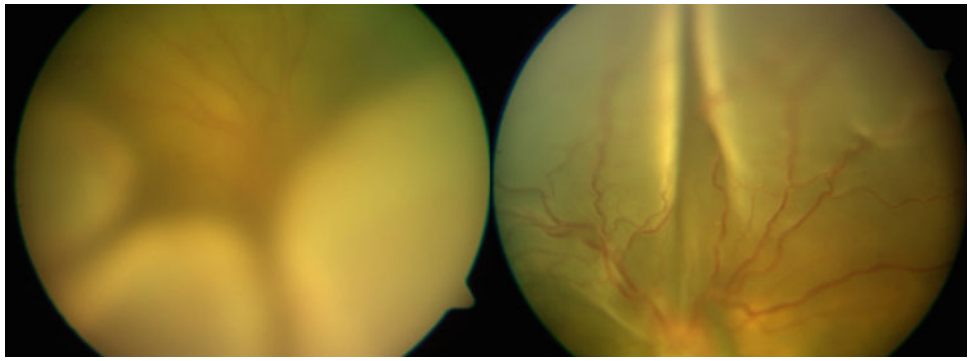

Fig. 19.1 Posterior pole at acute uveitic stage. Multiple serous retinal detachment and optic disk edema

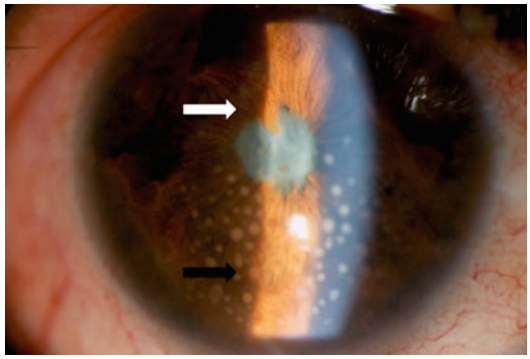

Fig. 19.2 Anterior segment at acute uveitic stage. Mutton fat keratic precipitates (*black arrow*) and posterior synechia (*white arrow*)

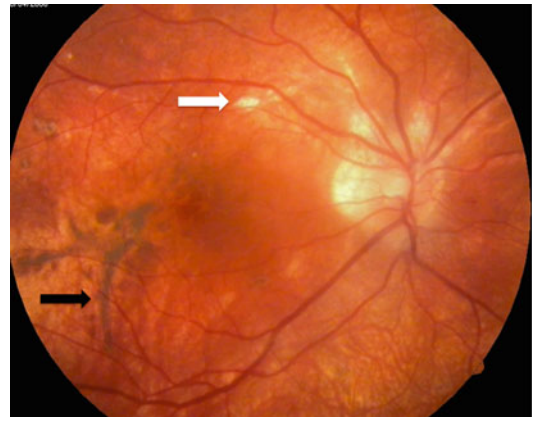

Fig. 19.3 Convalescent phase. "Sunset glow fundus," pseudo-Dalen-Fuchs nodules (*white arrow*), RPE migration (*black arrow*)

depigmentation [51] mainly in Japanese patients [69]. Cutaneous depigmentation may involve face, eyelids, and trunk [10].

- Two to three months after the uveitis stage, choroidal depigmentation develops. It is observed as an orange-red discoloration that simulates the image of sunset, with a pale disk, therefore known as "sunset glow fundus." It has been described more frequently in Asian [62] and Hispanic patients [70]. Numerous small, yellow, well-circumscribed areas of choroidal-retinal atrophy, known as "pseudo-Dalen-Fuchs nodules," appear in the inferior midperiphery of the fundus; RPE migration is clinically observed as areas of hyperpigmentation. Posterior uveitis reaches a smoldering stage as more melanocytes disappear from the choroid (Fig. 19.3).
- *Recurrent Phase*. It is characterized by a smoldering panuveitis with exacerbations of anterior or posterior uveitis. Anterior uveitis is granulomatous with mutton fat keratic precipitates and stromal iris nodules. Posterior uveitis can be seen as serous retinal detachments.
- Posterior segment recurrences are infrequent and may be related to late or suboptimal treatment, inadequate immunosuppression, premature withdrawal, or rapid tapering of steroids [71]. In these cases, there is still uveal pigment in the

choroid; therefore, a subclinical inflammation persists [72]. If chronic anterior uveitis ensues, severe chorioretinal atrophy may develop [73].

- Ocular hypotony has been described secondary to ciliary processes atrophy, cyclitis as part of the severe chronic anterior uveitis, and detachment of the ciliary body in patients without any systemic corticosteroid treatment [74]. In this phase, complications such as cataracts, glaucoma, subretinal neovascularization, and subretinal fibrosis may be observed. Arteriovenous anastomoses may develop [75], and linear streak fundus lesions simulating ocular histoplasmosis syndrome may be seen [76].

Extraocular Manifestations

In the prodromic phase, neurological manifestations are frequent. Sixty-seven percent of patients may present with generalized muscle weakness or headache [77]; periocular pain is referred in 73.9% of cases [78]. Meningismus, vertigo, tinnitus, and hearing loss can be found [79]. Mental changes range from mild confusion to psychosis, hemiparesis, dysarthria, and aphasia, and rarely seizures may occur [80]. In this stage, pleocytosis is reported in 80% of cases [65].

Auditory signs appear simultaneously with ocular inflammation even though they can be the first sign of the disease and are present in 75% of patients. Dysacusia may have a sudden onset and is associated with tinnitus and vertigo [81]; it may resolve weeks to years after onset. Deafness is reported in 30% of patients. Audiometry shows a central origin with cochlear involvement, mainly in the high frequency range (up to 30 dB); in early stages of the disease, all frequencies may be affected [21, 65, 82].

VKH should be considered in the differential diagnosis of patients with acute onset of headache followed by decreased visual acuity [83].

Integumentary signs are significant and more prevalent in Japanese than in Hispanic, Mexican-Mestizo, or Argentinian patients. In the prodromic phase, 27–72% of patients have an increased skin and scalp sensitivity [21].

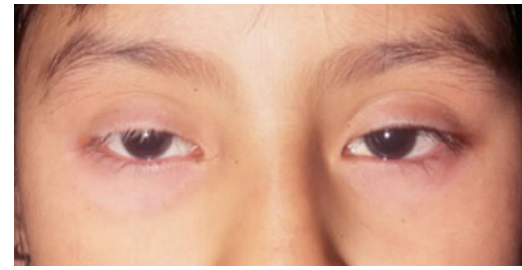

Fig. 19.4 Integumentary affection in convalescent stage. Cutaneous depigmentation of face and eyelids

In the convalescent stage, eyebrows, brows, and hair poliosis develop concurrent with posterior pole depigmentation. In these phases, vitiligo affecting eyelids, head, and trunk is observed (Fig. 19.4). Frequency depends on race, ranging between 10% and 63%; it is less frequent in Hispanic [77] than in Asian patients [65]. Alopecia has been reported in 35–73% of cases; it appears weeks to months after the onset of meningeal or ocular symptoms [84].

Ancillary Test

Diagnosis is based on clinical criteria (see Table 19.1); however, there are several tests that can help in diagnosis in atypical cases, when complications are seen and during follow-up.

Fluorescein Angiography (FA)

Patterns correlate with the stage of disease; in Table 19.2, the correlation of clinical and fluorescein angiographic findings is described. In the acute uveitis stage, the most common findings are optic disk hyperfluorescence and disseminated spotted choroidal hyperfluorescence (94.4% each), choroidal hypofluorescence (83.3%), and subretinal pooling of dye in 50% of patients [85]. Brinkley et al. suggested that subretinal pooling of dye and focal dye leaks at RPE level may be diagnostic angiographic features of VKH (Fig. 19.5) [86].

In the chronic uveitic stage, findings include spotted hyper- and hypofluorescence areas ("salt-and-pepper" appearance) and optic disk

Table 19.2 Correlation of clinical and fluorescein angiographic findings

Fluorescein fundus angiography patterns	Clinical correlation
Uveitic stage	
Disseminated spotted choroidal hyperfluorescence	Choroiditis
Subretinal pooling of dye	Subretinal fluid
Optic disk hyperfluorescence	Optic disk inflammation
Convalescent stage	
Spotted hyper- and hypofluorescence	
(Salt-and-pepper pattern)	RPE damage
Choroidal hypofluorescence	Delayed choroidal filling
Blockage of choroidal fluorescence	RPE migration
Retinal vascular wall hyperfluorescence	Retinal vasculitis
Localized choroidal hyperfluorescence	Choroidal neovascularization
Dot-like equatorial hyperfluorescence	Nummular whitish-yellow scars
Mixed bands of hyper- and hypofluorescence	Choroidal folds
Reticular band hypofluorescence (reticular pattern)	Unknown

RPE retinal pigment epithelium

hyperfluorescence in 72.7% of cases each, and blockage of choroidal fluorescence (63.6%).

In the convalescent stage, spotted hyper- and hypofluorescence is reported in 73.3% of eyes, blockage of choroidal fluorescence in 56.7%, and dot-like equatorial hyperfluorescence in 43.3%, which are the most common angiographic findings. In 40% of angiographies, optic disk hyperfluorescence secondary to residual optic disk capillary damage can be observed (Fig. 19.6) [85, 87].

Rao et al. suggested that subretinal bands of hyper- and hypofluorescence could be a manifestation of inflammatory thickening of the choroid and represent choroidal folds. They are seen in 27.8% of patients in acute stage and are less frequent during other stages [88, 89]. Hyperfluorescence of isolated segments of vessels may be observed at equatorial and peripheral veins (16.7–35%) [23, 85]. In cases of posterior recurrences, FA revealed multiple early hypofluorescent lesions of delayed choroidal filling with late hyperfluorescence [72].

Fluorescein angiography is also useful for detecting complications such as arteriovenous and retinochoroidal anastomosis, optic disk neovascularization, and choroidal neovascularization. Retinochoroidal and arteriovenous anastomoses represent collateral vessels over areas of RPE damage [65, 89]. In patients with VKH, angiographic findings are important to corroborate diagnosis (see Table 19.2).

Indocyanine Green Angiography (ICGA)

ICGA is the method of choice to evaluate choroidal disorders showing minimal and subclinical changes. In VKH it is useful for initial evaluation and follow-up. Findings include:

- Early hyperfluorescence and leakage of choroidal stromal vessels that indicates a severe choroidal stromal inflammatory vasculopathy.
- Hypofluorescent dark dots. This is the most constant and relevant pattern for follow-up purposes and is observed in all patients at disease onset. These are signs of altered vascular permeability and recur in 75% of patients. In ICGA they can be distinguished as follows:
  - A. Dark dots present in intermediate phase (8–12 min) and become isofluorescent in late phase. This pattern indicates the presence of small, partial thickness inflammatory foci (granuloma).
  - B. Dark dots present in the late phase (from 20 to 22 min onward). This pattern indicates whole thickness, large choroidal stromal foci (granuloma). The latter type of lesions can also cause additional choriocapillaris nonperfusion, a second cause of hypofluorescence. Obviously, both patterns do coexist, indicating inflammatory foci of different sizes [90].
- Fuzzy vascular patterns of large stromal vessels. They represent a diffuse inflammatory stromal vasculopathy. This pattern is seen in the intermediate ICG phase. In the late phases, a diffuse stromal hyperfluorescence is seen.

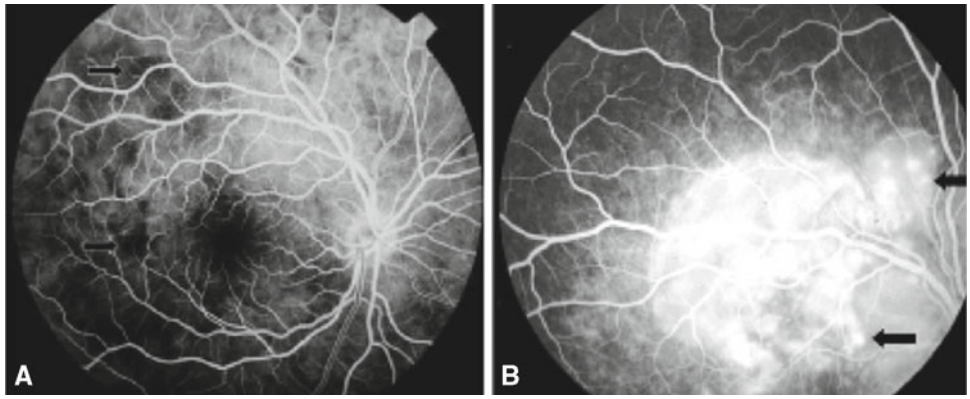

Fig. 19.5 Acute uveitic stage: (**a**) choroidal hypofluorescence due to delayed choroidal filling (*arrows*) and (**b**) spotted choroidal hyperfluorescence (*black arrows*) and subretinal pooling of dye

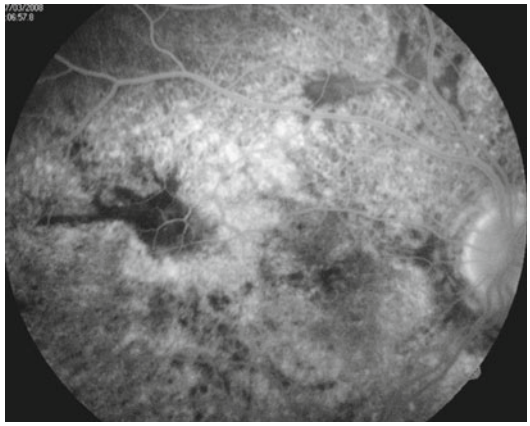

Fig. 19.6 Fluorescein angiography at convalescent stage. Spotted hyper- and hypofluorescence in salt-and-pepper pattern and blockage of choroidal fluorescence

- Disk hyperfluorescence is associated with severity of disease and is an important indicator of response to initial therapy.
- Disturbance/delay in early choriocapillaris circulation.
- Hyperfluorescent pinpoints and diffuse subretinal hyperfluorescence.
- Diffuse late hyperfluorescence. It is observed in acute and subacute disease [1].

Therefore, ICGA is a method used to determine the pattern of choroidal involvement and to evaluate subclinical disease and is an important tool for follow-up [91, 92]. ICG has also been used to confirm the presence of choroidal neovascular membrane and subretinal fibrosis that is shown as a late staining without any leakage of dye [91].

Cerebrospinal Fluid Analysis (CSF)

Cerebrospinal fluid analysis (CSF) is rarely needed, but it provides data to support the diagnosis; it has been considered as a major symptom/criterion in Sugiura's and AUS diagnostic criteria. It helps to diagnose atypical VKH and to rule out other diseases [93].

At prodromal stage of the disease, CSF will show pleocytosis in 71.6–100% of samples [92, 94, 95] composed mainly of lymphocyte cells, and a small number of macrophages with melanin basophilic granules [24]. These findings can be observed in 97% of VKH patients within 3 weeks of inflammation onset and may persist for about 8 weeks [29, 64]. Melanin-laden macrophages have been identified and suggest that these cells are responsible for the pleocytosis that is present in the early stages of the disease [24]. CSF is also valuable to make a differential diagnosis with sarcoidosis, meningoencephalitis, and lymphoma [10, 93].

Ultrasonography (USG)

Ultrasonography (USG) is of great importance when there is an inadequate pupillary dilatation

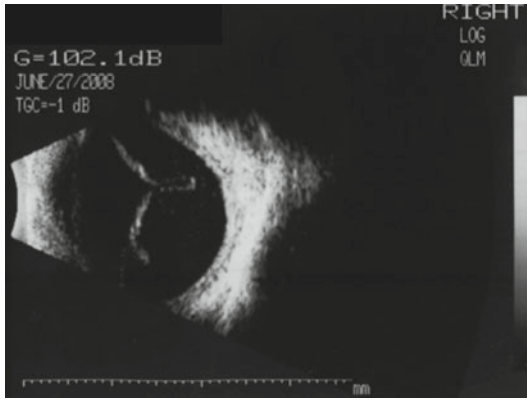

Fig. 19.7 B-scan ultrasound at uveitic stage showing diffuse low reflective choroidal thickening and serous retinal detachment

due to posterior synechiae that may obscure the view of the fundus or when presentation is atypical and extraocular manifestations are absent. USG manifestations were described by Forster et al. and include:

- Diffuse, low-to-medium reflective thickening of the posterior choroid
- Serous retinal detachment located in the posterior pole or inferiorly (Fig. 19.7)
- Some vitreous opacities with no posterior vitreous detachment
- Posterior thickening of the sclera or episclera

USG is an aid when other disorders need to be differentiated. For example, in posterior scleritis, the posterior wall of the globe is flattened, and an increased thickness of the posterior sclera and episclera and retrobulbar edema may be seen. USG has also been used to make differential diagnosis with benign reactive lymphoid hyperplasia of the uvea, choroidal melanoma, and other granulomatous disorders of the choroid such as tuberculosis or sarcoidosis [63].

Ultrasound Biomicroscopy (UBM)

Ultrasound biomicroscopy has been used to diagnose ciliochoroidal detachment and to follow up response to treatment. In chronic phases, ciliary body returns to normal thickness with homogeneous internal reflectivity and normal delineation of ciliary processes [94]. UBM also has been used to detect ciliary body edema, to demonstrate partial or complete angle closure, and to follow up pars plana decreasing thickness after treatment [9, 95]. Pars plana thickness is helpful for estimating the remaining inflammatory changes in the ciliary body [95].

Mantovani et al. demonstrated the presence of a supraciliary effusion which explained the myopization observed in early stages in some VKH patients [92].

Magnetic Resonance Image (MRI)

Andreoli et al. reported that magnetic resonance imaging (MRI) has not been useful in VKH diagnosis [87]; however, MRI has been used to differentiate VKH from scleritis, primary intraocular B-cell lymphoma, [96] sarcoidosis, [63], and multiple sclerosis [92].

Johnston and Teitelbaum described the advantages of MRI in VKH diagnosis: (1) excellent visualization of choroidal thickening; (2) differentiation from sclera, choroid, and retina; (3) detection of subclinical ocular disease or CNS affection. It has been reported that MRI may show bilateral annular choroidal detachment and choroidal thickening with scleral sparing [65].

Electrophysiology

Electrooculogram (EOG) and electroretinogram (ERG) present variable degrees of alteration based on disease stage. In ERG, a and b waves are slightly depressed in initial phases and can continue to be depressed for a long period of time, returning toward normal in the chronic and recurrent phases of the illness. In EOG, luminosity peak is decreased in prodromic and uveitic stages as reported by Jacobson [97]. Eventually, luminosity peak of EOG and amplitude of ERG return to basal values [98].

Our group [99] reviewed retinal function of eight VKH patients (16 eyes) with inactive disease (approximately 18 months without inflammation); we found that ERG in scotopic,

mesopic, and photopic phases showed b wave depression in 63.15% of patients. Color vision test (Farnsworth-Munsell D15, 100, anomaloscopy, and Ishihara Test) showed a severe dyschromatopsia with no axis in 45.94% of cases. Contrast sensitivity test was altered in 78.37% of the eyes, and automated Humphrey visual fields had a generalized, decreased retinal sensibility in 20.58% of eyes, concentric visual field reduction in 13.5%, and nasal defects in 5.88%. Multifocal ERG (mERG) had abnormal amplitude and implicit time in all patients.

Chee et al. studied visual function in patients with VKH with mERG and reported that in patients who do not have peripapillary atrophy, visual fields do not have alterations but have a subclinical retinal dysfunction; otherwise, in patients with chorioretinal atrophy, visual fields were abnormal and had a significant visual dysfunction. In these patients, mERG was reduced in amplitude with a retarded implicit time, while patients with sunset glow funds and with no peripapillary atrophy had diminished mERG amplitude but no affection of the implicit time [100]. If peripapillary atrophy is observed after the acute phase, then it may be useful to perform multifocal electroretinography to evaluate the amount of inflammation at that time point and hence modify immunosuppressant therapy as appropriate. Its occurrence would also be an indicator that these patients will need closer monitoring for recurrences [101].

Multifocal ERG studies used to evaluate macular function in uveitic stage demonstrated severe impairment. After treatment with immunosuppressive agents, although a good VA recovery was seen, a delayed and limited recovery of macular function was detected after 12 months of follow-up. This study demonstrated decreased amplitudes and prolonged latencies of N1 and P1 waves that reflect the function of photoreceptor cells. This behavior suggests that dysfunction of overlying photoreceptors (rod and cone cells) may be a hallmark in VKH syndrome or may be secondary to the diffuse pathologic changes in the choroid and/or retinal pigment epithelium. Yang et al. reported that VA improves sooner than mERG and that VA improvement was always better than mERG results [102].

Our ERG and visual field results suggest that photoreceptors are damaged, not only in the macular area, and that a diffuse pattern of alteration exists on ganglionar cells and external retina. This shows that even though visual acuity is good in patients with VKH, retinal function is severely altered [99].

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a helpful resource that can be used to diagnose and to monitor the resolution of serous retinal detachment. In the acute phase, is a diagnostic technique that evidence small serous retinal detachments that are not detected by slit-lamp biomicroscopy and can demonstrate intraretinal edema. In chronic phases, RPE thickening or proliferation may be observed [103].

Gupta et al. described four patients with VKH in uveitic stage who were studied using spectral-domain OCT. They found RPE undulations, with pockets of subretinal fluid (SRF) anterior to the trough of the undulations and multiple small bumps on the RPE surface. After treatment with corticosteroids, undulations resolved between 2 and 4 weeks with simultaneous resolution of the serous detachment. Undulations may be caused by a thickened choroid infiltrated with inflammatory cells that push the RPE forward and correspond to the hypofluorescent lines seen in FA. In five eyes, bands of moderate hyperreflectivity within the serous detachment were seen, probably representing fibrinous bands [104].

Maruyama reported evidence suggestive of retinal cystoid spaces in acute VKH syndrome. Intraretinal fluid accumulation was seen in the outer retina as well as serous retinal detachment [105]. Tsujikawa et al. found vertical thin walls of large cystoid spaces within the subretinal fluid in 43% of their VKH patients. They usually disappeared immediately after the onset of treatment, along with a reduction of the subretinal fluid. They assumed that these thin structures might represent subretinal fibrosis or fibrin membranes [106].

Yee et al. found cystoid spaces in 67.9% of the eyes using OCT3. They did not find a fibrin membrane, and the photoreceptor layer showed fluid

accumulation. In the acute stage, there is swelling of the photoreceptors that progressed from the junction of the inner and outer segments to the distal photoreceptors. If changes are reversible, outer segments can regain their normal folded structures and intraretinal space will be resolved [107].

Our group studied prospectively 70 eyes of 35 patients with VKH, 6 eyes (group 1) in uveitic stage, 61 in convalescent (group 2), and 3 in recurrent phase (group 3) using spectral-domain OCT. In group 1, all had serous retinal detachment, with worse VA in those where fovea was involved. In group 2, OCT was normal in 40.6%, retinal thinning was observed in 28.1%, epiretinal membrane in 10.8%, RPE hypertrophy in 9.3%, RPE detachment in 4.6%, and subretinal fibrosis in 10.8%. Worse VA was found in patients with subretinal fibrosis and RPE detachment. In group 3, two eyes had choroidal neovascularization and were the ones with worse VA and one had CME. We concluded that all phases of VKH diseases can be studied and that retinal and RPE characteristics, may be correlated with VA [108].

Anterior Segment Optical Coherence Tomography

Anterior segment OCT (AS-OCT) is a method to visualize the anterior segment noninvasively to obtain quantitative information. Yamamura et al. described a patient in which bilateral acute angle-closure glaucoma was diagnosed; AS-OCT images showed a shallow anterior chamber, narrow chamber angle, and supraciliary fluid in both eyes. The iris showed anterior bowing consistent with a pupillary block in both eyes. After treatment with systemic corticosteroids, anterior chamber returned to normal depth, ciliary body reverted to its normal position, and the supraciliary fluid disappeared in both eyes [109].

Differential Diagnosis

Differential diagnosis should include sympathetic ophthalmia, idiopathic central serous chorioretinopathy, acute leukemia, primary intraocular B-cell lymphoma, metastatic carcinoma, uveal melanocytic proliferation associated with systemic carcinoma, idiopathic uveal effusion syndrome, posterior scleritis, acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent white dot syndrome, Behcet's disease, Lyme disease, sarcoidosis, and benign reactive lymphoid hyperplasia of the uveal tract.

Systemic physical exam and blood workup to rule out systemic disease and malignancy should always be performed [87].

In the acute uveitic stage of VKH, disease choroiditis may cause papillitis, which is similar in appearance to optic neuritis [10]. Vogt–Koyanagi–Harada disease should be considered in the differential diagnosis of bilateral optic disk swelling, even in the absence of the characteristic extraocular manifestations of this disease. This is particularly true when the neuroimaging studies reveal no abnormality and when CSF analysis does not show pleocytosis. In such cases, fluorescein angiography of the retina is highly useful in the diagnosis of VKH disease [10].

Sympathetic Ophthalmia

It should always be considered, even though in most of these cases there is a previous history of ocular trauma penetrating (injury or surgical) or not penetrating (cyclocryotherapy, helium and proton YAG laser) in the contralateral eye.

Clinical signs are similar to those findings in VKH. In sympathetic ophthalmia (OS), granulomatous inflammation of the anterior segment is more common. Patients also have disk edema and hyperemia, choroidal thickening, and serous retinal detachments. Dalen-Fuchs nodules similar to the nummular lesions seen in VKH are frequently observed [63].

Primary Intraocular B-Cell Lymphoma

This disease must be suspected in patients older than 60 years, when there is a bilateral chronic uveitis associated with neurologic signs and symptoms. In general, lymphomas arising from

visceral organs tend to involve the uvea, in contrast with CNS lymphomas which affect vitreous, retina, and subretinal and sub-RPE areas [21]. On ophthalmologic examination, a multifocal, raised, lobulated, yellowish, subretinal, and sub-RPE lesion that involves the posterior pole is observed; it can be associated with satellite lesions, which may mimic Dalen-Fuchs nodules.

Posterior Scleritis

Posterior scleritis may present with decreased visual acuity and serous retinal detachment and pain with eye movements may be referred; it is usually unilateral. Clinical examination discloses the presence of a circumscribed mass, choroidal folds, retinal striae, choroidal and/or retinal detachment, and papillitis. When orbitary involvement is present, proptosis, palpebral edema or retraction, diploplia, and even ptosis can be seen. Ultrasound reveals flattening of the posterior aspect of the globe, retrobulbar edema, and high internal reflectivity of the thickened sclera [110]. In 45% of cases, a systemic disease is the cause of this entity, including systemic lupus erythematosus, rheumatoid arthritis, gout, and giant cell arteritis.

Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

Patients develop sudden loss of central vision after a viral prodrome. Clinically, multiple white-yellow flat-to-placoid lesions at the level of the RPE with minimal to no vitreous inflammation are seen. They resolve spontaneously and rapidly; VA returns to normal. On FA, lesions show early blocking of choroidal fluorescence, followed by late staining of the lesions [63].

Multiple Evanescent White Dot Syndrome (MEWDS)

It is a unilateral disease that affects young women and is characterized by a sudden drop in vision to the 20/200 range, often with an afferent pupillary defect. Clinically, multiple, small, and white lesions within vascular arcades are seen; sometimes a few vitreous cells can be found. It is self-limiting, and VA returns to normal within a few weeks. FA reveals multiple "wreath-like" areas of hyperfluorescence around the periphery of each of the white dots that fill in centrally in the late phases of the angiogram; staining of the optic disk and occasional perivascular sheathing may be observed [111].

Uveal Effusion Syndrome

It is a bilateral asymmetric disease; eye examination reveals a subacute serous retinal detachment that progresses slowly. It is associated with minimal intraocular inflammation, and sometimes a choroidal detachment can be found. Males between 34 and 66 years are more frequently affected. FA and ultrasound may mimic VKH. FA shows numerous fluorescent patches in the subretinal space during the serous detachment phase; later pigment migration resulting in a mottled fluorescence resembles the convalescent phase of VKH syndrome. These patients do not respond to corticosteroid treatment, and retinal detachment may become total and permanent [70, 112].

Sarcoidosis

Forty to fifty percent of patients with sarcoidosis develop ocular inflammation [113]. A bilateral, asymmetric, chronic granulomatous uveitis is observed [114]. Patients may present with meningoencephalitis in 5% of the cases; neurologic signs are focal, including cranial nerve palsies, peripheral neuropathies, and aseptic meningitis. Classical retinal signs of vasculitis are venous sheathing and candle wax drippings. CSF, CT, and MRI are useful in making the diagnosis [115]. Serum angiotensin converting enzyme level and lysozyme may be helpful; diagnosis is confirmed with a biopsy of the suspected granulomatous tissue [113].

Lyme Disease

Exudative retinal detachment has been described in these patients, as well as neuro-ophthalmic involvement that manifests as cranial neuropathies of the II, III, IV, VI, and VII cranial nerves and optic neuritis [116]. It is caused by a spirochete, *Borrelia burgdorferi*. Diagnosis is based on exposure, a skin rash, positive serologic test for *B. burgdorferi*, IgM in early stages, or high titers of IgG in later phases (after 4 weeks of onset). Sometimes lymphadenopathy is present [117, 119].

Other causes of serous retinal detachment should be included such as lupus erythematosus choroiditis, bilateral diffuse melanocytic hyperplasia, toxemia of pregnancy, and renal disease associated with anasarca [63].

Treatment

The goal of treatment for VKH is to suppress the active intraocular inflammation and prevent potential visual impairment [45]. The standard initial treatment for VKH is early, aggressive corticotherapy. Dosing regimens range from 1 to 2 mg/kg/day, with a slow tapering over 6 months. This has been shown to improve the prognosis by reducing length of disease and incidence of chronic phase and decreasing extraocular manifestations of VKH [62, 119].

Some authors [120, 121] analyzed the results of initial therapy with high-dose pulse intravenous (IV) corticosteroid in all patients. The authors found almost complete resolution of serous retinal detachment by day 7. These results suggest that IV corticosteroid may restore the permeability of chorioretinal vessels. Kitaichi et al. divided steroid treatment before 13 days and after 14 days of disease onset. The "early" group received systemic steroids for 10.9 months versus the "late" group who were treated for a mean of 24.2 months. Visual outcome was good in both groups [122]. Ohno et al. reported that patients who received systemic corticotherapy in the first 30 days of the disease had less multisystem involvement [123]. Recently, Jap et al. reported that the extent of pigmentary changes in VKH patients seemed to depend on the amount of corticosteroids received during the acute phase of the disease [101]. If patients were given an initial high dose of corticosteroid, this may preserve more melanocytes and may reduce the extent of pigmentary damage [124].

Even with appropriate treatment with steroid therapy, many patients experience recurrences and associated complications. For that reason, nonsteroidal immunosuppressive therapy (IMT) has been considered important in the treatment of VKH. The American Uveitis Society concluded that IMT is required to control the inflammation [125, 126]. The International Uveitis Study Group consensus panel included VKH in the group of diseases in which IMT treatment is "mandatory." However, until now the benefit of early nonsteroidal immunosuppressive treatment versus classic high-dose systemic corticosteroid treatment has not been clearly demonstrated. Rao has advocated the use immunomodulatory agents in chronic disease and chronic recurrent phases of VKH [127]. Paredes et al. analyzed visual outcomes in 13 patients who received steroids alone/delayed IMT or early initiation IMT. Of the first group, three of five patients had deterioration of VA and one showed improvement. In group 2, seven of the eight patients showed improvement, but the author did not describe in what stage of the disease patients were when treated [126]. Anterior segment inflammation is treated with topical steroid drops [87].

Cytostatic and cytotoxic agents such as cyclosporine, azathioprine, cyclophosphamide, chlorambucil, or mycophenolate mofetil have been used successfully in the treatment of VKH [63, 128–131]. Kim and Yu evaluated outcomes of azathioprine at low doses. They showed good results in 86.5–90% in the acute uveitic and chronic recurrent groups, respectively. They also showed that azathioprine may show superior outcome with less cumulative corticosteroid dose and that in patients with azathioprine most eyes without macular pathology or severe cataract showed good visual outcomes; visual prognosis mainly depended on the presence of complications [131]. Agarwal et al. used triple agent IMT

in patients that failed to respond to high-dose corticosteroid or were intolerant. They used azathioprine, cyclosporine, and steroids. Patients had a rapid resolution of retinal detachment with improvement of VA. They consider using this regimen early in the course of the disease before the development of any visually threatening complication of chronic inflammation to avoid prolonged steroid use [132].

Infliximab and daclizumab have been used successfully in some VKH patients [95, 133]. Intravenous immunoglobulin has been used in a case report were the patients were resistant and intolerant to long-term steroid therapy [134].

Sub-Tenon's corticosteroid injection has been used, which may be repeated several times; in many patients, clinical improvement may be seen faster. They are associated with a high risk of increased intraocular pressure and with an earlier development of cataract; so patients must be carefully monitored [135]. Triamcinolone acetonide and phosphate/acetate of betamethasone are some of the corticosteroids that are frequently used.

The use of intravitreal triamcinolone provides a short-term improvement in visual acuity and faster resolution of serous retinal detachment in the acute stage of the disease. Andrade and coworkers used 4-mg intravitreal triamcinolone acetonide injection in two eyes with VKH. They used this regimen because of the severity of the serous retinal detachment and because patients failed to respond to standard treatment [136]. Moreker et al. used the same dose of intravitreal triamcinolone in two injections at 3-month intervals; in these patients, oral corticosteroid treatment was shorter than usual [137]. Read et al. on a multicenter retrospective study compared the effect on outcomes of the route of administration of corticosteroids in acute VKH disease. They gave treatment either orally or intravenous followed by an oral taper. They did not find differences in final VA or on the development of visually significant complications between both groups [138].

In children, the use of combined methotrexate and steroids has been advocated because of the higher risk of developing complications such as RPE alterations, glaucoma, cataract, and subretinal neovascular membrane [15].

During pregnancy, immune function and severity of inflammation are influenced by the stage of pregnancy. Miyata et al. reported three patients in second trimester in which inflammation disappeared after treatment with steroids and did not recur. They did not have undesirable side effects [139].

Complications

Complications include cataract, glaucoma, choroidal neovascular membrane (CNVM), and subretinal fibrosis; they have been reported in at least 51% of affected eyes [21]. Several factors such as duration of disease and number of recurrences are associated with a higher risk of developing complications.

Cataract is the most common complication; it has been reported in 10–42% of cases and has been considered as the major cause of visual loss in 25% of patients [65, 140–143]. Severe inflammation and prolonged corticosteroid therapy are risk factors to develop this complication. In most cases, a posterior subcapsular cataract develops [119]. In eyes without active inflammation for at least 3 months, cataract surgery can be performed with relative safety and success if a strict perioperative control of inflammation is obtained and a trained and skillful surgeon is in charge. Common difficulties in these cases are presence of pupillary membranes, posterior synechiae, and small pupils. Ganesh et al. reported improvement of VA in 80% of their cases, although final visual outcome depends on posterior segment complications [143].

Glaucoma is reported in ranges from 6% to 45% [21, 119, 140]. Two forms have been reported, angle-closure glaucoma and open-angle glaucoma, and some may be related to the steroid therapy. Ocular hypertension that needs medical or surgical treatment is seen in one-third of patients with VKH.

Choroidal neovascular membranes (CNVM) are reported from 2.5% to 15% of affected eyes [21, 23, 65]. They must be suspected if there is

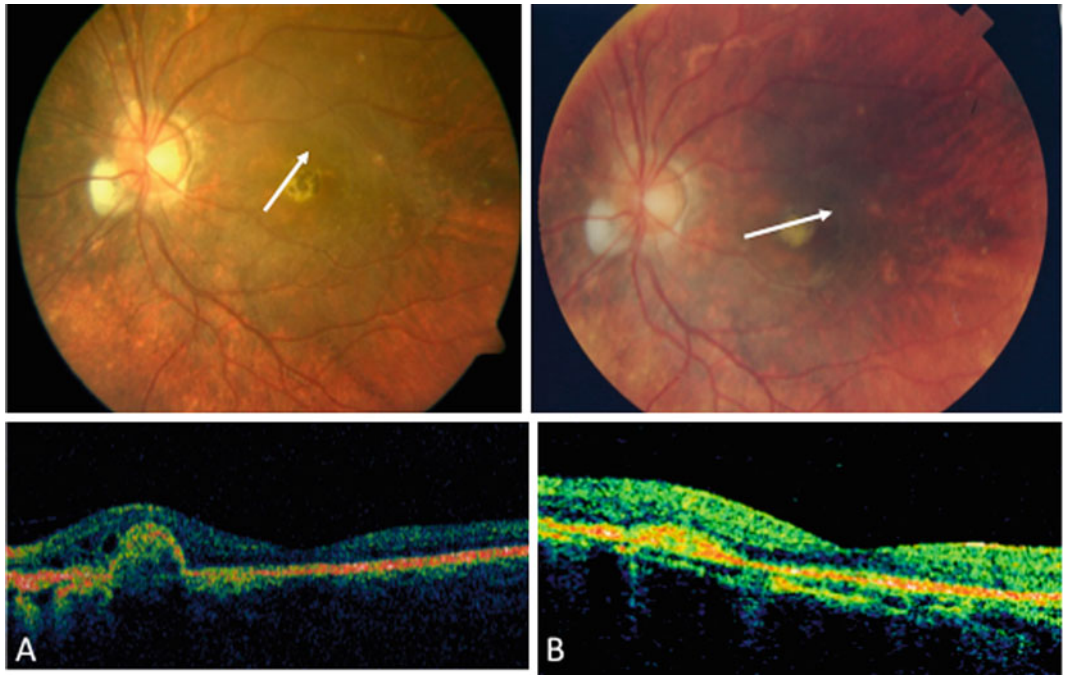

Fig. 19.8 Clinical picture of neovascular choroidal membrane and optical coherence tomograms. (**a**) In active phase, showing thickening with a small amount of retinal fluid. (**b**) After intravitreal bevacizumab application, RPE band in the choroidal neovascular membrane is no longer discontinuous

subretinal hemorrhage or exudate, and FA or ICG shows early and progressive leakage from subretinal vessels. VA alteration depends on CNVM localization. Treatment modalities include laser photocoagulation, surgical excision, systemic corticosteroid with or without immunosuppressors, intravitreal triamcinolone combined with photodynamic therapy (PDT), and PDT alone [144–149]. Treatment with bevacizumab alone or with laser photocoagulation has good results and leads to a fast resolution of both subretinal and intraretinal fluid with a concomitant improvement in VA. Final VA depends on CNVM localization, previous subretinal fibrosis, and cicatrization of CNVM (Fig. 19.8) [150, 151].

Subretinal fibrosis is found in 6–40% of cases [21, 152, 153]. Localization can be extrafoveal, juxtafoveal, subfoveal, and peripapillary. Patients with macular involvement have a poor VA [152]. Stenberg and coworkers suggested that retinal pigment epithelial migration and proliferation could lead to subretinal fibrosis in cases with chronic exudative retinal detachment [154]. Inflammatory cells have a major influence in the formation of subretinal fibrosis.

Prognosis

Final VA depends on age at onset of disease, initial VA, ethnicity, duration of disease, initial treatment, number of recurrences, and associated complications [21]. Final outcomes for VKH disease seem to depend also on long-term treatment strategies. To date, long-term management of VKH disease is not clearly defined and varies across centers and cases, including the dose of oral corticosteroids after the initial (first week) high-dose intravenous corticosteroid treatment, the tapering protocol, and the suitability of concomitant immunosuppressive therapy. There is evidence that submaximal treatment during the postacute period of VKH disease is associated with persistent choroidal inflammation, despite

apparent clinical control. On the other hand, sufficient high-dose postacute therapy completely suppressed choroidal inflammatory disease within 2–4 months [155].

Since the use of systemic steroids, visual outcome has improved dramatically. Bykhovskaya et al. suggest that treatment with oral steroids reduced the risk of subretinal neovascularization or fibrosis by 82% and of VA loss (less than 20/200) in the better-seeing eye by 67%. In addition, these authors suggested that the use of immunosuppressive drug therapy was associated with a risk reduction of 67% for vision loss to 20/50 or worse in better-seeing eyes and of 92% for vision loss to 20/200 or worse in better-seeing eyes [156].

Rubsamen and Gass detailed three factors that are predictive of poor visual outcome: (1) increasing age at the onset of inflammation, (2) chronic ocular inflammation requiring long-term treatment with corticosteroids, and (3) subretinal neovascular membranes [119].

There is a strong association between greater number of cumulative complications and worse final VA. In 74% of eyes with no complications, a VA of 20/40 or better was achieved. On the other hand, patients with three complications had a final VA of 20/200 or worse. Eyes with better final VA had fewer recurrences than those with a worse final VA [21].

In children, prognosis is very different from adults and within the different series. Ohno and associates reported that the younger the age at disease onset, the worse the final VA [141]. Tabbara et al. found a final VA of 20/200 or worse in 61% of their pediatric patients [16]. On the other hand, Rathinam and associates reported a final VA of 20/40 or better in 75% of their patients; 25% achieved 20/200 or worse [17]. In Read and associates' series, 85% of patients had a final VA of 20/40 [21]. Read and coworkers concluded that 50% of eyes with low VA at presentation (but without preexisting complications) were more likely to develop at least one complication. Same results were found by Ohno et al. [141]. This may be explained because a more severe disease initially will decrease VA faster. Rubsamen and Gass found no correlation between initial and final VA [119].

Duration of disease has not been proved to be a predictor of final VA [21]. Al-Kharashi et al. concluded that the development of extraocular manifestations was significantly associated with a worse final visual acuity, the development of glaucoma, and a greater number of recurrent episodes of inflammation [157]. Our group studied the relation among the presence of extraocular manifestations at the prodromic stage, the severity of ocular disease, frequency of extraocular manifestations at the convalescent stage, and frequency of complications. One hundred patients were included: 55 were in the uveitic stage, 14 in convalescence phase, and 31 in the recurrence stage at admittance. A higher frequency of retinal fibrosis was found in patients without extraocular manifestations and in those that presented extraocular manifestations in the prodromic stage; glaucoma was more frequently observed in patients with extraocular manifestations in the prodromic phase than in those patients with probable VKH (without extraocular manifestations). Few patients that presented with serous retinal detachment developed extraocular manifestations in the convalescent stage; this may be explained because patients with a more severe disease may seek medical treatment earlier and aggressive treatment may then diminish the frequency of integumentary manifestations. We failed to demonstrate a clear prognostic value of the extraocular manifestations in this group of 100 Vogt–Koyanagi–Harada patients, although convalescent manifestations are associated with a worst final visual outcome [158].

Controversies and Perspectives

VKH has been classified as complete, incomplete, or probable, depending on the presence or absence of extraocular manifestations. However, some Japanese authors only accept the diagnosis VKH in the complete and incomplete forms. In those classified as probable, they suggest to perform lumbar puncture or audiometric test to confirm the diagnosis.

Nowadays, during the uveitic acute phase of VKH, treatment of choice is high-dose, systemic

corticosteroids (methylprednisolone 1 g a day for 3 days administered intravenously or prednisone 1 mg/kg/day orally). Some groups have suggested to associate other immunosuppressors in this stage of treatment; however, most authors include other immunosuppressors only in the uveitic subacute or chronic phases when there is no good response to corticotherapy and when patient becomes dependent on corticosteroids or on corticosteroid sparing therapy.

In children, due to late diagnosis, poor visual outcome, and frequent adverse side effects of high-dose corticosteroid treatment, other immunosuppressors should be used from the beginning.

Traditionally, VKH recurrence phase was considered to affect only the anterior segment of the eye; widespread use of ICG has demonstrated that choroid is frequently involved. Efforts are now being made to find out how to decrease the frequency of recurrent posterior pole inflammation, which is commonly associated with more complications.

Focal Points

- VKH is a frequent bilateral panuveitis in pigmented races of Mongolian ancestry.
- Even though its mechanism is not well known, an autoimmune response causes intraocular inflammation; therefore, immunosuppressive therapy should be used.
- Ophthalmological clinical findings include severe bilateral iridocyclitis, serous retinal detachment, diffuse choroidal edema, and optic disk hyperemia. Vitritis is mild in most cases.
- Extraocular manifestations are seen in more than 60% of patients and include central nervous system alterations (headache, meningismus, skin/scalp hypersensibility, and occasionally focal neurologic signs) and auditory manifestations (tinnitus, hearing loss, and vertigo) in the prodromic stage. Dermatologic signs like alopecia, poliosis, and vitiligo are seen in the convalescent phase.
- Acute uveitic stage starts with a sudden drop of vision. In most cases, both eyes are affected at the same time; less frequently one eye is initially involved followed by the second eye in less than a week. At this point aggressive treatment with systemic corticosteroids is the treatment of choice and an important prognostic factor.
- Differential diagnosis is made with a variety of systemic and ocular diseases. A systemic physical exam and blood workup to rule out systemic disease and malignancy should always be performed.
- Complications are several and vary throughout the disease. Most common are cataracts, glaucoma, subretinal neovascularization, and subretinal fibrosis.

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Retinal Detachment and Lens Subluxation in Marfan Syndrome

20

Dinah Zur and Anat Loewenstein

Abstract

Marfan syndrome is an autosomal dominant inherited disorder of connective tissue. During the last two decades, the major role of mutation of the gene fibrillin 1 was shown. Ocular involvement in Marfan syndrome is very common, and in 41% of Marfan patients, ocular pathology is the presenting symptom. This chapter will detail the two main ocular features: ectopia lentis and retinal detachment—the most common and serious sight-endangering complications of the syndrome. Parallel to improved life expectancy of Marfan patients, the introduction of modern operative instruments changed the surgical approach and significantly improved operative results.

Keywords

Dislocated lens • Fibrillin • High myopia • Marfan syndrome • Retinal detachment

Introduction

The first description of the Marfan syndrome was probably given by E. Williams, an ophthalmologist, in 1875 [1]. He described two families who presented with dislocated lens and pupil, retinal detachment, and generalized loose-jointedness. In 1896, Marfan, a French pediatrician, reported on a 5-year-old child with long, thin extremities [2]. After being named "dolichostenomelia" and "arachnodactyly," the name Marfan syndrome was coined only in 1931 [3]. In 1943, cardiovascular abnormalities were recognized as part of the syndrome with aortic dilatation, dissecting aortic aneurysm, and floppy mitral valve as major complications [4, 5]. In 1990, the role of fibrillin in the pathogenesis was demonstrated [6].

Marfan syndrome is the second most common inherited connective tissue disorder after osteogenesis imperfecta [7]. Its incidence is estimated between 1 in 5,000 and 1 in 20,000, but the

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syndrome may be underdiagnosed due to its great variability [8–10].

The life expectancy of Marfan patients by 1972 was markedly shortened and the mean age was 32 years, with most deaths being due to cardiovascular causes [11]. Life expectancy by 1993 was increased by >25% and the prognosis of surgically treated patients was significantly improved [12].

Ocular involvement is frequent and accounts for a part of the major and minor diagnostic criteria for Marfan syndrome [13]. Almost every ocular structure can be involved. Forty-one percent of patients with Marfan syndrome are initially seen with ocular pathology and diagnosed by an ophthalmologist [14]. This number stresses the importance of alertness of the ophthalmologist when examining patients with suspicious findings—especially in light of improved surgical options and prophylaxis promising better chances in preservation of sight in Marfan patients.

General

Genetics

Marfan syndrome is inherited in an autosomal dominant manner with almost complete penetrance [3]. About one-fourth of patients with Marfan syndrome do have unaffected parents; i.e., the syndrome is caused by sporadic mutations [9].The majority of cases are induced by a mutation of the gene fibrillin 1 (FBN 1) on chromosome 15, q21.1 locus [15, 16]. The glycoprotein FBN 1 is a main component of the extracellular microfibrils. In Marfan syndrome, its integration into the matrix of connective tissue is impaired [6, 17, 18]. Most of the mutations found are unique to a patient or family. Altogether, more than 500 mutations of the FBN1 gene are known [19].

Beyond the structural function of microfibrils, they play a role in the regulation of cytokines [20]. The homology between FBN 1 and transforming growth factor-β(beta) (TGF-β)-binding proteins gave rise to the hypothesis that microfibrils are involved in the regulation of TGF-β(beta) activation. Indeed, recently a mutation of a further gene was discovered causing inactivation of the TGF-β(beta) receptor 2 (TGFBR2) [21]. This defect seems to end in a final common pathway for the development of the Marfan phenotype.

Pathogenesis

Elastic fibers are bundles of proteins found in the extracellular matrix of connective tissue, allowing its stretching and expansion. Those fibers are composed of an elastin core and surrounding microfibrils. As explained previously, FBN1 is a main component of the microfibrils, and a mutation of its gene is principally responsible for the pathology in Marfan syndrome. Still, more and more proteins containing pathological microfibrils others than FBN1 have been found, leading to the term *microfibrillopathy* [22].

Ocular Pathology

As mentioned, almost every part of the eye can be involved in Marfan syndrome. Pathology studies were described as early as 1940 and thereafter. A consistent finding is the increased axial length of the globe in affected patients. Remarkably, Maumenee found a significantly higher axial length in patients with dislocated lens compared to patients without dislocation [23]. The cornea is typically flat with decreased K and corneal thinning when measured by pachymetry. The main cause for corneal flattening seems to be an aberration of the cornea itself due to fibrillin gene mutations in combination with scleral thinning. A megalocornea may exist as well [24].

Dvorak-Theobald described an increased distance of the insertion of the rectus muscles from the limbus in a 27-month-old child, along with an enlarged globe [25].

The anterior chamber angle is typically wide open with an immature ciliary body, a broad trabecular meshwork, and displacement of Schlemm's canal [26]. The sphincter and dilator muscle of the iris are usually underdeveloped, causing eccentric pupil and poor mydriasis [23].

The iris itself shows a decreased number of circumferential folds and iridodonesis in cases of lens subluxation [27]. The sclera is thin.

There is little information available regarding the vitreous in Marfan syndrome. A frequent finding is liquefaction of the central and posterior vitreous. Evidently, in areas of lattice degeneration, the vitreous may be abnormally attached.

Strabismus is a frequent finding in Marfan patients, caused, among others, by abnormal connective tissue laxity due to missing fibrillin in the pulley. Consequentially, the rate of amblyopia is high (additionally increased by ametropia as well as axial changes).

Lens

The zonules and lens capsule in the healthy eye are rich in fibrillin, which is secreted by the nonpigmented epithelium of the ciliary body [28]. It stands to reason that alterations of fibrillin influence the lens development. In fact, capsular fibers and zonular fibrils are abnormal in size and structure in Marfan patients. The zonular fibers adjacent to the lens are few in number, and at times the lens capsule is almost devoid of zonules. Instead of radial bunches of fibrillin fibers, disorganized fibrillin-positive fragments are found dispersed on the anterior capsule [29]. Additionally, the fibers are weakened toward the lens capsule.

In most cases, the lens has normal size and shape, but microspherophakic lenses can be found, characterized by small size and spherical configuration with increased anteroposterior thickness [23].

Retina

The healthy retina contains fibrillin in the vessel walls only [30]. The eye in Marfan syndrome is in many ways similar to an eye with axial myopia. The peripheral retina shows myopic degenerative changes, lattice degeneration, atrophic holes, chorioretinal pigment proliferation, white without pressure, and vitreous traction syndromes. The choroid is mostly thin and the anterior retina stretched. Retinal breaks and scleral crescents can be seen. Though sharing many similar findings with myopia, in the observations of Maumenee, there was no Fuchs' spot present [23]. Furthermore, there was no posterior staphyloma seen in any patient. According to older publications, it seems that the macula is normally developed [31].

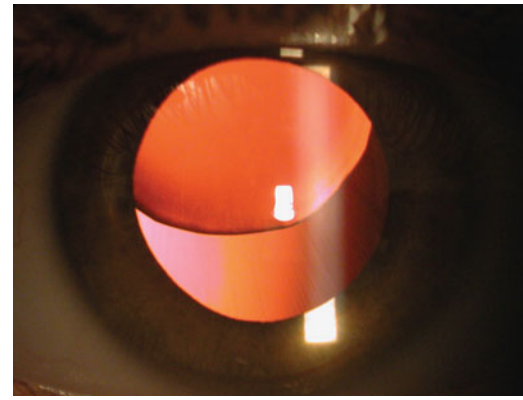

Fig. 20.1 Superotemporal subluxation of crystalline lens in a patient with Marfan syndrome. Note sparse zonular fibers

Lens Subluxation

Lenticular abnormalities are the most common ocular feature present in patients with Marfan syndrome; among them, ectopia lentis is the most frequent problem, with microspherophakia and lens opacities being less common.

In general, most cases of lens subluxation overall are caused by trauma. Among the heritable dislocations that are associated with skeletal dysplasias, Marfan syndrome is the most common one.

Clinical Findings

Lens subluxation occurs in about 60% of patients with Marfan syndrome [23], half of them bilateral and symmetric, presenting in early childhood (Figs. 20.1 and 20.2) [32]. Subluxation remains mostly stable since childhood; only 7.5% of all patients progress with increasing age until complete luxation.

Symptoms include decreased vision and monocular diplopia. Apart from lens dislocation, ophthalmologic examination may reveal iridodonesis and irregular astigmatism. Cross et al. found a

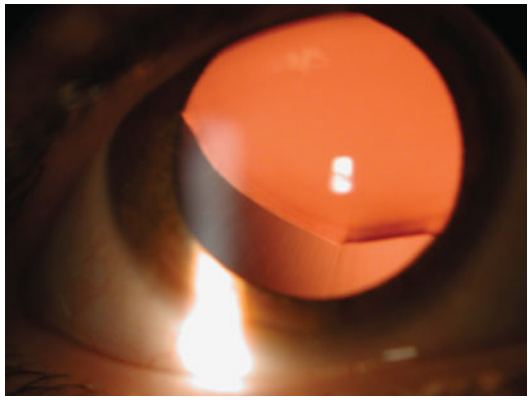

Fig. 20.2 Superonasal subluxation of crystalline lens in another patient with Marfan syndrome. A single inferior zonular bundle is still intact

Table 20.1 Ectopia lentis—differential diagnosis

Genetic
With systemic manifestation
Marfan syndrome
Homocystinuria
Weill-Marchesani syndrome
Sulfite oxidase deficiency
Hyperlysinemia
Isolated
Simple ectopia lentis (congenital/delayed)
Ectopia lentis et pupillae
Aniridia
Megalocornea
Nongenetic
Trauma
Lues
Persistent hyperplastic

superotemporal direction of dislocation in 67% of all cases; dislocations into the vitreous or anterior chamber were rare [31]. Another relative common feature is a backward dislocation of the lens, causing a gap between the pupillary border of the iris and the anterior lens surface [23].

Pathogenesis

Lens subluxation occurs due to an asymmetrical excess of laxity in zonular fibers. In the presence of dislocation, the zonules are stretched. In cases of localized stretching, the edge of the lens can be notched (pseudo lens coloboma).

The subluxation causes anterior shift of the lens/iris diaphragm and thus anterior displacement of the focal point of the eye. This leads to myopic shift, which is aggravated by thickening of the lens, bringing along an increased refractive power [33].

Differential Diagnosis

Several systemic conditions can be associated with lens subluxation (Table 20.1). The most important one to be differentiated from Marfan syndrome is surely homocystinuria. In this syndrome, affected patients present with similar marfanoid skeletal features and cardiovascular abnormalities. After the age of 5 years, myopia is rapidly developing; lens dislocation is usually downward—atypical for Marfan syndrome. Histologic examination shows deficiency of zonular fibers adjacent to the lens and atrophy of the ciliary body [34]. This differential diagnosis should be considered in patients with negative family history. The diagnosis is made by laboratory testing.

Weill-Marchesani syndrome can come along with ectopia lentis as well. The typical presentation is with shallow anterior chamber and microspherophakia, complicated by papillary block glaucoma.

Rare conditions associated with lens subluxation are hyperlysinemia, sulfite oxidase deficiency, and isolated familial ectopia lentis.

Treatment

Mild stable subluxation may be corrected by glasses or contact lenses. But progressive dislocation, worsening cataract, or development of glaucoma might necessitate surgical intervention.

In the past, surgical removal was not an accepted method due to severe and frequent complications as postoperative retinal detachment [35]. Alternative treatment strategies as peripheral iridectomy and photocoagulation of the iris provided only slight visual improvement and did not treat lens-associated complications [36]. The introduction of modern operative technique and instruments significantly decreased the rate of retinal detachment by avoiding vitreous incarceration and removing vitreoretinal adhesions.

Accepted indications for surgical treatment include luxation of the lens into the anterior chamber or into the vitreous, progressive subluxation accompanied by worsening visual acuity or uncorrectable refractive changes, and prevention of amblyopia.

In the past, according to the patient's age and the surgeon's experience, lensectomy was performed using a limbal or pars plana access or by vitrectomy—leaving the patient aphakic [37, 38]. In 1979, it was Peyman et al. who reported on 32 cases of lens subluxation and dislocation due to several causes, two of which were secondary to Marfan syndrome [39]. The lens was removed by a vitrectomy using a pars plana access, achieving significant visual improvement.

In 1996, Halpert et al. presented a group of 59 eyes that underwent pars plana lensectomy combined with anterior vitrectomy [40]. The long-term follow-up results were encouraging: 84% reached a postoperative visual acuity better than 20/40. Retinal detachment occurred in 1 out of 18 eyes, which completed more than 11 years of follow-up. More recently, the same group published 38 eyes with hereditary lens subluxation (22 of them due to Marfan syndrome) that underwent within-the-bag lensectomy with similar results [41].

Shortt et al. showed pars plana lensectomy to be safe in the management of ectopia lentis in children [42]. Seventy-seven percent reached a visual acuity of 6/9 and better. Thirteen out of 24 cases were secondary to Marfan syndrome.

The issue of refractive correction of aphakia is another challenging problem in Marfan patients—especially in children for preventing amblyopia. Glasses or contact lenses can present a nonsurgical solution, but aniseikonia, intolerance, and noncompliance frequently limit their use. In those cases, secondary intraocular lens (IOL) placement can be chosen. Today, secondary IOL implantation is not the method of choice, although it still presents an option in prepuberty and high myopia. Hence, primary implantation of an IOL is desirable and has become the accepted treatment.

In cases of secondary IOL placement or in eyes without adequate capsular support, an anterior chamber IOL, scleral-fixated IOL, or iris-fixated posterior chamber IOL can be inserted.

Aspiotis described a series of seven eyes with subluxated lens due to Marfan syndrome that underwent lensectomy, anterior vitrectomy, and implantation of Artisan intraocular lens to the anterior chamber [43]. He achieved good refractive correction; all patients reached a visual acuity better than 20/40. Minimal complications, nonsignificant endothelial cell loss, and easy implantation were reported.

A review of the literature could not state the superiority of one lens type or fixation site in the capsular bag or ciliary sulcus [44].

Retinal Detachment

Retinal detachment is the most serious ocular complication in Marfan syndrome. Marfan patients are predisposed to develop retinal detachment; the incidence lies between 8% and 25.6% [23, 45]. It is more common in the younger age, with an average age of 22 years.

Clinical Findings

As discussed previously, the changes in eyes of patients with Marfan syndrome resemble myopic changes. Retinal holes and tears are frequent findings. The prevalence of giant retinal tears is significantly increased compared to the general population [46]. Retinal detachment is estimated to occur in about 10% of Marfan patients (Fig. 20.3). In the presence of a dislocated lens, the prevalence is significantly higher [23]. The rate of bilateral retinal detachment varies between different reports from 17.7% to 69% [47, 48]. Sharma et al. described anatomic findings of 53 eyes with retinal detachment in Marfan patients and their surgical results: 71% had associated ectopia lentis; in three-thirds, retinal detachment was complete; and in half of the cases, proliferative vitreoretinopathy was present. The vast majority of retinal breaks were found in the temporal half.

Poor mydriasis, lens opacities, and lens dislocation can impair visualization and make retinal examination difficult [49].

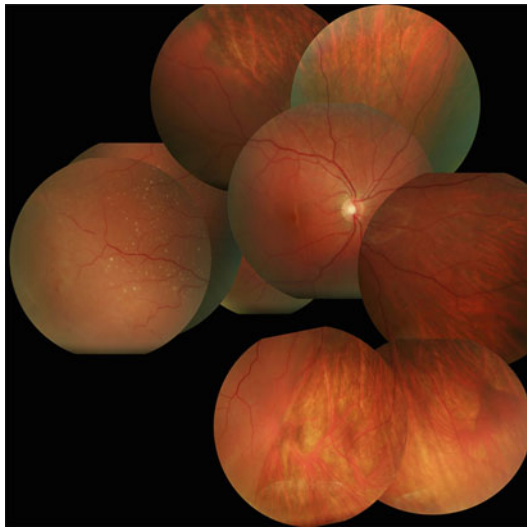

Fig. 20.3 A 15-year-old boy with high myopia, Marfan syndrome, and macula-off retinal detachment. Visual acuity was 20/200 (Courtesy of Manuel Diaz-LLopis, M.D. and Roberto Gallego-Pinazo, M.D.)

Pathogenesis

Myopia and increased axial length are evident risk factors for developing retinal tears. Furthermore, vitreous liquefaction is a frequent finding in Marfan patients and involves the central and posterior vitreous body. Posterior vitreous detachment in absence of dehiscence at the vitreoretinal interface and abnormal vitreoretinal adhesions at the equator forward the development of large retinal tears by causing traction.

Ectopia lentis and zonular deficiency cause additional traction on the ora serrata, leading to small tears or holes in the retinal periphery. The high prevalence of retinal breaks in the temporal half could indeed be connected to the frequent direction of lens subluxation in the superior temporal quadrant. Zonules deficiency in the lower nasal quadrant may cause free movement of vitreous, resulting in traction on the opposite site, hereby producing more breaks.

In fact, most of the patients with retinal detachment have a subluxated lens. Retinal detachment in these cases has features resembling those of retinal detachment in aphakic and pseudophakic patients.

Cataract extraction and removal of subluxated lens were shown to raise the risk of retinal detachment [23, 35]. As previously mentioned, vitreous loss and incarceration were frequent complications of earlier lens surgery and presented a major risk factor for developing retinal detachment. Modern operation techniques and instruments significantly reduced this complication.

Therapy

Management of retinal detachment in Marfan patients is difficult for several reasons: Multiple breaks in different meridians can be present. Surgery is complicated in these patients by young age, lattice degeneration, thin sclera, poorly dilating pupils, and possible ectopia lentis demanding high surgical skills.

Visual outcome was poor in the first reports of surgical repair. Almost half of the cases shown by Jarrett in 1967 ended with a visual acuity of no light perception; in the report of Maumenee, it was a third [23, 35]. Advancement of operative instruments and methods improved the visual and anatomic outcome during the last decades.

In 1993, Greco and Ambrosino showed successful pars plana lensectomy and vitrectomy in five out of six eyes [50]. Dotrelova et al. reported 18 eyes; retinal reattachment was achieved in 89% of uncomplicated and in 56% of complicated retinal detachments [51]. These results were comparable with the outcome in patients without Marfan syndrome. A part of those cases was managed without removal of the dislocated lens.

Abboud showed good long-term results with a 75% reattachment rate after combined scleral buckling and vitrectomy [47]. Proliferative vitreoretinopathy was the main cause for failure of attachment.

In the previously cited study of Sharma et al., 45% of the cases were treated by scleral buckle operation. The reattachment rate following the primary surgical intervention was 62%; eight eyes needed additional operative correction. The overall anatomical success in this group, including reoperation, was 87.5%. The other group underwent pars plana vitrectomy with scleral buckle. The overall anatomical success in those cases was 86.2%. In half of the cases, the eye was filled with air or gas, and in the other half, with silicone oil. In all phakic eyes that had vitrectomy,

the lens was removed. Besides facilitating intraoperative maneuvers, performing lensectomy also improved intraoperative visualization, particularly during fluid-gas exchange.

Loewenstein et al. described postsurgical findings in Marfan patients with retinal detachment; one of the two groups reported was operated several years earlier [52]. In the recent group, there was no significant difference between phakic and aphakic or pseudophakic eyes. However, in the earlier group, the results for aphakic and pseudophakic eyes were considerably worse than for phakic eyes. Only 29% had a flat retina and 71% had a final visual acuity of no light perception.

Lee et al. reported 13 cases of retinal detachment [53]. Ten eyes underwent scleral buckle with successful retinal attachment in all; one patient was additionally managed with a radial plomb. The remaining three patients underwent pars plana vitrectomy with scleral buckle combined with lensectomy due to posterior dislocation of lens or number and location of breaks. Anatomic success was achieved in all cases. Seven eyes had a best-corrected visual acuity (BCVA) better than 20/40 six months after surgery.

A case of scleral buckle erosion in a Marfan patient was described, which was promoted by thin and abnormal sclera [54].

Choosing the adequate surgical procedure depends on several factors. Preoperatively, the complexity of the detachment and the status of the vitreous and the lens have to be evaluated thoroughly. Scleral buckling can be recommended as a primary surgical procedure if there is no lens opacity and only minimal lens displacement interfering with the fundus details. Retinal breaks should be located at or anterior to the equator [51]. Patients who have undergone lensectomy prior to the detachment can often be managed with scleral buckling. In cases of failed scleral buckling, proliferative vitreoretinopathy, giant retinal tears, posterior dislocation of lens, and inadequate visualization of the fundus periphery because of dislocated lens or cataract, vitreous surgery is necessary. According to the circumstances, vitrectomy should be combined with lens removal as discussed previously. Perfluorocarbon is commonly used for reattaching the retina and additionally helpful in retrieving a posteriorly dislocated lens. Vitrectomy is usually performed in combination with scleral buckling in order to reduce anterior vitreous traction and hereby avoid recurrent detachment. Proliferative vitreoretinopathy has to be treated adequately.

As the rate of bilateral retinal detachment is high, thorough examination of the fellow eye on a regular basis is crucial. Prophylactic treatment of the fellow eye has been proposed, but its benefit has not been proven.

Furthermore, when planning surgery in Marfan patients, one should keep in mind cardiovascular problems, which raise the risk during general anesthesia.

Controversies and Perspectives

Of all the ocular complications in Marfan syndrome, retinal detachment continues to be the most severe and difficult to manage. The coexisting pathology in Marfan syndrome, namely, ectopia lentis, can by itself cause serious visual impairment, but is also one of the predisposing factors for retinal detachment. Whereas former generations of ophthalmic surgeons had to deal with severe intra- and postoperative complications and poor visual outcome in Marfan patients, significant advancement and modern operative technologies and instruments significantly improved surgical prognosis with resultant higher potential for successful anatomic and visual results. Specifically, the introduction and sophistication of vitrectomy techniques has radically changed the treatment of retinal detachment and is accepted as standard of care for most cases.

Similarly, the fundamental controversy of whether to operate ectopia lentis in Marfan patients seems to be solved. Nowadays, lensectomy is established as the treatment of choice. Still, the optimal anatomic site for implantation of an intraocular lens is undetermined. Anterior chamber intraocular lenses can easily be used in the absence of capsular support but bear the risk of corneal endothelial loss, iris sphincter erosion, glaucoma, chronic inflammation, and hyphema. It should be

noted, however, that with modern open-loop anterior chamber lenses, the safety aspect has improved. Still, many surgeons will prefer a scleral sutured intraocular lens in case of deficient capsular support because of its anatomic location in the posterior chamber. Indeed, this type of intraocular lens is less irritating to the eye but requires high technical skills and is more time consuming. At last, iris-sutured posterior chamber lenses are an option but require a normally developed anterior segment, and their implantation is as difficult to perform as suturing to the sclera. Artisan lenses are a good option in children and adults with Marfan syndrome because of easy handling, less complications, and corneal endothelium safety.

Altogether, the prognosis for lens subluxation and retinal detachment in Marfan patients has enormously improved.

Focal Points

- As for all congenital syndromes, early detection of suspicious findings and referral for systemic workup are essential. Potential lethal systemic involvement points out the importance of alertness of the ophthalmologist. Suspect patients should be referred for full medical and orthopedic evaluation. First-grade relatives should be examined as well.
- Prevention of amblyopia is one of the main goals. Especially in children, the follow-up has to be close and includes complete ophthalmologic examination and repeated refraction measurements. Refractive errors need to be corrected accurately. In case of uncorrectable aberrance, surgery should be considered in a timely manner.
- Pars plana lensectomy is a safe and effective way to treat ectopia lentis, providing good visual acuity and bearing a low incidence of complications.
- Retinal detachment will be treated with pars plana vitrectomy and gas or oil tamponade combined with scleral buckling, in most of the cases.
- The prognosis for Marfan patients has enormously improved during the last decades. Life expectancy and quality got better continually thanks to modern cardiac and vascular surgery. Early detection of ocular pathology and appropriate treatment meliorated the expectation for preservation of sight in a radical manner.

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Diabetic Retinopathy

21

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David G. Zeballos, and Sergio Bonafonte-Royo

Abstract

Diabetic retinopathy remains a major threat to sight in the working-age population in the developed world. In proliferative diabetic retinopathy (PDR), the growth of new vessels is thought to occur as a result of vascular endothelial growth factor (VEGF) release into the vitreous cavity as a response to ischemia, which facilitates the process of angiogenesis and macular edema. In these patients, the introduction of new therapies, such as VEGF inhibitors, may have a beneficial effect on diabetic retinopathy including diabetic macular edema and retinal neovascularization, and these therapies could complement laser photocoagulation treatment.

Keywords

Diffuse diabetic macular edema • Nonproliferative diabetic retinopathy • Proliferative diabetic retinopathy • Retinal photocoagulation • Tractional retinal detachment • Vascular endothelial growth factor • VEGF inhibitors

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Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the B cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action [1].

The vast majority of cases of diabetes fall into two etiopathogenetic categories. In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. This form of diabetes, insulin-dependent diabetes or juvenile-onset diabetes, which accounts for only 5–10% of those with diabetes, results from a cellular-mediated autoimmune destruction of the B cells of the pancreas. For the other category, a much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. This form of diabetes, non-insulin-dependent diabetes or adult-onset diabetes, which accounts for ~90–95% of those with diabetes, results from an insulin resistance and usually has relative insulin deficiency. At least initially, and often throughout their lifetimes, these individuals do not need insulin treatment to survive [1]. Currently, there are approximately 13 million Americans with diagnosed diabetes and millions more who remain unaware that they have the disease. This number is expected to increase to 29 million by the year 2050 [2].

Diabetic retinopathy (DR) is a highly specific vascular complication of both type 1 and type 2 diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. After 20 years of diabetes, nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes have some degree of retinopathy. Diabetic retinopathy poses a serious threat to vision. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger-onset patients (aged <30 years at diagnosis, an operational definition of type 1 diabetes) and 1.6% of older-onset patients (aged ≥30 years at diagnosis, an operational definition of type 2 diabetes) were legally blind. In the younger-onset group, 86% of blindness was attributable to diabetic retinopathy. In the older-onset group, where other eye diseases were common, one-third of the cases of legal blindness were due to diabetic retinopathy. Overall, diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20–74 years. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. Macular edema within 1 disk diameter of the fovea is present in 9% of the diabetic population [3]. Although visual loss secondary to proliferative changes is more common in patients with type 1 diabetes, visual loss in patients with type 2 diabetes is more commonly due to macular edema [4].

The objective of this chapter is to describe the clinical findings of DR as well as its epidemiology, pathogenesis, risk factors, diagnosis, classification, and current management.

Pathogenesis

The pathogenesis of diabetic retinopathy begins with prolonged hyperglycemia, which results in expression of factors that activates the β(beta)2 isoform of protein kinase C and stimulates vascular endothelial proliferation and increases capillary permeability. Other mechanisms may also be involved such as increased glucose metabolism via the polyol pathway (aldose reductase) or the accumulation of advanced glycation end products. High concentrations of glucose increase flux through the polyol pathway with the enzymatic activity of aldose reductase, leading to an

elevation of intracellular sorbitol concentrations. This rise in intracellular sorbitol accumulation has been hypothesized to cause osmotic damage to vascular cells.

Diabetes mellitus causes abnormal glucose metabolism as a result of decreased levels or activity of insulin. Increased levels of blood glucose are thought to have a structural and physiologic effect on retinal capillaries causing them to be both functionally and anatomically incompetent. A persistent increase in blood glucose levels shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (e.g., glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of its primary function (i.e., autoregulation of retinal capillaries).

Loss of function of pericytes results in weakness and eventual saccular outpouching of capillary walls. These microaneurysms are the earliest detectable signs of DR. Ruptured microaneurysms (MA) result in retinal hemorrhages either superficially (flame-shaped hemorrhages) or in deeper layers of the retina (blot and dot hemorrhages). Increased permeability of these vessels results in leakage of fluid and proteinaceous material, which clinically appears as retinal thickening and exudates (Fig. 21.1). If the swelling and exudation would happen to involve the macula, a diminution in central vision may be experienced. Macular edema is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy (NPDR). However, it is not exclusively seen only in patients with NPDR, but it also may complicate cases of proliferative diabetic retinopathy (PDR).

It has also been postulated that platelet abnormalities in diabetics may contribute to diabetic retinopathy. There are three steps in platelet coagulation: initial adhesion, secretion, and further aggregation. It has been shown that the platelets in diabetic patients are "stickier" than platelets of nondiabetics. They secrete prostaglandins that cause other platelets to adhere to them (aggregation) with blockage of the vessel and endothelial damage. The variety of hematologic abnormalities seen in diabetes, such as increased erythrocyte aggregation, decreased red blood cell (RBC) deformability, increased platelet aggregation, and adhesion, predispose to sluggish circulation, endothelial damage, and focal capillary occlusion. This leads to retinal ischemia, which, in turn, contributes to the development of diabetic retinopathy.

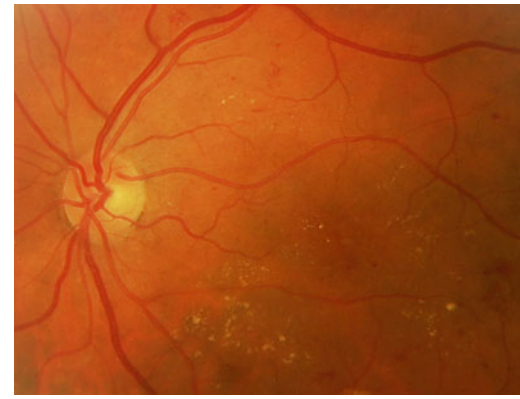

Fig. 21.1 The vascular lesions that are identified with the onset of retinopathy include the formation of saccular capillary aneurysms, disappearance of pericytes from capillaries having endothelial cells, nonperfusion and obliteration of capillaries and small arterioles, gradual thickening of vascular basement membrane, and associated changes such as vessel leakage, exudates, and hemorrhage

The vascular lesions that are identified with the onset of retinopathy include the formation of saccular capillary aneurysms**,** disappearance of pericytes from capillaries having endothelial cells, nonperfusion and obliteration of capillaries and small arterioles, gradual thickening of vascular basement membrane, and associated changes such as vessel leakage, exudate, and hemorrhage (Fig. 21.1) [5]. Progressive capillary narrowing and/or microthrombosis leads to impairment of retinal blood flow. When a large segment of the retina is affected, retinal ischemia occurs and stimulates growth factor production; vascular endothelial growth factor (VEGF) is the most extensively studied. VEGF is a homodimeric glycoprotein produced by the vascular smooth muscle. VEGF expression is induced by hypoxia and by various metabolic stimuli such as platelet-derived growth factor, angiotensin II [6], and high

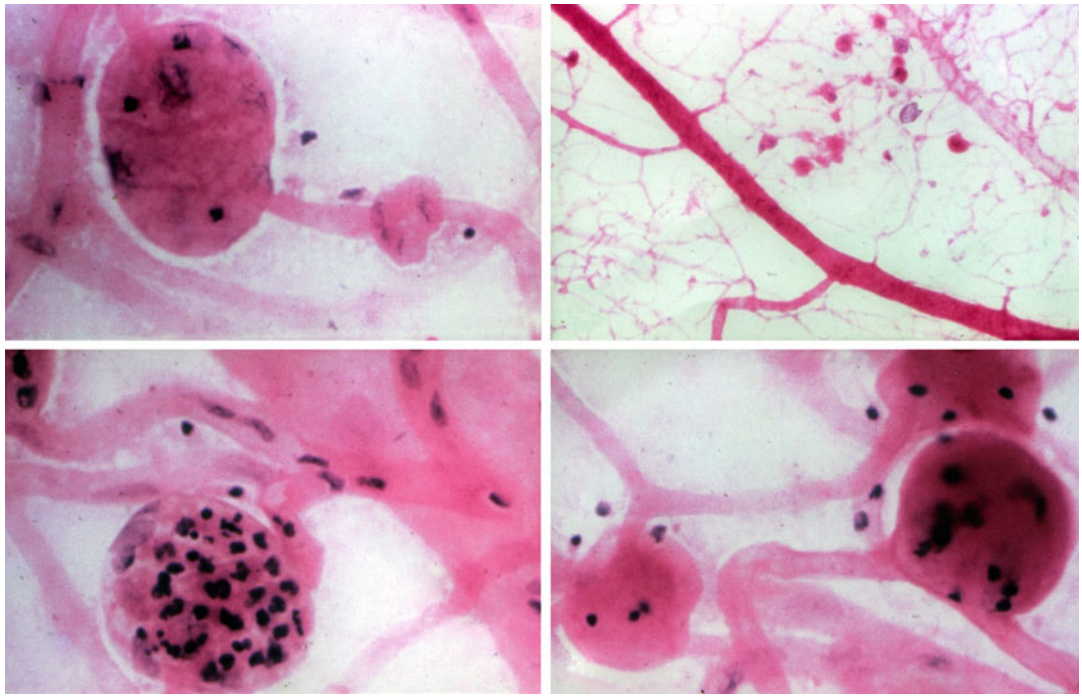

Fig. 21.2 In diabetic patients with retinopathy, pericyte ghosts have been found to be rare or absent from capillaries of the optic nerve and cerebral cortex but numerous in the retinal capillaries (Courtesy of Dario Savino-Zari, M.D.)

extracellular glucose. By virtue of its powerful angiogenic effect and potent permeability properties, VEGF is strongly implicated in the development of neovascularization and retinal leakage (macular edema).

The histological finding of diabetic retinopathy is typical capillaries with endothelial cells but few or no pericytes. In diabetic patients with retinopathy, pericyte ghosts have been found to be rare or absent from capillaries of the optic nerve and cerebral cortex but numerous in the retinal capillaries (Fig. 21.2).

Risk Factors

Duration of Disease

In patients with type 1 diabetes, no clinically significant retinopathy can be seen in the first 5 years after the initial diagnosis of diabetes is made. After 10–15 years, 25–50% of patients show some signs of retinopathy. This prevalence increases to 75–95% after 15 years and approaches 100% after 30 years of diabetes. In patients with type 2 diabetes, the incidence of diabetic retinopathy increases with the duration of the disease. Of patients with type 2 diabetes, 23% have NPDR after 11–13 years, 41% have NPDR after 14–16 years, and 60% have NPDR after 16 years.

Glucose Control

The Diabetic Complications Control Trial (DCCT) [7] and the United Kingdom Prospective Diabetes Study (UKPDS) [8] conclusively demonstrated that intensive glycemic control significantly reduces the risk of DR development and progression in both type 1 and type 2 diabetes, though not preventing retinopathy completely. Although no similar trials for patients with non-insulin-dependent diabetes mellitus (NIDDM) have been completed, the American

Diabetes Association (ADA) has suggested that glycosylated hemoglobin levels of less than 7% (reflecting long-term glucose levels) should be the goal in all patients to prevent or slow down the onset of diabetes-related complications.

Blood Pressure Control

Systemic hypertension, in the setting of diabetic nephropathy, correlates well with the presence of retinopathy. Hypertension might contribute to worsening of DR by increasing endothelial shear stress and the release of VEGF that follows stretching of the vessel walls, leading to altered retinal autoregulation and increased perfusion pressure [9].

Lipid Control

Elevated serum lipid levels are positively associated with retinal hard exudates in DR. Hard exudates, in turn, are associated with visual impairment and subretinal fibrosis from macular edema. Proper management of hyperlipidemia may result in less retinal vessel leakage and less hard exudate formation. The reason behind this is unclear. Sen et al. [10] demonstrated that simvastatin inhibited progression of retinopathy in diabetic patients with dyslipidemia.

Other Factors

Other factors that affect the progression of diabetic retinopathy are renal disease proteinuria and pregnancy. Renal disease, as evidenced by proteinuria and elevated *blood urea nitrogen (*BUN)/creatinine levels, is an excellent predictor of the presence of retinopathy. This probably is due to the fact that both conditions are caused by DM-related microangiopathies such that the presence and severity of one reflects that of the other. Pregnant women without any diabetic retinopathy run a 10% risk of developing NPDR during their pregnancy. Of those with preexisting NPDR, 4% progress to the proliferative type.

Table 21.1 International Clinical Diabetic Retinopathy Disease Severity Scale (Modified from [12])

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: • 20 Intraretinal hemorrhages in each of four quadrants • Definite venous beading in two quadrants • Prominent intraretinal microvascular abnormalities in 1+ quadrant And no signs of proliferative retinopathy
PDR	One or more of the following: • Neovascularization • Vitreous/preretinal hemorrhage

NPDR nonproliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

Classification and Natural History

Diabetic retinopathy is generally classified into NPDR and PDR, both of which are further graded into different levels. Diabetic macular edema (DME) can occur at any stage. Accurate diagnosis of the stage of the disease is critical because of the varying risk of progression to PDR.

The Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale was based on the modified Airlie House classification of diabetic retinopathy and was used to grade fundus photographs [11]. Although it is recognized as the gold standard for grading the severity of diabetic retinopathy in clinical trials, its use in everyday clinical practice has not proven to be easy or practical. The levels of diabetic retinopathy disease severity scale are listed in Table 21.1 [12] and consist of five scales with increasing risks of retinopathy.

The first level is "no apparent retinopathy," and the second level, "mild NPDR," includes ETDRS stage 20 (microaneurysms only). The risk of significant progression over several years is very low in both groups. The third level, "moderate NPDR," includes eyes with ETDRS levels 35–47,

Table 21.2 International Clinical Classification of Diabetic Retinopathy, Severity of Diabetic Macular Edema[a] (Modified from [12])

Proposed disease severity level	Findings observable upon dilated ophthalmoscopy[b]
DME apparently absent	No apparent retinal thickening or hard exudates in posterior pole
DME apparently present	Some apparent retinal thickening or hard exudates in posterior pole
DME present	Mild DME (some retinal thickening or hard exudates in posterior pole but distant from the center of the macula)
	Moderate DME (retinal thickening or hard exudates approaching the center of the macula but not involving the center)
	Severe DME (retinal thickening or hard exudates involving the center of the macula)

[a]*DME* diabetic macular edemaa
[b]Hard exudates are a sign of current or previous macular edema. DME is defined as retinal thickening requiring a three-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography

and the risk of progression increases significantly by level 47. Still, the fourth level, "severe NPDR" (ETDRS stage 53), carries with it the most ominous prognosis for progression to PDR. The fifth level, "PDR," includes all eyes with definite neovascularization or vitreous/preretinal hemorrhage. There was no attempt to subdivide level 5 as a function of ETDRS "high-risk characteristics" because significant rates of progression are expected to occur in all of these cases [13].

Diabetic macular edema involves the breakdown of the blood-retinal barrier, with increased vascular permeability resulting in central retinal thickening (edema) and lipid deposits (hard exudates). This is termed clinically significant macular edema (CSME), when it is present close to the central macula. Both CSME and PDR are the predominant causes of visual loss in DR. The DME disease severity scale is listed in Table 21.2 [12]. The initial and most important designation is to separate eyes with "apparent DME" from those with "no apparent thickening or lipid" in the macula. The first level is determined by the presence or absence of apparent retinal thickening or lipid in the posterior pole. A second-level evaluation documents details related to the distance of retinal thickening and/or lipid from the fovea. Eyes with obvious foveal involvement by edema or lipid are categorized as "severe DME." Eyes with edema and/or lipid relatively distant from the macula are graded as "mild DME." "Moderate DME" was used to identify cases in which retinal thickening and/or lipid is close to (or "threatening") the fovea [14].

Nonproliferative Diabetic Retinopathy

The earliest stage of DR (or NPDR) is characterized by retinal vascular abnormalities including microaneurysms (saccular outpouchings from the capillary wall), intraretinal hemorrhages, and cotton wool spots (nerve fiber layer infarctions). As the disease progresses, the gradual closure of retinal vessels results in retinal ischemia, giving rise to signs including venous abnormalities (beading, loops), intraretinal microvascular abnormalities, and increasing retinal hemorrhage and exudation. Nonproliferative diabetic retinopathy is graded as mild, moderate, and severe, according to the presence and extent of the aforementioned lesions.

Microaneurysms are the first alterations detectable by ophthalmoscopy (Figs. 21.1, 21.3, and 21.4). They present as small red dots in the middle retinal layers. Fluorescein angiography shows microaneurysms as pinpoint hyperfluorescent lesions that fade in the later phases of the angiogram. The hypofluorescence of dot and blot hemorrhages distinguishes them from the hyperfluorescent microaneurysms. The earliest change in diabetics is an increased vascular permeability, which is seen as late hyperfluorescence emanating from the retinal vessels (Fig. 21.4). The microaneurysms may rupture when the wall of the aneurysm becomes weak, giving rise to an intraretinal hemorrhage. If this intraretinal hemorrhage is deep within the inner nuclear or outer plexiform layers, it presents as a round-oval or

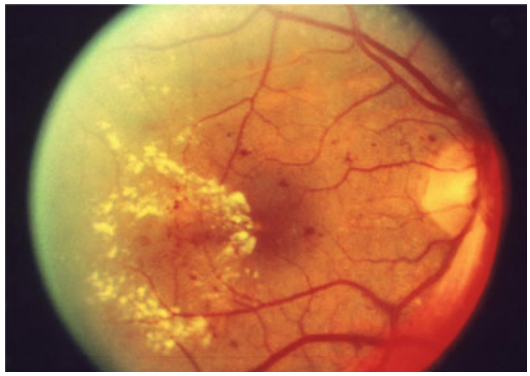

Fig. 21.3 Microaneurysms are the first alterations detectable by ophthalmoscopy. They present as *small red dots* in the middle retinal layers. They tend to leak serous fluid and lipid sometimes in a circinate pattern as shown here

dot-blot hemorrhage. Fluorescein angiography of the hemorrhage shows hypofluorescent dots by blockage (Fig. 21.5).

Also, intracellular fluid collection, coming from leaky microaneurysms, leads to macular edema, the leading factor in diabetes-related legal blindness. These signs, in addition to cotton wool spots, are indicative of ischemia within the nerve fiber layer, leading to stasis of fluid. Hard exudates are yellow lipid deposits with relatively discrete margins. They commonly occur at the edges of microvascular leakage and may form a circinate pattern around leaking microaneurysms (Fig. 21.3). They may coalesce to form extensive sheets of exudates. Vision is affected when hard exudates encroach on the macula. Fluorescein angiography shows hypofluorescence by blockage (Fig. 21.6).

Retinal edema is due to microvascular leakage and indicates breakdown of the inner blood-retinal barrier. It appears as grayish areas of retinal thickening. The thickening may look like a petal-shaped cyst on the macula, and this can cause severe visual deterioration. Fluorescein angiography shows diffuse late hyperfluorescence due to leakage, which may assume a flower-petal pattern if a cystoid macular edema (CME) is present. Optical coherence tomography (OCT) may show three patterns of diabetic macular edema: retinal swelling, cystoid macular edema, and serous retinal detachment (Fig. 21.7).

Cotton wool spots are caused by precapillary arteriolar occlusion within the retinal nerve fiber layer. The interruption of axoplasmic transport, caused by the ischemia and subsequent buildup of transported material within the nerve axons, is responsible for the white appearance of these lesions. Fluorescein angiography shows hypofluorescence due to blockage, which is frequently associated with an area of adjacent capillary nonperfusion.

As hyperglycemia persists, microaneurysms, hemorrhages, and cotton wool spots become more widespread, and the disease progresses to moderate and severe forms. Furthermore, moderate NPDR may present with venous beading, which suggests decreased retinal circulation, and intraretinal microvascular abnormalities (IRMA), indicating dilated capillaries. Fluorescein angiography of IRMA shows hyperfluorescence with mild leakage (Fig. 21.8). Venous loops are almost always adjacent to large areas of capillary nonperfusion, while IRMAs seem to function as collateral channels for blood flow [15].

In short, advanced NPDR is characterized by increased ischemia, resulting in more severe vascular permeability, widespread hemorrhaging, venous abnormalities, and IRMAs (Fig. 21.9).

Proliferative Diabetic Retinopathy

The more advanced stage of DR (or PDR) involves the formation of new blood vessels, induced by the retinal ischemia, which spreads out either from the disk (neovascularization of the disk, NVD) or from elsewhere in the retina (neovascularization elsewhere, NVE). New vessels extending into the vitreous can cause vitreous hemorrhage and tractional retinal detachments (associated with accompanying contractile fibrous tissue). Fluorescein angiography stands out the neovascularization during the early phases of the angiogram and shows hyperfluorescence during the later stages due to intensive leakage of dye from the neovascular tissue (Fig. 21.10).

Approximately 50% of patients with very severe NPDR progress to proliferative retinopathy within 1 year [15]. Areas of capillary nonper-

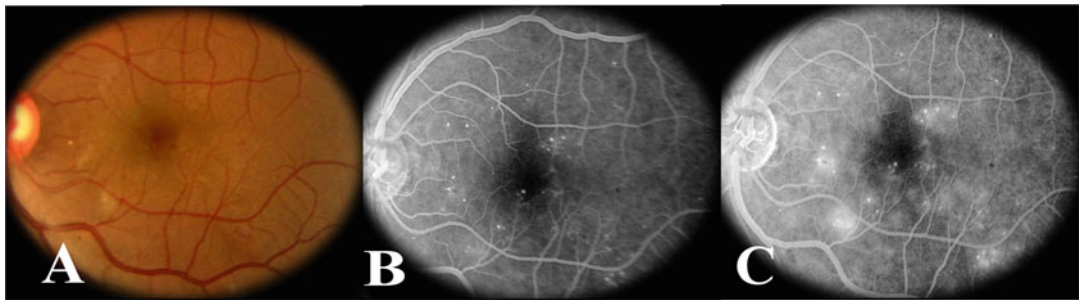

Fig. 21.4 (**a**) Color fundus photograph shows few subtle microaneurysms (MA) on the posterior pole. (**b**) MA are seen as *white dots* due to hyperfluorescence on fluorescein angiography. (**c**) If the wall of the MA is weak, leakage of dye from the MA is observed in the late phase of the angiogram. This is the mechanism by which macular edema develops. The adjacent edematous retinal tissue is seen as diffusely stained

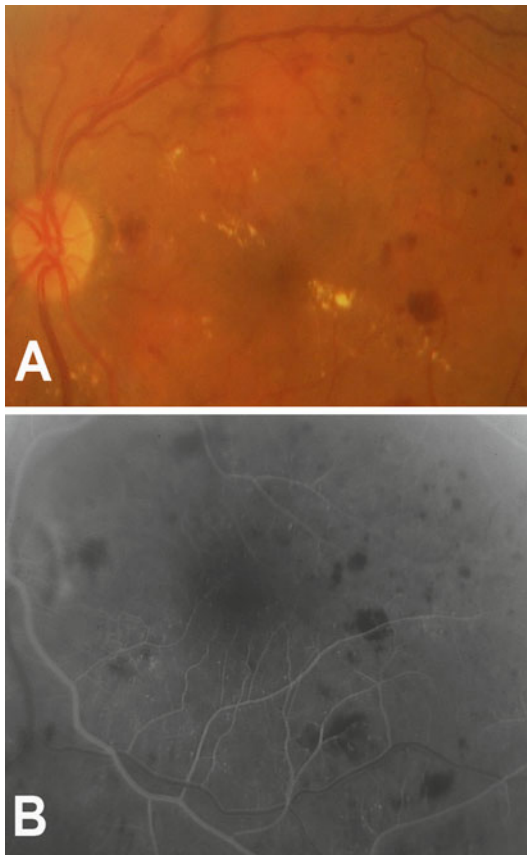

Fig. 21.5 (**a**) Color photograph in nonproliferative diabetic retinopathy. (**b**) Fluorescein angiography of the hemorrhage shows *hypofluorescent dots* by blockage

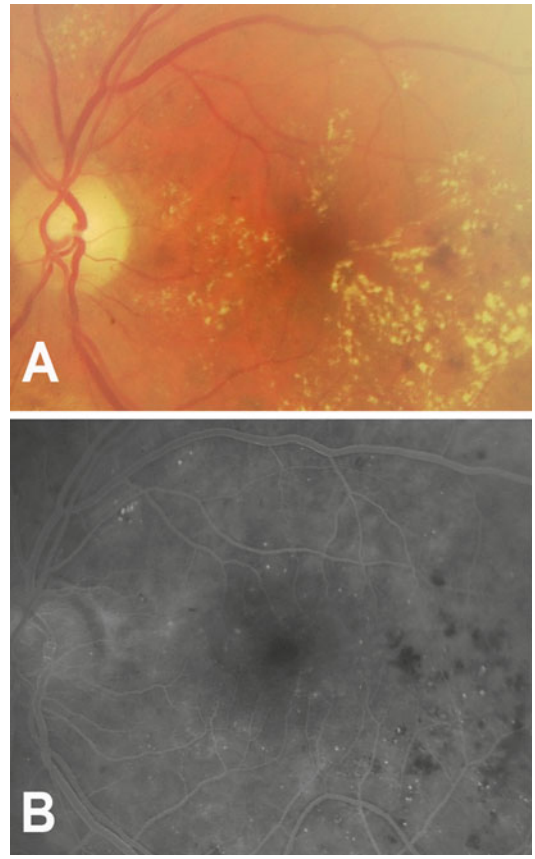

Fig. 21.6 (**a**) Vision is affected when hard exudates encroach on the macula. (**b**) Fluorescein angiography shows hypofluorescence by blockage

fusion are seen as homogenous dark patches (Fig. 21.11). As the degree of ischemia increases, PDR will develop. Proliferation begins when retinal veins give rise to a collection of new, fine vessels that are weak and leaky. Because neovascularization appears to occur with less effort on a preformed connective tissue framework, a shallowly detached posterior vitreous face is

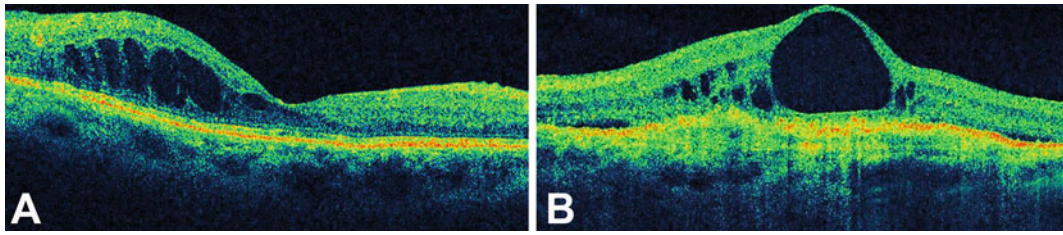

Fig. 21.7 Optical coherence tomography (OCT) may show three patterns of diabetic macular edema: retinal swelling, cystoid macular edema, and serous retinal detachment. (**a**) Typical pattern of diabetic macular edema of the cystoid macular edema (CME) type on OCT. Retinal swelling shows increased retinal thickness with reduced intraretinal reflectivity and expanded areas of lower reflectivity. (**b**) Typical pattern of diabetic macular edema of the CME type on OCT. Eyes with well-established CME, which has persisted for more than 1 year, the cystoid spaces fuse to form a large cystoid cavity

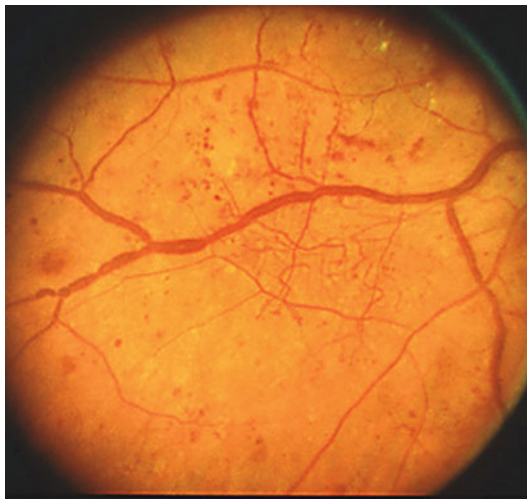

Fig. 21.8 Moderate nonproliferative diabetic retinopathy may present with venous beading, which suggests decreased retinal circulation, and intraretinal microvascular abnormalities (IRMA), indicating dilated capillaries. Fluorescein angiography of IRMA shows hyperfluorescence with mild leakage (not shown)

frequently the site for new vessel growth. Intraretinal microvascular abnormalities may be confused with early neovascularization. Prior to the appearance of frank neovascularization, IRMA develops. A fluorescein angiogram differentiates both conditions. The angiographic appearance of IRMA is that of collateral vessels that do not leak. On the other hand, neovascularization is characterized by hyperfluorescent leaking areas that increase in size and intensity as the study progresses. In the event that these vessels arise on or within one disk diameter of the optic nerve head, they are referred to as NVD (Fig. 21.12a, b); when these vessels arise anywhere else on the retina, they are called NVE (Fig. 21.13a, b). As new vessel growth continues, the fibrous component becomes more prominent, with the fibrotic tissue being either vascular or avascular. The fibrovascular variety is usually found in association with vessels that extend into the vitreous cavity or with abnormal new vessels on the surface of the retina or disk. The avascular variety usually results from thickening of the posterior hyaloid. Vitreous traction is transmitted to the retina along these proliferations and may lead to traction retinal detachment [15]. Eyes with significant fibrous proliferation are less likely to bleed, but carry an increased risk of tractional retinal detachment.

Advanced Eye Disease

In advanced PDR, progressive fibrovascular proliferation leads to blindness due to vitreous hemorrhage and traction retinal detachment. Bleeding may occur into the vitreous or, more frequently, into the retrohyaloid space (preretinal hemorrhage). This has a crescentic shape, which demarcates the level of posterior vitreous detachment (Fig. 21.14). Occasionally, a preretinal hemorrhage may penetrate into the vitreous gel. Tractional retinal detachment is caused by progressive contraction of fibrovascular membranes over large areas of vitreoretinal adhesion (Fig. 21.15). The retinal detachment has a concave configuration with the highest elevation occurring at points of vitreoretinal traction (Fig. 21.16). Diabetic tractional retinal detachment

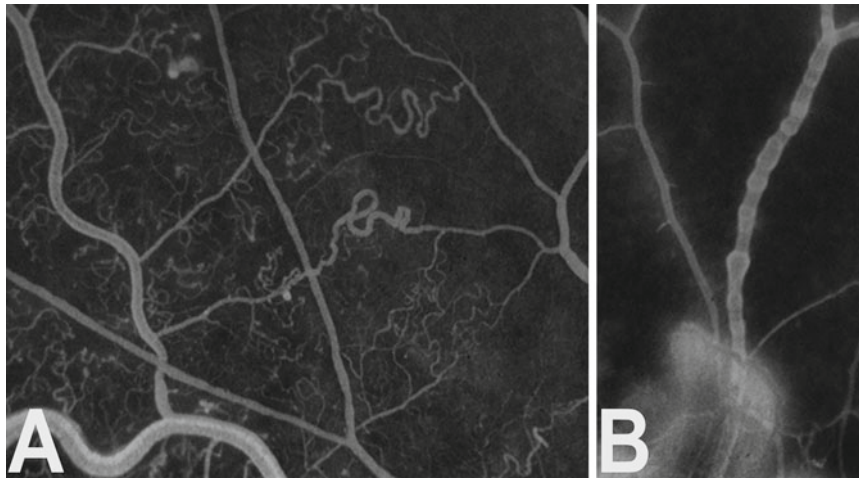

Fig. 21.9 Fluorescein angiography of advanced nonproliferative diabetic retinopathy is characterized by increased ischemia, resulting in more severe vascular permeability, widespread hemorrhaging, venous abnormalities, and intraretinal microvascular abnormalities (IRMA) (**a**). Fluorescein angiography of IRMA shows hyperfluorescence with wall-vessel staining (**b**)

may remain localized for a long time without involving the macula (Fig. 21.17).

Rubeosis iridis and neovascular glaucoma occur when new vessels form on the iris and in the anterior chamber angle, leading to a painful blind eye that occasionally requires enucleation. Rubeosis is usually common in eyes with severe retinal ischemia or persistent retinal detachment following unsuccessful vitrectomy. Ghost cell glaucoma resulting from vitreous hemorrhage can occur. Small full-thickness retinal holes may be seen near the proliferation; these sometimes lead to combined rhegmatogenous and tractional retinal detachment. Late in the course of the disease, neovascular glaucoma can result from new vessels growing on the iris and anterior chamber angle structures.

Diabetic Macular Edema

Clinically significant macular edema develops with time in 10–15% of diabetic patients [16].

DME can occur at any stage of diabetic retinopathy and is caused by excessive vascular permeability resulting in the leakage of fluid and plasma constituents, such as lipoproteins, and a secondary thickening and distortion of the central retina, together with stretching of neurons and an initial reversible loss of vision. Since in the course of time these disturbed neurons can die off, permanent sight reduction can also result [17].

Clinically significant macular edema (CSME) occurs if there is thickening of the retina involving the center of the retina (macula) or the area within 500 μ(mu)m of it, if there are hard exudates at or within 500 μm of the center of the retina with thickening of the adjacent retina, or if there is a zone of retinal thickening one disk area or larger in size, any part of which is within one disk diameter of the center of the retina (Fig. 21.18). The definition of CSME refers to the threshold level at which laser photocoagulation is carried out [18].

The International Clinical Diabetic Macular Edema Disease Severity Scale includes two major levels: absent and present. If DME is present (Table 21.2) [12], it is divided into mild (some retinal thickening or hard exudates in the posterior pole, but distant from the center of the macula), moderate (retinal thickening or hard exudates approaching the center of the macula, but not the center), and severe (involving retinal thickening or hard exudates involving the center) [19].

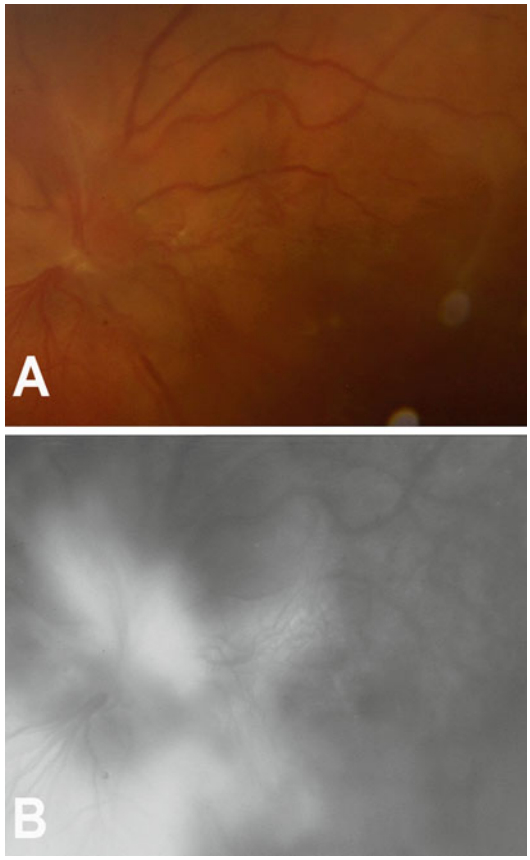

Fig. 21.10 (**a**) Color photograph. (**b**) Fluorescein angiography stands out the neovascularization on the optic disk (NVD) during the early phases of the angiogram and shows hyperfluorescence during the later stages due to intensive leakage of dye from the neovascular tissue

The Pan-American Collaborative Retina Study Group (PACORES) has come up with a definition of diffuse diabetic macular edema (DDME) for their studies, and it requires evidence of diffuse retinal thickening and/or hard exudates (without a circinate ring pattern) involving the center of the macula (clinically significant DME as defined by the ETDRS on slit-lamp biomicroscopic examination) and diffuse fluorescein leakage involving the center of the macula on fluorescein angiography (FA) with less than 33% of leakage associated with microaneurysms [20].

Macular edema is best evaluated by dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography. In addition, serial FA and OCT play an important role in guiding treatment of diabetic macular edema (DME). Optical coherence tomography (OCT) provides images by projecting a pair of near-infrared light beams into the eye. The resulting interference pattern from these beams is dependent of the thickness and reflectivity of the retinal structures and is detected by the measuring system. The images produced appear to be cross sections of the retina and allow the thickness of the retina to be measured. The thickness of the retina may allow DME to be followed in a quantitative manner. The OCT method is analogous to ultrasound B-scanning in that distance information is extracted from the time delays of reflected signals.

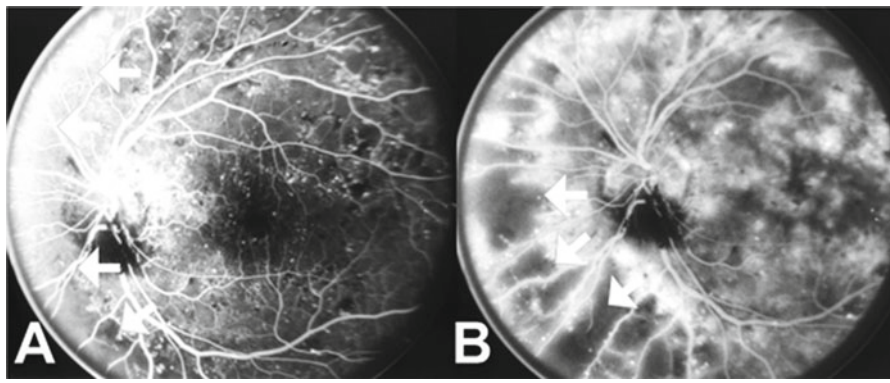

Fig. 21.11 A 69-year-old woman with diabetic retinopathy presented with a visual acuity of 20/400 in her left eye. Retinal examination showed scattered dot and blot hemorrhages, microaneurysms, and clinical significant macular edema. (**a**) Early-phase fluorescein angiogram (FA) demonstrated microaneurysms as pinpoint hyperfluorescent lesions and capillary nonperfusion seen as hypofluorescent areas (*arrows* in a and b). (**b**) Late-phase FA revealed hyperfluorescent spots and leakage corresponding to diffuse macular edema

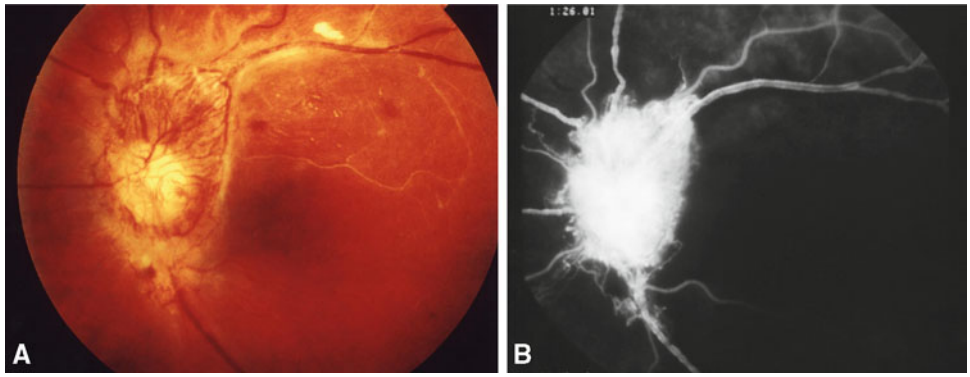

Fig. 21.12 In the event that these vessels arise on or within one disk diameter of the optic nerve head, they are referred to as neovascularization of the disk (NVD). (**a**) Color photograph. (**b**) Fluorescein angiography

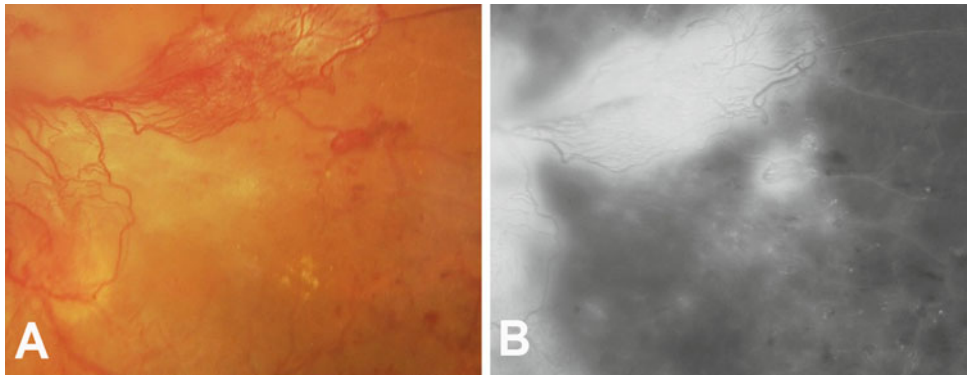

Fig. 21.13 In the event that these vessels arise anywhere else on the retina, they are called neovascularization elsewhere (NVE). (**a**) Color photograph. (**b**) Fluorescein angiography

Optical (laser) instead of acoustic waves are used in OCT, which allows a much higher resolution (3–5 μm) and thereby a more precise assessment of retinal thickness (Fig. 21.19).

Management

Diabetic retinopathy remains a major cause of worldwide preventable blindness. Fluorescein angiography has become a very important tool to study, diagnose, assist in the management, and assess treatment response in patients with diabetic retinopathy. Optical coherence tomography facilitates quantification of the retinal thickness and allows precise follow-up to evaluate the effect of the management of diabetic patients with different degrees of diabetic

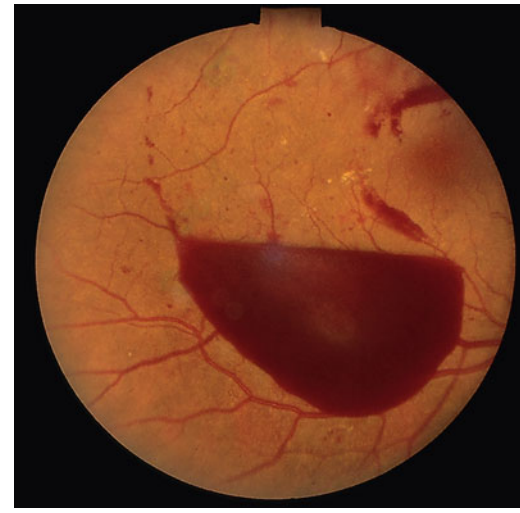

Fig. 21.14 Dilated fundus photographs showing exudates, microaneurysms, and preretinal hemorrhages from bleeding neovascularization

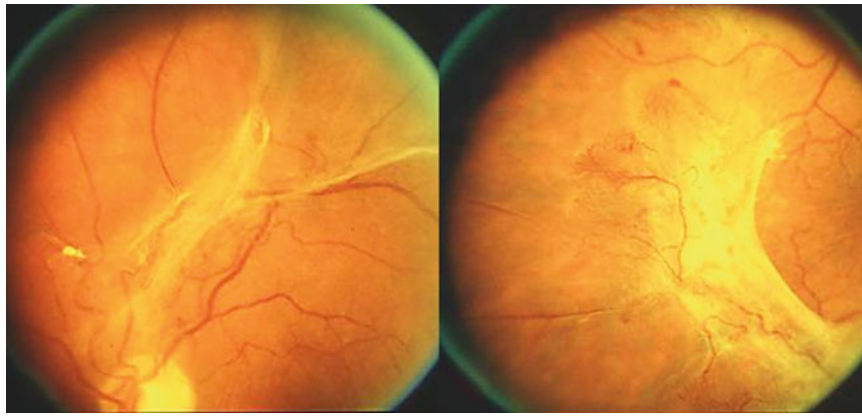

Fig. 21.15 Proliferative diabetic retinopathy: tractional retinal detachment is caused by progressive contraction of fibrovascular membranes over large areas of vitreoretinal adhesion

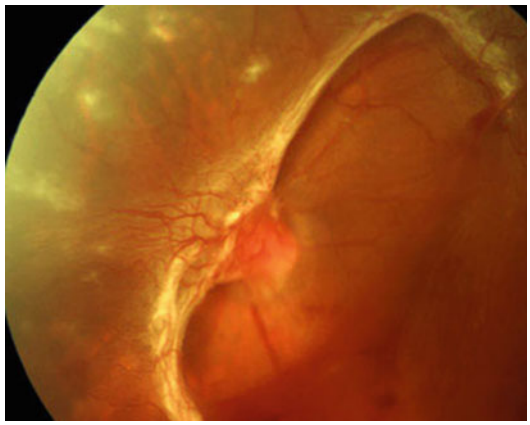

Fig. 21.16 Proliferative diabetic retinopathy: fibrous tissue with localized traction retinal detachment

retinopathy with CSDME in an objective way. In addition, OCT may be very useful in the evaluation of the vitreoretinal and vitreopapillary interface.

Measures to avoid blindness include medical management (control of blood sugar, blood pressure, and serum lipids) and ocular management (laser photocoagulation and pars plana vitrectomy). Adjunctive pharmacologic therapies (intravitreal triamcinolone acetonide and anti-VEGF agents) have shown early promise in the treatment of both DME and PDR. Other medications under investigation include the fluocinolone acetonide implantable device, the extended-release dexamethasone implant, and oral ruboxistaurin.

Glycemic Control

The most effective medical treatment to slow the progression of diabetic retinopathy is glycemic control. The relationship between hyperglycemia and retinopathy has been reported in well-conducted observational studies. The Diabetes Control and Complications Trial (DCCT) [7] and the United Kingdom Prospective Diabetes Study (UKPDS) [8] showed that optimal metabolic control could reduce the incidence and progression of DR. The results of the DCCT and UKPDS showed that while intensive therapy does not prevent retinopathy completely, it reduces the risk of the development and progression of diabetic retinopathy. This can be translated clinically to a preservation of eyesight and reduced need for laser treatment. The review concluded that while keeping the HbA1c targets (HbA1c <7.0%, preprandial plasma glucose 90–130 mg/dl and postprandial plasma glucose <180 mg/dl) in mind, health-care providers should individualize the glycemic goals with the understanding that more stringent targets, such as a HbAIc <6%, may further reduce complications while subsequently increasing the risk of hypoglycemia. Currently, the recommendation is for maintenance of glucose levels as near normal as possible. There does

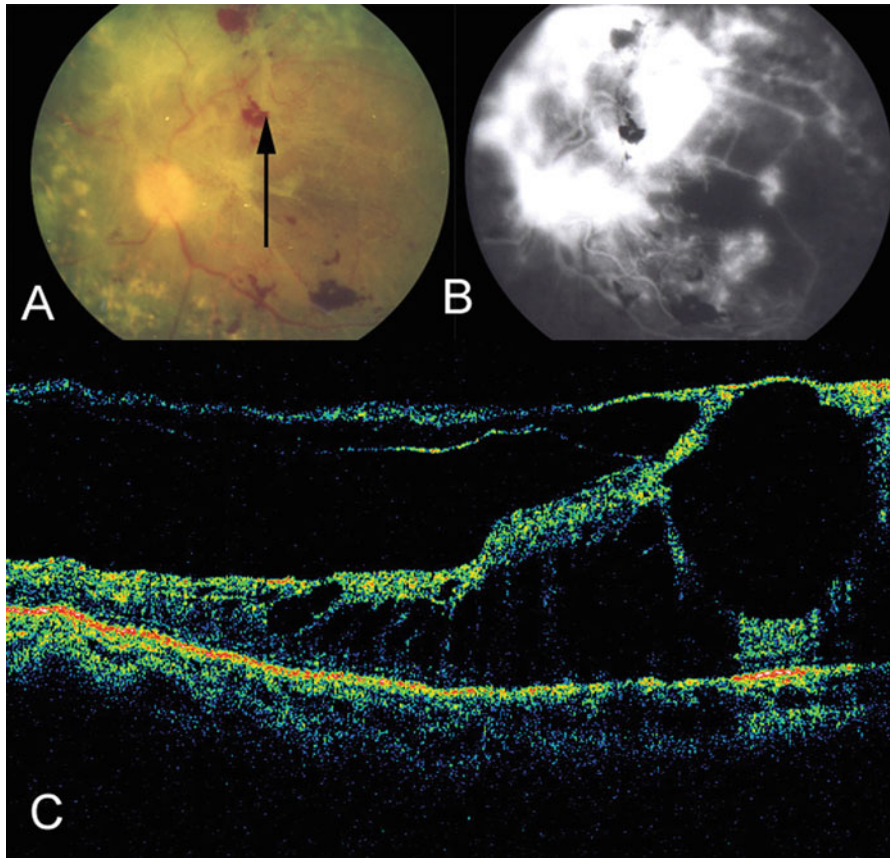

Fig. 21.17 Diabetic tractional retinal detachment may remain localized for a long time without involving the macula. Cystoid macular edema (CME) developed in this case. (**a**) Fundus photography, (**b**) angiofluoresceinography, and (**c**) optical coherence tomography of proliferative diabetic retinopathy with preretinal membranes (thin, reflective bands anterior to the retina) and CME

not appear to be a level below which there is not a reduction of microvascular complications.

Blood Pressure Control

Epidemiological observations suggest that hypertension increases the risk and/or progression of diabetic retinopathy and macular edema. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), progression of retinopathy was associated with higher diastolic blood pressure at baseline and an increase in diastolic blood pressure over a 4-year follow-up period.

The UKPDS Study Group reported the effectiveness of tight blood pressure control [21]. The UKPDS randomized 1,148 hypertensive patients with type 2 diabetes to less tight (<180/105 mmHg) and tight (<150/85 mmHg) blood pressure control with the use of an angiotensin-converting enzyme (ACE) inhibitor or a β-blocker. With a median follow-up of 8.4 years, a mean blood pressure of 144/82 was achieved in the tight and 154/87 in the less tight control group. Patients in the tight control group had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity of three lines compared with the less tight control group. In addition, there were reductions in deaths related to diabetes and stroke. The UKPDS data showed no difference in the efficacy of ACE inhibitors or β-blockers with

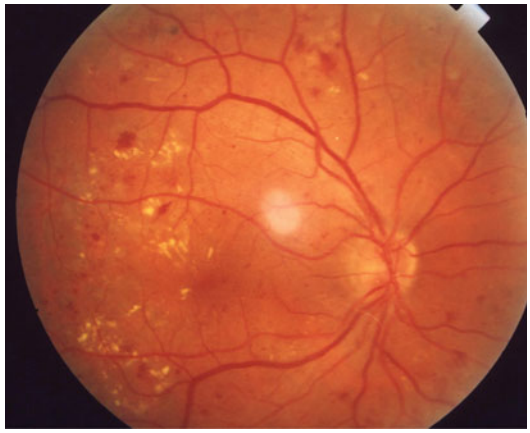

Fig. 21.18 Clinically significant macular edema occurs if there is thickening of the retina involving the center of the retina (macula) or the area within 500 μ from the center of the fovea, if there are hard exudates at or within 500 μ of the center of the retina with thickening of the adjacent retina, or if there is a zone of retinal thickening one disk area or larger in size, any part of which is within one disk diameter of the center of the retina

regard to progression of diabetic retinopathy in type 2 diabetic subjects, suggesting that blood pressure control and not the type of medication is most important in those with hypertension.

Serum Lipid Control

Hyperlipidemia has been linked to the presence of retinal hard exudates in patients with DR, and some evidence suggests that lipid-lowering therapy may reduce hard exudates and microaneurysms. There is observational evidence that elevated lipids may increase the morbidity of macular edema and affect the severity of diabetic retinopathy. Severe hard exudates can lead to the development of subretinal fibrosis, a complication that can lead to permanent loss of vision. A study found that simvastatin inhibited progression of retinopathy in diabetic patients

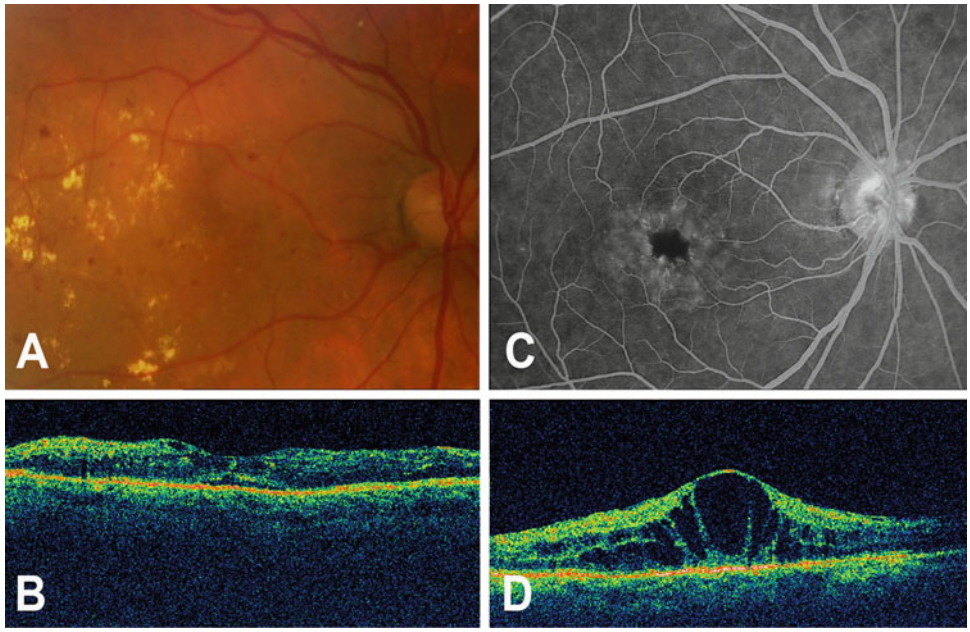

Fig. 21.19 Light instead of acoustic waves are used in optical coherence tomography, which allows a much higher resolution (<8 μ) and thereby a more precise assessment of retinal thickness. (**a**) Diffuse diabetic macular edema with OCT (**b**) demonstrating diffuse thickening and subretinal fluid. Cystoid macular edema demonstrated both on (**c**) fluorescein angiogram and (**d**) OCT

with dyslipidemia [10]. Further clinical trials are currently underway examining the effects of statins.

Aspirin Treatment

The Early Treatment Diabetic Retinopathy Study (ETDRS) investigated whether aspirin (650 mg/day) could retard the progression of retinopathy. After examining progression of retinopathy, development of vitreous hemorrhage, or duration of vitreous hemorrhage, aspirin was shown to have no effect on retinopathy, and there are no ocular contraindications to the use when required for cardiovascular disease or other medical medications.

Laser Photocoagulation

Laser photocoagulation therapy has proven effective in reducing DR progression, and pars plana vitrectomy can in many cases prevent severe vision loss in patients with advanced stages of DR [22]. Unfortunately, both treatments carry a risk of additional vision loss, and neither is effective at reversing loss of visual acuity.

Panretinal Photocoagulation and Focal/Grid Laser Photocoagulation

Therapeutic retinal photocoagulation has been practiced for more than 50 years. Since the 1960s, the treatment has become gradually more refined, effective, and safe as new wavelengths and treatments have entered clinical practice.

Two large National Institutes of Health-sponsored trials, and the Early Treatment Diabetic Retinopathy Study (ETDRS), provide the strongest support for the therapeutic benefit of photocoagulation. The DRS tested whether scatter (panretinal) photocoagulation (PRP) surgery could reduce the risk of vision loss from PDR [23]. There were 1,758 participating patients. After only 2 years, photocoagulation surgery was shown to significantly reduce visual loss (i.e., best acuity of 5/200 or worse) in 15.9% of untreated eyes versus 6.4% of treated eyes. The benefit persisted through the entire duration of follow-up and was greatest among patients whose baseline evaluation revealed high-risk characteristics (HRCs) (disk neovascularization or vitreous hemorrhage with any retinal neovascularization). Of control eyes with HRC, 26% progressed to severe visual loss versus 11% of treated eyes. The absolute benefit of photocoagulation was much smaller for eyes that did not have HRC.

To determine the timing of photocoagulation, the ETDRS examined the effect of treating eyes with mild NPDR to early PDR. The rates of visual loss were low with either treatment applied early or delayed until development of HRCs. Because of this low rate and the risk of complications, the report suggested that scattered photocoagulation be deferred in eyes with mild-to-moderate NPDR. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed, if the eye has reached the high-risk proliferative stage.

The ETDRS also demonstrated the effectiveness of focal photocoagulation in eyes with macular edema. In patients with clinically significant macular edema, 24% of untreated eyes, compared with 12% of treated eyes, developed doubling of the visual angle (e.g., 20/50 to 20/100). Laser photocoagulation in both the DRS and the ETDRS was beneficial in reducing the risk of further visual loss, but generally not beneficial in reversing already diminished acuity.

The recommended therapy is either 1,200–2,000 burns 500 μ in diameter delivered through the Goldmann lens or 1,200–2,000 burns 200 μ in diameter delivered through the Rodenstock panfundoscope or Volk SuperQuad lenses. The burns should be intense enough to whiten the overlying retina, which often requires a power of 200–600 mW and duration of 0.1 s (Fig. 21.20).

Focal and grid laser photocoagulation is indicated for CSME, the goal being to limit vascular leakage through a series of focal laser burns at leaking microaneurysms or grid laser burns in regions of diffuse breakdown of the blood-retinal barrier (Fig. 21.21). In some patients with less than high-risk PDR or with severe or very severe NPDR, PRP may be indicated under certain circumstances. The latter include presence of rapidly

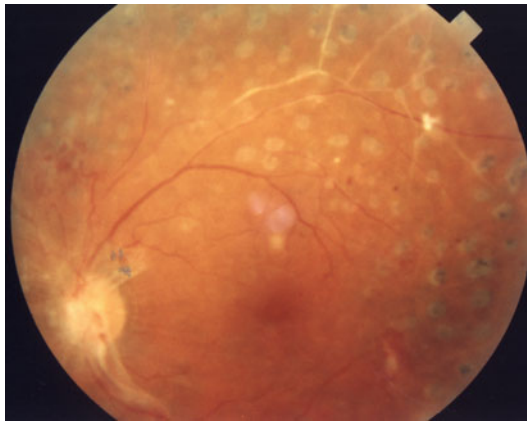

Fig. 21.20 Panphotocoagulation in an eye with neovascularization of the optic disk (NVD). Notice the chorioretinal scars outside the arcades

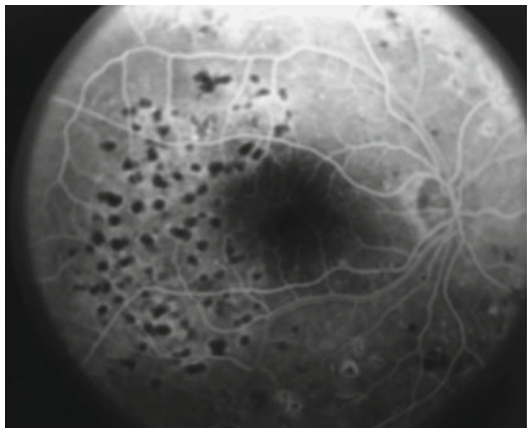

Fig. 21.21 Focal laser for diabetic macular edema in the same patient as Fig. 21.15. Fluorescein angiogram frame showing laser scars in a grid pattern temporal to the fovea

advancing retinal disease, history of poor patient follow-up, type 1 or 2 diabetes mellitus of long duration, a strong family history of diabetes mellitus, or concurrent medical status suggesting rapid progression of DR. Recently, a prospective randomized controlled double-masked trial was performed to compare subthreshold micropulse diode laser photocoagulation (MPDL) with conventional green laser photocoagulation (CGL) in the treatment of clinically significant diabetic macular edema (CSME). This study has shown that subthreshold micropulse diode laser photocoagulation is equally as effective as CGL treatment for CSME [24].

Focal or grid laser photocoagulation may result in an initial decrease in central vision; rarely, they may induce subretinal fibrosis with choroidal neovascularization. On the other hand, peripheral visual field constrictions with poor dark adaptation are the side effects of extensive PRP. In the presence of neovascularisation, vitreous hemorrhage may occur during the course of treatment.

Vitrectomy

Nasrallah et al. [25] observed in 1988 a lower incidence of posterior vitreous detachment in eyes with diabetic macular edema compared with eyes without edema. Lewis et al. [26] described the first encouraging results after vitrectomy in diabetic eyes with macular traction in 1992. Hikichi et al. [27] observed spontaneous resolution of edema in 55% of eyes with posterior vitreous separation, compared with 25% of eyes with or without incomplete posterior vitreous detachment.

The prevalence of posterior vitreous detachment in patients with diabetic macular edema is significantly lower than in diabetic patients without macular edema. Vitrectomy seems to be beneficial for patients with macular edema and traction that are associated with posterior hyaloid thickening [28].

The Diabetic Retinopathy Vitrectomy Study (DRVS) was an important trial evaluating the role of vitrectomy in the management of advanced DR. It found that compared to deferred vitrectomy (after 1 year), early vitrectomy (within the first 6 months) conferred more benefit for patients with visual acuity (VA) ≥20/400 plus one of the following: (1) severe neovascularization and fibrous proliferation, (2) fibrous proliferation and moderate vitreous hemorrhage, or (3) moderate neovascularization with severe fibrous proliferation and moderate vitreous hemorrhage. Among such patients, 44% with early vitrectomy and 28% with deferral treatment had VA ≥20/40 after 4 years follow-up [29].

The main objectives of vitrectomy are to remove media opacities, completely relieve all tractional adhesions (Fig. 21.22), and manage

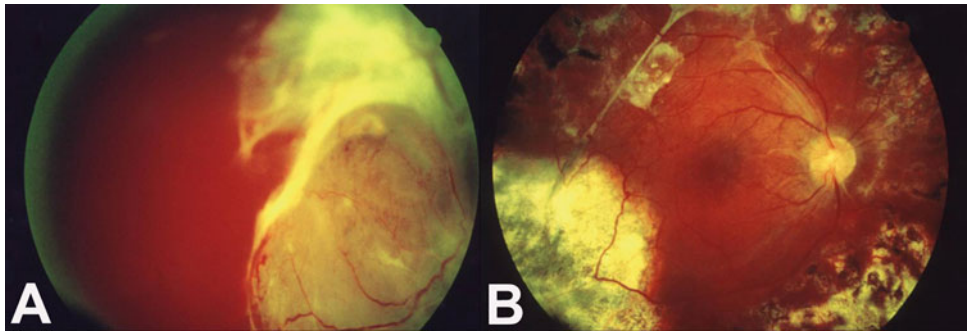

Fig. 21.22 (**a**) Preoperative fundus photograph. Proliferative diabetic retinopathy with extensive vitreous and retinal hemorrhage. A great fibrovascular membrane is observed before treatment. (**b**) Five weeks after the intravitreal injection of bevacizumab and 1 month after vitrectomy with bimanual dissection, retinal panphotocoagulation, and gas endotamponade

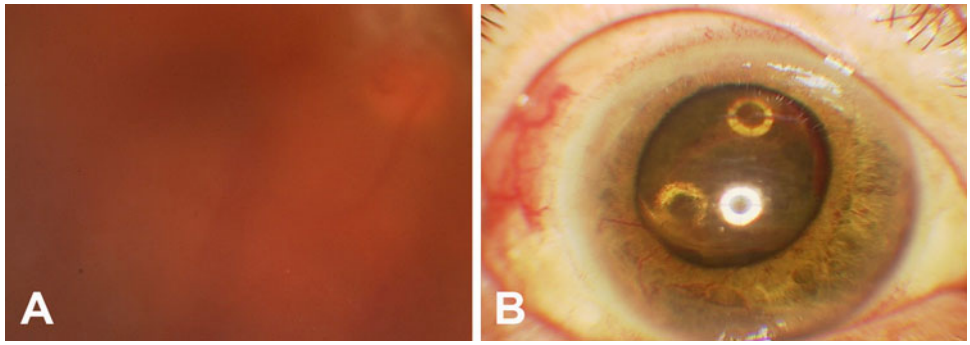

Fig. 21.23 The most frequent short-term postoperative complication of vitrectomy is recurrent vitreous hemorrhage (**a**), while the premature development of cataract is the most common long-term complication (**b**). Rubeosis iridis with secondary glaucoma is another important complication (**b**)

recurrent complications from previous vitrectomy. Some side effects—such as loss of peripheral, night, or color vision—are rarely noted by some photocoagulation-treated patients. The most frequent short-term postoperative complication of vitrectomy is recurrent vitreous hemorrhage, while the premature development of cataract is the most common long-term complication. Rubeosis iridis with secondary glaucoma, endophthalmitis, retinal tear, and detachment are other important complications (Fig. 21.23). Currently, a vitrectomy is performed much earlier, and a diabetic vitreous hemorrhage is observed for about a month before offering early vitrectomy with small-gauge instrumentation to perform what has been called minimally invasive sutureless vitreoretinal surgery.

Twenty-three-gauge transconjunctival sutureless vitrectomy (TSV) was first described by Claus Eckardt [30] as an alternative to the previously described 25-gauge TSV reported by Fujii et al. [31]. The use of sutureless pars plana vitrectomy (PPV) with 23-gauge vitrectors is gaining acceptance and offers advantages versus 25-gauge vitrectomy. The characteristics of the vitrector, particularly the fact that the cutting tip is closer to the edge of the vitrector, facilitate dissection of the fibrovascular proliferations occurring in diabetic retinopathy. In addition, an accessory 25-gauge wide-field endoillumination can be placed on a fourth sclerotomy, permitting bimanual dissection.

A current variation of vitrectomy for proliferative diabetic retinopathy is the use of intravitreally injected anti-VEGF medication as an adjuvant. A recent study demonstrated that preoperative intravitreal bevacizumab (IVB) injection was associated with reduced intraocular bleeding during 23-gauge PPV for diabetic

macula-involving tractional retinal detachment (TRD) [32]. However, another study suggests that surgery should be performed 4 days after intravitreal bevacizumab as most TRD cases occur or progress ≥5 days after the injection [33].

Recently, Parolini et al. [34] reported the rate of postoperative complications in 943 consecutive eyes operated on with 23-gauge transconjunctival pars plana vitrectomy. This report showed that 831 eyes (88%) did not have either significant intra- or postoperative complications. Sclerotomy leakage requiring suture occurred in 37 eyes (3.9%). One choroidal detachment (0.1%) spontaneously resolved 1 week after surgery. At postoperative day 1, 31 eyes (3.3%) experienced transient hypotony. Forty-five eyes (4.8%) presented a subtle vitreous hemorrhage that resolved spontaneously. Two retinal detachments (0.2%) occurred, one at 1 month and one at 3 months. They concluded that 23-gauge complete vitrectomy and peripheral laser seem safe for a variety of vitreoretinal surgical procedures. The rate of post- and intraoperative complications compares favorably with 25-gauge and with the standard 20-gauge vitrectomy [34].

Kim et al. [35] included 11 cases of vitreous hemorrhages, 10 cases of diabetic macular edema, and 1 case of tractional retinal detachment treated with 23-gauge transconjunctival sutureless vitrectomy (TSV). The median BCVA improved from 20/400 (LogMAR, 1.21+/–0.63) to 20/140 (LogMAR, 0.83+/–0.48) at 1 week (p=0.003), 20/100 (LogMAR, 0.85+/–0.65) at 1 month (p=0.002), and 20/100 (LogMAR, 0.73+/–0.6) at 3 months (p=0.001). Intraoperative suture placement was necessary in 7.5%, and the authors reported no serious postoperative complications [35].

Current preliminary results have confirmed the safety and practicality of the 27-gauge instrument system for transconjunctival sutureless MIVS in selected cases. The favorable wound-sealing structures with few postoperative complications and acceptable operating time suggest the potential of the 27-gauge system for treating macular diseases, simple vitreous opacity or diabetic vitreous hemorrhage, and moderately severe diabetic retinopathy. Similar to the recent evolution of other small-gauge systems, further development and refinement of the 27-gauge instrument functionality and rigidity are under way and are critical to the widespread use of this system for the full spectrum of vitreoretinal diseases in the future [36].

Pharmacotherapy

In recent years, further advances in pharmacotherapy have shown promise in the treatment of diabetic retinopathy. The three major classes of medications currently being studied are corticosteroids, VEGF antagonists, and miscellaneous agents.

Corticosteroids

Corticosteroids, a class of substances with anti-inflammatory properties, have been demonstrated to inhibit the expression of the VEGF gene [37]. Corticosteroids are known to reduce vascular permeability, reduce blood-retinal barrier breakdown, downregulate the production of VEGF, and inhibit certain matrix metalloproteinases. Intravitreal triamcinolone (IVTA) has been studied experimentally in the prevention or treatment of choroidal neovascularization, retinal neovascularization, and proliferative vitreoretinopathy and for the treatment of refractory cystoid macular edema (CME) [38].

Triamcinolone Acetonide

Intravitreal triamcinolone has been used for the treatment of diffuse diabetic macular edema, which is characterized by diffuse leakage from extensive areas of posterior capillary bed, a scarcity of hard exudates, and a poor response to grid laser treatment [39]. Intravitreal injection of 1 or 4 mg of triamcinolone acetonide may be beneficial as a treatment for diabetes macular edema with few complications [40].

Using a dosage of about 20 mg IVTA, the increase in VA was most marked during the first 3–6 months after injection and was evident for about 6–9 months [41]. Using a dosage of 4 mg, the duration of the effect (as measured by a reduction in macular thickness by OCT) was less than

6 months. These results lead to clinical trials comparing the efficacy of different IVTA doses, which confirmed that, in general, the duration of the effect increased with increasing dosage. Since the beneficial effects of IVTA are transient, with recurrence of macular edema, in a proportion of eyes, repeated injections may be necessary.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) has completed enrollment on a 3-year, randomized, prospective, multicenter clinical trial comparing two doses (1 and 4 mg) of preservative-free IVTA (Allergan, Irvine, CA, USA) with modified ETDRS photocoagulation for DME [42]. A recently published multicenter study, funded by the National Eye Institute and conducted through the DRCR.net, studied 840 eyes of 693 subjects with DME involving the fovea and with VA of 20/40 to 20/320. This 2-year study demonstrated that focal/grid photocoagulation is more effective and has fewer side effects than 1- or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME who have characteristics similar to the cohort in this clinical trial. The results of this study also support that focal/grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of DME [43].

The most important complication of IVTA is increased intraocular pressure (IOP) resulting in secondary open-angle glaucoma, which sometimes may be severe and intractable [44]. Elevation of IOP up to 24 mmHg may occur in about 4% of patients, usually within about 3 months. The second most important complication of IVTA is cataract formation, which may become visually significant in about half of eyes within 1 year [45]. The rates of injection-related endophthalmitis following IVTA have been reported to be in the range of 0.099–0.87% per injection [46]. The incidence of pseudoendophthalmitis, due to migration of triamcinolone acetonide crystals into the anterior chamber, is probably higher than that of infectious endophthalmitis. Other reported complications of IVTA (and of any intravitreal injection) include retinal detachment, lens trauma, and vitreous hemorrhage.

Peribulbar triamcinolone acetonide may have some limited efficacy for patients with DME although the bulk of the current literature appears to indicate that IVTA is more effective [47].

Fluocinolone Acetonide

In order to avoid the systemic toxicity of corticosteroids and immunomodulary therapy (IMT) or the repeated injections of local steroids necessary to control ocular inflammation, and to prevent development of cumulative damage resulting from recurrent episodes of inflammation, researchers have developed a number of local corticosteroid sustained-release devices that can be implanted directly into the vitreous of the eye, at the site of the inflammatory disease. Preliminary studies of such a device, the fluocinolone acetonide implant (Retisert, Bausch & Lomb, Rochester, NY, USA), have shown significant reductions in the number of inflammatory episodes and decreased reliance on systemic corticosteroids or other IMT [48].

The fluocinolone acetonide intravitreal implant is US Food and Drug Administration (FDA)-approved for the treatment of chronic, noninfectious uveitis affecting the posterior segment [49] and is currently in clinical trials for the treatment of macular edema.

Extended-Release Dexamethasone

The extended-release dexamethasone implant (Ozurdex, Allergan, Irvine, CA, USA) is a biodegradable copolymer of PLGA (poly [lactic-glycolic] acid) and is designed for intravitreal delivery of dexamethasone for approximately 35 days. It has shown favorable outcomes in the treatment of macular edema due to various etiologies, including diabetic retinopathy, retinal vein occlusions, pseudophakic CME, and uveitis, in a phase II study with randomized 306 patients 1:1:1 to Ozurdex 350 ug, Ozurdex 750 ug, or observation [50]. The primary efficacy endpoint was ≥2-line improvement in BCVA. Secondary endpoints included changes in retinal thickness by OCT measurement, change in contrast sensitivity, and improvement in angiographic leakage. Currently, Allergan completed the initial analysis of data from its phase III studies of Ozurdex® for macular edema associated with retinal vein occlusion (RVO) [51, 52]. Patients receiving either the 350 μg or the 700 μg dose of Ozurdex® demonstrated a statistically significant increase in vision based on a 3-line

or better improvement in visual acuity compared to a sham treatment. In addition, both doses of Ozurdex® were well tolerated in the studies. Less than 7% of patients receiving 700 or 350 μm of Ozurdex® experienced an elevation of intraocular pressure greater than 35 mmHg at any time during the 6-month study, and at 6 months, less than 1% of patients had an IOP above 25 mmHg. This new delivery system involves a single-use applicator that delivers the implant via pars plana injection and is performed in the office setting similar to an intravitreal injection. Ozurdex (dexamethasone intravitreal implant) has been approved by the FDA as first-line therapy for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion

Vascular Endothelial Growth Factor Inhibitors

Vascular endothelial growth factor (VEGF) is thought to be a primary mediator of the vascular alterations in diabetic retinopathy. Vascular endothelial growth factor is produced in response to hypoxia from capillary loss and/or microaneurysm formation. It is a key mediator of angiogenesis and blood-retinal barrier breakdown in the ischemic retina. VEGF is upregulated in diabetic retinopathy and is present in increased levels in the aqueous and vitreous humor of patients with PDR [52, 53]. At least five isoforms of VEGF are known. At the moment of this writing, there are four main anti-VEGF agents in clinical use: (1) pegaptanib sodium (Macugen; OSI Eyetech Pharmaceuticals Inc., New York, NY; and Pfizer Inc., New York, NY, USA), (2) ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA, USA), (3) bevacizumab (Avastin; Genentech, South San Francisco, CA, USA), and (4) Aflibercept, previously known as VEGF-Trap eye (Eylea®, Regeneron Pharmaceutics Inc., Tarrytown, NY).

Pegaptanib

Pegaptanib is a modified 28-base pegylated RNA aptamer that binds VEGF165 and the longer VEGF isoforms. It was the first FDA-approved ophthalmologic anti-VEGF agent for the treatment of choroidal neovascularization from age-related macular degeneration (AMD) [54]. A phase II clinical trial of pegaptanib in patients with DME followed up for 36 weeks resulted in better VA outcomes, reduced central retinal thickness, and reduced resort to additional photocoagulation therapy when compared with sham injections [55]. The retrospective analysis of a randomized clinical trial that aimed to study the effect of pegaptanib on diabetic macular edema suggested that pegaptanib might also induce neovascular regression [56].

Ranibizumab

Ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF. This quality makes it a powerful drug for VEGF inhibition. Intravitreal ranibizumab is FDA-approved for the treatment of exudative AMD. A pilot study in patients with CSME showed that therapy with this drug has the potential to maintain or improve VA and reduce retinal thickness [57]. The early experience in animal models with proliferative retinopathy and neovascular glaucoma shows that posterior and anterior neovascularizations are very sensitive to anti-VEGF therapy.

In a recent study, Nguyen et al. [58] compared the use of intravitreal ranibizumab (group 1, 42 patients) with focal/grid laser (group 2, 42 patients) or a combination of both (group 3, 42 patients) in diabetic macular edema (DME). At month 6 of follow-up, they observed that the mean gain in BCVA was significantly greater in group 1 (+7.24 letters, $p=0.01$, analysis of variance) compared with group 2 (–0.43 letters), and group 3 (+3.80 letters) was not statistically different from groups 1 or 2. Excess foveal thickness was reduced by 50%, 33%, and 45% in groups 1, 2, and 3, respectively. These results indicated that during 6 months of follow-up, the application of intravitreal ranibizumab (0.5 mg) administered at baseline and months 1, 3, and 5 had a significantly better visual outcome than focal/grid laser treatment (at baseline and month 3 if needed) or a combination of 0.5 mg of ranibizumab and focal/grid laser at baseline and month 3 in patients with DME [58].

The outcome of two phase III clinical trials will increase our knowledge of the role of ranibizumab in the treatment of DME [59].

Bevacizumab

Bevacizumab is a full-length humanized monoclonal antibody against VEGF, which binds to all isoforms of human VEGF and its biologically active by-products. It is FDA-approved as an adjunctive systemic treatment for metastatic colorectal cancer. The angiogenic properties of bevacizumab, administered via intravenous infusion or intravitreal injection, have been studied in patients with choroidal neovascularization, macular edema, vitreous hemorrhage, and iris neovascularization [60, 61].

Vascular endothelial growth factor plays an important role in many diseases of the posterior pole that are characterized by macular edema and/or intraocular neovascularization. In most parts of the world, both pegaptanib sodium and ranibizumab are not readily available. Therefore, bevacizumab has been proposed as an alternative treatment option.

The Pan-American Collaborative Retina Study Group (PACORES) previously reported on their results on primary intravitreal bevacizumab at doses of 1.25–2.5 mg. Intravitreal bevacizumab seems to provide stability or improvement in VA, OCT, and FA in DME at 6 months [62] and appears to be safe and well tolerated during the first year [63]. In addition, PACORES recently reported the 24-month anatomic and BCVA response after primary intravitreal bevacizumab (IVB) in patients with DME [20]. The results of this retrospective study demonstrated the efficacy of 1.25 or 2.5 mg of intravitreal bevacizumab as primary treatment for DME as 51.8% of eyes showed anatomical as well as functional improvement. In addition, these results suggest a reduced risk of VA loss in eyes with DME treated with intravitreal bevacizumab (97.1% of eyes). All eyes received an intravitreal injection at the initial visit; however, recurrences were retreated at the discretion of the treating physician. There were a total of 807 IVB injections performed. The mean number of IVB injections per eye was 5.8 (range 1–15 injections) at a mean interval of 12.2 ± 10.4 weeks.

These results indicate that intravitreal bevacizumab injections may have a beneficial effect on macular thickness and VA for diffuse diabetic macular edema (DDME). Optical coherence tomography results were available for 139 eyes. At 1 month, the mean 1-mm CMT measurements decreased from 446.4 μm ± 154.4 μm to 333.75 μm ± 117 μm ($p < 0.001$), and this overall improvement continued throughout the 24-month follow-up (Figs. 21.24 and 21.25). Therefore, in the future, this new treatment modality could replace or complement focal/grid laser photocoagulation. Furthermore, focal/grid laser photocoagulation could be used to consolidate the results obtained with one intravitreal bevacizumab injection and decrease the need for reinjections.

Fig. 21.24 (continued) bevacizumab at a dose of 2.5 mg in this eye. (**b**) OCT reveals decrease of macular edema and SRF at 1 month after bevacizumab injection. The retinal map analysis indicates a central foveal thickness of 421 μm. Visual acuity (VA) improved to 10/200. (**c**) Three months after the injection, the OCT scan shows improvement in foveal thickness (354 μm) and almost complete resolution of the SRF. VA improved to 20/200. (**d**) Four months after the first injection, his VA diminished to 20/400, and OCT scan demonstrated the reappearance of macular edema associated to increase of intraretinal cysts and SRF. Central foveal thickness increased to 861 μm. He received a second injection of intravitreal bevacizumab at a dose of 2.5 mg at this point. (**e**–**g**) OCT scans at 5, 6, and 9 months showed a progressive decrease in macular edema, intraretinal cysts, and SRF, which were confirmed with decreased of central foveal thickness (723, 436, and 397 μm, respectively). VA also improved progressively (20/200, 20/160, and 20/125, respectively). (**h**) Twelve months after the first injection, OCT scan showed resolution of DME, with complete reabsorption of SRF and restoration of foveal anatomy. Central foveal thickness decreased to 200 μm, and visual acuity was 20/80. (**i**) OCT scans at 24 months showed a marked resolution of DME, with complete reabsorption of SRF and restoration of foveal anatomy. Central foveal thickness was 157 μm, and the visual acuity improved to 20/50 (Reprinted with permission from Arevalo JF, Sanchez JG, Wu L, Maia M, Alezzandrini AA, Brito M, Bonafonte S, Lujan S, Diaz-Llopis M, Restrepo N, Rodríguez FJ, Udaondo-Mirete P; Pan-American Collaborative Retina Study Group. Primary intravitreal bevacizumab for diffuse diabetic macular edema the Pan-American Collaborative Retina Study Group at 24 months. Ophthalmology 2009 Jun 20 [Epub ahead of print])

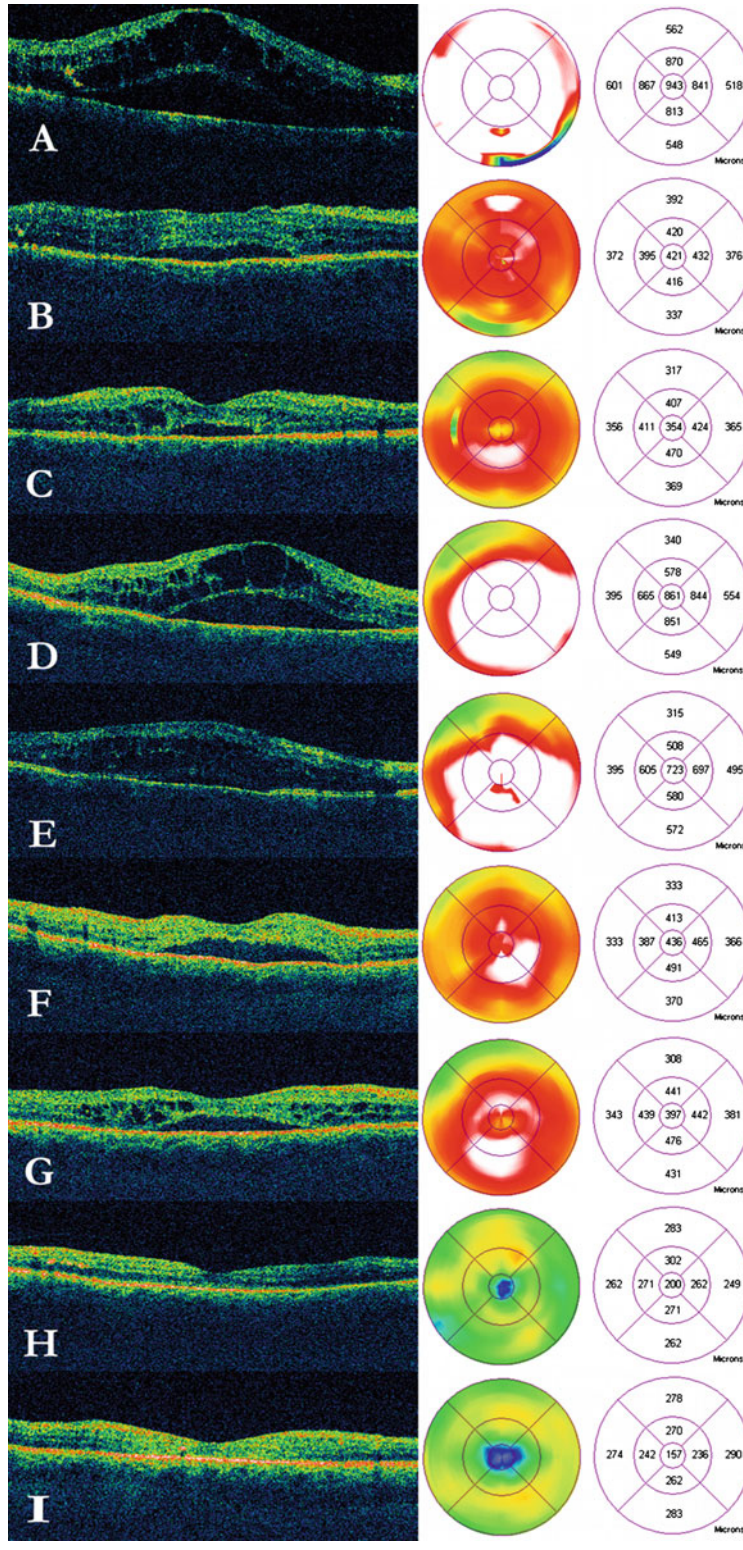

Fig. 21.24 Sequential optical coherence tomography (OCT) of a 32-year-old diabetic man with a 3-month history of loss of vision to counting fingers (CF) in his right eye that had developed diabetic macular edema (DME). (**a**) A horizontal OCT scan obtained through the fovea revealed loss of the normal foveal contour, diffuse macular thickening, areas of low intraretinal reflectivity consistent with intraretinal cysts, and subretinal fluid (SRF). The retinal map analysis revealed a foveal thickness of 943 μm. The patient underwent an intravitreal injection of

Aflibercept

Aflibercept is a recombinant fusion protein that consists of portions of human VEGF receptors 1 and 2 that allows it to bind to VEGF-A, VEGF-B and placental growth factor. Aflibercept has been recently approved for the treatment of Age-related macular degeneration.

The Da Vinci Study randomized 221 eyes with DME to 0.5 mg of aflibercept every 4 weeks vs 2 mg of aflibercept every 4 weeks vs 2 mg of aflibercept monthly for 3 consecutive monthly doses and then every 2 months vs 2 mg of aflibercept monthly for 3 consecutive monthly doses and then on an as needed basis (prn) vs macular laser photocoagulation. At the 6 month follow-up, aflibercept treated eyes had a gain of 8.5 to 11.4 letters compared to 2.5 letters in the laser group [64].

Controversies and Perspectives

There are several reports published on the intravitreal administration of anti-VEGF compounds for retinal neovascularization (RN) in diabetic retinopathy [56, 65]. In addition, there are several case reports on the use of intravitreal bevacizumab in RN in diabetic retinopathy demonstrating regression of RN in PDR [66–70].

The PACORES group conducted a retrospective study in 43 eyes of 39 patients with PDR that had RN, who were treated with off-label intravitreal bevacizumab. Patients were followed for 24 months. Of the total of 43 eyes, 17 (39.5%) eyes treated showed total regression of RN on fundus examination with absence of fluorescein leakage (Fig. 21.26a, b), 15 (34.9%) eyes demonstrated partial regression of RN on fundus examination and FA, and 11 (25.6%) eyes showed no regression of RN. They have demonstrated that intravitreal bevacizumab resulted in marked regression and then stability of RN on fundus examination and FA in patients with PDR and previous PRP [33].

Regression of neovascularization and decrease of retinal thickening occurred in some injected eyes as soon as 7–15 days after the intravitreal injection of bevacizumab. Twenty-one eyes (47.7%) needed a second injection due to recurrence of neovascularization at a mean of 12.4 weeks, and seven eyes (15.9%) needed a third injection due to recurrence of neovascularization at a mean of 17.3 weeks. They elected to defer reinjection only when there was a recurrence of RN. Optimum dose and dosing sequence for IVB is still undetermined. An interesting finding at 24 months is an increase in the number of eyes that did not respond to IVB with complete RN regression as compared with previously published 6-month data [71]. It is possible that over time the effect of IVB on RN diminishes and that other means to control RN will be necessary including PRP and vitrectomy. Although one tractional retinal detachment was reported (1 eye; 2.3%) and one (2.3%) eye developed a vitreous hemorrhage in these series, further studies are needed to assess the efficacy and safety of IVB in the management of PDR. The authors concluded that intravitreal bevacizumab seems to be a useful treatment for PDR, minimizing the risk for exudative complications, progression of retinal neovascularization, vitreous hemorrhage, and decreased vision caused by macular edema. Intravitreal bevacizumab may potentially be used as an adjuvant agent to PRP for PDR.

In addition, anti-VEGF drugs may be employed as an adjuvant therapy to the surgical treatment in diabetic retinopathy [72]. Their potential applications in this field are as follows:

1. Prior to surgery. The intravitreal injection of anti-VEGF drugs leads to a significant reduction of neovascularization, with a reduction in the adherence of the fibrovascular complex to the retina. This simplifies viscodelamination and reduces intraoperative bleeding during delamination and

Fig. 21.25 (continued) injection, OCT showed a marked resolution in macular edema and restoration of foveal anatomy. Central foveal thickness was 125 μm, and VA improved to 20/160 (Reprinted with permission from Arevalo JF, Sanchez JG, Wu L, Maia M, Alezzandrini AA, Brito M, Bonafonte S, Lujan S, Diaz-Llopis M, Restrepo N, Rodríguez FJ, Udaondo-Mirete P; Pan-American Collaborative Retina Study Group. Primary intravitreal bevacizumab for diffuse diabetic macular edema the Pan-American Collaborative Retina Study Group at 24 months. Ophthalmology 2009 Jun 20 [Epub ahead of print])

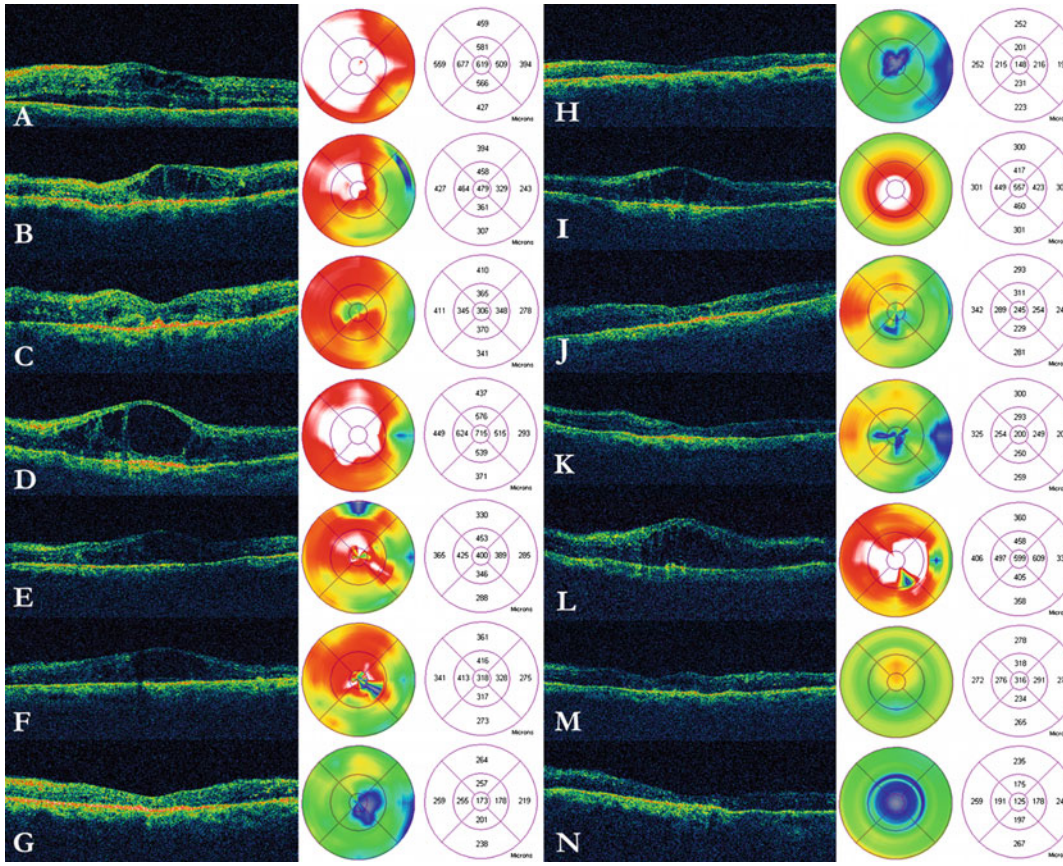

Fig. 21.25 Sequential optical coherence tomography (OCT) of a 69-year-old diabetic woman with a 6-month history of loss of vision to counting fingers (CF) in her left eye that had developed diabetic macular edema (DME). (**a**) A horizontal OCT scan obtained through the fovea revealed loss of the normal foveal contour, diffuse macular thickening, areas of low intraretinal reflectivity consistent with intraretinal cysts, and subretinal fluid (SRF). The retinal map analysis revealed a foveal thickness of 619 μm. The patient underwent an intravitreal injection of bevacizumab at a dose of 2.5 mg in this eye. (**b**) OCT reveals partial resolution of intraretinal macular edema and complete reabsorption of SRF at 1 month after bevacizumab injection. The retinal map analysis indicates a central foveal thickness of 479 μm. Visual acuity (VA) improved to 20/400. (**c**) Three months after the injection, the OCT scan shows improvement in foveal thickness (306 μm). VA improved to 20/200. (**d**) Four months after the first injection, her VA diminished to CF, and OCT scan showed the reappearance of macular edema associated to increase of intraretinal cysts. Central foveal thickness increased to 715 μm. She received a second injection of intravitreal bevacizumab at a dose of 2.5 mg at this point. (**e**–**g**) At month 6, she received a third injection of intravitreal bevacizumab at dose of 2.5 mg. OCT scans at 5, 6, and 9 months showed a progressive resolution in macular edema and intraretinal cysts, which were confirmed with decrease of central foveal thickness (400, 318, and 173 μm, respectively). VA also improves progressively (20/200, 20/200, and 20/125, respectively). (**h**) Twelve months after the first injection, the OCT scan showed resolution of DME, with complete reabsorption of SRF and restoration of foveal anatomy. Foveal thickness decreased to 148 μm, and visual acuity was 20/125. (**i**) Sixteen months after the first injection, her VA diminished to 20/400, and the OCT scan showed a reappearance of macular edema associated to increase of intraretinal cysts. Central foveal thickness increased to 557 μm. She received a fourth injection of intravitreal bevacizumab at dose of 2.5 mg. (**j**) OCT scan at 17 months showed a resolution in macular edema and intraretinal cysts. Central foveal thickness decreased to 245 μm, and VA was 20/160. (**k**) 18 months after the first injection (2 months after the previous injection), the OCT scan shows improvement in foveal thickness (200 μm). VA improved to 20/125. (**l**) Nineteen months after the first injection, her visual acuity diminished to 20/400, and the OCT scan showed the reappearance of macular edema. The retinal map analysis indicates a central foveal thickness of 599 μm. She received a fifth injection of intravitreal bevacizumab at a dose of 2.5 mg at this point. (**m**) OCT scan at 20 months showed resolution in macular edema and intraretinal cysts. Central foveal thickness decreased to 316 μm. VA improved to 20/200. (**n**) Twenty-four months after the first

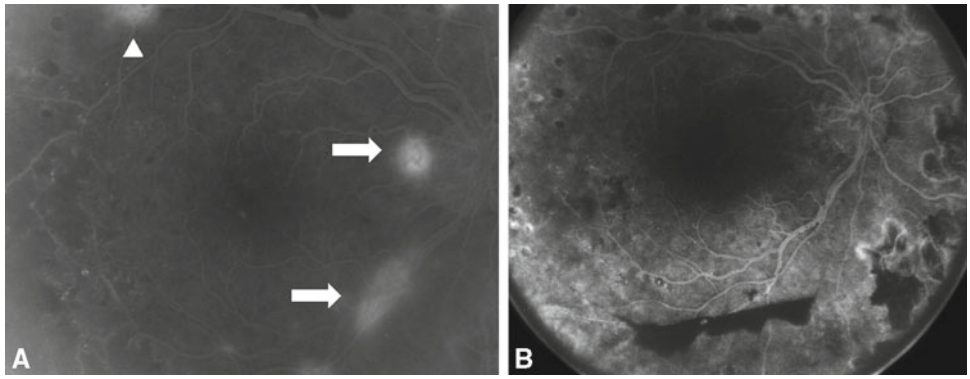

Fig. 21.26 A 53-year-old man had a 2-month history of visual loss to 20/60 in his right eye. We had performed panretinal photocoagulation (PRP) in his right eye 2 years previously. Fundus examination revealed a mild vitreous hemorrhage. (**a**) Fluorescein leakage from neovascularization of the disk (NVD) at baseline (*arrows*) between retinal vessels crossing the optic disk was demonstrated. In addition, fluorescein angiography (FA) showed magnification of retinal neovascularization elsewhere (NVE) in the superonasal retina (*arrowhead*). (**b**) At week 1 after intravitreal bevacizumab, total resolution of leakage from NVD and NVE is shown. His visual acuity returned to 20/32 one month later. He needed a reinjection at months 6, 14, and 24 of follow-up. A PRP was performed at 24 months

segmentation. To minimize the risk of tractional retinal detachment due to the contraction of fibrovascular tissue, vitrectomy must be performed within 1 week after the injection.

2. To decrease the risk of postoperative bleeding. Recurrent vitreous hemorrhages after vitrectomy are often due to small bleeding from persistent neovascularization. The injection of anti-VEGF drugs at the end of vitrectomy could prevent bleeding from these vessels by blocking the proinflammatory stimulus of the surgical procedure.
3. To treat postoperative vitreous hemorrhage. The intravitreal injection of anti-VEGF drugs in patients with postoperative bleeding leads to resolution of the hemorrhage.
4. To treat rubeosis iridis. In eyes with complete panretinal photocoagulation, the combination of cryotherapy and intravitreal anti-VEGF injection in the same surgical procedure produces disappearance of iris neovascularization together with a long-term effect with no recurrences. In neovascular glaucoma, anti-VEGF drugs can also facilitate filtrating surgery [72].

The PACORES group has identified 25 eyes (patients) out of 698 IVT injections that developed or had progression of tractional retinal detachment (TRD) with decreased BCVA after intravitreal bevacizumab prior to vitrectomy for the management of PDR (Fig. 21.27) [33]. The natural course of PDR is characterized by a cycle of proliferation and regression typical of new vessels, proliferation of fibrous tissue accompanying new vessels, formation of adhesions between the fibrovascular proliferations and the posterior vitreous surface, and contraction of the posterior vitreous surface and associated proliferation. The development or progression of TRD in PDR following intravitreal bevacizumab in our patients could have happened by natural history or rapid neovascular involution with accelerated fibrosis and posterior hyaloidal contraction as a response to decreased levels of VEGF. In the current study, eleven (44%) patients used insulin administration as sole therapy for glycemic control, seven (28%) diabetic patients controlled glycemic levels with oral therapy, and the remainder seven (28%) patients used combination therapy with insulin and oral hypoglycemic agents for glycemic control. They all had uncontrolled diabetes associated with elevated glycosylated hemoglobin (HbA1c mean=9.2%). Results of this study suggest that TRD in PDR may occur or progress after intravitreal bevacizumab used as an adjuvant to vitrectomy. However, in the eyes that underwent vitrectomy, they had the impression that there was a reduced risk of intraoperative bleeding facilitating the removal of fibrovascular membranes. When neovascularization regresses, the fibrovascular complex becomes a fibrous tissue that can be removed through slight traction or

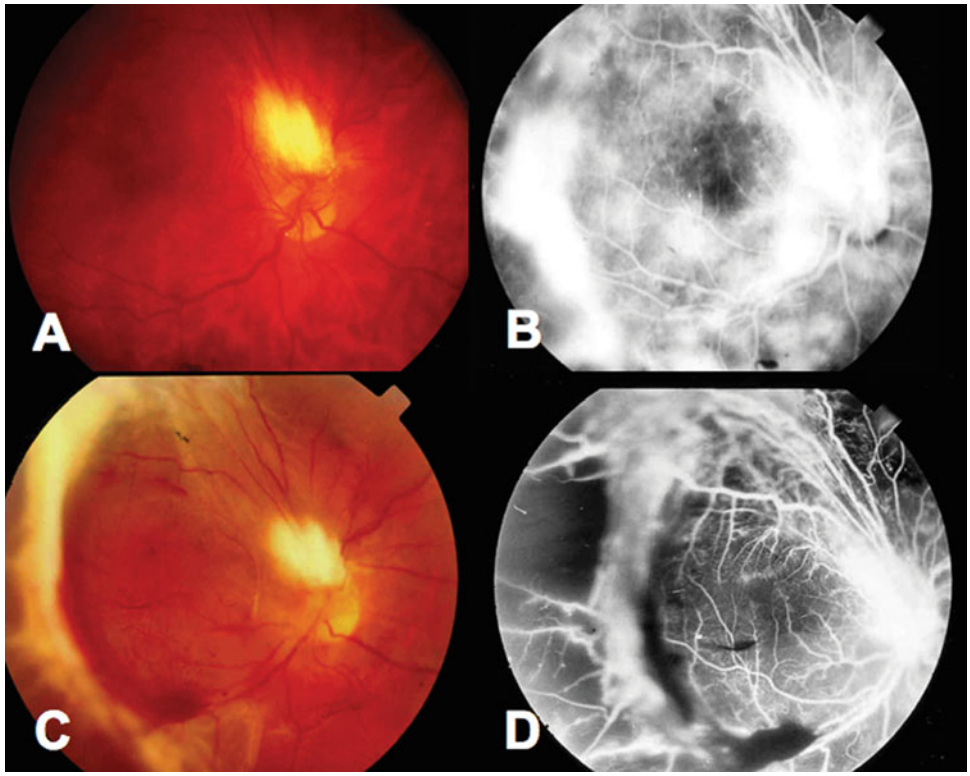

Fig. 21.27 (**a**) Color photograph and (**b**) fluorescein angiogram (FA) before intravitreal bevacizumab. FA revealed marked hyperfluorescence resulting from leakage of dye from new vessels and fibrous tissue on the disk (NVD), new vessels and fibrous tissue temporal to the fovea (NVE), and diffuse macular edema. The retina is attached, and best-corrected visual acuity (BCVA) is 20/80. (**c**) Color photograph and (**d**) FA 1 week after 2.5 mg of intravitreal bevacizumab demonstrating dense fibrous tissue contraction and tractional retinal detachment temporal to the fovea and along the superotemporal vascular arcade. BCVA is hand motions at 2 m (Courtesy of Jans Fromow-Guerra, M.D., and Virgilio Morales-Canton, M.D.)

segmented with a vitrectomy probe with minimal bleeding. As we know, a bloodless field allows for better visibility, and the surgeon may be less likely to create an iatrogenic retinal break. In addition, the chances of postoperative complications such as rebleeding or fibrinoid syndrome may be decreased. Although one case report suggests that the injection of pegaptanib before vitrectomy for proliferative diabetic retinopathy facilitates surgery [73], the most common anti-VEGF drug employed for this purpose is bevacizumab [63–71]. All these advantages may allow the surgeon to save more eyes utilizing preoperative intravitreal bevacizumab regardless of increased traction on some severe PDR cases. Moreover, most patients with development or progression of TRD had poorly controlled diabetes mellitus associated with elevated HbA1c, insulin administration, PDR refractory to panretinal photocoagulation, and longer time between intravitreal bevacizumab and vitrectomy. These factors need to be studied to determine if they are indeed risk factors for the development or progression of TRD after preoperative intravitreal bevacizumab in PDR. Surgery should be performed 4 days after intravitreal bevacizumab as most TRD cases occur ≥5 days after the injection.

Focal Points

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. Diabetic retinopathy is still a cause of blindness. Diabetic eye disease severely affects quality of life for patients with

diabetes by decreasing visual acuity and increasing the risk of blindness.

Treatment modalities that exist can prevent or delay the onset of diabetic retinopathy, as well as prevent loss of vision, in a large proportion of patients with diabetes. The DCCT and the UKPDS [21] established that intensive diabetes management to obtain near-euglycemic control can prevent and delay the progression of diabetic retinopathy. The treatment involves not just laser photocoagulation and vitrectomy surgery but now also includes control of blood glucose, hypertension, and serum lipids.

Pharmacotherapy is making an impact on the treatment of diabetic retinopathy, and many treatments are currently under investigation. The future holds promise with improved pharmacotherapies that may decrease the progression of diabetic retinopathy and diabetic macula edema and help with the treatment of the many complications than can occur due to PDR. The results from clinical trials with protein kinase C (PKC) inhibitors, intravitreal steroids, ACE inhibitors, hyaluronidase, and specially anti-VEGF agents are promising, and further clinical trials are ongoing, and the role of pharmacologic treatments will become clearer for the treatment and reduction of visual loss of DR.

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Retinal and Choroidal Manifestations of Systemic Hypertension

22

Stephen G. Schwartz, Susan Schneider, and William F. Mieler

Abstract

Systemic (essential) hypertension is common and has well-described effects on the retinal and choroidal vasculature. Because systemic hypertension is frequently asymptomatic, the presenting signs and symptoms may be visual. Hypertensive retinopathy has been linked to increased vascular morbidity and mortality. Therefore, early detection of ophthalmologic changes may lead to intensified blood pressure management, thus preserving vision and improving general health. In addition, hypertension is associated with several important retinal diseases, including retinal vascular occlusion, diabetic retinopathy, and anterior ischemic optic neuropathy.

Keywords

Hypertensive retinopathy • Hypertensive choroidopathy • Hypertensive optic neuropathy

Introduction

Systemic (essential) hypertension, which affects almost one-third of adults in the United States, is a major risk factor for cardiovascular disease, stroke, and death [1].

Hypertension directly affects the retinal and choroidal circulations, causing hypertensive retinopathy and choroidopathy. In addition, hypertension is associated with acceleration of diabetic retinopathy and also increases the risk of retinal vascular occlusion, ischemic optic neuropathy, retinal artery macroaneurysm, and other diseases. Because hypertension is frequently asymptomatic, the presenting signs or symptoms may be visual. Thus, the practicing ophthalmologist should possess a familiarity with this disease and its myriad effects on the posterior segment of the eye.

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Hypertensive Retinopathy

"Albuminuric retinitis" was initially noted by Leibreich in 1859 [2], and Marcus Gunn published detailed case descriptions in 1892 [3]. Hypertensive retinopathy is the most common ophthalmic manifestation of hypertension [4], with a reported prevalence of 2–14% in nondiabetic adults over age 40 years [5]. Detection of hypertensive retinopathy is important to preserve vision and to guide treatment of the underlying systemic disease [1].

Multiple clinical grading systems have been published. The four-stage Keith-Wagener-Barker classification was described in 1939 [6], and the five-stage Scheie classification was described in 1953 [7]. More recently, a simpler three-stage classification has been proposed (Table 22.1) [8]. Regardless of the classification scheme, the progression of the disease generally follows the known pathophysiology [9]. Initially, retinal arteriolar constriction occurs as part of an autoregulatory mechanism [10]. With continued disease, breakdown of the inner blood-retinal barrier occurs, with subsequent hemorrhages and exudates, followed by retinal edema (Fig. 22.1a, b). In advanced cases, optic nerve edema (hypertensive optic neuropathy) may ensue, which is caused by ischemia leading to axonal edema [11] (Fig. 22.2a, b).

The differential diagnosis of hypertensive retinopathy is listed in Table 22.2 [12]. Selected reported risk factors for hypertensive retinopathy are listed in Table 22.3.

Table 22.1 Classification of hypertensive retinopathy (Adapted from [8])

Degree	Associated findings
Mild	Arteriovenous crossing changes ("nicking")
	Generalized or focal arteriolar attenuation
	Widening or accentuation of arteriolar light reflex ("copper wiring")
Moderate	Retinal hemorrhages
	Cotton-wool spots
	Microaneurysms
	Hard exudates
Malignant	Optic disk edema

Hypertensive retinopathy is typically bilateral, although unilateral disease has been reported in the setting of contralateral carotid disease [13]. Optical coherence tomography of advanced cases typically may demonstrate cystoid macular edema and subretinal fluid [14, 15].

Hypertensive retinopathy may predict increased risks of systemic morbidity and mortality. Large population-based studies have documented statistically significant associations between worsening degrees of hypertensive retinopathy and risks of stroke [16], cognitive impairment [17], and cardiovascular death [18].

Hypertensive Choroidopathy

Hypertensive choroidopathy is more common in younger patients, whose retinal vessels are not yet sclerotic from exposure to chronic hypertension [9]. Although there is no formal grading system for hypertensive choroidopathy, the clinical manifestations follow the histopathology [19]. Initial ischemia is followed by chronic choroidal vascular occlusion and ultimately recanalization of the choroidal vessels.

Clinically, choroidal infarcts may manifest as Elschnig spots [20] (Fig. 22.3a, b, c) or less commonly as Siegrist's streaks. If the choroidopathy involves the macula, permanent visual loss may result [21]. Continued ischemia of the retinal pigment epithelium may lead to exudative (serous) retinal detachment (Fig. 22.4). In severe cases, massive suprachoroidal hemorrhage may occur, with associated anterior displacement of the lens-iris diaphragm and nonpupillary block angle closure [22].

Indirect Effects

Hypertension is a risk factor for a variety of retinal and choroidal diseases, summarized in Table 22.4 (Fig. 22.5a, b, c). For many of these diseases, an association is well documented, while for others, an association is suspected but has not been conclusively demonstrated [5].

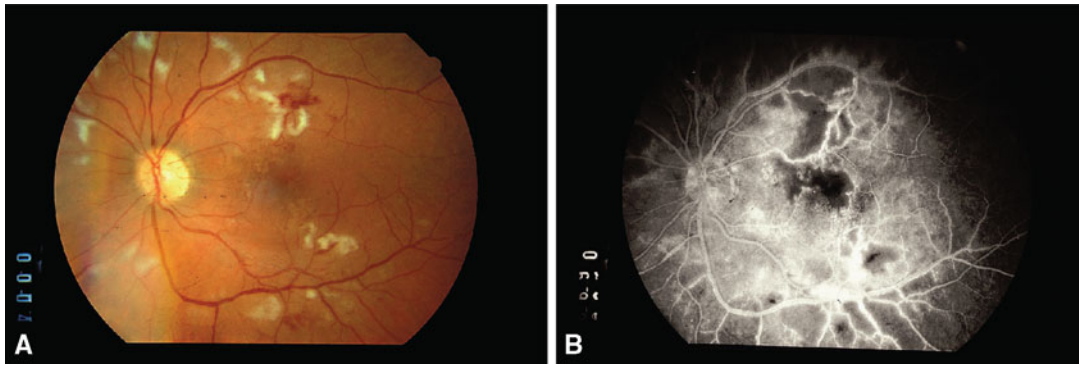

Fig. 22.1 (**a**) Color photograph of hypertensive patient depicting features of moderate hypertensive retinopathy, including generalized arteriolar narrowing, cotton-wool spots, and small intraretinal hemorrhages. (**b**) Fluorescein angiogram (FA) reveals localized areas of capillary nonperfusion

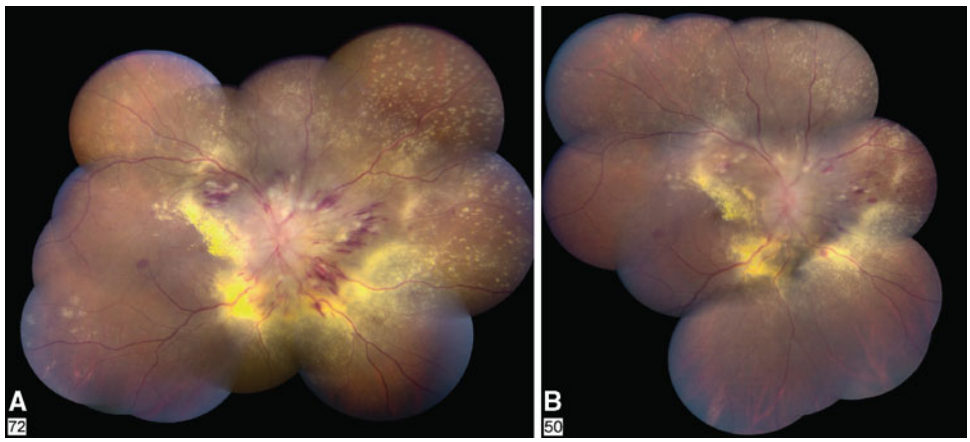

Fig. 22.2 (**a**) Color photograph documenting hypertension-induced optic neuropathy, along with hypertensive retinopathy and choroidopathy. Intraretinal hemorrhages, cotton-wool spots, exudates, and areas of choroidal ischemia are readily apparent. The patient was admitted to the emergency department for management of markedly elevated blood pressure of 240/120. (**b**) Color photograph of same patient, showing early resolution of hypertensive features now 2 weeks following control of systemic hypertension (BP 120/72)

Table 22.2 Differential diagnosis of hypertensive retinopathy (Adapted from [12])

Differential diagnosis	Reference
Age-related retinal vascular arteriosclerosis	[30]
Collagen vascular disease	
Diabetic retinopathy	
High-altitude retinopathy	[31]
Macular telangiectasis	
Ocular ischemic syndrome	
Radiation retinopathy	[32]
Venous occlusive disease	

Table 22.3 Selected reported risk factors for hypertensive retinopathy

Risk factor	Reference
Female gender	[33]
African ancestry	[34]
Deletion polymorphism in the angiotensin-1-converting enzyme gene	[35]
Low plasma adiponectin levels	[36]

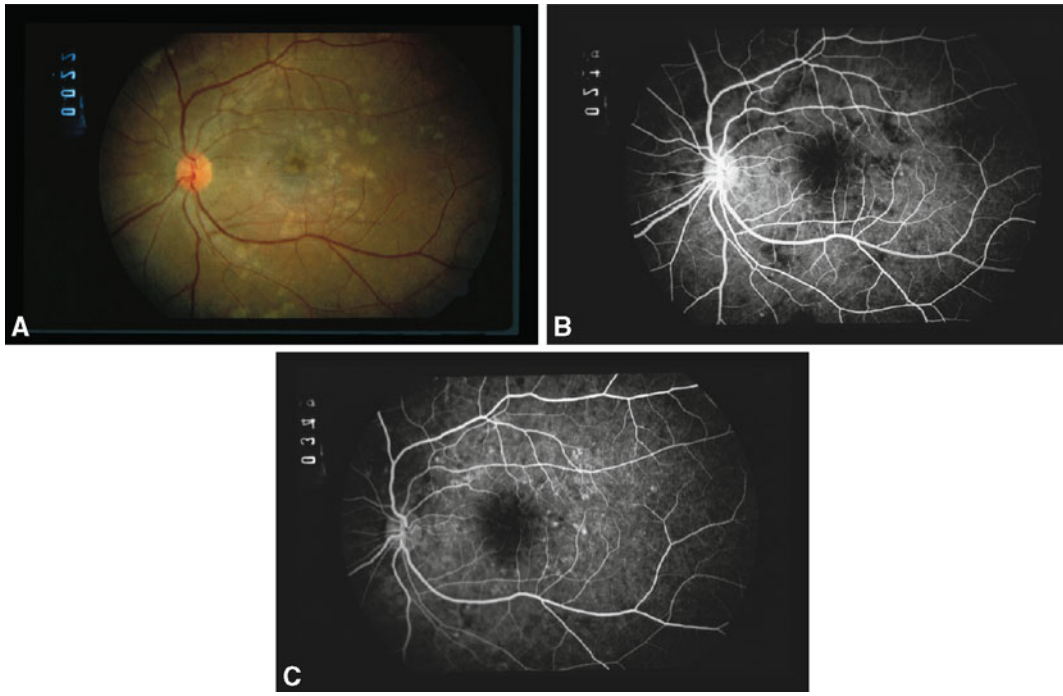

Fig. 22.3 (**a**) Color photograph showing multiple punctate areas of choroidal ischemia (Elschnig spots) in a young patient with acute hypertension. The patient had mild visual blurring. (**b**) Early frame of FA documenting punctate areas of blocked fluorescence corresponding to the regions of choroidal ischemia. (**c**) Later frame of the FA revealing punctate spots of hyperfluorescence corresponding to the areas of choroidal ischemia

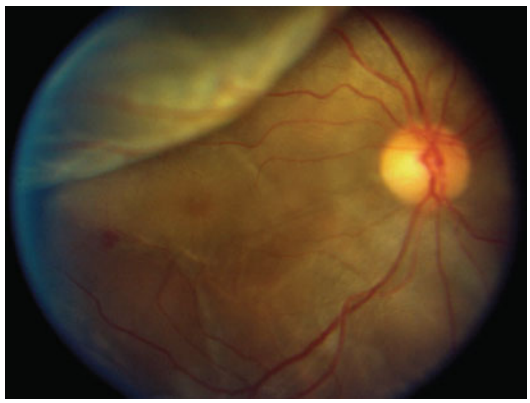

Fig. 22.4 Color photograph revealing an exudative, serous retinal detachment in a patient with extreme choroidal ischemia secondary to hypertension

Table 22.4 Retinal and choroidal diseases associated with hypertension (Adapted from [5])

Well-documented associations	Reference
Anterior ischemic optic neuropathy	[37]
Diabetic retinopathy	[38]
Retinal arterial macroaneurysm	[39]
Retinal artery occlusion	[40]
Retinal emboli	[41]
Retinal vein occlusion	[42]
Suspected associations	
Age-related macular degeneration	[43]
Open-angle glaucoma	[44]
Rarely reported associations	
Macular hole	[45]

Controversies and Perspectives

After 150 years, there remains no consensus clinical grading system for hypertensive retinopathy. The three-step classification discussed here is straightforward but not universally accepted.

Because most patients with hypertensive retinopathy are asymptomatic, there are legitimate questions regarding screening. Some authors have suggested that all hypertensive patients undergo regular dilated fundus examinations, although

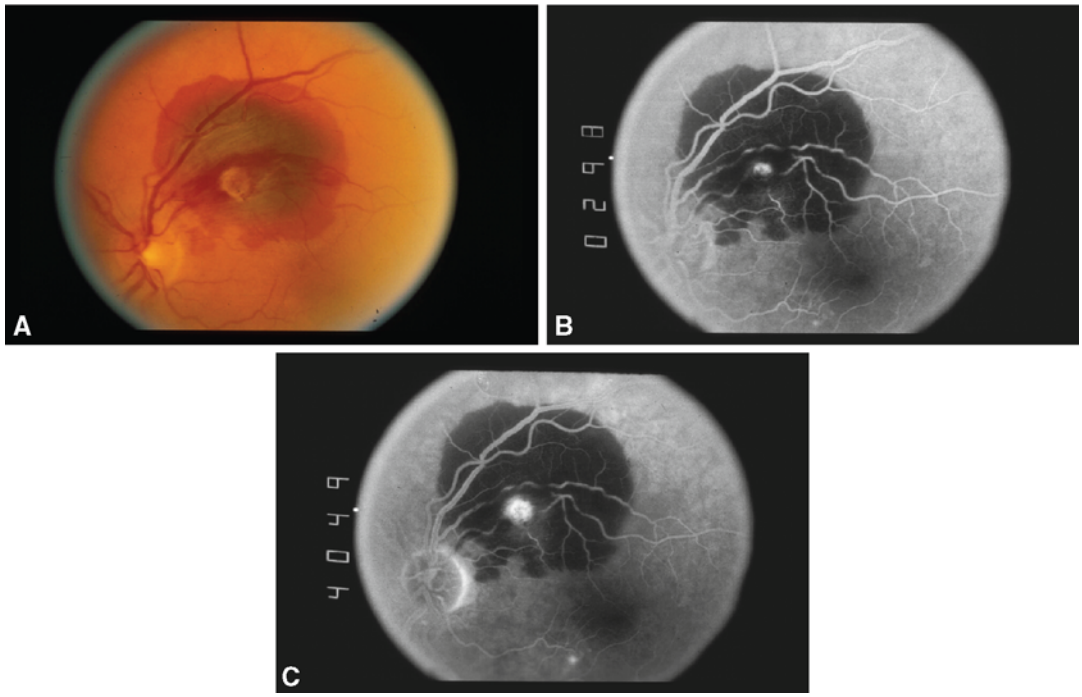

Fig. 22.5 (**a**) Color photograph of a hypertensive patient who developed a retinal arterial macroaneurysm, surrounded by intra- and subretinal hemorrhage, superonasal to the macula. (**b**) Early frame of the FA showing hyperfluorescence at the site of the macroaneurysm, surrounded by blockage of fluorescence secondary to the hemorrhage. (**c**) Later frame of the FA showing leakage at the site of the macroaneurysm

there is no convincing evidence in support of this recommendation [5]. The National High Blood Pressure Education Program Education Working Group recommends screening hypertensive children for retinopathy [23], although one study of hypertensive children showed a low rate of retinal findings, all of which were mild [24].

Using retinal findings to guide systemic treatment is an imperfect strategy. Direct ophthalmoscopy has been reported to correlate poorly with blood pressure measurements in patients with mild to moderate hypertension, with significant interobserver and intraobserver variability [25]. Digital fundus photography and automated image analysis may improve the diagnostic accuracy of retinal imaging in the future [26].

Summary

It has been suggested that treatment of the underlying hypertension may lead to improvement of hypertensive retinopathy [27], yet there are no data from randomized clinical trials regarding this [28]. Calcium channel blockers have been proposed as possible neuroprotective agents to treat hypertensive retinopathy [29], but at the present time, evidence of their effectiveness in hypertensive patients is lacking.

Focal Points

- Hypertension is common among adults in the United States.
- Posterior segment manifestations are common in hypertensive patients.
- Hypertensive retinopathy is associated with increased risks of stroke, cognitive impairment, and cardiovascular death.
- Hypertension increases the risks of other retinal diseases, including retinal vascular occlusions, diabetic retinopathy, and anterior ischemic optic neuropathy.

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Posterior Pole Manifestations of Hematologic Diseases

23

Eric S. Ahn, Ahmad Bakir Tarabishy, and Andrew P. Schachat

Abstract

Hematologic diseases often share clinical features within the choroid and retina because of the limited number of cell line or lines affected. No one chorioretinal change is specific for a particular hematologic anomaly; rather, it is the context and pattern that help guide clinical diagnoses. Retinal and choroidal manifestations of hematologic illness may be critical not only in identifying new or recurrent illness but also in ultimately reducing patient morbidity and mortality. Therefore, it is paramount that an open and regular dialogue be maintained between a patient's hematologist and ophthalmologist.

Keywords

Anemia • Histiocytic • Hyperviscosity • Leukemia • Lymphoid • Lymphoma • Multiple myeloma • Myelodysplasia • Myeloid • Myeloproliferative • Neoplasm • Sickle • Thalassemia • Thrombocytopenia • Waldenstrom

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Introduction

Mankind's understanding of illness, including hematologic disease, can first be credited to Hippocrates, who attributed physiologic maladies to humoral excess or deficiency. Further understanding stalled until the development of the microscope by Anthony Van Leeuwenhoek in 1642 and the first observation of a cell by Robert Hooke in 1665 [1]. William Hewson, the father of hematology, was the first to describe leukocytes and clotting factors during the late

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eighteenth century [2]. The relative explosion of discovery and knowledge during this era would result in the elucidation of thalassemia by Thomas Cooley, leukemia by Rudolph Virchow, and the development of cell theory by Schwann, Schleiden, and Virchow in the mid-nineteenth century [3]. Yet hematologic disease, despite advancements in diagnostics and therapeutics, still remains a significant cause of morbidity and mortality.

The treatment arm of medicine has evolved beyond bloodletting, but this has not changed the overall idea of eradicating or replacing overpopulating or overacting cells without devastating normal host physiology. In recent years, advances in medical and radiation oncology have increased survival time for many blood dyscrasias, yet one challenge still remains. The detection of these illnesses requires symptomatic patients or the fortune of asymptomatic detection during routine evaluation, such as an abnormal complete blood count or palpable mass. Therefore, although most patients with hematologic disease are referred to ophthalmology with known diagnoses, on occasion, the presenting symptoms of such illnesses can be ocular. In fact, the ocular findings described by Liebreich in 1863 and by Moore in 1925 remain accurate for many hematologic diseases [4]. The fundus findings, though, may often not be diagnostic for a specific blood dyscrasia because these neoplasms arise from aberrations occurring at particular points in cellular development of common precursors. Nevertheless, the ultimate goal in recognizing these clinical sequelae is the need to promptly treat new or recurrent disease with the tools at hand today.

Anemia

Anemia is a common laboratory finding associated with a variety of hematologic and nonhematologic disorders and is defined as a decreased circulating red blood cell (RBC) mass. Anemia can be divided into those caused by decreased RBC production and those caused by increased RBC destruction. Decreased production may be caused by decreased bone marrow stimulation by erythropoietin, as occurs in renal failure; decreased marrow cellularity, such as myelofibrosis and aplastic anemia; component deficiencies in hemoglobin production, such as iron deficiency or vitamin B12 deficiency; and abnormal or deficient hemoglobin, as is seen with the thalassemias or sickle cell disease. Increased RBC destruction is caused by blood loss or hemolysis. Hemolysis may occur by mechanical forces, such as mechanical heart valves and microangiopathic hemolytic anemias, abnormal RBC structures, such as spherocytosis and elliptocytosis, or immune-mediated RBC destruction, such as autoimmune hemolytic anemia. Anemia is also a frequent finding in chronic infections, malignancies, autoimmune disorders, and hepatic and renal insufficiency (Table 23.1) [5].

Table 23.1 Various causes of anemia[a]

I.Acute blood loss
II.Hypoproliferative
(a) Low erythropoietin states (renal disease)
(b) Anemia of chronic disease
(c) Component deficiency
(i) Iron deficiency
(ii) Vitamin B12 deficiency
(iii) Folate deficiency
(d) Bone marrow failure
(i) Aplastic anemia
(ii) Pure red cell aplasia
(iii) Myelophthisis
(iv) Myelofibrosis
III. Hyperproliferative
(a) Hemolytic anemia
(i) G6PD deficiency
(ii) Autoimmune hemolytic anemia
(iii) Microangiopathic hemolytic anemia
1. TTP/HUS
2. DIC
3. Mechanical heart valve
(iv) Hemoglobinopathies
1. Thalassemia
2. Sickle cell disease
(v) Spherocytosis
(vi) Paroxysmal nocturnal hemoglobinuria

[a]*TTP/HUS* thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, *DIC* disseminated intravascular coagulation

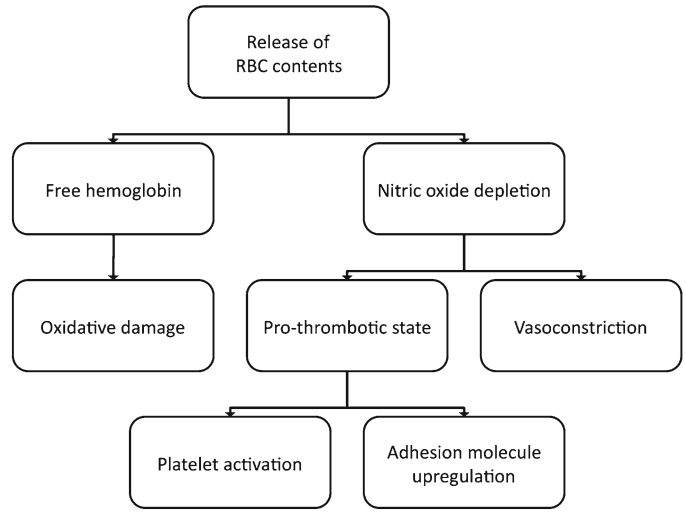

Fig. 23.1 Hemolysis cascade

Fundus findings in severe anemia may include optic disk swelling, intraretinal hemorrhages, retinal edema, and cotton-wool spots (CWS). These findings are frequently present in patients with a hematocrit less than 30% and are present in many patients with coexisting thrombocytopenia [6–8].

Anemia can cause retinal and choroidal pathology through a variety of mechanisms. Severe anemia causes end-organ hypoxia that can lead to vascular remodeling and endothelial dysfunction. Compensatory vasodilation can explain the vascular tortuosity that is seen in some cases of severe anemia [9]. Hemolysis of various etiologies creates a pro-thrombotic state through a complex interaction of extracellular hemoglobin, nitric oxide depletion, and vascular dysregulation. Nitric oxide (NO) is a potent free radical and vasodilator that is derived from arginine and produced by the enzyme nitric oxide synthase. Intravascular hemolysis causes release of free hemoglobin, which rapidly reacts with and destroys circulating nitric oxide. Additionally, release of intracellular enzymes such as erythrocyte arginase converts circulating arginine to other amino acids, leading to decreased NO production by shunting arginine away from the nitric oxide synthase (NOS) pathway (Fig. 23.1) [10]. A resultant hypercoagulable effect may explain findings sometimes found in patients with anemia such as cotton-wool spots, retinal edema, and neovascularization. Choroidal thrombosis and vascular stasis may explain the serous macular detachment that is reported in various anemia-associated disorders.

Erythropoietin is a glycoprotein hormone produced in the kidney that promotes erythrocyte differentiation from bone marrow precursor cells. While anemia due to renal insufficiency is a common cause of anemia due to depressed erythropoietin production, most etiologies of anemia result in compensatory overexpression of erythropoietin, and this may play a role in promoting neovascularization in patients with anemia due to various causes. Increased erythropoietin stimulates retinal neovascularization in diabetic retinopathy and other ischemic retinal processes and may incite neovascularization in certain cases of severe anemia [11].

Many causes of anemia have associated platelet and coagulation disorders. Aplastic anemia is commonly part of a pancytopenia with severe deficiencies of platelets and white blood cells. There is an increased prevalence of retinal hemorrhages in anemia patients with an associated thrombocytopenia. Thrombotic microangiopathies, such as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) and disseminated intravascular coagulation (DIC), often have an associated consumptive thrombocytopenia, caused by widespread platelet activation and microvascular thrombosis. Consumption, and in severe cases depletion, of

clotting factors results in a paradoxical promotion of widespread bleeding. Iron deficiency anemia is often accompanied with a reactive thrombocytosis, although the effect of the increased platelets on the retinal and choroidal vasculature is unclear.

Aplastic Anemia

Aplastic anemia is characterized by decreased or absent hematopoietic precursor cells in the bone marrow, resulting in severe deficiencies of RBCs, platelets, myeloid, and lymphoid cells. Severe anemia and thrombocytopenia can result in intraretinal, preretinal, and vitreous hemorrhage, in addition to white-centered hemorrhages and cotton-wool spots [12]. Severe intraretinal hemorrhage in the setting of profound thrombocytopenia can result in a hemorrhagic retinoschisis [13]. An occlusive vasculopathy has been reported in association with Fanconi anemia, a rare inherited form of aplastic anemia [14–16].

Hemoglobinopathies

Sickle Cell Disease

Adult hemoglobin is formed from a tetramer of two alpha-like globulin chains and two beta-like globulin chains. Subtle differences in the alpha-like and beta-like chains result in the formation of different hemoglobins, such as embryonic and fetal hemoglobin, that possess an oxygen dissociation curve appropriate for various phases of prenatal and postnatal life. Normal adult hemoglobin is composed of two alpha globulins and two beta globulins and is characterized by high solubility. Minor structural alterations can result in dramatic changes in solubility.

Hemoglobin S is a result of a mutation in the beta globulin gene, which results in the substitution of valine for glutamic acid. Structurally, hemoglobin S in its deoxygenized state forms long polymers that damage cell membranes and results in the sickled microscopic appearance of red blood cells. These sickled RBCs result in vascular occlusion, intravascular and extravascular hemolysis, and ischemia in organs where RBCs are commonly sequestered, such as the lungs, spleen, kidney, and liver. In addition, RBC hemolysis can alter key vascular homeostatic mechanisms, such as the NO pathway as discussed previously. Altered expression of cell membrane proteins may also contribute to vascular stasis and thrombosis. Reticulocytes—immature RBCs released from a compensating bone marrow—have increased expression of surface integrins, which bind to vascular cell adhesion molecule-1 (VCAM-1) on activated vascular endothelial cells. Endothelial cells also have increased expression of adhesion molecules leading to cellular stasis, increased oxygen extraction from RBCs, and promotion of sickling, leading to a downward spiral of hemostasis, sickling, acidosis, and ischemia [17].

Patients homozygous for HbS (SS disease) will have sickle cell disease with chronic anemia and multisystem ischemic complications, such as bone necrosis, hypoxia, and strokes. Proliferative and non-proliferative sickle cell retinopathies are more common in patients with heterozygous HbS mutations combined with other hemoglobinopathies such as patients with hemoglobin SC disease or those with sickle cell thalassemia.

Ocular complications of sickle cell disease are often described as non-proliferative and proliferative. Angioid streaks are present in approximately 1–2% of patients with sickle cell disease and may be more common in patients with HbSS and S-Thal disease [18, 19]. Nonspecific vascular alterations such as arteriolosclerosis and vascular tortuosity are common. “Salmon patch” lesions and “black sunbursts” are considered hallmark findings of non-proliferative sickle retinopathy. Salmon patch hemorrhages are intraretinal or preretinal hemorrhages with a bright red “salmon” color that often will change with time, representing ongoing hemoglobin metabolism. Old lesions that resolve may leave behind a schisis cavity containing refractile particles [20]. Histologic analysis reveals intra- and extracellular iron deposits in the schisis cavities [21]. “Black sunbursts” are areas of subretinal hemorrhage that lead to reactive retinal pigment epithelium (RPE)

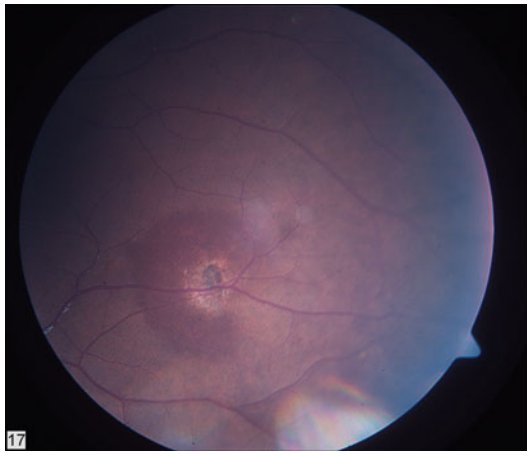

Fig. 23.2 A black sunburst lesion in a boy with sickle cell retinopathy

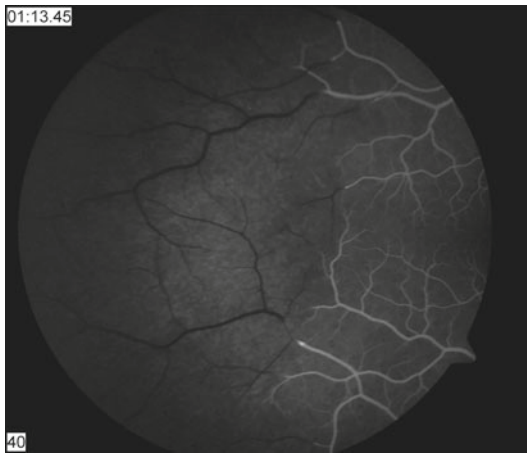

Fig. 23.3 Stage 1 proliferative sickle retinopathy consists of peripheral nonperfusion

hyperplasia (Fig. 23.2). Vision loss due to macular ischemia can be diagnosed with fluorescein angiography showing an enlarged foveal avascular zone. The "macular depression sign" has been described by Goldbaum and is thought to represent thinning of the inner retina as a result of macular ischemia [22]. Choroidal ischemia can also be demonstrated with angiography [23].

Branch and central retinal arterial occlusion can spontaneously occur in patients with sickle cell disease in the absence of typical findings of sickle cell retinopathy [24–26]. Rarely, retinal ischemia may result in a visual field defect that mimics an optic neuropathy [27].

Proliferative sickle retinopathy (PSR) occurs in approximately 40% of HbSC patients and only 20% of SS patients [28]. PSR has been classified into five stages by Goldberg [29]. Stage 1 consists of the presence of peripheral nonperfusion (Fig. 23.3). Stage 2 demonstrates peripheral arteriovenous anastamoses. Stage 3 is characterized by the presence of "sea-fan" neovascularization (Fig. 23.4a, b). Stage 4 is defined by the presence of vitreous hemorrhage. Patients with stage 5 disease have a tractional or rhegmatogenous retinal detachment.

Treatment focuses primarily on preventing progression of PSR. In patients with active neovascularization, scatter retinal photocoagulation reduces the likelihood of progression to stage 4 and 5 disease. Although patients with small areas of neovascularization can be observed safely, some authors argue that any apparent neovascularization should be treated as the risk of complications associated with laser photocoagulation is small. Several treatment strategies have been described. One is to apply laser burns to the area of retina immediately anterior to the area of neovascularization [30]. Another is circumferential application of laser to the peripheral retina, which is preferred in cases with extensive neovascularization and in patients whose compliance with follow-up may be poor [31]. Feeder vessel photocoagulation is highly effective in causing involution of sea fans but has fallen out of favor because of a high risk of complications, such as secondary retinal-choroidal neovascularization and retinal detachment [32, 33]. It is important to recognize that approximately 60% of sea fans will involute over time without treatment [20].

Vitreous levels of vascular endothelial growth factor (VEGF) are elevated in patients with PSR, making intravitreal anti-VEGF treatment an attractive therapeutic option [34]. There are two reported cases in the literature showing regression of active neovascularization following intravitreal injection of bevacizumab in patients with proliferative sickle retinopathy [35, 36].

Surgical treatments for retinal complications of PSR are fraught with difficulty for a variety of reasons [20, 37]. First, compromise of choroidal circulation puts patients at risk for anterior segment ischemia following scleral buckling

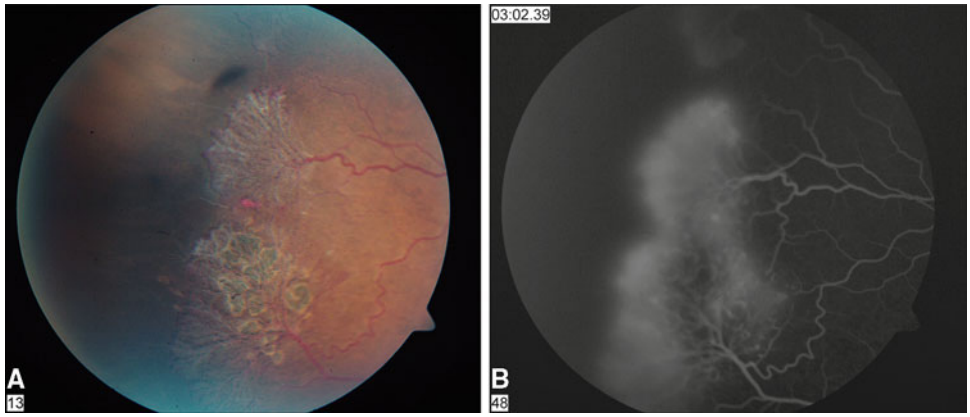

Fig. 23.4 (**a**, **b**) "Sea-fan" neovascularization with dye leakage at the border of an area of nonperfused retina in a late-frame fluorescein angiogram

procedures [38, 39]. Second, compromised retinal and optic nerve microvasculature introduces a risk of macular and/or optic nerve infarction as the eye is pressurized intraoperatively [40]. During surgery, inadvertent retinal breaks occur with relative ease because of the presence of thin, ischemic peripheral retina, ischemic retina, as is vitreous hemorrhage from traction on sea-fan neovascularization. Vitreoretinal surgery is also complicated in sickle cell patients because of an increased risk of postoperative glaucoma caused by sickled RBCs clogging the trabecular meshwork. Acetozolamide is contraindicated intra- or postoperatively because it lowers serum pH and contributes to increased sickling [41]. Routine exchange transfusion is advocated by some to decrease the risk of sickling perioperatively, though other authors believe this is probably unnecessary [42–44].

Several systemic treatments are used to address the complications of SCD. Hydroxyurea is a commonly used agent in the management of SCD and has been shown to decrease hospitalization rates and prolong survival. Transfusions are used to lower the percentage of sickle hemoglobin in the circulation and may help prevent pain crises and stroke. Deferoxamine, an iron chelator used to prevent iron overload, is associated with a toxic retinopathy. There are no effective available treatments for non-proliferative complications of sickle cell retinopathy, although insights into the pathogenesis of sickle cell vasculopathy may promote new treatments that can prevent sickling and end-organ ischemia. Sildenafil, which increases intracellular cyclic guanosine monophosphate; bosentan, an endothelin receptor blocker already in use for treatment of pulmonary hypertension; and other treatments that are aimed at raising nitric oxide levels are being evaluated in clinical trials [45]. Allogeneic hematopoietic stem cell transplantation appears to be a dramatic but promising method that can reverse the sickle phenotype in severely affected patients [46]. Case reports have reported improvement in ischemic maculopathy with transfusion exchange [47, 48].

Thalassemia

The thalassemias are a group of diseases characterized by decreased production of alpha or beta chains that comprise normal adult hemoglobin, resulting in an imbalance in the alpha to beta chain ratio and decreased hemoglobin production. The minor thalassemias are characterized by decreased production of one alpha or beta chain and are largely asymptomatic. Patients with intermediate thalassemia syndromes are frequently asymptomatic until adolescence and have a decreased production of one of the alpha and beta chains in addition to an abnormal hemoglobin (e.g., sickle cell thalassemia, HbE/

beta-thalassemia). Patients with beta-thalassemia major lack both beta chains and are dependent on regular blood transfusions for survival.

Ocular findings include venous tortuosity, degenerative RPE changes, and angioid streaks. RPE degeneration is more common in patients with thalassemia major than thalassemia intermediate and is likely related to deferoxamine rather than anemia [49].

Deferoxamine Toxicity

Deferoxamine is used as treatment of iron overload in transfusion-dependent patients with thalassemia. Deferoxamine-associated pigmentary retinopathy and optic neuropathy may be reversible upon discontinuation [50–52]. Routine screening for retinopathy in patients on chronic treatment with deferoxamine is recommended [53]. In patients on continuous intravenous infusion for severe iron overload, retinopathy may reach advanced stages over as little as 3 weeks [54].

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common enzyme deficiency that leads to acute intravascular hemolysis upon exposure to certain foods, drugs, and infections that overload the G6PD pathway, which is essential to maintain reduced glutathione necessary to protect RBCs against oxidative damage. G6PD deficiency appears to be associated with a lower risk of retinal venous occlusion than in patients with normal levels. The mechanism behind this protective effect is unclear, though alteration in intracellular cholesterol metabolism has been proposed [55].

Paroxysmal Nocturnal Hemoglobinuria

The molecular pathophysiology in paroxysmal nocturnal hemoglobinura (PNH) points to a defect in the glycosylphosphatidylinositol (GPI) anchor, leading to an absence of GPI-anchored membrane proteins, resulting in increased complement activation. Hemolysis, thrombophilia, and bone marrow failure are the main clinical features. Retinal venous and arterial occlusive diseases have been described [56]. Serous retinal detachment has also been reported [57]. Venous sinus thrombosis can occur secondary to the general hypercoagulable state with resultant fundus findings [58]. Eculizumab, a humanized monoclonal antibody that targets C5 and prevents assembly of the membrane attack complex, has recently been shown to be effective in reducing hemolysis and thrombosis [59].

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is characterized by antibodies against RBC components resulting in splenic sequestration and extravascular destruction. Retinal hemorrhage and serous macular detachments have been described in case reports [60, 61]. Phlebitis has been reported, although this may have been due to coexisting autoimmune conditions—which are common in patients with AIHA [62].

Thrombotic Thrombocytopenic Purpura

Microangiopathic hemolytic anemia and thrombocytopenia, in association with renal or neurologic dysfunction, are the defining features of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). TTP and HUS, the former characterized by neurologic dysfunction, the latter by renal failure, are now thought to be related clinical syndromes of the same underlying pathology. Demonstrating schistocytosis (mechanically fractured RBCs) on a peripheral blood smear is essential to the diagnosis. ADAMTS13 deficiency, a von Willebrand factor (vWF) protease, has been implicated in cases of TTP. Deficiency of ADAMTS13 leads to a rise in vWF multimers with resultant platelet aggregation and formation of platelet thrombi in the

microvasculature—a hallmark histologic feature of TTP [63]. HUS, a common cause of renal failure in children, is primarily caused by Shiga-like toxin associated with foodborne infection with *Escherichia coli* E157:H7 [64].

Other disorders, such as disseminated intravascular coagulation, connective tissue disease such as lupus or scleroderma, antiphospholipid antibody syndrome, or malignant hypertension, may mimic HUS/TTP and should be considered in the differential diagnosis. Kidney biopsy is sometimes necessary to establish the diagnosis. Timely diagnosis is essential as plasma exchange therapy is usually curative.

Fundus findings in patients with TTP/HUS include serous macular detachment, retinal hemorrhages, cotton-wool spots, a Purtscher-like retinopathy, and retinal artery and vein occlusions [65–68]. Ocular findings often resolve after plasma exchange therapy [69]. Panretinal photocoagulation and anti-VEGF agents have been successfully used in treating associated neovascularization [70].

Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies (APL) are associated with a vaso-occlusive vasculopathy. Common features are cotton-wool spots, arteriolar nonperfusion, neovascularization, and vitreous hemorrhage [71]. Retinal vein and artery occlusions have also been reported [72]. However, antiphospholipid antibodies are frequently a nonspecific finding. They may be found in asymptomatic patients or can be seen in association with other systemic autoimmune disorders such as systemic lupus erythematosus. The incidence of ocular pathology in patients with antiphospholipid antibodies is not clear. However, there does appear to be an increased risk for the presence of antiphospholipid antibodies in patients with retinal vein or artery occlusions, particularly in the absence of other risk factors for vascular occlusions [73, 74].

A portion of patients with detectable APL will have the antiphospholipid antibody syndrome (APLS). APLS is defined as vascular (arterial or venous) thrombosis or pregnancy loss in the presence of two positive laboratory tests performed at least 6 weeks apart [75]. Castanon et al. studied 17 patients with APLS, and fundus abnormalities were present in 15 of them. Choroidal ischemia was detected in 2/17 patients, and areas of retinal nonperfusion were seen in 5/17 patients [76]. Other findings included venous tortuosity, optic nerve swelling, cotton-wool spots, vitreous hemorrhage, and serous macular detachment. APLS has also been reported to mimic serpiginous chorioretinitis with an occlusive vasculitis [77].

Patients with APLS should be maintained on antiplatelet and anticoagulant therapy with aspirin and Coumadin, with a target international normalized ratio (INR) between 2.0 and 3.0 [78]. Patients with severe acute vision loss due to vaso-occlusive retinopathy may respond to acute treatment with cytotoxics and/or plasmapheresis [79].

Hemophilia and Platelet Disorders

Platelet disorders result in spontaneous intraretinal hemorrhages, similar to the way platelet disorders characteristically produce skin petechiae. Hemophilia and other clotting factor disorders may cause spontaneous hemorrhage if the factor deficiency is severe; however, in most cases, hemorrhage occurs following trauma or surgery [80]. Vitreous, retinal, and choroidal hemorrhage have all been reported [81–83].

Surgery can be performed safely in patients with inherited deficiencies if accompanied with administration of ddAVP (desmopressin acetate tablets) and infusions of clotting factor concentrate [84, 85]. Acquired factor deficiency, or resistance to circulating factor sometimes caused by autoantibodies, can be treated with clotting factor infusion and systemic immunosuppression [86].

Myelodysplastic Disorders

It is the development of dysplasia, or "bad formation," along with ineffective hematopoiesis that characterizes this group. The hematologic findings manifest as a cytopenia in one or more

myeloid lines usually with increased bone marrow cellularity and normal or increased blasts up to 20%. The incidence in the USA is approximately 10,000 new cases per year; risk increases with age and slightly with male gender [87]. The prevalence of myelodysplastic syndrome (MDS) is estimated to be 4.1/100,000 and the median age is 71 [88, 89]. Although predominantly a primary process, treatment-induced MDS accounts for 10% of cases [89]. Childhood MDS is much more unusual and is most commonly associated with monosomy 7 [90]. Transformation to acute leukemia is variable largely because of different clinical and biological features, with MDS more a disorder of increased apoptosis versus uncontrolled proliferation in leukemia with some overlap between the two [91].

Most, if not all, of the retinal and choroidal changes due to MDS are secondary effects caused by anemia, thrombocytopenia, or neutropenia. A study of ocular complications in those with MDS was found in 19/41 patients, with one case each of vitreous hemorrhage, central retinal vein occlusion (CRVO), and cotton-wool spots, ten subjects with retinal hemorrhages (red and white centered), and two with optic neuritis, with some patients having more than one complication [92]. Retinal hemorrhages were associated with low platelet counts of $27{,}000 \pm 29{,}000$ ($p < 0.006$), while hemoglobin concentration was not found to be significant. As expected, higher rates of retinal hemorrhage were associated with refractory anemia with excess blasts due to the higher degree of neoplastic change. Unlike in acute leukemia, where evidence has been equivocal regarding platelet counts and retinal hemorrhages, MDS has morphologic and maturational platelet defects that predispose to bleeding independent of platelet count [93]. One reported case of birdshot retinochoroidopathy in an HLA-A29-negative individual with trisomy 8 MDS was thought to be an autoimmune response, possibly related to S-antigen [94, 95]. Very rare cellular infiltration has been reported, including increased optic nerve thickness, ciliochoroidal effusion, and non-arteritic anterior ischemic optic neuropathy (AION) [96–98].

Myeloproliferative Disorders

The myeloproliferative neoplasms (MPN) are a proliferation of one or more myeloid lineages with proliferation of bone marrow progenitor cells. In contrast to MDS, MPN usually have effective hematopoiesis with more terminally differentiated cell line or lines. These manifestations can be classified as classic, including chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PCV), and primary myelofibrosis (PMF); as atypical, including systemic mastocytosis, hypereosinophilic syndrome, chronic neutrophilic and basophilic leukemia; as well as many others including unclassifiable types and MPN/MDS overlaps. These diseases often share mutations resulting in overexpression of tyrosine kinase activity such as BCR-ABL in CML and Janus kinase 2 (JAK2) or thrombopoietin receptor (MPL) in the other classic MPN, resulting in growth factor–independent proliferation [99].

Chronic Myelogenous Leukemia

This MPN is associated with the Philadelphia chromosome, a by-product of a t(9;22) resulting in a fusion protein of BCR and c-ABL (nonreceptor tyrosine kinase), which results in uncontrolled production of mature granulocytes. The incidence is 0.6–2 per 100,000 persons and accounts for 15–20% of adult leukemias, with a slight male predominance [100]. Median age at presentation is 50 years with no familial predisposition, and there is an increased risk with ionizing radiation.

The intraocular sequelae of CML may be subtle until blast crises where it takes the appearance of acute leukemia. During the chronic phase, with repeated vascular injury and nonperfusion, there appears to be a higher prevalence of peripheral microaneurysms and neovascularization in contrast to other leukemias [101, 102]. A rare occurrence of bilateral peripheral retinal nonperfusion with arteriovenous anastomosis and sea-fan neovascularizations in the setting of a CBC within

normal limits and no other retinal findings has been reported [103]. Thrombotic microangiopathy or papilledema can be manifestations of this disease, in addition to optic disk edema possibly secondary to imatinib therapy or ocular infections after bone marrow transplant (BMT) [104–107].

Polycythemia Vera

Polycythemia vera involves a clonal proliferation of myeloid cells with a primary increase in red cell mass and has been defined as a hemoglobin concentration greater than 16.5 g/dl in females, 18.5 g/dl in males, and a low serum erythropoietin level [108, 109]. The age of onset typically ranges from 20 to 85, with a median of 60 years, and the incidence is 1.9/100,000 per year with a female predominance except in men over 70 years [110, 111]. It has been postulated that erythroid progenitors develop signaling defects downstream of cytokine receptors that are unrelated to erythropoietin or its receptor. There is increased tyrosine kinase activity via the insulin-like growth factor 1 system or decreased tyrosine phosphatase activity resulting in overexuberant red cell production [112–114].

Systemic manifestations characteristically involve pruritus especially after a warm bath, erythromelalgia, dyspepsia, and thrombotic events. The pathogenesis of thrombosis appears to be related to platelet hyperfunction and thromboxane overexpression, while the increased risk of hemorrhage may be related to membrane receptor abnormalities, acquired von Willebrand syndrome, or other defects of function/structure [115, 116]. In general, the ocular effects of PCV are mostly secondary to hyperviscosity and thrombosis resulting in amaurosis fugax, migraine, arteriospasm or arteriosclerosis, and sometimes a cyanotic hue in the eyelids and conjunctiva [117]. The retinal arteries attenuate and veins can become engorged and tortuous, with a variable amount of flame-shaped hemorrhages and/or CWS. This can progress to vein or artery obstruction. Vasomotor symptoms include headache, amaurosis fugax, transient ischemic attack, ophthalmic migraine, scintillating scotomata, and thrombotic or embolic phenomena [118, 119]. There are also more uncommon reports of PCV presenting as isolated monocular visual loss secondary to profound retinal ischemia; bilateral CRVO, isolated papilledema, or AION; an orbital mass from extramedullary hematopoiesis; and/or impaired dark adaptation [120–125].

Essential Thrombocythemia

This is a clonal stem cell disorder resulting in chronic primary thrombocytosis with platelet count >450,000/uL that by definition is not reactive, not a result of the other myeloproliferative disorders, and occurs in the setting of normal iron stores [126]. In fact, neither thrombopoietin nor its receptor, c-Mpl, appears to be involved in the pathogenesis of this disorder, unlike other familial thrombopoietin/c-Mpl-related thrombocytoses, and appears to be more often related to JAK2 mutations [127]. The incidence has been reported to be 2.5 per 100,000 individuals per year, with a prevalence of approximately 24/100,000, a male to female ratio of 0.69, and median age at diagnosis of 60 years and occurring rarely in children [128–130]. Retinal artery and vein occlusions, peripheral ischemia, and neovascular complications have all been reported [119, 131–133].

Primary Myelofibrosis

Primary myelofibrosis is characterized by chronic clonal proliferation derived from multipotent myeloid stem cells with atypical megakaryocytic hyperplasia with secondary fibrosis, osteosclerosis, and angiogenesis of the bone marrow causing eventual failure with extramedullary hematopoiesis as anemia progresses along with constitutional symptoms [134, 135]. Platelet and leukocyte counts can be variable, although thrombocytopenia tends to develop as the disease progresses with platelet hypofunction [136]. Bone marrow biopsy ultimately shows fibrosis and the absence of granulomatous disease or foci

of malignant cells, with a peripheral smear showing sequelae of myelophthisis. Approximately 50% of patients with PMF show JAK2 mutations, while the remainder may have other mutations related to the JAK-STAT pathway or as yet unrecognized molecular etiologies [137–139]. The incidence is reported to be 1.5 per 100,000 individuals per year with median age being 67; the disease rarely occurs in children [111].

This disorder is more commonly associated with ocular adnexal involvement, such as extramedullary hematopoiesis with secondary effects related to immunosuppression from bone marrow transplantation, with a reported case of CMV retinitis [140] and hemorrhagic retinopathy due to anemia [141]. Otherwise, the literature is sparse, and treatment-related effects from supportive therapies such as prednisone, etanercept, or radiation may manifest.

Leukemias

Acute Myeloid Leukemia

This is a clonal proliferation of myeloid precursors that lack the ability to differentiate into mature forms resulting in the accumulation of immature or blast cells. It is the most common cause of leukemia in adults but comprises less than 10% of leukemias in children [142]. The incidence is approximately 3–5/100,000 individuals per year, with a median age of 65 years and slight male predominance [142]. It is classified based on World Health Organization (WHO) criteria into four groups: acute myeloid leukemia (AML) with recurrent genetic abnormalities, AML with myelodysplasia-related features, therapy-related AML and MDS, and AML not otherwise specified [143].

Lymphoid

Lymphoid neoplasms derive from T or B cell lineages and are classically grouped as deriving from lymphoid precursors, mature lymphocytes, or plasma cells. These can present as a mass, or lymphoma, or have blood and bone marrow involvement (greater than 25% blasts) and be termed leukemia. Yet any lymphoma can evolve into leukemia, and sometimes, leukemia can present as an extramedullary mass; therefore, lymphoid neoplasms should be classified based on morphology, genetics, and immunophenotype rather than anatomic location [144].

The precursor B leukemias/lymphomas, tdt positive and cd3 negative, are more common in childhood and have an overall incidence of 2% per population with a male predominance [145, 146]. They typically present acutely as leukemias, commonly with central nervous system (CNS) and nodal involvement. In contrast, precursor T leukemia/lymphoma, cd3 and 7 positive, tends to affect young adult males who often have diffuse lymphadenopathy and a bulky mediastinal mass. There may be CNS involvement, especially if in the leukemic form.

The prevalence of leukemic ocular involvement in the literature varies from 9% to 90%, with one prospective study showing leukemic infiltration in 3% of patients, leukemia-related findings in 39%, and unrelated abnormalities in 20% [147, 148]. The characteristic findings of leukemia are the result of direct organ invasion, abnormal hematopoiesis, altered blood viscosity, or immune suppression. Within the choroid, leukemic infiltration is often perivascular but can be patchy or diffuse with increased thickness [149]. Cellular infiltration can also extend subretinally and intraretinally, appearing as yellow infiltrates that may resemble viral or fungal infections, especially in the immunosuppressed, or as perivascular sheathing and optic nerve infiltration. It has been speculated that infection may have a closer association with patients in remission with prior bone marrow transplantation (BMT) rather than those with newly diagnosed leukemia [150]. An analysis of patients with BMT showed a posterior segment complication rate of 12.8%, with 2% having developed infectious retinitis or endophthalmitis that had a temporal correlation showing that fungal infection typically occurred within 120 days of BMT while viral or parasitic infection generally arose much later [151].

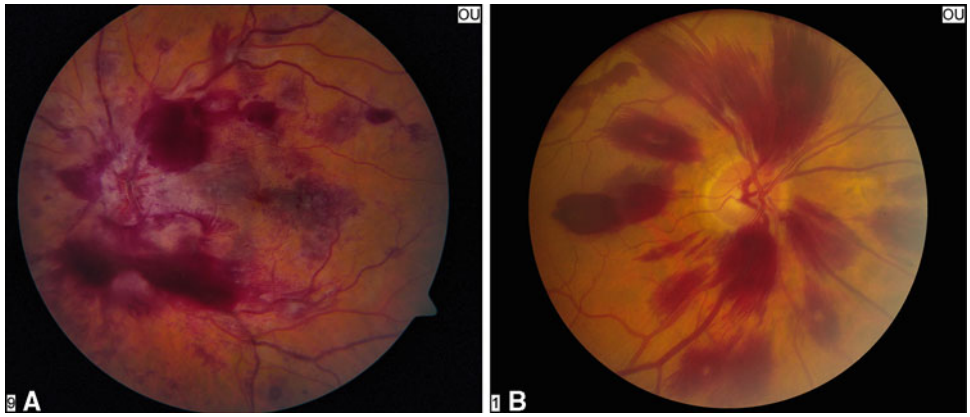

Fig. 23.5 (**a**, **b**) Retinal hemorrhages and Roth spots in two patients with relapsed acute myeloid leukemia

More commonly, leukemia presents with a characteristic retinopathy related to anemia, thrombocytopenia, and hyperviscosity (Fig. 23.5a, b). Venous dilation and tortuosity may be present along with intraretinal or vitreous hemorrhage. The intraretinal hemorrhages can be flame- or blot-shaped and have a white center that may represent leukocyte aggregates or a platelet-fibrin hemostatic plug [146]. The presence of hemorrhage has been shown to correlate most with severe thrombocytopenia, with possibly a lesser component due to anemia [152]. Cotton-wool spots can also be observed as a result of local arteriole obstruction, although hematologic parameters do not seem to be associated with their presence and may be more a result of cellular occlusion. Within this background, there may be RPE changes such as hypertrophy, atrophy, or migration, in addition to photoreceptor injury and sensory retinal detachment [153, 154]. Retinal neovascularization appears to be more common in CML, as does the development of microaneurysms, both of which tend to be found in the peripheral retina and thought to be secondary to chronic leukocytosis and subsequent vascular injury and capillary dropout [155, 156]. Those with other concurrent medical illness may be at higher risk of the leukemic complications, such as the acceleration of diabetic retinopathy [157] or from treatment-related effects as in the case of cyclosporine-induced retinopathy [158].

There are more specific reports of bilateral central retinal artery occlusion (CRAO) or macular hemorrhage associated with an increased risk of intracranial hemorrhage in AML [159, 160]. CML has also presented as bilateral retinal and optic disk neovascularization, while subretinal hypopyon and bilateral serous macular detachments have been described in lymphoid leukemias [161–163]. In general, retinal or choroidal involvement with chronic lymphocytic leukemia (CLL) is uncommon, with findings more often related to immunosuppression such as acute retinal necrosis, *Aspergillus* endophthalmitis, or *Nocardia* choroid abscess [164–167].

T cell lymphoma/leukemia is unusual, though it can manifest as vitreous seeding and chorioretinal involvement, retinal detachment and CNS involvement, and retinocerebral vasculitis [168–171]. In children, the presence of a CRAO should raise suspicion for systemic or ocular causes other than atherosclerotic disease, such as lymphoma [172]. An isolated report also showed the presence of unilateral vasculitis in hairy cell leukemia [173].

Lymphomas

Lymphomas are often synonymously associated with visceral or nodal disease and can be divided into Hodgkin and non-Hodgkin types (NHL), with NHL having B and T cell subtypes. The clonal

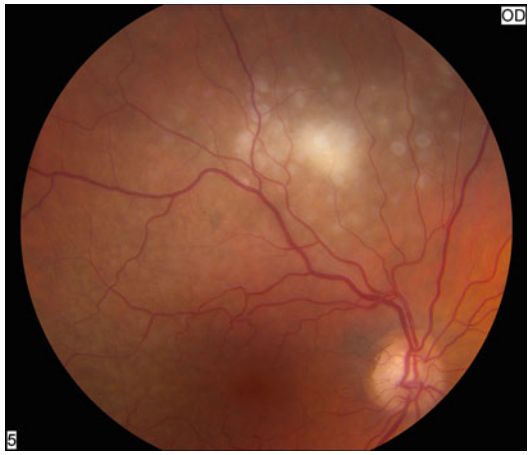

Fig. 23.6 Systemic diffuse large B cell lymphoma with uveal involvement

lines that lymphomas derive from usually involve cells that represent a more mature form with respect to immunohistochemical markers, cytology, and genetic features, representing a continuum from pre- to post-germinal lymphocyte development.

B Cell Lymphoma

Mature B cell neoplasms involve cells that have fulfilled at least antigen-independent development and are thought to arise from mutations just prior to or during somatic hypermutation [174, 175]. This is a broad class that includes chronic lymphocytic leukemia/lymphoma (CLL), mantle cell lymphoma (MCL), follicular cell lymphoma (FCL), diffuse large B cell lymphoma (DLBCL) (Fig. 23.6), Burkitt's lymphoma (BL), marginal zone lymphoma (MZL), plasma cell neoplasms, and other iterations. CLL is the most common leukemia and is often asymptomatic except for the presence of lymphadenopathy, like FCL. MCL and DLBCL demonstrate aggressive behavior and often present at an advanced stage at diagnosis, MCL presenting with nodal and gastrointestinal (GI) tract involvement and DLBCL, the most common NHL, presenting as a rapidly enlarging mass with wide-ranging extranodal involvement [176]. BL is another aggressive neoplasm with endemic, sporadic, and immunodeficiency-associated forms that are characterized by high tumor burden, tumor lysis, and the presence of a translocation of c-MYC on chromosome 8 to an immunoglobulin locus [177]. MZL can be extranodal, where it is associated with mucosa-associated lymphoid tissue, or nodal, and is typically low grade and asymptomatic unless there is local tissue injury as in the case of extranodal MZL.

Intraocular lymphomas are rare and, when present, often represent a systemic lymphoma rather than a true primary neoplasm. They can be anatomically categorized as primarily having retinal, choroidal, ciliary, or iridal involvement, with each location associated with varying prognoses [178]. Classically though, intraocular lymphoma is clinically recognized as either a vitreoretinal type, which is more commonly associated with CNS lymphoma, and a less common uveal type that is usually secondary to a more peripheral primary lymphoma. Vitreoretinal intraocular lymphoma has features that belong to the uveitis masquerade syndromes, including chorioretinal infiltrates, vitritis, perivascular sheathing with later development of RPE atrophy, and mottling.

Chorioretinal involvement by uveal intraocular lymphoma usually is from metastatic spread, with primary neoplasms uncommon. These lesions typically appear as uni- or multifocal yellow-white choroid infiltrates with moderately defined borders (Fig. 23.7a, b) showing persistent hypofluorescence on indocyanine green (ICG) angiography and no tumor vessels on (FA) fluorescein angiography [179]. On occasion, the lesions can result in exudative retinal detachment (RD) or appear as a larger contiguous lesion when in close approximation, causing a thickened appearance to subretinal tissue. They typically involve the posterior pole predominantly and can mimic fungal and autoimmune chorioretinitis, but the lymphoma cells are beneath the level of the RPE and the vitreous is clear. Uncommon findings such as artery or vein occlusion, and optic nerve infiltration may also occur in addition to variant presentations

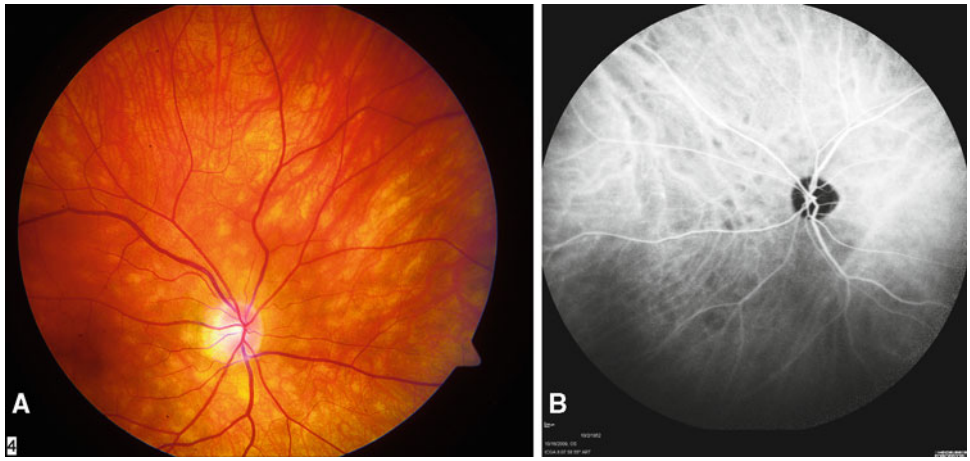

Fig. 23.7 Systemic mantle cell lymphoma with uveal involvement. (**a**) Yellow circular choroidal lesions. (**b**) Corresponding areas of hypofluorescence on indocyanine green (ICG) angiography

such as choroidal masses or serous macular detachments [180–182].

Hodgkin's Lymphoma

Hodgkin's lymphoma (HL) arises from the clonal proliferation of germinal/post-germinal center B cells or rarely T cells better known as Reed-Sternberg cells (RS), set upon a varying background of lymphocytes, granulocytes, and plasma cells. Its classification can be divided into classical and nonclassical forms based on RS cell appearance, with the most common type being nodular sclerosing HL. As a whole, HL accounts for 10% of all lymphomas, exhibiting a bimodal distribution in developed countries and having an association with Epstein-Barr virus (EBV), immunosuppression, autoimmune disease, and genetic and environmental factors [183–187].

Various reports have demonstrated findings of panuveitis, optic nerve infiltration, branch retinal artery occlusion (BRAO), macular detachment, cotton-wool spots, periphlebitis, and yellow-white retinal and chorioretinal lesions, although more commonly HL has an overall appearance similar to hypertensive retinopathy [102, 188–190]. The occurrence of HL within the retina and choroid is extremely rare and should prompt additional diagnostic or confirmatory testing to ensure other etiologies are ruled out. On occasion, HL has been associated with infectious etiologies such as cytomegalovirus (CMV), nocardia, toxoplasma gondii, and herpes virus [191–194].

Plasma Cell Disorders

After completion of antigen-independent development, B cells are exposed to antigen presentation that can lead to the development of plasma cells. As a result of their ability to secrete antibodies, normally predominantly IgG, pathology can result from either the accumulation of excess antibody or antibody components and/or the direct effects of neoplastic proliferation.

Monoclonal Gammopathy of Undetermined Significance

Aberrant clonal proliferation can occur asymptomatically in the case of monoclonal gammopathy of undetermined significance (MGUS), with a prevalence of 3% and 5% in those over 50 and 70 years of age, respectively [195], and twice as common in those of African ancestry [196]. This condition is usually detected as part of a broad evaluation of many clinical signs and symptoms and is characterized by the absence of proliferative plasma cell effects such as lytic bone lesions, hypercalcemia, renal injury, or anemia; serum monoclonal protein (IgG, A, or M) less than 3 g per deciliter; and a bone marrow showing less

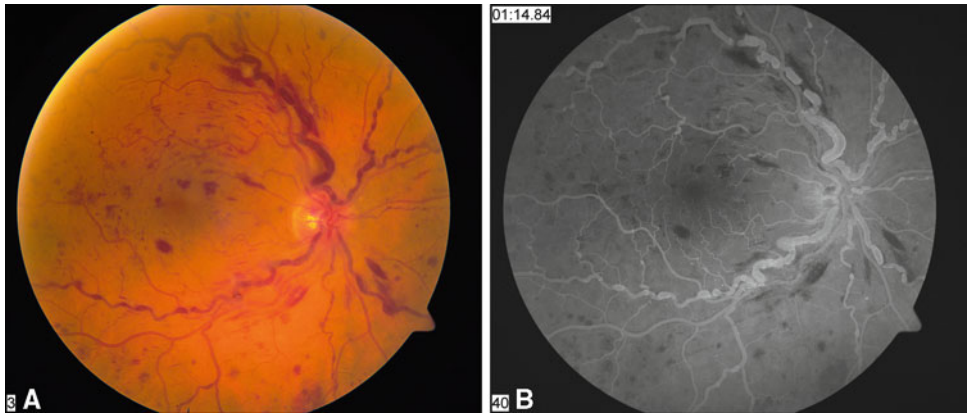

Fig. 23.8 (**a**) Hyperviscosity and hemorrhage due to Waldenstrom's macroglobulinemia. (**b**) "Sausage-link" appearance of venous circulation

than 10% clonal plasma cells [197]. Genetic abnormalities including translocations, aneuploidy, and deletions affecting cell cycle genes like cyclin D or tyrosine kinase–based receptors appear to contribute to clonal pathology [198–200]. A small case series reported the occurrence of bilateral retinal hemorrhages, CWS, and a unilateral macular detachment with no leakage on FA in one patient with benign polyclonal gammopathy, but for the most part, those with MGUS are expected to be clinically undetectable [201].

The main concern of MGUS, then, is the 1% per year risk of symptomatic transformation, resulting in Waldenstrom's macroglobulinemia (WM), primary amyloidosis, or multiple myeloma (MM) [202]. In addition, MGUS has been associated with higher rates of systemic lupus erythematosus and idiopathic thrombocytopenic purpura [203].

Waldenstrom's Macroglobulinemia/ Hyperviscosity

Macroglobulinemia is the excess occurrence of IgM monoclonal protein that can be produced by neoplasms associated with lymphoproliferative or plasma cell disorders. When secondary to a lymphoplasmacytic lymphoma, the condition is called Waldenstrom's macroglobulinemia, a disorder with clinical findings due to hyperviscosity, autoimmunity, or direct infiltration of lymphoreticular organs [204]. Specifically, WM has an incidence of 3 per million per year with a slight male predominance and overall is more common in Caucasians [205, 206]. The exact cause of WM is unclear, although somatic and cytogenetic anomalies have been detected, possibly a result of repeated B cell stimulation by chronic inflammation, like hepatitis C, or autoimmunity [207–209]. Pathophysiology is related to the pentameric structure of IgM that increases viscosity and commonly causes neurologic deficits, while its antigen binding domain confers autoimmunogenicity reportedly to red blood cells and nervous tissue components [210, 211].

The effects of hyperviscosity can cause a variety of findings on fundoscopic exam, occurring in up to 17% in WM, with the earliest retinal changes occurring at an IgM plasma level of approximately 5,442 mg/dl [212, 213]. Classically, WM results in bilateral vascular dilatation resulting in venous tortuosity with a sausage-like appearance and retinal hemorrhages that improve with plasmapheresis (Fig. 23.8a, b). Increasing vascular stasis can lead to fluid extravasation and hypoperfusion, causing retina and disk edema, subretinal fluid accumulation, nonperfusion, and even CRVO, which has a very similar appearance [214–216]. In more subtle cases, mid-peripheral hemorrhages may be the only finding as vascular diameter decreases and the volumetric flow rate drops. Rarely, WM can

cause a paraneoplastic retinopathy resulting in changes similar to retinitis pigmentosa [217].

Plasmacytoma/Multiple Myeloma

Plasma cell myelomas (PCM) can be grouped based on whether they arise from the bone or are extramedullary and if they manifest as single (plasmacytoma) or multiple bone lesions (multiple myeloma). These share in common the over-secretion of monoclonal protein, most commonly excess IgG comprising about half of all affected, while Bence Jones protein (kappa or lambda light chains only) accounts for only 16% [218]. Systemic findings include lytic skeletal lesions, hypercalcemia, anemia of chronic disease, and acute renal failure, although there is a form of MM, smoldering MM, that can be entirely asymptomatic [197]. MM accounts for approximately 10% of all hematologic malignancies, with an incidence of 4 per 100,000 persons that increases with age and a slight male predominance [184, 219].

When the posterior pole is involved, the findings of MM are predominantly secondary to its systemic effects or from chemotherapy. Severe anemia may result in a non-proliferative diabetic retinopathy like fundus but with nerve fiber layer hemorrhages that may include white centers, occurring regardless of serum monoclonal protein levels [220]. The latter point may be due to the fact that like the IgM encountered in WM, but rarely, a hyperviscosity syndrome or CRVO can occur despite the presence of IgG protein [221].

MM seems to lack a strong tropism for the eye, but direct infiltration of the choroid and retina, temporal arteritis, vasculitis, peripheral cysts, and exudate macular detachments have been reported [222, 223]. Very rarely, a plasmacytoma may arise primarily in the choroid as an amelanotic mass [224].

Plasma Cell Leukemia

Plasma cell leukemias are rare and arise primarily or as a progression of multiple myeloma, with an overall incidence of 0.02 cases per 100,000 persons [142]. The diagnosis requires kappa or lambda light chain restriction and an absolute plasma cell count greater than 2,000/μl or 20% of the peripheral white blood count [225]. Presenting signs and symptoms can include those of both multiple myeloma and leukemia. Therefore, leukemic findings, such as hemorrhage, CWS, perivasculitis, and chorioretinal infiltration, or features characteristic of multiple myeloma may become apparent.

T Cell Lymphomas

The T cell lymphomas are a small group of neoplasms that include adult T cell lymphoma/leukemia, cutaneous T cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T cell lymphoma, and T-prolymphocytic lymphoma. The intraocular manifestations of T cell lymphoma are rare and, when present, have been more commonly associated with systemic involvement of primary cutaneous peripheral T cell lymphoma or adult T cell lymphoma/leukemia rather than primary intraocular lymphoma, although clinically they may have a similar appearance and therefore require tissue or fluid specimens [169, 226].

In particular, adult T cell lymphoma/leukemia is the only T cell lymphoma due to human T-lymphotropic virus type 1 [144]. It is rare in the United States with 0.05 cases per 100,000 population and is more prevalent in the Caribbean and southern Japan with a slight male predominance [142, 227]. The exact mechanism of tumorigenesis is unclear although a viral oncoprotein, tax, appears to decrease apoptosis and favor cellular survival and proliferation [228]. Ocular involvement usually involves wide-ranging findings from vitritis, yellow-white choroidal or retinal infiltration, hemorrhage, edema, and rarely vasculitis and optic nerve infiltration, although the most frequent finding is vitritis [171, 226, 229].

Mycosis fungoides and its more aggressive variant, Sezary syndrome, characterize a unique and extremely rare subset of primary cutaneous T cell lymphomas of unclear cause with incidences of 6 and 0.3 cases per million population per year, respectively [230]. Although ocular involvement is rare, it can present with vitritis and white subretinal lesions between RPE and Bruch's

membrane or direct invasion from an external cutaneous lesion [231, 232].

Other rare T cell lymphomas, like natural killer (NK) neoplasms, also show marked vitritis but may additionally have serous retinal and choroidal detachments, while atypical findings like CRAO may be the initial presenting symptom of lymphoma in children [172, 233].

Controversies/Perspectives

Roth Spots

Confusion regarding Roth spots (RS), or white-centered hemorrhages, seems to permeate throughout the medical community. This is partly due to a strong stereotype associating RS with subacute bacterial endocarditis, in addition to a lack of understanding of RS pathophysiology. Speculation persisted that these lesions may have also represented leukemic cells or nerve fiber layer injury. In fact, studies have shown that RS lesions are rather the result of platelet-fibrin thrombi formed as a result of capillary rupture probably from acute systemic insults [13, 146, 234].

In addition, RS can occur in a wide variety of clinical settings, ranging from ocular hypotony; to shaken baby syndrome; human immunodeficiency virus; intracranial hemorrhage; traumatic delivery; blood dyscrasias such as anemia, thrombocytopenia, and leukemia; anoxic or hypoxic states like carbon monoxide poisoning; and relative ischemic conditions such as diabetes mellitus, hypertension, and preeclampsia [236]. Therefore, although RS are most commonly due to emboli from subacute bacterial endocarditis, other traumatic, ischemic, or hemodynamic causes should be considered based on clinical context.

Anti-VEGF Therapy

Anti-VEGF treatment is finding an increasingly prominent role in the treatment of various ocular neovascular disorders. Bevacizumab is commonly used as a treatment of neovascular glaucoma and is used by some as an adjuvant treatment in patients undergoing surgical repair of tractional retinal detachments due to proliferative diabetic retinopathy. Despite the evidence that VEGF plays an important role in proliferative sickle retinopathy (PSR), the data on the use of anti-VEGF agents is slim, with only two reported cases to our knowledge in the published literature.

There are theoretical and practical advantages and disadvantages to the use of anti-VEGF agents for PSR. One theoretically avoids the risk of choroidal neovascularization and retinal tear that is associated with argon laser photocoagulation. However, one set of complications is traded for another, as intravitreal injection is associated with a small, but definite, risk of endophthalmitis and also the risk that the rapid regression may be associated with traction or traction-rhegmatogenous detachment. In addition, the risk for potential systemic ischemic events associated with intravitreal anti-VEGF treatment should not be taken lightly in sickle cell patients, who already face an increased risk of stroke and other systemic ischemic events. Intravitreal injection can be useful in the setting of vitreous hemorrhage precluding laser treatment. In most cases, however, vitreous hemorrhage in PSR resolves spontaneously, and it is unclear if intravitreal treatment will make it go away any faster. Finally, intravitreal injection has the disadvantage of needing recurrent treatments, whereas photocoagulation effective ablates the area of treated retina.

Ultimately, judgment on anti-VEGF treatment of PSR should be reserved until there is reliable data in the form of controlled clinical trials. Until then, well-intended treatments with intravitreal bevacizumab or ranibizumab may in fact simply be shots in the dark.

Focal Points

Close communication with hematologist.

Anemia

- Ischemic changes such as intraretinal hemorrhages, retinal edema, and CWS.
- Fundus manifestations more common with a hematocrit less than 30%, often with coexistent thrombocytopenia.
- Erythropoietin may help stimulate neovascularization.

Hemoglobinopathies

Sickle Cell
- Commonly with arteriolosclerosis and vascular tortuosity, rarely angioid streaks
- Proliferative: Sea-fan neovascularization, overall more common in HbSC disease
- Non-proliferative: Salmon patches, intra- or preretinal hemorrhages, and black sunbursts, pre-hyperplasia secondary to subretinal hemorrhages

Thalassemia
- Degenerative RPE changes more common in thalassemia major and may be due to deferoxamine therapy
- Venous tortuosity, angioid streaks

Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome

- Purtscher-like retinopathy
- Vascular occlusions

Myelodysplastic Syndrome

- Retinal and choroidal changes almost always due to cytopenia of one or more cell lines causing anemia, thrombocytopenia, and/or neutropenia

Myeloproliferative Neoplasms

Myelogenous Leukemia
- Recurrent, predominantly peripheral vascular injury and nonperfusion with possible neovascularization

Polycythemia Vera
- Hyperviscosity and thrombotic symptoms with vascular engorgement, NFL infarcts, and retinal hemorrhages

Essential Thrombocythemia
- Ischemic changes secondary to higher risk of thrombosis.

Leukemia

- Most commonly a retinopathy due to characteristic changes from anemia, thrombocytopenia, and hyperviscosity
- Patchy or diffuse choroidal involvement with direct infiltration that can extend sub- or intraretinally appearing as yellow-white infiltrates
- Roth spots

Lymphoma

Yellow retinal lesions in a patient with known lymphoma more often represent infection due to bacterial, fungal, CMV, or other viral causes.

B Cell
- Vitreoretinal type more common and associated with CNS lymphoma.
- Uveal type more associated with peripheral lymphomas.
- Metastasis from systemic lymphoma may appear as uni- or multifocal yellow-white choroid lesions.

Hodgkin's Lymphoma
- Rule out other etiologies as this is extremely rare.

Plasma Cell
- MGUS is essentially clinically undetectable.

Waldenstrom
- CRVO-like appearance but bilateral, possible neurologic symptoms, and responds to plasmapheresis
- Sausage-link venous tortuosity

Multiple Myeloma
- Manifests mainly with retinal findings of anemia, less commonly hyperviscosity as most patients' M-protein consists of the smaller IgG

T Cell

- Extremely rare and can have varying ocular findings, although vitritis is the most recognized

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The Ocular Ischemic Syndrome

24

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Abstract

The ocular ischemic syndrome encompasses the ocular symptoms and signs attributable to severe carotid artery stenosis, generally ≥90%. The symptoms include decreased vision in most eyes and ocular/orbital pain in 40%. Iris neovascularization is present in 67% of eyes, while the posterior segment findings include narrowed retinal arteries, dilated (but not tortuous) retinal veins, and microaneurysms in most eyes. Other posterior signs include dot and blot retinal hemorrhages (80%), posterior neovascularization, (35%), and macular edema (14%). Fluorescein angiography discloses delayed arteriovenous transit time (95%), delayed choroidal filling (60%), and late arterial staining (85%). Therapy includes carotid endarterectomy and carotid stenting, while direct ocular therapy includes panretinal photocoagulation for ocular neovascularization.

Keywords

Ocular ischemic syndrome • Carotid artery stenosis • Ocular symptoms and signs

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Introduction

In 1963, Kearns and Hollenhorst [1] described the ocular symptoms and signs associated with severe carotid artery obstructive disease (Table 24.1). They called the entity "venous stasis retinopathy" and noted a prevalence of approximately 5% in their patients with carotid artery obstruction. Misunderstanding has since arisen with the term "venous stasis retinopathy" because the name has also been used to denote a mild central retinal vein obstruction [2]—an

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Table 24.1 Symptoms and signs associated with the ocular ischemic syndrome [5, 6, 32]

Symptoms	Incidence
Anterior segment	
Vision loss	~90%
Periorbital pain	40%
Signs	
Anterior segment	
Iris neovascularization	67%
Anterior chamber flare	67%
Anterior chamber cells	20%
Posterior segment	
Narrowed retinal arteries	90% +
Dilated retinal veins	90% +
Microaneurysms	80%
Retinal hemorrhages	80%
Optic disk/retinal neovascularization	35%
Macular edema	14%
Cherry-red spot	12%
Neovascularization of the retina	8%
Vitreous hemorrhage	4%
Spontaneous retinal arterial pulsations	4%
Anterior ischemic optic neuropathy	2%
Retinal arterial emboli, cholesterol	2%
Retinal arteriovenous communications	Rare
Ancillary tests	
Fluorescein angiography	
Delayed retinal arteriovenous transit time	95%
Late retinal arterial staining	86%
Delayed choroidal filling	60%
Macular edema	16%
Electroretinography	
Decreased a- and b-wave amplitudes	Most eyes

outflow condition versus the inflow problem seen with carotid artery obstruction. Alternative names proposed include ischemic coagulopathy [3] and ischemic ocular inflammation [4, 5]. Nonetheless, in the majority of cases, clinical and histopathologic examinations of eyes with ocular ischemic disease due to carotid artery obstruction generally fail to demonstrate inflammation [5–8]. The descriptive term proposed by Magargal and Brown [5, 6] is the *ocular ischemic syndrome (OIS)* [5, 6], an entity not to be confused with mild central retinal vein obstruction and other posterior segment vasculopathies.

Demography

The mean age of patients with the OIS is approximately 65 years, with a range from the 50s to the 80s [5]. No racial predilection has been shown, but males outnumber females by a ratio of 2:1. In approximately 20% of patients, the OIS is bilateral [5].

Sturrock and Mueller [9] reported the annual incidence of the OIS in the UK to be 7.5 cases/million persons. Extrapolation of these data to the USA suggests an annual incidence of 2,200 cases. Nonetheless, the incidence may be falsely low since it is possible that some cases are misdiagnosed.

Etiology

Typically, a stenosis of 90% or greater in the ipsilateral common carotid and/or internal carotid arterial system is necessary to cause the OIS (Fig. 24.1), while a 50% stenosis is not [5]. It has been shown that a 90% carotid stenosis reduces the central retinal artery perfusion pressure by about 50% [10, 11]. In approximately 50% of cases, the affected carotid vessel is 100% occluded [5].

Obstruction as distally as the ipsilateral ophthalmic artery can also cause the OIS [5, 12, 13]. Rarely, an isolated obstruction of the central retinal artery alone can mimic the dilated retinal veins and retinal hemorrhages seen in eyes with the ocular ischemic syndrome [14]. In this instance, the choroid appears to be unaffected on fluorescein angiography.

Atherosclerosis within the carotid artery is the cause of the majority of OIS cases (Fig. 24.2) [5]. Dissecting aneurysm of the carotid artery has been reported as a cause [15], as has giant cell arteritis [16]. Hypothetically, entities such as fibromuscular dysplasia [17], Behçet's disease [18], trauma [19], and inflammatory conditions that cause carotid artery obstruction could lead to the OIS.

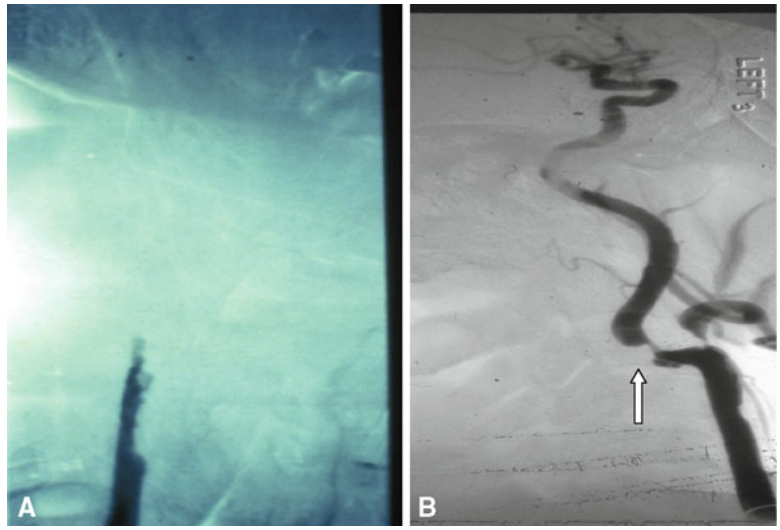

Fig. 24.1 (**a**) *Upper left*. Carotid arteriogram of a 65-year-old patient discloses a 100% blockage of the right common carotid artery. (**b**) *Upper right*. The left internal carotid artery demonstrates a 95% blockage of the internal carotid artery (*arrow*)

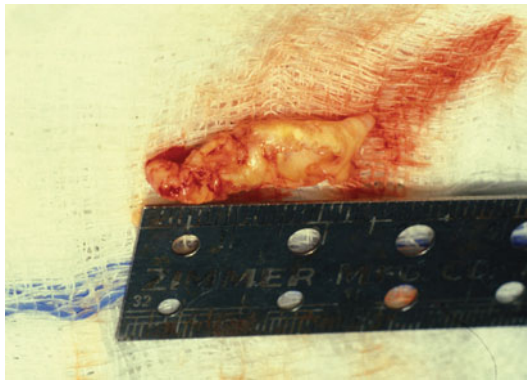

Fig. 24.2 Atherosclerotic plaque composed of fibrous tissue, cholesterol and calcium from a patient who underwent endarterectomy (Courtesy of Ms. Karen Albert)

Symptoms

Loss of Vision

Over 90% of patients with the OIS relate a history of visual loss in the affected eye(s) [5]. In two-thirds of cases it occurs over a period of weeks to months, while it is abrupt in approximately 12%. In the abrupt vision loss cohort there is often a cherry-red spot present on funduscopic examination.

Prolonged recovery following exposure to a bright light has been described in patients with severe carotid artery obstruction [20]. Concurrent attenuation of the visual evoked response after light exposure has also been observed in these cases [20]. With instances of bilateral, severe carotid artery obstruction, the visual loss after exposure to bright light occurs in both eyes, thus mimicking occipital lobe ischemia due to vertebrobasilar disease [21].

Amaurosis Fugax

A history of amaurosis fugax is elicited in about 10% of OIS patients [5]. Amaurosis fugax, or fleeting loss of vision for seconds to minutes, is thought to be predominantly caused by emboli to the central retinal arterial system, although vasospasm may also play a role [22], as can giant cell arteritis [23]. While the majority of people with amaurosis fugax alone do not have the OIS, it can be an indicator of concomitant, ipsilateral carotid artery obstructive disease. Approximately one-third of patients with amaurosis fugax have an ipsilateral carotid artery obstruction of 75% or greater [24]. Rarely, amaurosis fugax has been

associated with stenosis of the ipsilateral ophthalmic artery [24].

Pain

Pain is present in the affected eye or orbital region in about 40% of OIS cases [5]. We have referred to this pain as "ocular angina" [5]. Most often, it is described as an intermittent dull ache. Neovascular glaucoma can be the cause, although in those eyes with normal intraocular pressure, the cause may be ischemia to the globe and/or ipsilateral dura.

Visual Acuity

The presenting visual acuities of eyes with the OIS are bimodally distributed, with 43% of affected eyes having vision ranging from 20/20 to 20/50 and 37% having counting fingers or worse vision [25]. Absence of light perception is generally not seen early but can occur in the later stages of the disease, usually secondary to neovascular glaucoma. Among all eyes, treated and untreated, with the OIS at the end of 1 year of follow-up, 24% remain in the 20/20–20/50 group, while a large 58% have counting fingers or worse.

Signs

External

A prominent superficial temporal artery can occasionally be seen with the OIS (Fig. 24.3). This vessel is typically a collateral artery that allows blood flow from the ipsilateral external carotid system to pass across the midline and supply an occluded, contralateral, carotid arterial system. Giant cell arteritis can also cause an enlarged superficial temporal artery, although it is typically tender and irregular, while that associated with the OIS is not. Caution should be exercised if an enlarged superficial temporal artery is encountered with OIS symptoms and signs since a temporal artery biopsy to confirm giant cell arteritis could suddenly interrupt blood flow to the contralateral brain and result in a cerebrovascular accident.

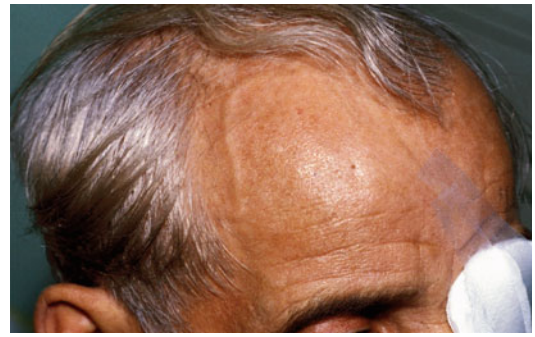

Fig. 24.3 A prominent superficial temporal artery in a patient with the ocular ischemic syndrome with a 100% left common carotid obstruction. Blood from this vessel crosses over to supply the left carotid arterial system

Anterior Segment Changes

Unfortunately, neovascularization of the iris is already seen in approximately two-thirds of eyes with the OIS at the time of presentation (Fig. 24.4a, b) [5]. This finding is associated with a 90% incidence of counting fingers vision at 1 year [25]. Nevertheless, only half of these eyes have or develop increased intraocular pressure, even if the anterior chamber angle is closed by fibrovascular tissue [5]. Impaired ciliary body perfusion, with a subsequent decrease in aqueous production, likely accounts for this phenomenon.

Flare in the anterior chamber is present in most eyes with iris neovascularization. An anterior chamber cellular response is seen in about one-fifth of eyes with the OIS [5] but rarely exceeds grade 2 using the Schlaegel classification [26]. Keratic precipitates can be present but are unusual.

In unilateral cases, there is generally little difference between the degree of cataractous lens change in each eye. As the disease progresses, however, cataractous changes can develop. In advanced cases, the lens may become mature.

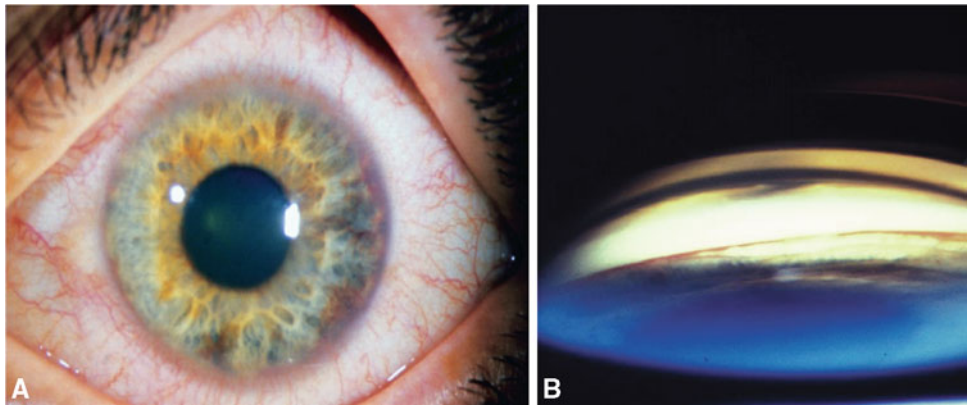

Fig. 24.4 (**a**) Neovascularization of the peripheral iris in a patient with the ocular ischemic syndrome. (**b**) Gonioscopy of the anterior chamber angle reveals neovascular, peripheral, anterior synechiae closing the anterior chamber angle

Posterior Segment Findings

The retinal arteries are usually narrowed in OIS eyes, while the retinal veins are most often dilated but not tortuous (Fig. 24.5) [5]. The venous dilation may be accompanied by beading but usually not to the extent seen in eyes with marked preproliferative or proliferative diabetic retinopathy. Dilation of the veins seems to be a nonspecific response to ischemia in the OIS, diabetic retinopathy, threshold retinopathy of prematurity, and other vasculopathies.

In contrast to OIS eyes, those with central retinal vein obstruction usually have generally dilated veins that are also tortuous. The fact that the OIS occurs secondary to impaired inflow, while a central retinal vein obstruction is associated with compromised outflow from thrombus formation at or near the lamina cribrosa [27], differentiates the ocular response to inflow and outflow vasculopathies.

Retinal hemorrhages are seen in about 80% of affected eyes. They are most commonly seen in the mid-periphery (Fig. 24.6) but can also extend into the posterior pole. While dot and blot hemorrhages are the most common variant, superficial retinal hemorrhages in the nerve fiber layer are occasionally seen. The hemorrhages likely arise secondary to leakage from the smaller retinal vessels with endothelial damage secondary to ischemia. Similar to the case with diabetic retinopathy, these hemorrhages may also result from the rupture of microaneurysms. In general, the hemorrhages seen with the ocular ischemic syndrome are considerably less numerous than those accompanying central retinal vein obstruction. They are virtually never confluent in OIS eyes.

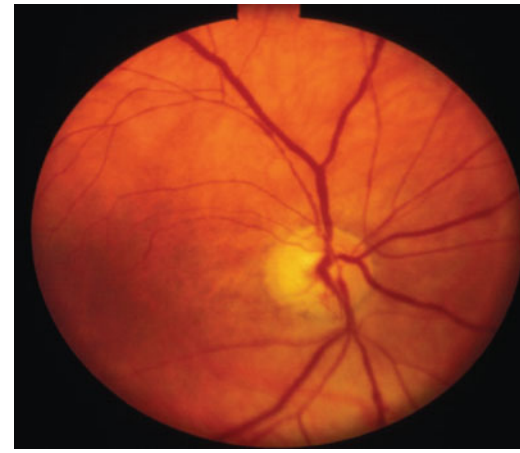

Fig. 24.5 Posterior pole of the right fundus of an ocular ischemic syndrome in a patient with a 100% internal carotid occlusion. The retinal arteries are narrowed and the retinal veins are dilated and slightly beaded, but the tortuosity seen with outflow occlusions, such as central retinal vein occlusion, is absent

Microaneurysms are frequently observed outside the posterior pole but can be seen in the macular region as well. Hyperfluorescence with fluorescein angiography (Fig. 24.7a, b) differentiates these abnormalities from hypofluorescent retinal hemorrhages. Retinal telangiectasia has also been described [28].

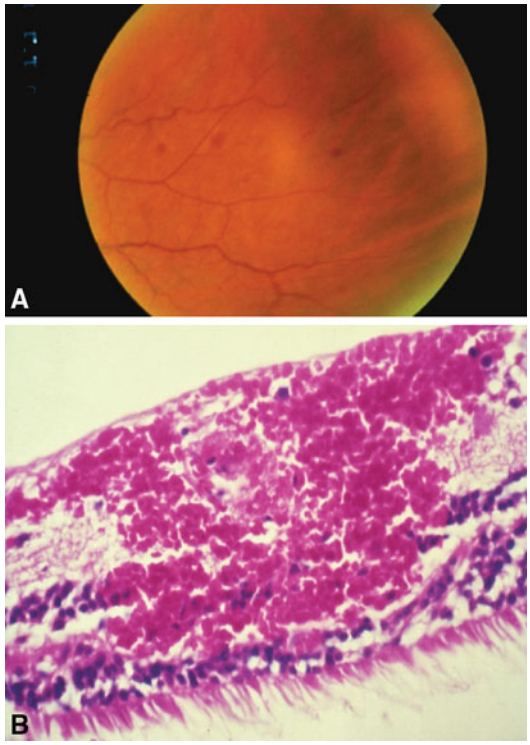

Fig. 24.6 (**a**) Dot and blot hemorrhages in the mid-peripheral fundus of a patient with the ocular ischemic syndrome. (**b**) Histopathologic correlate of dot and blot hemorrhages in association with the ocular ischemic syndrome. Blood, typically present in the inner nuclear/outer plexiform layer, has spread through almost the full thickness of the retina (Fig. 24.6b Hematoxylin-eosin ×100; courtesy of Dr. W. Richard Green)

Posterior segment neovascularization can occur on the optic disk (Figs. 24.8 and 24.9) and/or on the retina (Figs. 24.10 and 24.11). Neovascularization of the disk is encountered in about 35% of eyes, while neovascularization of the retina is seen in about 8% [5]. Vitreous hemorrhage arising from traction upon the neovascularization by the vitreous gel (Fig. 24.9) has been reported to occur in 4% of eyes with the ocular ischemic syndrome in a retrospective study [5]. Rarely, the neovascularization can progress to severe preretinal fibrovascular proliferation.

A cherry-red spot characteristic of acute central retinal occlusion is seen in approximately 12% of eyes with the OIS [5]. It can occur secondary to inner layer retinal ischemia from embolic obstruction or hemorrhage under an atherosclerotic plaque in the central retinal artery. Nonetheless, it probably develops more often when the intraocular pressure exceeds the perfusion pressure within the central retinal artery, especially in eyes with neovascular glaucoma. When iris neovascularization develops several weeks after central retinal artery obstruction, severe carotid artery obstruction may or may not be present. When iris neovascularization is present, however, at time of presentation of a central retinal artery obstruction, a severe obstruction of the ipsilateral carotid arterial system should be suspected.

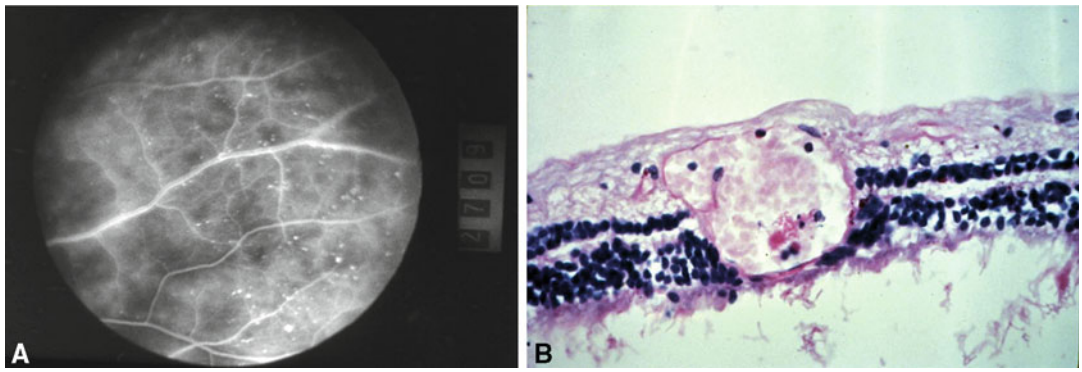

Fig. 24.7 (**a**) Positive intravenous fluorescein angiogram in an ocular ischemic syndrome eye at 4.5 min after injection shows multiple small hyperfluorescent dots corresponding to microaneurysms in the mid-peripheral retina. (**b**) Histopathologic correlation of a large microaneurysm (MA) from an eye with the ocular ischemic syndrome (Fig. 24.7b Hematoxylin-eosin ×100; courtesy of Dr. W. Richard Green)

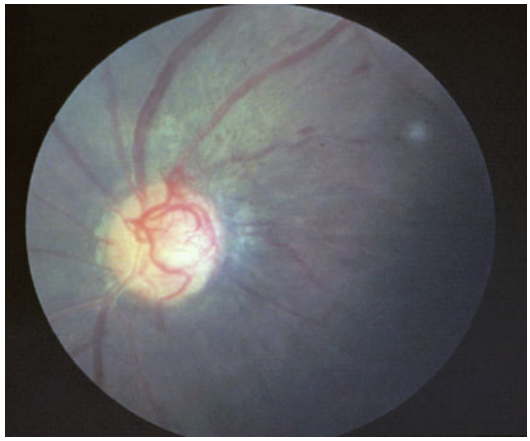

Fig. 24.8 Neovascularization of the optic disk in an 80-year-old, nondiabetic man with a 95% left internal carotid artery obstruction

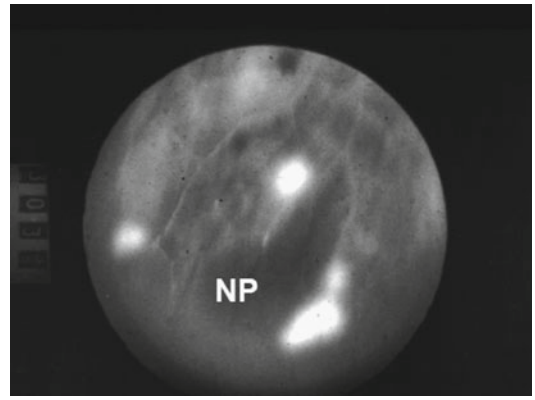

Fig. 24.10 Hyperfluorescence corresponding to three separate foci of neovascularization of the retina in the mid-peripheral fundus of a nondiabetic man with bilateral 95% internal carotid artery obstructions. NP corresponds to retinal capillary nonperfusion adjacent to the foci of retinal neovascularization

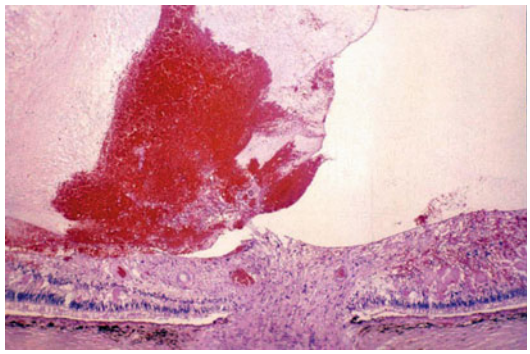

Fig. 24.9 Histopathologic correlate of vitreous hemorrhage occurring secondary to traction on neovascularization of the optic nerve head (hematoxylin-eosin ×40)

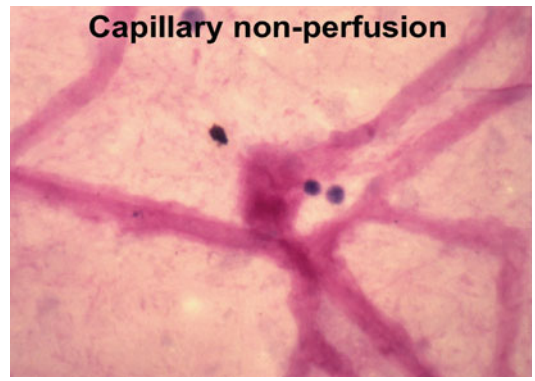

Fig. 24.11 Trypsin digest (×160) corresponding to retinal capillary nonperfusion. The capillaries are acellular tubules with no endothelial cells or pericytes. Reperfusion does not occur through these "dead" vessels

Additional posterior segment signs [5] include cotton-wool spots in 6% of eyes, spontaneous retinal arterial pulsations in 4%, and cholesterol emboli within the retinal arteries in 2%. In contrast to spontaneous retinal venous pulsations, which are a normal variant and located at the base of the large veins on the optic disk, the arterial pulsations are usually more pronounced and may extend a disk diameter or more out from the optic disk into the surrounding retina. Anterior ischemic optic neuropathy has also been reported in OIS eyes [5, 29, 30]. Acquired arteriovenous communications of the retina are rarely seen [31].

Diagnostic Studies

Fluorescein Angiography

Delayed arm-to-choroid and arm-to-retina circulation times are frequently observed in OIS eyes [5]. Nonetheless these measurements can be difficult to assess since they depend upon whether the dye was injected in the antecubital fossa or hand as well as the rapidity of injection. The observation of a well-demarcated, leading edge of fluorescein dye within a retinal artery after an

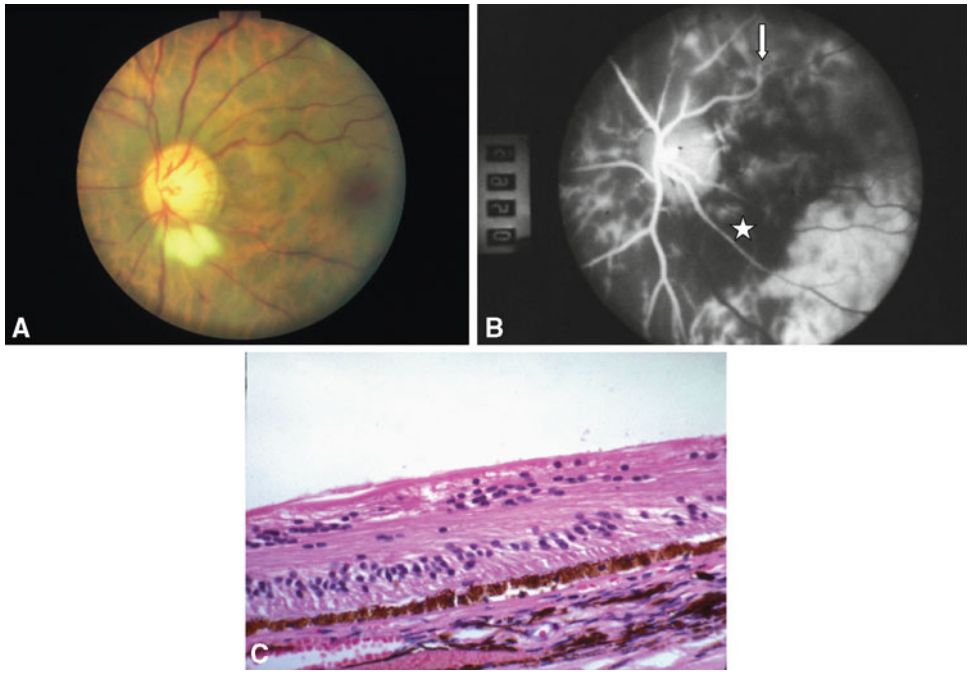

Fig. 24.12 (**a**) Left fundus of an ocular ischemic syndrome eye with 20/20 vision. The retinal arteries are narrowed, and the retinal veins are dilated and beaded but not tortuous. Superficial, *yellow–white*, myelinated nerve fibers are an incidental finding adjacent to the inferior optic disk. (**b**) Fluorescein angiogram at approximately 1 min after injection discloses choroidal hypoperfusion (*star*), as well as leading edges of dye within the retinal arterial system (*arrow*). (**c**) Histopathology of an ocular ischemic syndrome eye reveals damage to the inner and outer retinal layers. The retinal pigment epithelium is relatively intact, as might be expected, since the clinical observation of retinal pigment epithelial hyperplasia and/or retinal pigment epithelial loss is uncommon with the ocular ischemic syndrome (Fig. 24.12c Hematoxylin-eosin ×100; courtesy of Dr. W. Richard Green)

intravenous injection is a distinctly unusual finding that can be seen in eyes with the OIS (Fig. 24.12a, b, c).

Normally, choroidal filling is completed within 5 s after the first appearance of dye. Sixty percent of eyes with the OIS demonstrate patchy and/or delayed choroidal filling (Fig. 24.12b). In some instances, the filling is delayed for a minute or longer. Although not the most sensitive sign, abnormal choroidal filling is the most specific fluorescein angiographic sign in OIS eyes.

Prolongation of the retinal arteriovenous transit time is seen in 95% of eyes with the OIS (high sensitivity) but can also be seen in eyes with central retinal artery obstruction and central retinal vein obstruction (low specificity). The major retinal veins in the temporal vascular arcade completely fill within 10–11 s after the first appearance of dye within the corresponding retinal arteries. In extreme cases of the OIS, the retinal veins fail to fill throughout the study.

Staining of the retinal vessels in the later phases of the study is seen in about 85% of eyes (Figs. 24.13 and 24.14). Both larger and smaller vessels can be involved, the arteries preferentially more so than the veins. Chronic hypoxic damage to endothelial cells may account for the staining. In contrast, staining of the retinal vessels is uncommon with central retinal artery obstruction alone. With central retinal vein obstruction, the veins often demonstrate late staining but the retinal arteries are generally not affected.

Macular edema with fluorescein angiography is seen in about 14% of eyes with the OIS [32]. Hypoxia and subsequent endothelial damage within the smaller retinal vessels, as well as leakage from microaneurysms, account for this phenomenon.

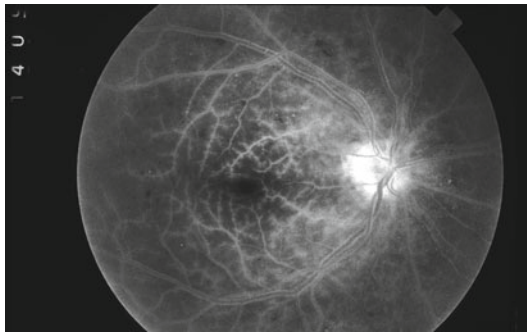

Fig. 24.13 Fluorescein angiogram of an ocular ischemic syndrome eye at greater than 2 min after injection demonstrates staining of midsized retinal arteries and less so the retinal veins

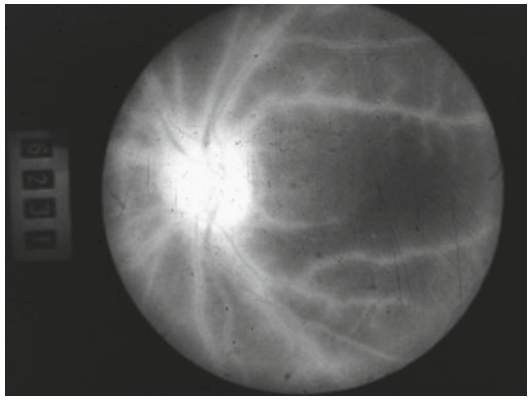

Fig. 24.14 Fluorescein angiogram of an ocular ischemic syndrome eye at greater than 10 min after injection demonstrates pronounced staining of the retinal arteries and less so the retinal veins

Dye accumulation can be mild or severe and is usually associated with hyperfluorescence of the optic disk. The disk, however, is generally not swollen ophthalmoscopically.

Retinal capillary nonperfusion can be seen in some eyes (Figs. 24.10 and 24.11). The histopathologically observed absence of endothelial cells and pericytes within the retinal capillaries corresponds to areas of nonperfusion seen with fluorescein angiography [5, 33]. Bilateral, simultaneous, intravenous fluorescein angiography is a technique that has been reported to be helpful diagnostically in patients with unilateral ocular ischemic syndrome [34]. The technique, however, requires specialized equipment and is not generally available.

Electroretinography

The electroretinogram typically discloses a diminution, or absence, of both a- and b-wave amplitudes in eyes with the OIS [5, 6]. The b-wave corresponds to activity in the inner retinal layers, while the a-wave correlates with activity of the photoreceptors in the outer retina [35, 36]. Reduction in the amplitude of the oscillatory potential of the b-wave has also been noted in eyes with retinal ischemia secondary to carotid artery stenosis [37]. This can be seen in patients with proven carotid artery disease even in the presence of a normal fluorescein angiogram.

Carotid Artery Imaging

Carotid angiography usually discloses a 90% or greater obstruction of the ipsilateral internal or common carotid artery in persons with the OIS (Fig. 24.1). Given that noninvasive tests, such as duplex ultrasonography and oculoplethysmography, have an accuracy of approximately between 88% and 95% for detecting carotid stenosis of 75% or greater [38–40], and that angiography has a potential for serious complications, these noninvasive studies should be considered before angiography is obtained.

Others

Visual evoked potentials have been used to study eyes with severe carotid artery stenosis. The recovery time of the amplitude of the major positive peak after photostress has been shown to improve in patients with severe stenosis after endarterectomy [41].

Ophthalmodynamometry can be of benefit in detecting decreased ocular perfusion in cases of unilateral OIS [10, 42]. In the absence of an ophthalmodynamometer, Kearns [42] has advocated light digital pressure on the upper lid of the affected eye. Digital pressure frequently produces pronounced arterial pulsations on the disk that can be seen extending several millimeters into the retina. Unlike spontaneous venous pulsations

Table 24.2 Systemic abnormalities associated with the ocular ischemic syndrome at baseline [43]

Abnormality	Prevalence (%)
Systemic arterial hypertension	73
Diabetes mellitus	56
S/P myocardial infarction	50
Stroke	27
S/P arterial bypass surgery	19
Five-year mortality	40

S/P status post

on the optic disk, retinal arterial pulsations are always abnormal.

Systemic Associations

The OIS is associated with systemic abnormalities related in some way to atherogenesis (Table 24.2) [43]. The prevalence of systemic arterial hypertension in OIS patients is 73%. Diabetes mellitus is found in 56% of patients, while 50% have had a myocardial infarction, the latter demonstrating that arterial atherosclerosis in an OIS population is not confined to only the eye. Approximately 27% of OIS patients have had a previous stroke, while the stroke rate for people with the OIS is approximately 4% per year [43]. At the time of presentation, almost one-fifth of patients relate a history of having peripheral vascular disease for which previous bypass surgery was required [43].

Mortality data [43] have shown that the 5-year death rate for patients with the OIS is 40% (Fig. 24.15). The leading cause of death is cardiovascular disease, which accounts for about two-thirds of cases. Stroke is the second leading cause of death.

Differential Diagnosis

The differential diagnosis for the OIS includes primarily mild (nonischemic) central retinal vein obstruction, diabetic retinopathy, radiation retinopathy, hypertensive retinopathy, and vasculopathies such as those encountered with polycythemia and collagen vascular diseases.

Treatment

Systemic Therapy: Carotid Artery

The natural course of vision loss with the ocular ischemic syndrome is uncertain. Nonetheless, most eyes with the fully developed entity probably have a poor long-term outcome. When iris neovascularization is present, over 90% of eyes become legally blind within a year of discovery [25].

When a carotid artery is 100% obstructed, endarterectomy is generally not effective since a thrombus can propagate anterograde and/or retrograde. In these cases, extracranial to intracranial bypass surgery, usually from the superficial temporal artery to the middle cerebral artery, has been attempted to alleviate the obstruction. Although this procedure was of benefit in 20% (3/15) of cases in salvaging vision in eyes with the OIS, the visual prognosis at 1 year after the surgery was universally poor [25]. Additionally, the procedure has not been shown in a large randomized study to be of benefit in preventing the risk of ischemic stroke [44].

Although there are no randomized studies that compare the natural history of the disease to the course after carotid endarterectomy, this surgery may also stabilize or improve vision in the eyes of patients who undergo successful endarterectomy prior to the development of iris neovascularization [25, 45]. Notwithstanding, the visual results associated with this treatment are fair at best. In the series of Sivalingam et al. [25] at the end of 1 year, 7% of eyes with the ocular ischemic syndrome that underwent endarterectomy experienced visual improvement or stabilization, 33% were unchanged, and 60% had worse vision. Among the 60 total OIS eyes in the group, an endarterectomy was performed for only 3 without iris neovascularization. At the end of 1-year follow-up the vision was better in one, stable in one, and worse in the third.

Endarterectomy appears to rarely cause regression of iris neovascularization eyes with the OIS [46]. It should be noted that eyes with the OIS will occasionally develop a severe increase in intraocular pressure after ipsilateral carotid

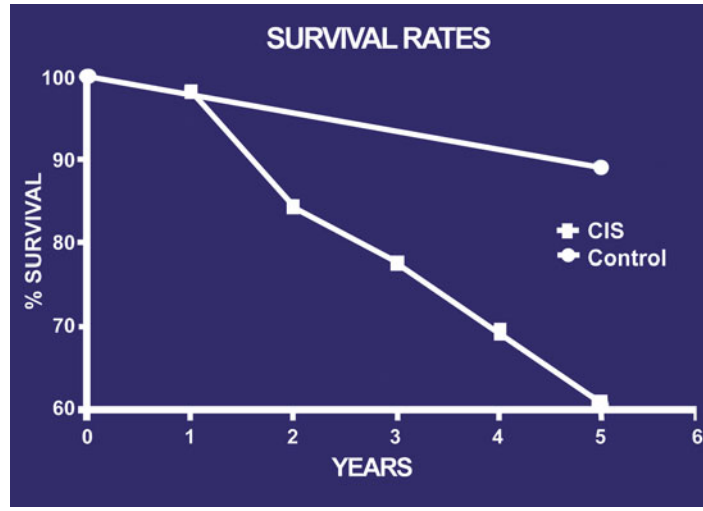

Fig. 24.15 Survival rates of ocular ischemic syndrome (OIS) patients and an age-matched control group without the OIS. The 5-year mortality rate for OIS patients is 40%, three to four times greater than expected in the age-matched control patients

endarterectomy. This is most likely to occur in eyes with iris neovascularization and anterior chamber angle compromise from fibrovascular tissue formation. Although aqueous outflow is impaired in such eyes, ciliary body perfusion and aqueous humor formation are also decreased secondary to the carotid stenosis. When the carotid obstruction is suddenly reversed, ciliary body perfusion and aqueous humor formation increase, but the outflow obstruction in the anterior chamber angle is still present. Thus, the intraocular pressure rises drastically. Ciliary body destructive procedures or glaucoma filtering surgery may be required in these cases [47, 48].

Several large randomized studies have recently been published concerning the indications for carotid endarterectomy in general [49–52]. Carotid endarterectomy has been proven to be efficacious both in symptomatic patients with high-grade (70–99%) carotid artery stenosis and in asymptomatic patients with greater than (or equal to) 60% stenosis. Specifically, the investigators of the North American Symptomatic Carotid Endarterectomy Trial [50] noted a 17% absolute risk reduction in the cumulative 2-year risk of ipsilateral stroke and a 10% absolute risk reduction in fatal ipsilateral stroke when those randomized to endarterectomy were compared to those who were treated medically. The European Carotid Surgery Trialists' Collaborative Group [49] also was able to demonstrate a similar treatment effect of carotid endarterectomy for patients with 70–99% stenosis (sixfold reduction in 3-year risk of ipsilateral stroke) but also found that in the 0–29% stenosis group the early risks of surgery (2.3% died or had a disabling stroke within 30 days of surgery) outweighed the 3-year benefit when compared to medical therapy.

The investigators of the Asymptomatic Carotid Atherosclerosis Study [51] were able to demonstrate an aggregate risk reduction of 53% in the incidence of death or stroke, when those randomized to surgery were compared to those who received medical treatment. Asymptomatic patients with carotid artery stenosis of 60% or greater reduction in diameter were eligible to benefit. Accordingly, any patient with the OIS and severe carotid artery stenosis should be considered for carotid endarterectomy.

Marx et al. [53] demonstrated that percutaneous carotid artery angioplasty with stenting stabilized or improved vision in each of three cases, while Kawaguchi et al. [54] demonstrated that stenting of the carotid artery improved the OIS in seven of eight patients. Stenting for restenosis of the carotid artery and the OIS has also been reported [55].

Ophthalmic Therapy

Full scatter panretinal laser photocoagulation has been advocated for OIS eyes with iris neovascularization and/or posterior segment neovascularization

[25, 56–58]. This generally consists of 1,500–2,000 500-μm burns with the argon green laser. Unlike the situation when iris neovascularization occurs secondary to diabetic retinopathy, in which there is regression in a majority of cases with full scatter panretinal photocoagulation, approximately 36% of ocular ischemic syndrome eyes will demonstrate regression of the iris neovascularization after full scatter treatment [25]. If the anterior chamber angle is completely closed by fibrovascular tissue and there is no posterior segment neovascularization, panretinal photocoagulation is probably not indicated unless a glaucoma filtering procedure is being considered, as higher success rates of filtration surgery have been reported when PRP has been performed [58].

While there is little in the reported literature regarding the management of macular edema secondary to this condition, Klais and Spaide [59] recently reported excellent clinical resolution of fluid and dramatic improvement in vision in a patient treated with intravitreal triamcinolone acetonide. Intravitreal bevacizumab has been utilized to successfully treat iris neovascularization occurring secondary to the OIS, although long-term data are lacking [60].

Controversies and Perspectives

The greatest controversy concerns the effect of reversal of the carotid artery stenosis by endarterectomy or stenting. Clinical trial data are lacking in regard to visual results obtained following carotid surgical interventions. Since the visual prognosis is grim if the patient already has iris neovascularization, it seems important that vascular surgery be undertaken at an earlier time. Obtaining noninvasive carotid studies should be considered in the appropriate clinical scenario, preferably prior to the development of iris neovascularization.

While somewhat controversial, oral rosuvastatin has been shown to decrease atherosclerosis in coronary patients [61]. This form of therapy might well benefit those with the atherosclerosis encountered with the OIS.

Focal Points

- The OIS is associated with dilated and beaded retinal veins that *are not tortuous*, while nonischemic central retinal vein obstruction is associated with dilated, beaded veins that *are tortuous*.
- The OIS is the most common cause of spontaneous arterial pulsations.
- Among the fluorescein angiographic signs associated with the OIS, delayed choroidal filling is the most specific. Increased arteriovenous transit time is the least specific.
- In patients with carotid stenosis and diabetic retinopathy, it can be difficult to differentiate which disease accounts for the ocular changes.
- Light digital pressure on the upper lid typically produces dramatic spontaneous retinal arterial pulsations in OIS eyes, while the same or greater pressure in nonischemic central retinal vein obstruction fails to produce retinal arterial pulsations.
- If the clinical symptoms and signs of the OIS are present and a severe carotid stenosis is absent, obstruction of the ophthalmic may be present.
- The effect of high dose oral rosuvastatin, which has been shown to reverse coronary atherosclerosis, may be of benefit for the treatment of the atherosclerosis associated with the OIS.

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Ocular Manifestations of Pregnancy

25

Derek Kuhl, Stephen G. Schwartz, Bhavna P. Sheth, and William F. Mieler

Abstract

Pregnancy may be associated with ocular changes, which most often are transient in nature. It can exacerbate preexisting conditions or be associated with development of new conditions. The ocular effects of pregnancy may be divided into physiologic changes, pathologic conditions, or modifications of preexisting conditions. Pathologic conditions include entities such as preeclampsia and eclampsia, along with conditions that are seen with increased frequency during pregnancy such as central serous chorioretinopathy. The most significant modified preexisting condition is diabetes mellitus. The various effects of pregnancy on the eye will be reviewed throughout this chapter.

Keywords

Ocular manifestations of pregnancy • Pregnancy-induced hypertension • Preeclampsia • Eclampsia • HELLP syndrome • Central serous choroidopathy • Purtscher's-like retinopathy • Amniotic fluid emboli • Disseminated intravascular coagulation (DIC) • Thrombotic thrombocytopenic purpura (TTP)

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Introduction

The effects of pregnancy on the eye as well as the use of ophthalmic medications in pregnancy will be reviewed. The ocular effects of pregnancy may be divided into physiologic changes, pathologic conditions, or modifications of preexisting conditions [1]. Pathologic conditions include the ocular effects of pregnancy-specific conditions, such as preeclampsia and eclampsia, as well as conditions that are seen in increased frequency during

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pregnancy, such as central serous retinopathy and other vasculopathies. Modifications of preexisting conditions include ocular changes seen in conjunction with diabetes mellitus as well as in patients with certain intraocular tumors.

Physiologic Changes

Intraocular Pressure

The intraocular pressure has been reported to decrease in the second half of pregnancy, presumably due to an increase in the facility of outflow and uveoscleral outflow [2, 3] and a decrease in episcleral venous pressure [4]. The intraocular pressure returns to prepregnancy levels by 2 months postpartum [5].

Cornea

The cornea may demonstrate a decrease in sensitivity [6], an increase in thickness [7], and an increase in corneal curvature during pregnancy [8]. All of these factors may contribute to contact lens intolerance [9]. The change in thickness may also alter the refractive index of the cornea, thereby changing the refraction [10]. Pregnant women should therefore wait for at least a few weeks postpartum before obtaining a new spectacle prescription.

Pathologic Conditions

Pregnancy-Induced Hypertension

Clinical Features

Pregnancy-induced hypertension (PIH) includes preeclampsia and eclampsia, and occurs in approximately 5% of pregnancies. It may be associated with a variety of ocular abnormalities. Hypertension, peripheral edema, and proteinuria characterize preeclampsia, while eclampsia is basically preeclampsia with seizures.

PIH generally occurs after the 20th week of pregnancy. Risk factors for its occurrence include first and multifetal pregnancies, very old or young maternal age, mothers with vascular disease, and certain fetal abnormalities. The systemic symptoms include headache, epigastric pain, vomiting, and visual disturbances.

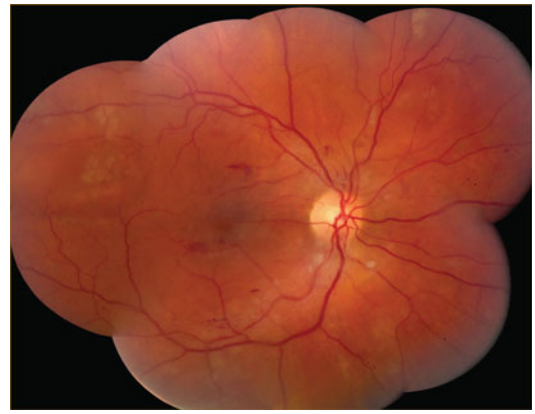

Fig. 25.1 Color photograph OD depicts a preeclamptic female with visual acuity of 20/400 OD. There is generalized arteriolar attenuation, with punctate hemorrhages, and an occasional cotton-wool spot

Ocular Manifestations

The most common symptoms of PIH are blurred vision, photopsias, scotomata, and diplopia. The ocular signs include retinal arteriolar abnormalities, serous retinal detachments, and ischemic optic neuropathy. The most common retinal abnormality seen in preeclampsia is focal arteriolar spasm and narrowing [11, 12] (Fig. 25.1). This may be associated with peripapillary or focal areas of retinal edema (Fig. 25.2a, b). As the vessel changes return to normal after delivery, visual loss is unusual, though permanent loss does occur on occasion.

Serous retinal detachments are seen in approximately 1% of preeclamptic patients and about 10% of eclamptic patients [13, 14]. Choroidal ischemia is believed to play a role in the pathogenesis of these serous detachments [15] (Fig. 25.3a, b). The bullous serous elevations, which may be bilateral, occur in the absence of significant retinal vascular abnormalities. Most patients experience resolution of the detachments shortly after delivery. Although the visual prognosis is quite good, residual pigment epithelial

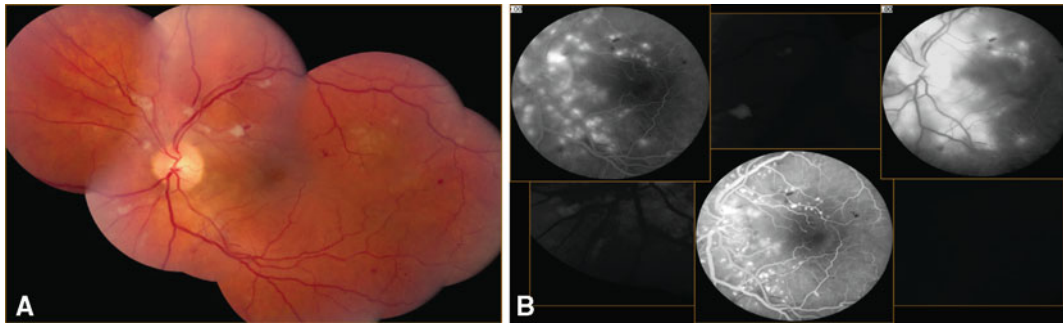

Fig. 25.2 (**a**) Color photograph in an eclamptic patient revealing vascular narrowing, mild peripapillary edema, choroidal ischemia, and localized serous detachments. The visual acuity was counting fingers OU. (**b**) Fluorescein angiogram (FA) reveals punctate areas of retinal and choroidal ischemia, with gradual leakage in the peripapillary region in the late frames of the study

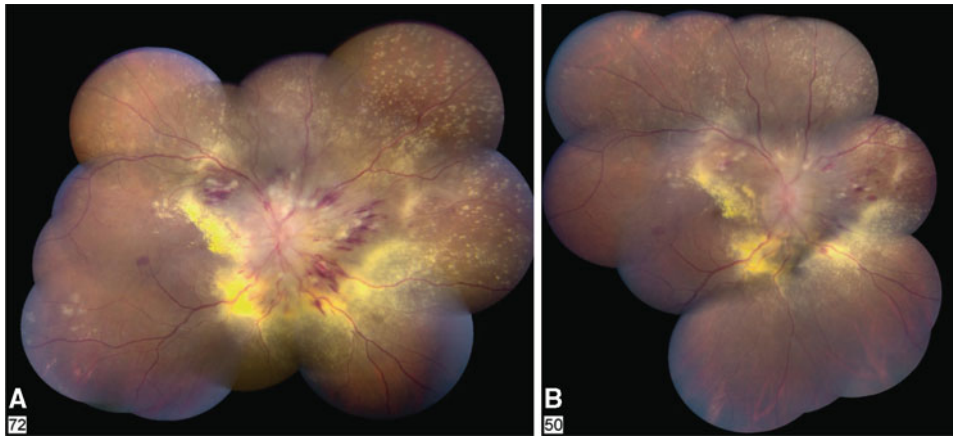

Fig. 25.3 (**a**) Color photograph taken during the third trimester in an eclamptic patient, showing optic disk swelling, peripapillary hemorrhages, and exudate, with areas of choroidal infarction. (**b**) Color photograph taken 2 weeks following delivery, documenting partial resolution of the peripapillary swelling and edema

alterations and optic atrophy may limit the visual acuity [16, 17]. Acute anterior ischemic optic neuropathy (AION) has been reported to occur in severe preeclampsia. The pathophysiology remains speculative [18]. Cortical blindness due to cerebral arteriolar vasospasm and cerebral edema may also be seen in PIH [19, 20]. The vision usually recovers completely.

HELLP Syndrome

In approximately 10% of patients with severe PIH, the HELLP syndrome occurs. The HELLP syndrome, which is characterized by hemolysis, elevated liver enzymes and low platelets, is associated with a poor maternal and fetal outcome. The ocular findings in this disorder include bilateral serous retinal detachments with yellow-white subretinal opacities [21] (Fig. 25.4a, b, c) as well as vitreous hemorrhage [22].

Management of PIH

With regard to the management of PIH, the immediate delivery of the fetus is advantageous to the mother in the majority of cases. However, the maturity of the fetus needs to be taken into account when determining the timing of the delivery. Medical management includes controlling the blood pressure and electrolyte imbalances. The perinatal mortality rate of patients with PIH is 13–30% [23]. Death usually results

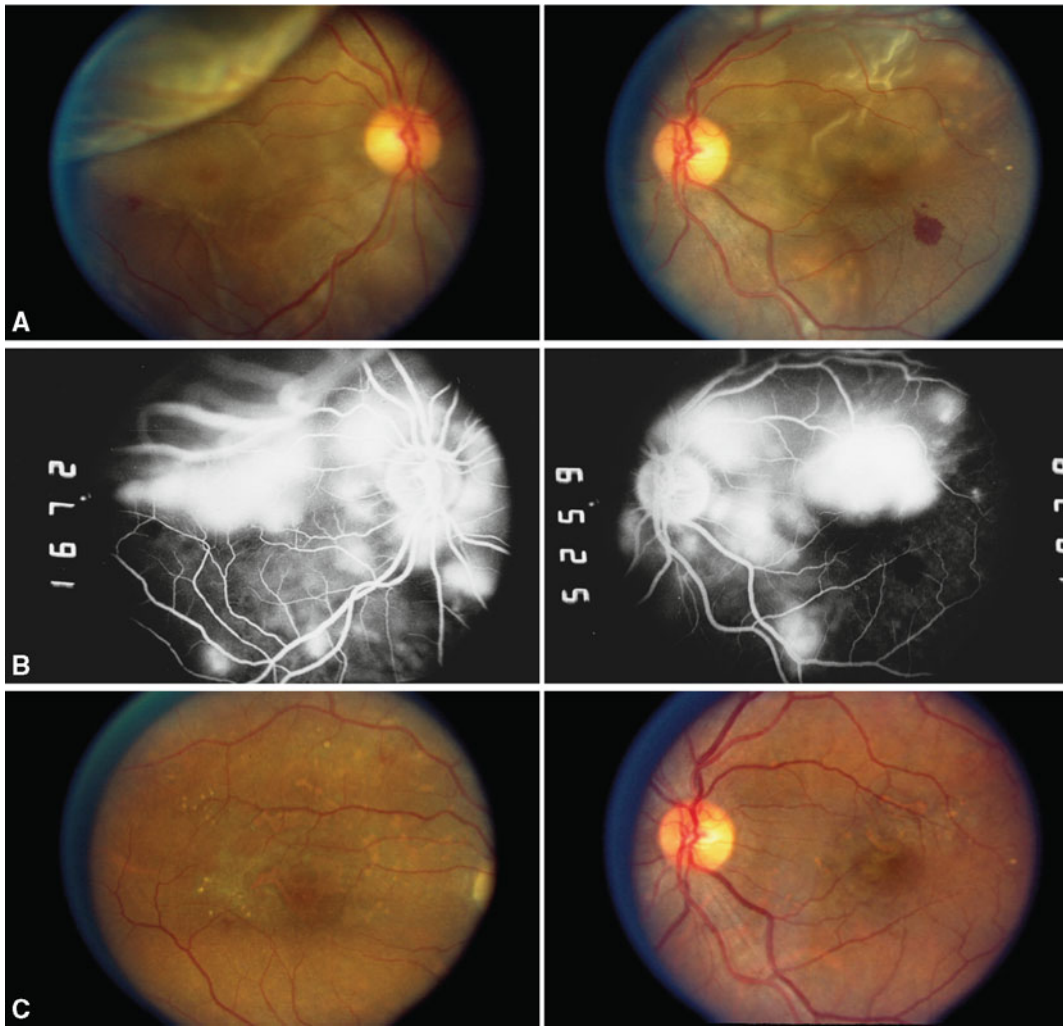

Fig. 25.4 (**a**) Color photographs of a patient with HELLP syndrome, documenting a serous retinal detachment OD, with extensive bilateral choroidal ischemia OU. (**b**) The FA documents numerous foci of choroidal leakage along with areas of peripheral non-perfusion. (**c**) Following delivery, color photographs OU show resolution of the serous retinal detachment OD, though there is residual pigment mottling throughout the posterior pole of both eyes (Photographs courtesy of David Sarraf, M.D., Los Angeles, CA)

from pulmonary edema, central nervous system hemorrhage, or cardiac, liver, or renal failure.

Prognosis

Overall, the incidence of visual and retinal abnormalities has decreased due to the continued improvement in the medical management of PIH. The majority of the ocular abnormalities improve with systemic medical care or with delivery of the fetus.

Central Serous Retinopathy

Central serous retinopathy (CSR) is characterized by a spontaneous, localized serous retinal detachment causing symptoms of decreased vision, metamorphopsia and micropsia. Generally, in the nonpregnant setting, the condition affects males (8–10:1), in the second to fourth decade of life. In pregnancy, there is an increased frequency of CSR, and it has been known to occur in any

trimester [24]. The etiology of CSR in pregnancy is unknown, though hormonal [25], coagulation, and hemodynamic changes may play a role [26].

The presence of subretinal exudates and/or fibrin with the serous retinal detachment is more commonly seen in CSR associated with pregnancy (90%) than in nonpregnant females and males (less than 20%) [27] (Fig. 25.5a–d). This exudate appears white or gray-white and represents fibrin in the subretinal space [27]. The diagnosis can usually be made by clinical presentation; thus, diagnostic fluorescein angiography is rarely necessary, and one can avoid the concerns of obtaining an FA in the setting of pregnancy (see discussion of Diagnostic Agents [fluorescein angiography] at the end of this chapter).

Both the serous detachment and the subretinal exudates tend to resolve near the end of pregnancy or early in the postpartum period. Patients who have experienced an episode of CSR in pregnancy may have a recurrence outside of pregnancy or in a subsequent pregnancy [24] (Fig. 25.5a–d).

Occlusive Vascular Disorders

A variety of occlusive vascular disorders may occur during pregnancy. These disorders include a Purtscher's-like retinopathy or ocular changes associated with disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), and amniotic fluid embolism.

Purtscher's-Like Retinopathy

A Purtscher's-like retinopathy has been reported within 24 h of childbirth [28]. It is usually associated with complications of the late stages of pregnancy, such as preeclampsia or pancreatitis. Patients experience severe, bilateral vision loss shortly after delivery.

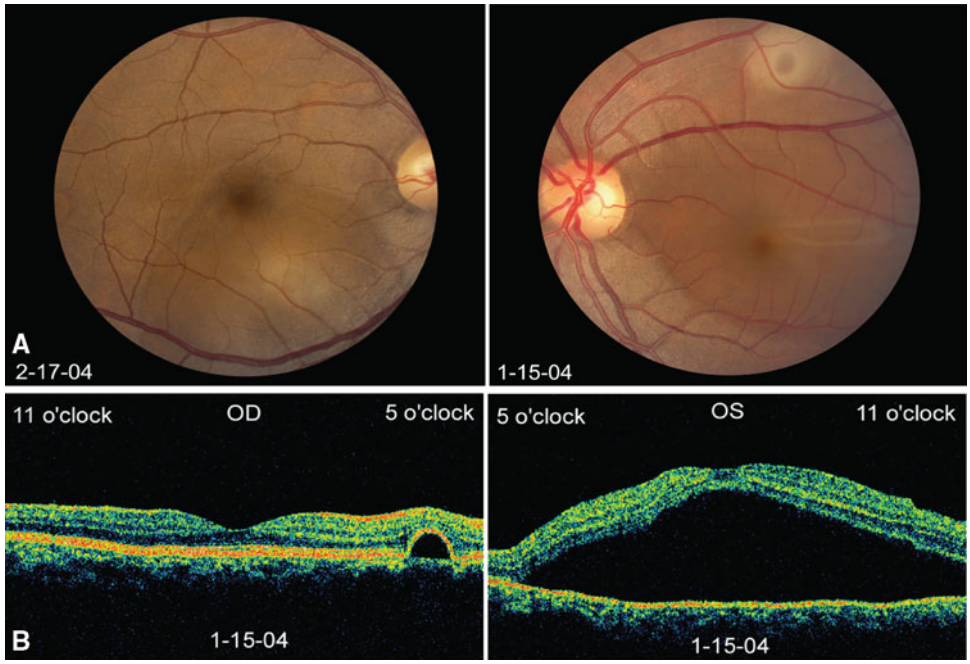

Fig. 25.5 (**a**) Color photographs OU in a female taken near the end of her first trimester. She has bilateral serous retinal detachments, with subretinal fibrin. This was her first pregnancy, and it had been uncomplicated. The visual acuity was 20/25 OD and 20/100 OS. (**b**) Time domain OCTs show a small PED OD and a prominent serous retinal detachment OS. The patient was observed. (**c**) Color photographs show gradual worsening of the serous RD with subretinal fibrin OD, though it normalized early in the postpartum time frame. (**d**) The OCTs also normalized. The visual acuity returned to 20/20 OU within 1 month following delivery of the child

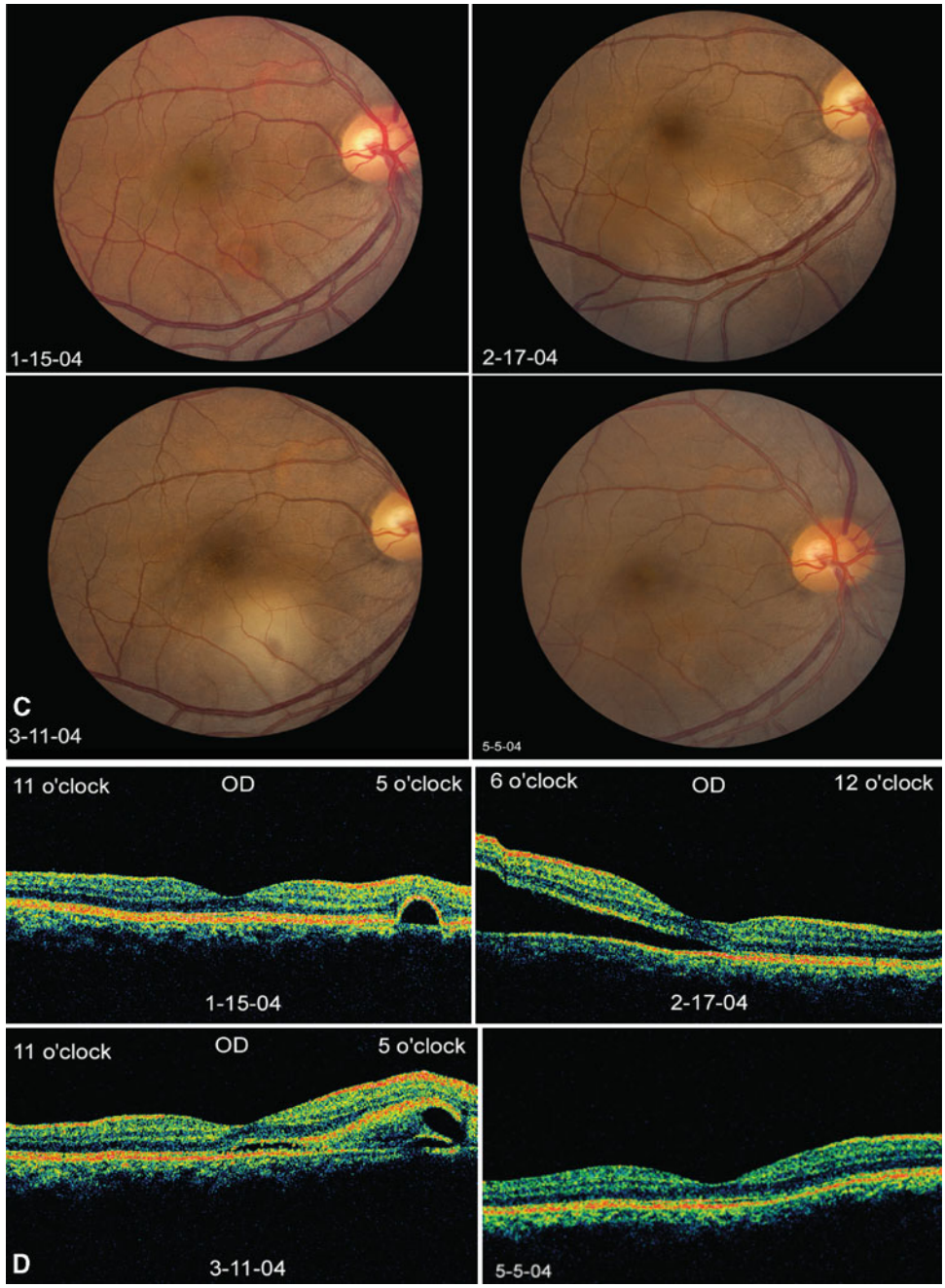

Fig. 25.5 (continued)

Funduscopic changes include widespread cotton-wool spots with or without intraretinal hemorrhages (Fig. 25.6a, b). Fluorescein angiography demonstrates focal areas of arteriolar obstruction and varying degrees of retinal vascular leakage. The retinal changes tend to resolve spontaneously, and vision recovers in most cases. The etiology of this disorder is

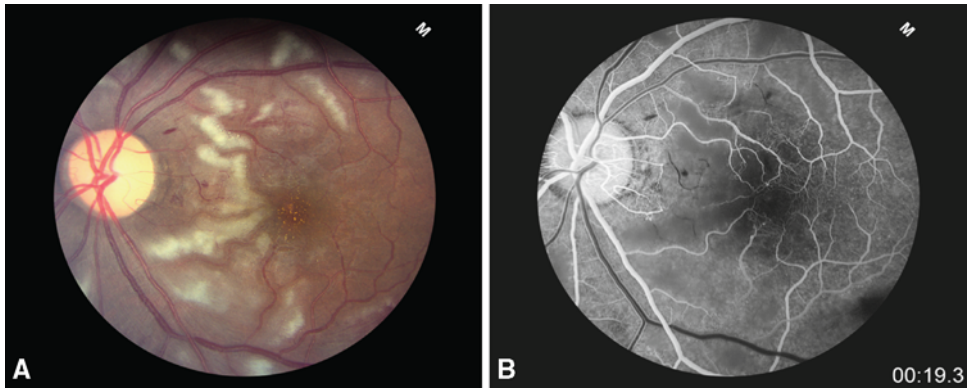

Fig. 25.6 (**a**) Color photograph in a patient with eclampsia, who developed Purtscher's-like retinopathy within 2 days of childbirth, with significant painless loss of vision OU. Multiple peripapillary cotton-wool spots were seen, along with an occasional intraretinal hemorrhage. (**b**) The FA revealed mild areas of capillary non-perfusion. The findings spontaneously improved, and the patient's vision returned to normal

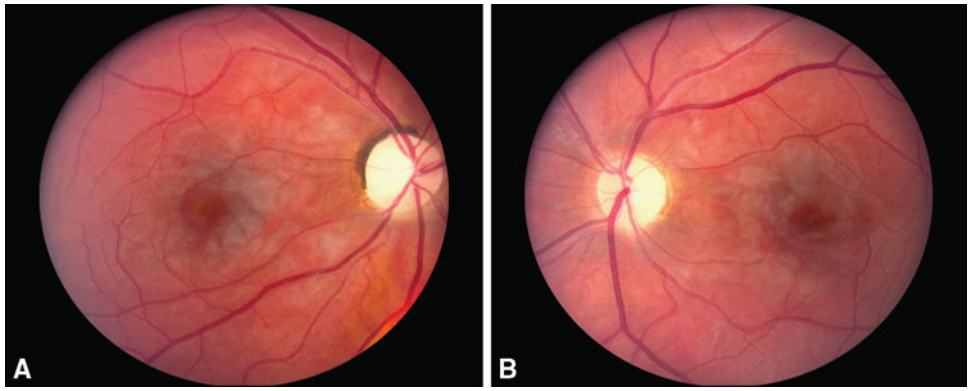

Fig. 25.7 (**a**, **b**) Color photographs OU from a patient who experienced a complicated, induced abortion. She developed disseminated intravascular coagulation (DIC). While photographs were not available during the acute course of the disease, these images are from 2 months later showing residual pigment mottling secondary to areas of presumed choroidal ischemia. Vision was 20/50 OD and 20/60 OS

related to complement-induced granulocyte aggregation and vascular occlusion.

Disseminated Intravascular Coagulation (DIC)

Disseminated intravascular coagulation (DIC) may occur in complicated abortions, abruptio placenta, severe preeclampsia, and retained dead fetus. DIC is characterized by widespread thrombus formation. The choroid is the most common intraocular structure involved [29, 30]. Occlusion of the choriocapillaris by a thrombus leads to disruption of the overlying retinal pigment epithelium causing a serous retinal detachment. With resolution of DIC, the serous detachment resolves. However, residual retinal pigment epithelial changes may be present (Fig. 25.7a, b), and visual recovery may be incomplete.

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) may also be seen in the setting of pregnancy. It is characterized by thrombus deposition in vessels, hemolytic anemia, thrombocytopenia, neurologic changes, fever, and renal dysfunction. Ocular changes in this disorder include retinal vascular occlusions, retinal hemorrhages, serous retinal

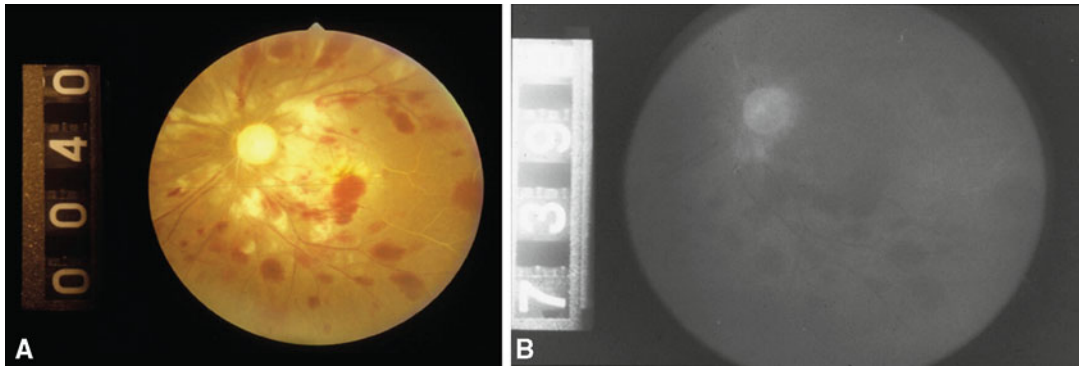

Fig. 25.8 (**a**) Color photograph OS from a patient with thrombotic thrombocytopenic purpura (TTP). The patient experienced severe bilateral loss of vision secondary to occlusive vasculopathy. (**b**) The FA shows virtually complete shutdown of blood flow

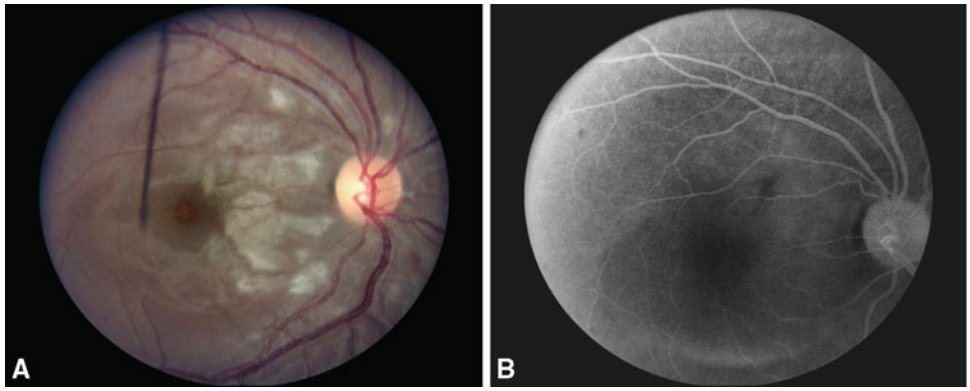

Fig. 25.9 (**a**) Color photograph OD depicting findings from a patient with amniotic fluid embolization. Multiple cotton-wool spots are noted, along with areas of retinal ischemia. (**b**) The FA confirms a moderate degree of capillary non-perfusion

detachments, and optic disk neovascularization [31–34] (Fig. 25.8a, b). A Purtscher's-like retinopathy has also been reported with TTP [35].

Amniotic Fluid Embolism

Amniotic fluid embolism is a serious complication of pregnancy, with an 80% mortality rate. It occurs during labor, delivery, or in the immediate postpartum period. Particulate matter from the amniotic fluid enters the maternal circulation, causing cardiopulmonary failure. Ophthalmic manifestations include retinal artery occlusions [36] and capillary non-perfusion (Fig. 25.9a, b).

Preexisting Conditions

Diabetic Retinopathy

Progression

Pregnancy is a major risk factor for the progression of diabetic retinopathy, as has been reported by Klein and associates [37]. Several studies have outlined the degree of the retinopathy progression during the course of pregnancy [1, 37–40]. Axer-Seigel and coworkers examined 65 patients with insulin-dependent diabetes mellitus who became pregnant [37]. They reported that 26% of

patients without diabetic retinopathy at conception developed mild non-proliferative diabetic retinopathy (NPDR) during the course of pregnancy. Fifty-five percent of patients with initial NPDR had progression of their non-proliferative retinopathy, while 22.5% of patients with initial NPDR progressed to proliferative diabetic retinopathy (PDR) necessitating the need for panretinal photocoagulation.

Both NPDR and PDR occurring during the course of pregnancy have a high rate of spontaneous regression in the third trimester or in the postpartum period. As reported by Axer-Seigel [37], of the patients with no retinopathy at conception who then developed mild NPDR during pregnancy, 50% experienced total regression of their retinopathy and 30% had partial regression of their retinopathy after delivery. The rate of total regression was not as high in patients with more advanced disease at the onset of pregnancy. Total regression was noted in only 17% of patients with NPDR initially who progressed to severe NPDR during pregnancy.

Diabetic macular edema may also occur during pregnancy [41, 42], and as noted with other forms of retinopathy, there is a high rate of spontaneous regression postpartum.

Factors Associated with Progression

The progression of diabetic retinopathy is influenced by various factors, including the duration of diabetes mellitus, metabolic control before and during pregnancy, severity of retinopathy at conception, and the presence of coexisting hypertension. Diabetic retinopathy progression is more likely to occur in pregnant women who have had diabetes for a longer period of time, as is also the case for nonpregnant diabetics [38].

Several studies have also shown that both higher glycosylated hemoglobin levels at conception and rapid tightening of glycemic control during pregnancy have been associated with a higher risk of progression of retinopathy [39, 43]. In contrast, Axer-Seigel and associates found no association between the retinopathy status and the levels of glycosylated hemoglobin at conception or with the institution of tighter metabolic control during the pregnancy [38]. They did note that the glycosylated hemoglobin levels were higher in patients who had progression of their retinopathy as compared to those who did not have progression, but this difference was statistically significant only in the third trimester. Lauszus and coworkers found no association between the progression of retinopathy and the glycosylated hemoglobin [44].

Another factor that influences the progression of diabetic retinopathy during pregnancy is the degree of retinopathy at conception. Those patients with preexisting diabetic retinopathy are at a high risk of progression of their disease during pregnancy [1, 38, 45]. Progression to proliferative retinopathy without the initial presence of non-proliferative retinopathy in early pregnancy is rare but has been reported in three pregnant diabetic patients who were treated with a specific type of insulin, insulin lispro [46].

Finally, both high diastolic and systolic blood pressure have been reported to be associated independently with diabetic retinopathy progression [37, 38].

Pathophysiology of Progression

The pathogenesis for the acceleration of diabetic retinopathy during pregnancy is unclear. Several investigators have studied retinal circulatory changes in diabetic and control subjects during pregnancy. Chen and associates found an increase in retinal blood flow in pregnant women who had worsening of their diabetic retinopathy [47]. In contrast, Schocket and coworkers noted that the retinal venous diameter and retinal blood flow decreased to a greater degree in diabetic mothers compared to nondiabetic mothers [48]. Thus, they proposed that the decrease in blood flow might exacerbate retinal ischemia and hypoxia, leading to the acceleration of diabetic retinopathy.

Treatment Criteria for Diabetic Retinopathy

The treatment of proliferative diabetic retinopathy during pregnancy is based on the same criteria, as defined by the Diabetic Retinopathy Study, as in nonpregnant patients [49]. Diabetic macular edema is often observed without treatment due to

the high rate of spontaneous regression in the postpartum period [50].

Follow-up Guidelines

The American Academy of Ophthalmology has guidelines for the monitoring of pregnant diabetic patients in its Preferred Practice Patterns for diabetic retinopathy [51]. Ideally, pregnant diabetic women should receive an ophthalmologic examination prior to conception and then again in the first trimester. Subsequent exams should be at the discretion of the examiner but at least every 3 months until delivery.

Intraocular Tumors

Uveal Melanoma

The growth of uveal melanomas in pregnancy has been reported [52–54]. Shields et al. reviewed the clinical course of 16 pregnant patients with uveal melanomas [54]. Seven patients were diagnosed with active melanomas at initial presentation and treated immediately. Of the remaining nine patients who had been followed for various lengths of time with suspicious choroidal nevi or dormant uveal melanomas, seven patients demonstrated growth into active melanomas during the course of pregnancy. The histopathology of the tumors in pregnant women was no different than in nonpregnant women. Also, the 5-year survival rate in these women was similar to nonpregnant women with uveal melanomas. The mechanism of tumor growth in pregnancy is not known.

Choroidal Osteoma

There have been several case reports of choroidal osteomas presenting during pregnancy. McLeod described a patient who developed visual blurring during the first trimester of pregnancy due to a juxtapapillary choroidal osteoma [55]. Gass also reported a patient who presented in the ninth month of pregnancy with visual loss due to a choroidal osteoma with an associated choroidal neovascular membrane [56]. The etiology for the exacerbation of the choroidal osteoma during pregnancy is unknown.

Choroidal Hemangioma

The rapid growth of choroidal hemangioma during pregnancy and its subsequent spontaneous regression after delivery have been reported [57].

Ocular Medications

Topical Drops

Topical medications may pass through the placenta or be excreted in breast milk, creating a potential risk to the fetus. Little data has been published regarding the use of topical ophthalmic medications in pregnant or nursing mothers.

There have been no teratogenic effects reported with the use of topical anesthetics [58]. Dilating drops probably should not be used without indication. The systemic use of phenylephrine, atropine, homatropine, and scopolamine has been reported to be associated with minor fetal abnormalities, such as inguinal hernia and club foot [59].

With regards to glaucoma medications, no studies have been performed in pregnant women. All glaucoma medications are category C medications, with the exception of brimonidine and dipivefrin. Category C medications include those for which animal studies have shown adverse effects to the fetus, but no studies in women are present. Category C medications also include those that have not been studied in animals or humans. A case report has been described of a patient using timolol 0.25% during the second and third trimester without adverse effects on the pregnancy [60]. Topical timolol is secreted in breast milk and should be avoided in nursing mothers [61].

Brimonidine and dipivefrin are category B medications. These drugs have been tested in animals and revealed no harm to the fetus. However, no controlled studies have been performed on pregnant women.

In general, all routine and nonessential medications should be avoided during pregnancy. The decision to use medications, with the potential risks and benefits, should be reviewed with the patient. If administration is

required, then nasolacrimal sac occlusion should be performed to limit the systemic absorption of the medication.

Diagnostic Agents

Fluorescein dye crosses the placenta and is present in breast milk for at least 3 days after administration [62]. No teratogenic or embryocidal effects have been reported in animals [63, 64]. Also, no adverse effects have been reported in humans. Halperin and coworkers reviewed the use of fluorescein angiography in pregnant patients [65]. A retrospective study of neonatal outcomes in 105 pregnant patients who underwent fluorescein angiography revealed that there was not a high rate of birth anomalies or complications. Nonetheless, most vitreoretinal specialists likely would avoid obtaining an angiogram during pregnancy unless a sight-threatening lesion, such as a choroidal neovascular membrane, is suspected.

Indocyanine green (ICG) has been used in pregnant women for non-ophthalmic purposes, such as for measuring hepatic blood flow, without adverse effect on the mother or fetus. It does not cross the placenta, and it is not known whether it is present in breast milk [66]. Fineman and coworkers conducted a survey of 1,101 members of the Retina, Macula, and Vitreous Societies regarding the use of ICG in pregnant women [67]. The survey revealed that there is widespread hesitation to use ICG for retinal angiography in pregnant women, despite its documented safety when used for non-ophthalmic purposes.

Summary

Pregnancy may be associated with a variety of ocular manifestations. The majority of these changes resolve after pregnancy, though occasionally, they may lead to permanent visual impairment. An understanding of these changes will help to establish the diagnosis as well as to plan the optimum treatment regimen when evaluating the pregnant female.

Focal Points

- Hypertensive-related conditions are the most commonly encountered abnormalities during pregnancy (pregnancy-induced hypertension, preeclampsia, eclampsia, HELLP syndrome).
- Pregnancy may exacerbate preexisting conditions, particularly diabetes mellitus, or may cause new conditions to arise such as central serous choroidopathy.
- A variety of vascular occlusive disorders may rarely be encountered (DIC, TTP).

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Retinal and Choroidal Manifestations of Systemic Medications

26

Stephen G. Schwartz and William F. Mieler

Abstract

Retinal and choroidal manifestations/toxicity may be seen in patients exposed to a variety of systemic medications. Toxicity may manifest itself via a variety of means, including disruption of the retina and retinal pigment epithelium, vascular damage, cystoid macular edema, retinal folds, crystalline retinopathy, uveitis, and subjective visual changes (without objective findings). Examples of all of these forms of toxicity will be presented. With a high index of suspicion, the correct diagnosis can almost always be established.

Keywords

Retinal and choroidal toxicity • Diffuse retinal pigment epithelium changes • Vascular damage • Cystoid macular edema • Retinal folds • Crystalline maculopathy • Uveitis • Subjective visual changes without objective findings

Introduction

Posterior segment toxicity is a rare but important potential complication of certain systemic medications. Retinal and choroidal toxicity may be associated with permanent visual loss or may represent potentially severe systemic complications. Timely diagnosis, and discontinuation of the inciting agent, may restore vision and in some cases improve overall health.

In this chapter, retinal and choroidal toxicities are divided primarily into one of the following categories: diffuse retinal changes, crystalline deposits, subjective visual changes without objective findings, primarily vascular changes, primarily macular changes, and particular syndromes including induced retinal folds.

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Toxicity with Diffuse Retinal Changes

Toxicity with Pigmentary Degeneration

Quinolines

Chloroquine (Aralen, Sanofi Winthrop Pharmaceuticals, New York, NY), a member of the quinoline family of agents, and the less toxic derivative hydroxychloroquine (Plaquenil, Sanofi Winthrop Pharmaceuticals, New York, NY) are antimalarial agents also used to treat certain rheumatologic diseases.

Quinoline retinal toxicity has been recognized for over 50 years [1–4]. Initially, the patient may be asymptomatic, and the first sign may be a loss of the foveal light reflex. Verticillata-like changes of the cornea may be noted. Nonspecific macular pigmentary alterations typically ensue, ultimately leading to the classic bull's eye lesion (Fig. 26.1a, b). In advanced cases, diffuse retinal pigmentary changes may develop, associated with retinal vascular attenuation and optic atrophy (Fig. 26.2a–d).

In mild cases, discontinuation of the agent may cause stabilization or even amelioration of toxicity, although patients with more advanced disease may continue to progress [5]. Quinolines are associated with an exceptionally long clearance time [6], and toxicity 7 years following discontinuation of chloroquine has been reported [7].

In 2002, a task force of the American Academy of Ophthalmology (AAO) established guidelines for screening patients being treated with quinoline antimalarials, particularly hydroxychloroquine. The task force recommended risk stratification based on a baseline examination, including assessment of daily dosage, dilated fundus examination, and either Amsler grid testing or automated macular perimetry [8]. Patients being treated with a daily dose less than 3 mg/kg of chloroquine or 6.5 mg/kg of hydroxychloroquine, with no other systemic or ocular risk factors, were considered unlikely to develop retinal toxicity and could be followed as per the AAO Preferred Practice Patterns for otherwise healthy adult patients [9]. The daily dose should be calculated based on ideal body weight, rather than actual weight, because quinolones are stored to a greater degree in lean body tissues. Obese patients may require more frequent monitoring [10].

These guidelines are well established and straightforward, but there appear to be challenges in their practical implementation. In one study, about one-third of patients being treated with hydroxychloroquine had not received an eye examination [11]. More recently, screening roles have been proposed for spectral domain optical coherence tomography (OCT) [12], fundus autofluorescence [13], and multifocal electroretinography (ERG) [14]. The precise roles of these ancillary tests are yet to be fully determined, along with microperimetry.

In early 2011, the screening guidelines for monitoring patients on hydroxychloroquine were updated by a task force from the American Academy of Ophthalmology [15]. These guidelines included recommendation of a baseline

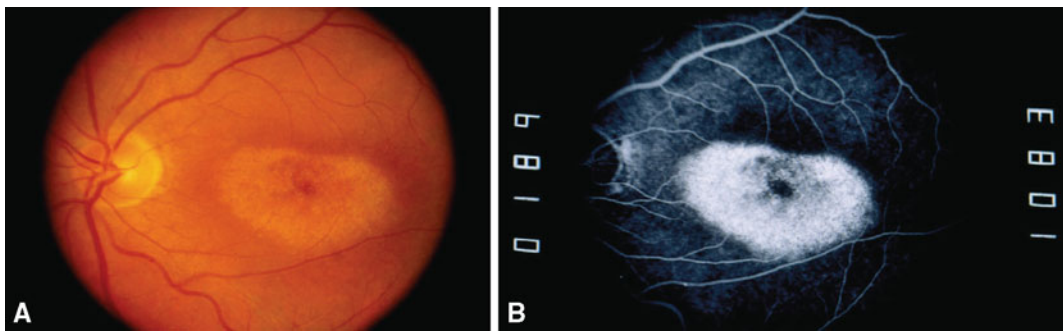

Fig. 26.1 (**a**) Color photograph showing a typical bull's eye form of maculopathy secondary to chloroquine. (**b**) Fluorescein angiogram (FA) depicting a transmission defect highlighting the area of pigment loss

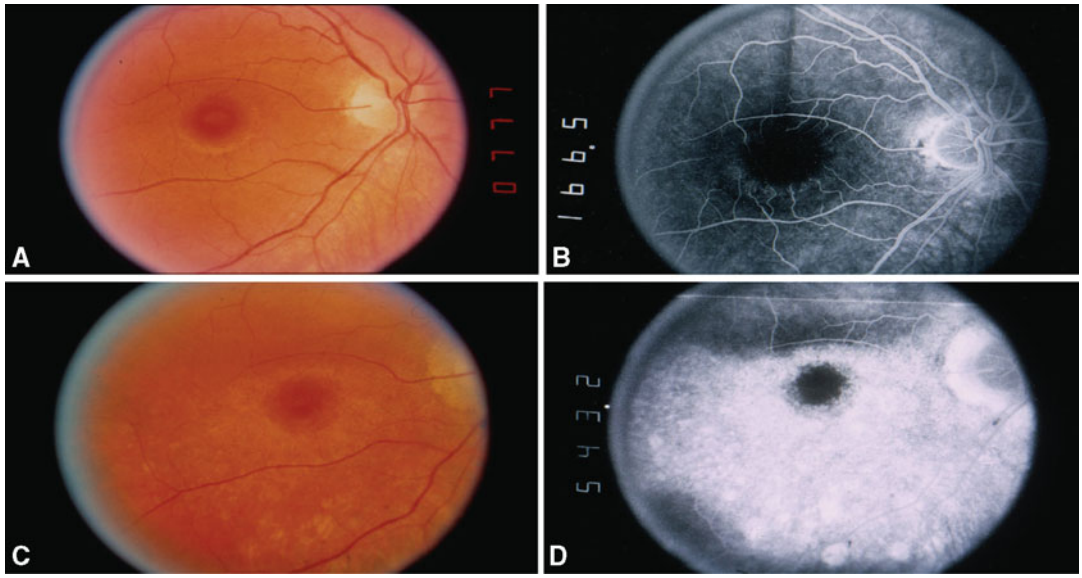

Fig. 26.2 (**a**) Color photograph showing a bull's eye pattern of maculopathy. (**b**) Corresponding FA highlighting the area of pigment loss. (**c**) Color photograph of the same patient several years later, having been off of chloroquine in the interim, documenting progression of disease even in the absence of supplemental medication. (**d**) FA highlighting the expanded area of pigment loss

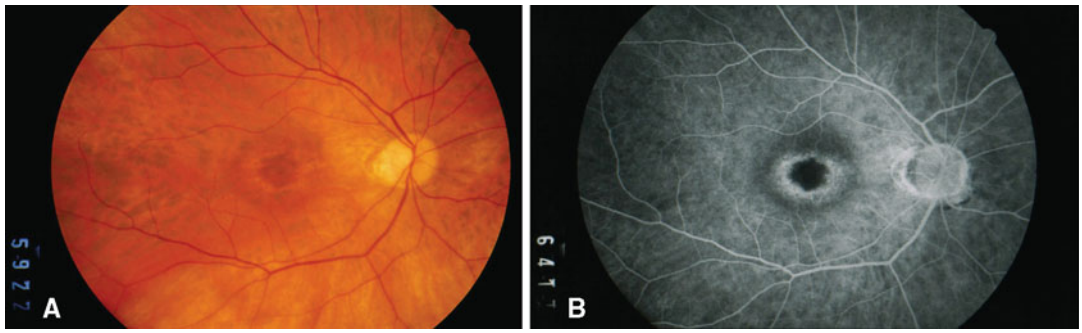

Fig. 26.3 (**a**) Color photograph of hydroxychloroquine toxicity, (**b**) with associated FA. The patient had been treated with a standard dosage of 400 mg/day, for approximately 5 years, and the patient was of short stature

examination performed at the commencement of therapy. Screening examinations during the first 5 years of therapy can be performed during routine ophthalmic examination (interval to be determined by the age of the patient and the presence or absence of retinal or macular disease). Earlier recommendations emphasized dosing by weight, as most patients are given 400 mg/day of hydroxychloroquine. This dose is generally acceptable for all patients except for those of short stature (generally 5 ft 2 in. or less in height). These patients should be given a dose based on their ideal body weight, as otherwise overdosage may occur (Fig. 26.3a, b). Furthermore, the dosage may need to be altered if the patient has renal or liver dysfunction.

After 5 years of therapy, screening should be performed at least annually. Current guidelines are centered around tests found to detect early toxicity often prior to any appreciable fundus findings. Patients should have a Humphrey 10-2 automated visual field (HVF) test with a white

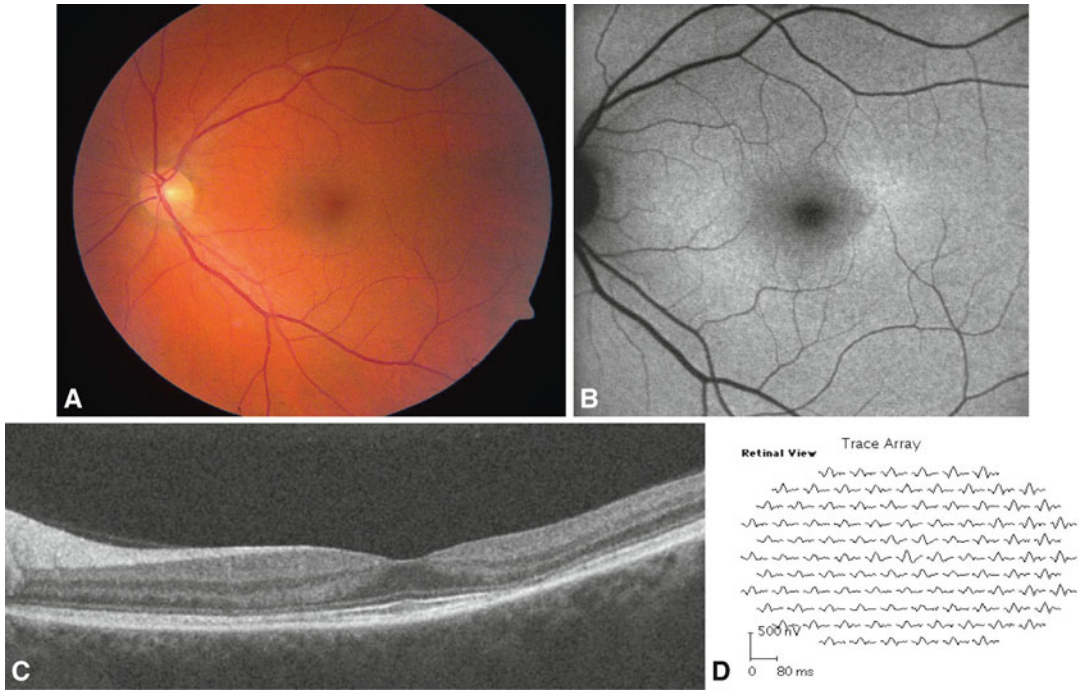

Fig. 26.4 Screening tests for hydroxychloroquine toxicity. (**a**) Color photograph showing very minimal macular pigment mottling in a patient on hydroxychloroquine for 5 years. (**b**) Fundus autofluorescence shows a minimal degree of abnormality in the macular region. (**c**) Spectral domain OCT shows minimal disruption of the inner segment/outer segment (IS/OS) junction. (**d**) Multifocal ERG (D) shows normal waveforms (Images courtesy of Michael Marmor, M.D., Stanford, CA)

test object and in addition should have one of three objective tests at each screening: spectral domain OCT (SD-OCT), multifocal electroretinogram (mfERG), and/or fundus autofluorescence (FAF) (Fig. 26.4a–d). Any abnormalities of the pattern deviation on the HVF need to be taken seriously. In most situations, SD-OCT should also be obtained. While abnormalities on FAF are generally associated with concerns for active disease, the test has not yet been shown to be reliably predictable as a screening tool for future toxicity. While mfERG is most likely the most sensitive test, it is still not uniformly available to all patients.

As noted in the preceding paragraph, it is imperative to discuss the risk of toxicity with patients and the rationale for screening (to detect, but not necessarily prevent visual loss). If ocular toxicity occurs and is recognized at an early stage, efforts should be made to communicate this directly to the prescribing physician so that alternative treatment options can be discussed with the patient. In almost all cases, cessation of the drug should be suggested.

The related medication quinine (Quinamm, Marion Merrell Dow, Inc., Kansas City, MO) is used to treat benign nocturnal muscle cramps and may be associated with distinct toxicity. Acute overdose is associated with headache, nausea/vomiting, tremor, hypotension, and loss of consciousness, associated with severe visual loss [16]. Acutely, there may be mild retinal edema with mild venous dilation. Over several weeks, arteriolar attenuation and optic atrophy develop (Fig. 26.5a, b). Diffuse retinal damage is indicated by abnormalities on full-field ERG and other electrophysiologic tests [17, 18]. More recently, it was reported that therapeutic doses of quinine used to treat cerebral malaria in children were associated with asymptomatic and transient evidence of photoreceptor dysfunction, as measured by full-field ERG [19].

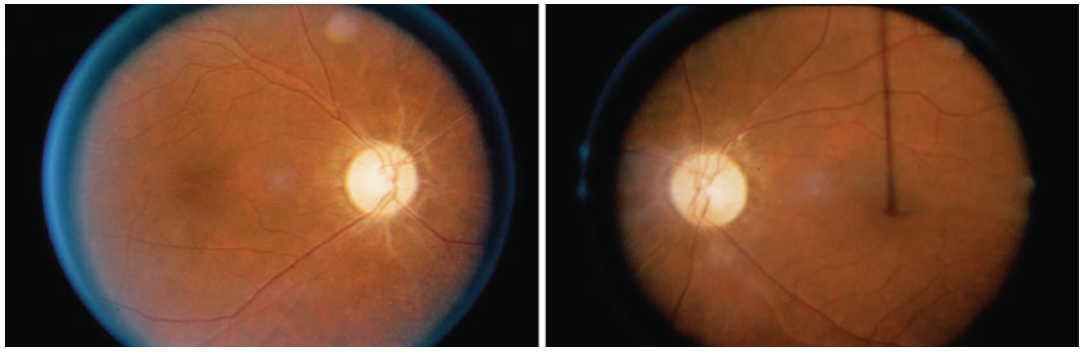

Fig. 26.5 Color photographs, showing late-onset optic disk pallor, along with vascular attenuation. The photos were taken 2 months after intentional overingestion of quinine in an attempted suicide

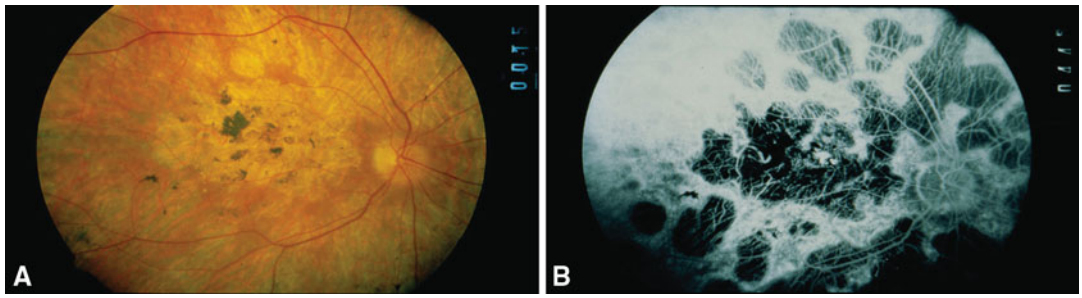

Fig. 26.6 (**a**) Color photograph showing intermediate thioridazine toxicity with nummular areas of pigment loss. (**b**) FA highlights areas of central and peripheral loss of retinal pigment epithelium and choriocapillaris

Phenothiazines

Historically, the phenothiazines were commonly used antipsychotic medications. The piperidine phenothiazines, such as thioridazine (Mellaril, Sandoz Pharmaceuticals, East Hanover, NJ), are associated with a characteristic retinal toxicity. Symptoms include impaired vision, nyctalopia, and dyschromatopsia (red or brown) [20]. Early signs include nonspecific macular pigmentary changes, which may progress to widespread, nummular atrophy of the retinal pigment epithelium (RPE) and choriocapillaris [21] (Fig. 26.6a, b). Advanced cases may manifest diffuse retinal pigmentary alterations with vascular attenuation and optic atrophy [22] (Fig. 26.7a, b). Discontinuation of the medication in milder cases may allow for stabilization or improvement of vision. In some cases, visual loss may continue to progress due to a continued decline of previously damaged retinal tissue [23]. For example, a recent report documented progressive visual loss 30 years after discontinuing thioridazine [24].

Deferoxamine

Deferoxamine (desferrioxamine, Desferal, Novartis, East Hanover, NJ) chelates iron and aluminum and is used to treat patients receiving repeated blood transfusions. Toxicity is unusual but generally manifests as decreased vision, nyctalopia, and visual field loss [25]. Initially, a gray discoloration of the macula may progress to diffuse pigmentary changes [26, 27] (Fig. 26.8a, b). A single dose may cause toxicity [28]. Visual loss typically resolves after discontinuation of the medication [29], but persistent visual loss has been reported [30].

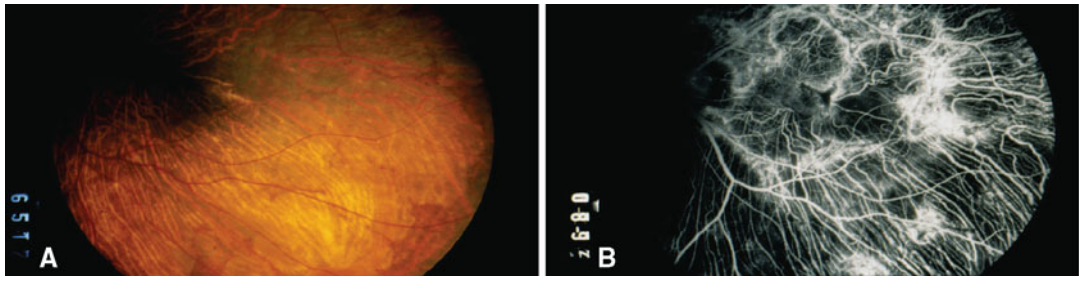

Fig. 26.7 (**a**) Color photograph showing end-stage thioridazine toxicity with diffuse loss of pigmentation. (**b**) FA shows diffuse atrophy of the retinal pigment epithelium and choriocapillaris, optic atrophy, and vascular attenuation. This severe end-stage disease resembles ocular findings seen in choroideremia

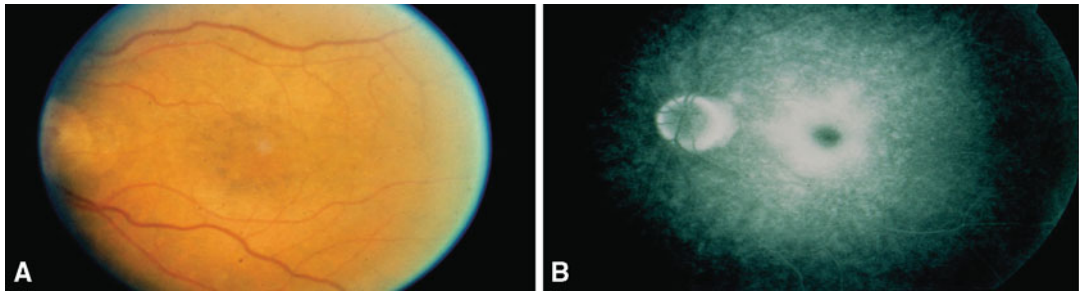

Fig. 26.8 (**a**) Color photograph of deferoxamine toxicity showing diffuse pigment mottling with mild grayish discoloration. (**b**) FA documenting diffuse pigmentary retinopathy with macular and retinal edema

Toxicity with Crystalline Deposits

Tamoxifen

Tamoxifen (Nolvadex, AstraZeneca, Wilmington, DE), an estrogen antagonist, is commonly used in the treatment of metastatic breast adenocarcinoma and more recently has been used at a higher dosage in the treatment of advanced glioblastoma. Toxicity is frequently asymptomatic, but may cause vision loss with dyschromatopsia [31]. White refractile deposits appear in the posterior pole (Fig. 26.9a, b), which may be associated with pigmentary changes and, in advanced cases, cystoid macular edema (CME) with angiographic leakage (Fig. 26.10). In patients receiving high-dose tamoxifen, peripheral retinal crystals may also develop [32].

Asymptomatic crystals may be observed closely, but discontinuation of the medication is generally recommended in patients with CME or visual loss [33]. The successful use of intravitreal pegaptanib (Macugen, Eyetech, New York, NY) and/or bevacizumab (Genentech, South San Francisco, CA) to treat CME associated with tamoxifen retinopathy has been reported [34].

Canthaxanthine

Canthaxanthine (Orobronze, Dewitte, Greenville, SC) is a carotenoid pigment used therapeutically for vitiligo and photosensitivity disorders. In some nations, the drug is sold as an over-the-counter oral tanning agent. Toxicity may be asymptomatic, but a ring of yellow-orange crystals is noted in the macula [35], (Fig. 26.11) associated with various abnormalities in electrophysiologic testing [36]. Imaging of the crystals with spectral domain OCT has been reported [37]. Upon discontinuation of the medication, the crystals typically resorb and the electrophysiologic parameters improve [38].

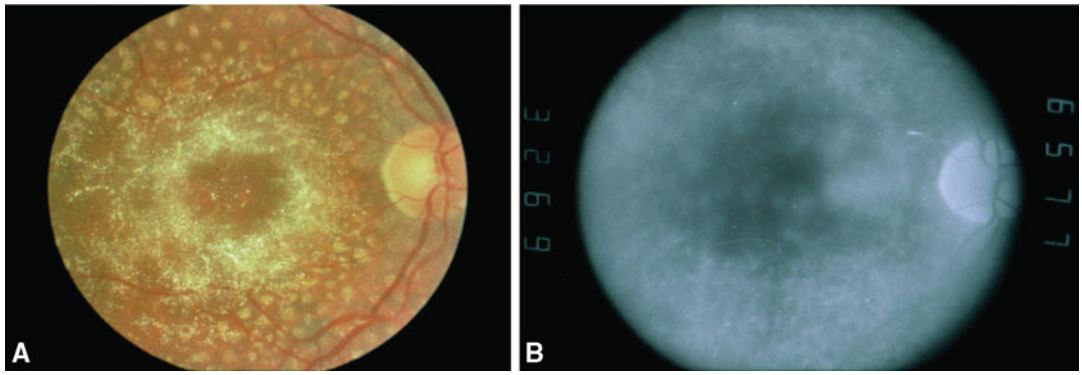

Fig. 26.9 (**a**) Color photograph showing a central perifoveal ring of tamoxifen-induced retinal crystals. (**b**) FA showing mild associated macular edema (though crystals are not seen). The patient was visually asymptomatic

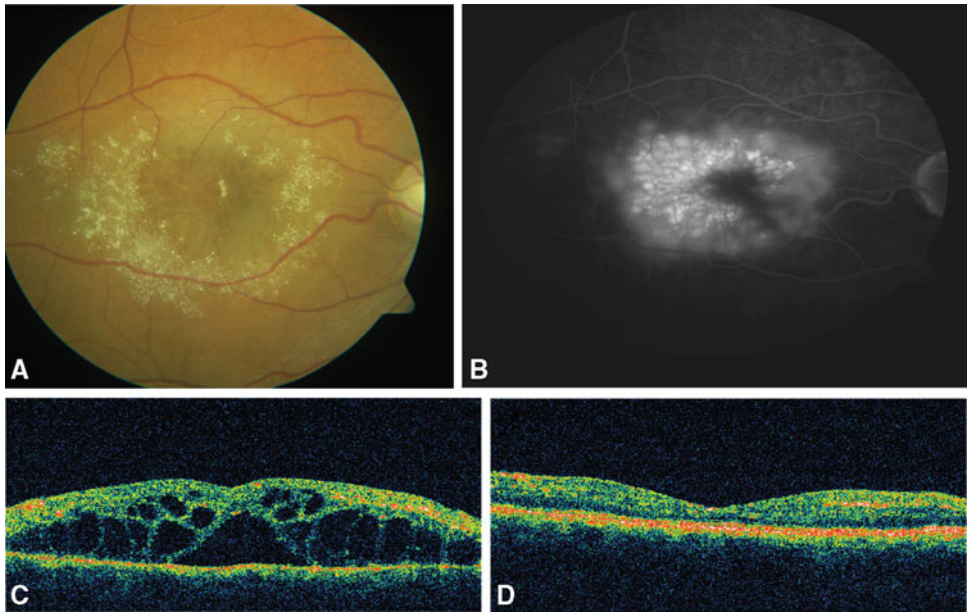

Fig. 26.10 (**a**) Color photograph of tamoxifen crystalline retinopathy in a patient with advanced glioblastoma being treated with high-dose tamoxifen. (**b**) FA documents diffuse cystoid macular edema (CME). (**c**) Time domain OCT confirms the findings of diffuse CME, while (**d**) a follow-up OCT several months later, following administration of intravitreal bevacizumab, shows resolution of the CME. The findings were bilateral (Images courtesy of David Sarraf, M.D., Los Angeles, CA)

Methoxyflurane

The inhalational anesthetic methoxyflurane (Penthrane) is rarely used today in the USA because of an associated renal toxicity characterized by deposition of calcium oxalate crystals in the renal tubules [39]. Similarly, methoxyflurane is associated with a yellow-white crystalline retinopathy. The crystals predominate in the macular area and along the arterioles, sometimes associated with cotton-wool spots [40, 41].

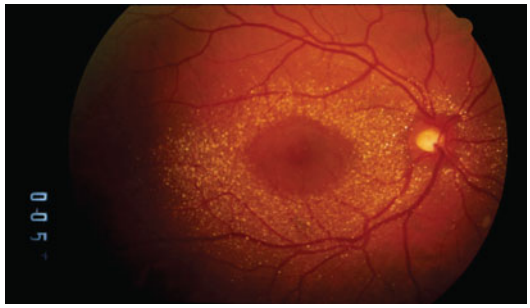

Fig. 26.11 Color photograph of canthaxanthine retinopathy. Prominent perifoveal punctate *yellow* deposits in a doughnut-shaped ring surrounding the macula (findings were bilateral)

Toxicity Without Fundus Changes

Cardiac Glycosides

The first published report associating xanthopsia with foxglove (*Digitalis purpurea*) was published in 1785 [42]. Modern cardiac glycosides, including digoxin (Lanoxin, GlaxoSmithKline, Brentford, Middlesex, UK), are associated with the same toxicity. Visual acuity may be reduced, and color vision is usually diminished. The examination is typically normal, but the full-field ERG shows characteristic and reversible abnormalities [43].

Phosphodiesterase Inhibitors

The phosphodiesterase (PDE) inhibitors sildenafil (Viagra, Pfizer, Inc., New York, NY), tadalafil (Cialis, Lilly, Indianapolis, IN), and vardenafil (Levitra, Bayer, Leverkusen, Germany) are widely used to treat erectile dysfunction. These agents inhibit PDE-5 in the penile corpora cavernosa but also act against PDE-6 in the photoreceptors [44]. A single therapeutic dose may cause reversible dyschromatopsia with full-field and multifocal ERG changes [45, 46]. Typically, the fundus examination is normal, but these agents are infrequently associated with retinal vascular occlusion [47], nonarteritic anterior ischemic optic neuropathy (NAION) [48], and other objective findings. A recent review of clinical trials data reported no statistically significant association between PDE inhibitor use and NAION or other adverse ocular events [49]. Long-term PDE inhibitor use typically causes no permanent visual loss [50], but patients with preexisting retinal disease may be at increased risk [51].

Toxicity with Retinal Edema

Methanol

Methanol has no indications for internal use, but is occasionally abused as an intoxicant or during a suicide attempt. Methanol ingestion is associated with severe visual loss, associated initially with retinal and optic disk edema, progressing to optic atrophy [52–54].

Toxicity with Retinal Vascular Changes

Talc

Magnesium silicate (talc) is used as a vehicle in the manufacture of many oral medications. Occasionally, patients abuse these medications by dissolving them and injecting them intravenously. When this occurs, talc enters the systemic vascular system and may enter the retina. Initially, small talc particles will traverse the pulmonary capillary network and enter the arterial system (Fig. 26.12). Chronic injection of talc may cause arteriovenous shunt formation in the lungs, so even relatively large talc particles may enter the retinal circulation [55, 56].

Initially, talc emboli may be asymptomatic [57], but repeated exposure may lead to a relatively typical ischemic retinopathy with capillary nonperfusion, microaneurysms, cotton-wool spots, and eventually retinal neovascularization [58–60].

Oral Contraceptives

Oral contraceptives are associated with retinal thromboembolic events, including retinal vascular occlusions [61] (Fig. 26.13). These complications

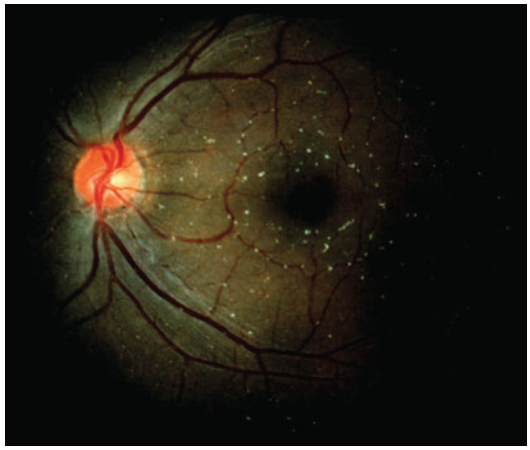

Fig. 26.12 Color photograph of talc retinopathy. Characteristic perifoveal *yellow-white* intra-arterial glistening crystals

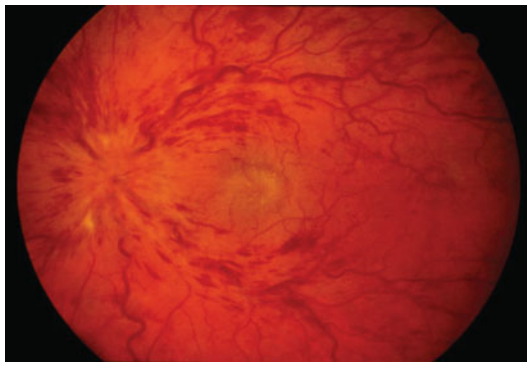

Fig. 26.13 Color photograph of a nonischemic central retinal vein occlusion (CRVO) in a 40-year-old hypertensive female on oral contraceptives. Upon stopping the oral contraceptives, the CRVO resolved without treatment

were more common with older medications, which contained higher concentrations of synthetic hormones [62, 63].

Interferon

The antivirals interferon alpha-2a (Roche Pharmaceuticals, Nutley, NY) and alpha-2b (Schering Corporation, Kenilworth, NJ) are used to treat chronic hepatitis and various malignancies. These agents are associated with a generally mild retinal vascular toxicity consisting of normal vision, cotton-wool spots, and intraretinal hemorrhages [64]. Visual loss may occur secondary to retinal vascular occlusion [65], CME [66], or NAION [67] (Fig. 26.14a, b). Systemic vascular disease, such as diabetes mellitus, increases the risk of interferon-associated retinopathy [68]. Successful treatment of retinopathy by lowering the blood pressure, without discontinuing the medication, has been recently reported [69].

Toxicity with Maculopathy

Niacin

Niacin (nicotinic acid, vitamin B3) is used to treat hyperlipidemia and hypertriglyceridemia. It causes a characteristic that resembles CME clinically and by OCT, but lacks fluorescein leakage on angiography [70, 71]. This pseudo-CME may be caused by intracellular fluid accumulation, as opposed to true edema, which is in the extracellular space [72] (Fig. 26.15).

Sympathomimetics

Intravenous sympathomimetics, including epinephrine, may be associated with a clinical picture similar to idiopathic acute macular neuroretinopathy [73, 74]. Visual loss or paracentral scotomas may occur, and reddish-brown wedge-shaped lesions may develop in the outer retina (Fig. 26.16). Toxicity may occur even with normal blood pressure [75].

Toxicity with Retinal Folds

Sulfanilamide-Like Medications

Several related medications may be associated with a syndrome including ciliary body swelling, choroidal effusion, and anterior displacement of the lens-iris diaphragm. Anterior segment complications include nonpupillary block angle closure, and posterior segment complications include induced myopia and retinal folds. The fluorescein angiogram shows no vascular leakage, indicating

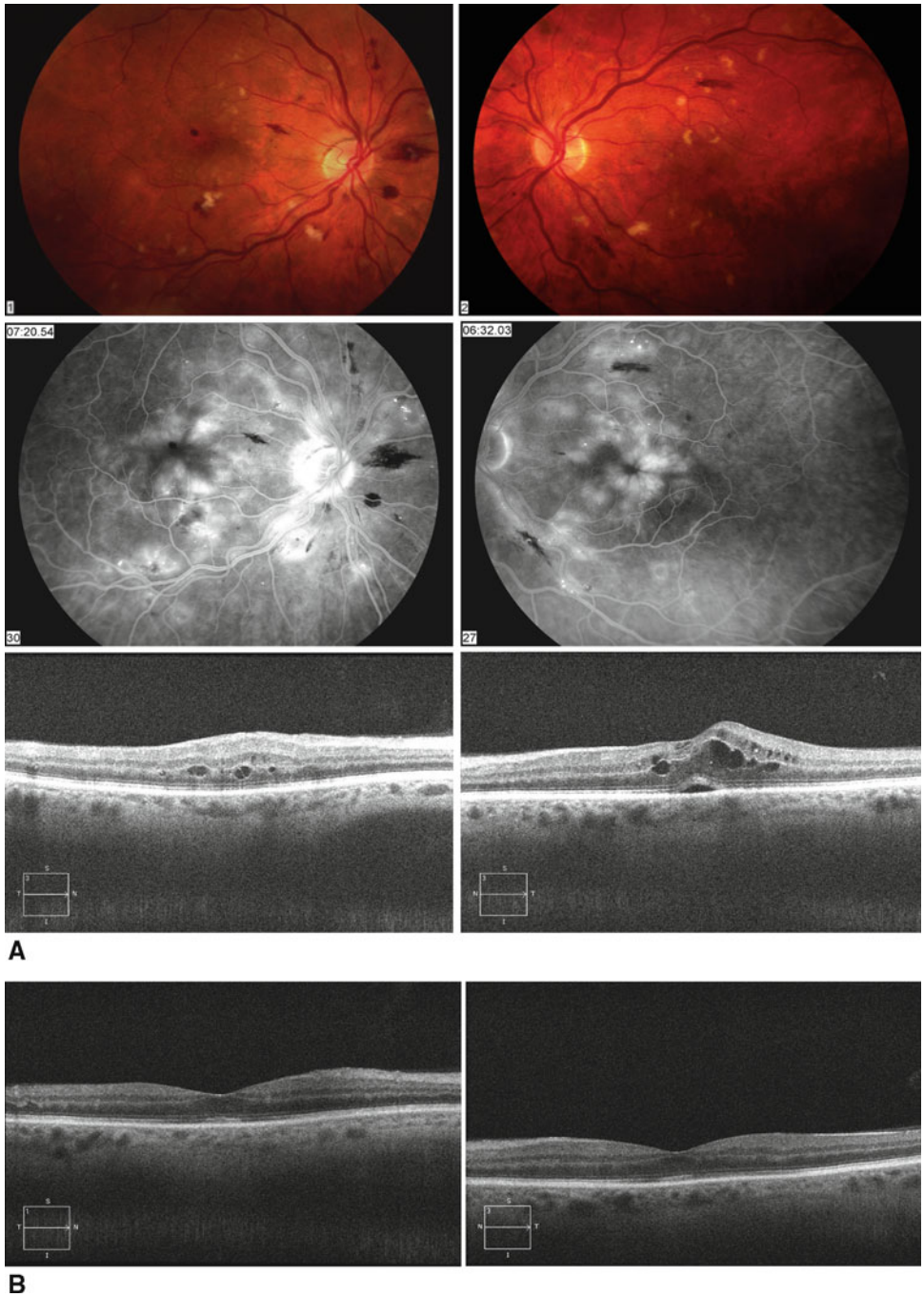

Fig. 26.14 (**a**) Color photograph and FA of a patient on interferon for treatment of hepatitis C, showing multiple cotton-wool spots and microangiopathy, and the SD-OCT documents mild cystoid macular edema. (**b**) Once the interferon was discontinued, 1 week later, the SD-OCT documents resolution of the CME (Images courtesy of Joseph Maguire, M.D., Philadelphia, PA)

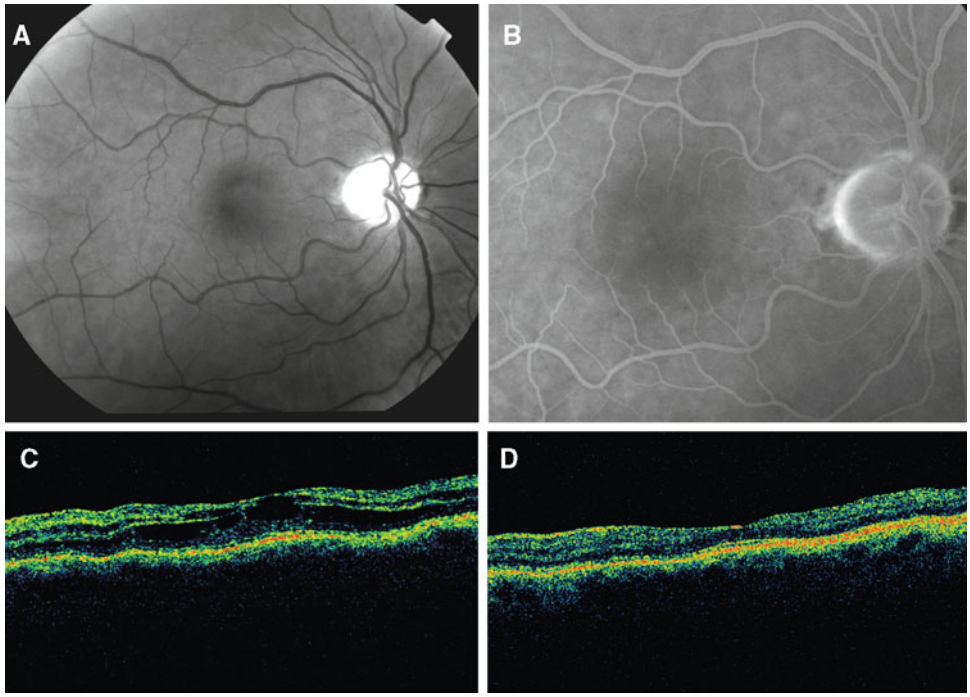

Fig. 26.15 (**a**) Red-free photograph of nicotinic acid maculopathy showing a blunted foveal reflex, while (**b**) the FA shows very minimal late leakage. (**c**) Time domain OCT reveals mild macular edema. (**d**) The nicotinic acid was discontinued, and 2 weeks later, the time domain OCT returned to normal. The findings were bilateral (Images courtesy of Lawrence A. Yannuzzi, M.D., New York City, NY)

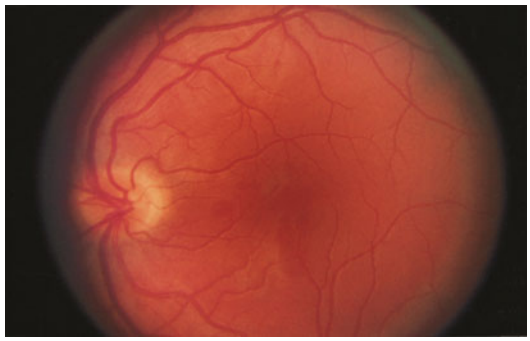

Fig. 26.16 Color photograph showing *reddish wedge-shaped* macular lesions in a patient exposed to intravenous sympathomimetic agents. The patient noted transient visual blurring

that the folds are caused by vitreous traction on the macula during axial elongation of the eye (Fig. 26.17a, b). Medications with a reported association with this syndrome include sulfanilamide [76], acetazolamide (Diamox, Lederle Pharmaceuticals, Inc., Pearl River, NJ) [77], metronidazole [78], hydrochlorothiazide [79], and topiramate (Topamax, Ortho-McNeil, Raritan, NJ) [80].

Summary

Pharmacologic retinal toxicity remains an unusual but important cause of visual morbidity. A high index of suspicion is necessary to make the proper diagnosis. Prompt recognition of toxicity, and discontinuation of the medication, may preserve vision and improve overall health in many of the cases.

Focal Points

- Certain systemic medications are associated with retinal or choroidal toxicity.
- Toxicity may manifest with generalized retinal pigment epithelial changes, vascular damage,

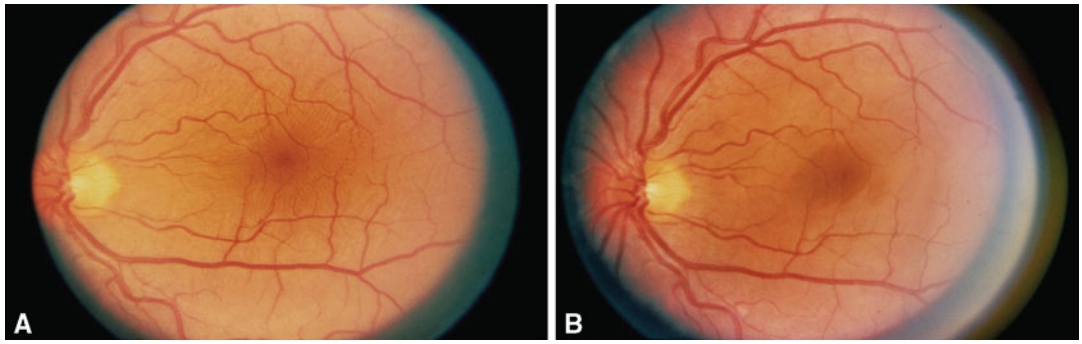

Fig. 26.17 (**a**) Color photograph of retinal folds induced by exposure to chlorthalidone. (**b**) Follow-up color photograph 2 weeks after discontinuation of the medication documents resolution of the folds

cystoid macular edema, retinal folds, uveitis, crystalline maculopathy, and with subjective visual symptoms.

- Discontinuation of the medication frequently, but not always, leads to stabilization or improvement of vision.
- Progression of ocular findings may be seen even after cessation of therapy with the quinolines.

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Retinal and Choroidal Manifestations of Renal Diseases

27

Leigh H. Spielberg and Anita M. Leys

Abstract

From widespread afflictions such as diabetes and hypertension to rare conditions like the ciliopathies, the kidney and retina are frequently affected by the same diseases. Factors ranging from genetic abnormalities and metabolic defects to vascular stress and neoplasia can have deleterious influence on these organs' structure and function. This chapter will discuss the pathological processes that link the kidney and the retina, focusing particularly on the identification of these conditions in a clinically relevant manner.

Keywords

Retinal disease • Choroid • Kidney • Hypertension • Diabetes • Oculorenal syndrome • Angiopathy • Vascular disease • von Hippel-Lindau • Papillorenal syndrome • Alport syndrome • Ciliopathy • Nephronophthisis • Cystinosis • Fabry

Introduction

The identification of associated kidney disease and retinal blindness has a long history that continues to the present day. At the forefront of this association stand two of the major diseases of modern times, namely arterial hypertension and diabetes. Moreover, the retina is one of the most common tissues involved in nonpolycystic kidney disease (PKD) types of cystic kidney disorders.

The kidney and the eye are closely linked in many diseases, both common and rare. Despite their vastly different functions, both the kidney and the retina are frequently vulnerable to the same systemic pathological processes such as vascular stress and complement pathway dysregulation. Several factors play a joint pathophysiological role in impaired kidney function and associated ocular disease, and mutual vulnerability of both retina and kidney underlies several syndromes and disease entities. Disorders involving both the eye and the kidney can result from

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developmental problems, metabolic defects, vascular disease, autoimmune conditions, infections, tumors, and pharmacological side effects. The term "oculorenal syndromes" points to a large and heterogeneous group of malformations and systemic diseases with particular and unusual ocular and renal features.

Patients with renal disease may require specific ophthalmic management, and vice versa. Several systemic diseases contribute to both retinal and renal pathology. The most widespread, and thus important, of these are diabetes mellitus and arterial hypertension, in which patients frequently develop both nephropathy and retinopathy. Both conditions can cause significant microvascular pathology that can injure the retinal and renal capillary beds and lead to structural and functional damage.

Diabetes

Diabetic retinopathy is a microangiopathic condition caused by hyperglycemia in its early stages and capillary closure as the condition progresses. Hyperglycemia causes vascular basement membrane thickening and a loss of both vascular endothelial cells and pericytes. Capillary nonperfusion results in retinal ischemia, which then determines the further course of the damage. Hypoxia induces preretinal neovascularization (Fig. 27.1), the development of which is modulated by angiogenic factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1). These new vessels are very fragile, predisposing them to microaneurysms and vascular leakage. Increased vascular permeability leads to several complications (Table 27.1), with macular edema representing the most debilitating problem in terms of visual function.

Both diabetic retinopathy and microalbuminuria, the telltale indication of early diabetic renal pathology, are expressions of microvascular damage. They are promoted by hypertension, hyperglycemia, dyslipidemia, and elevated levels of angiotensin II and are prevented and initially treated by adjusting these risk factors to the near-normal range. Due to structural similarities between the renal and retinal microvasculature, both organs are particularly susceptible. Angiotensin II leads to vascular constriction, increased capillary permeability, and increased blood pressure. This has a similar effect in both renal and retinal microvasculature, namely leakage. In the kidneys, increased filtration pressure in the glomerular capillaries causes leakage of albumin into the urine. In the retina, increased retinal capillary pressure and permeability lead to macular edema [1]. The association between high blood pressure and renal and retinal dysfunction is well recognized [2]. Similarly, microalbuminuria is associated with an increased risk of proliferative retinopathy and blindness [3].

The renin-angiotensin system (RAS) has been implicated in the pathogenesis of diabetic retinopathy [4]. Indeed, early blockade of the renin-angiotensin system in patients with type 1 diabetes has been shown to slow the progression of retinopathy [5]. Angiotensin II has been shown to be synthesized in the eye, particularly in those areas susceptible to diabetic retinopathy [6]. Further, there is a correlation between vitreous angiotensin-converting enzyme (ACE) activity and vitreous levels of VEGF [7], which is increased in the eyes of patients with proliferative

Fig. 27.1 (continued) (*asterisk*) and relatively mild leakage from the retinal vessels in the macular area, which is responsible for decreased visual acuity. In the left eye, the color fundus photograph (**e**) shows multifocal, peripheral neovascular tufts as well as neovascularization of the optic nerve head (*arrow*) and fibrosis (*asterisk*). In the macula and temporomacular region, vascular leakage has led to lipoid exudates (*arrowheads*) and edema with marked visual loss. Further temporal, hemorrhages and capillary nonperfusion are present. Capillary nonperfusion is better recognized on the red-free image (**f**), which also shows the extent of the neovascular tufts and of the fibrosis. FA (**g**) shows massive leakage from the neovascular membranes and, on the *upper left side* of the image, extensive capillary nonperfusion, indicated by a near-total lack fluorescence (*asterisk*). The late-stage FA (**h**) shows massive leakage in the posterior pole and capillary nonperfusion peripherally

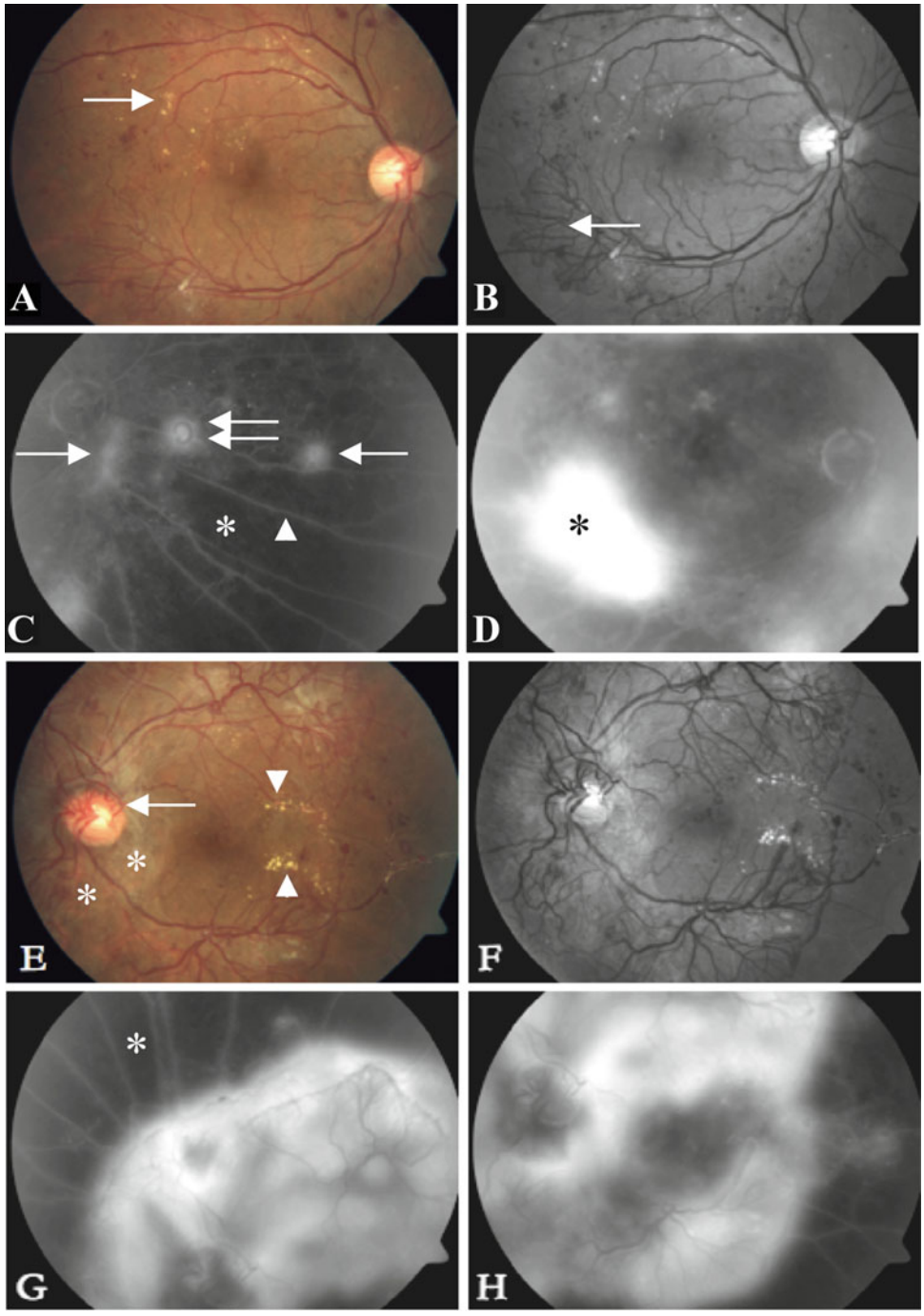

Fig. 27.1 Color fundus photograph (**a**) of the right eye of a diabetic patient with multifocal proliferative retinopathy and a relatively well-preserved macula, despite lipoid exudates temporal of the macula (*arrow*). The red-free photograph (**b**) better shows the fan-shaped neovascular membrane in the inferotemporal region (*arrow*). On the fluorescein angiograph (**c**), the darker area (*asterisk*) indicates peripheral capillary dropout. Fluorescence indicates leakage of fluorescein dye from the neovascular tufts (*arrows*) and from the veins (*arrowhead*), especially obvious in the omega-shaped venous dilatation (*double arrow*), nasal of the optic disk. Fluorescein angiography of the papillomacular region (**d**) shows pronounced leakage from the inferotemporal neovascular membrane

Table 27.1 Microangiopathic problems in diabetic retinopathy

Increased vascular permeability	Increased vascular fragility
Macular edema	Microaneurysms
Hard exudates	Intraretinal hemorrhage
Cotton-wool spots	Venous beading and loops

diabetic retinopathy [8]. The benefits of RAS blockade in diabetic retinopathy may represent direct effects on the eye, independent of effects of systemic blood pressure [5]. Large studies have shown that angiotensin II blockade with sartans leads to an absolute reduction of both renal events and the progression of retinopathy [9, 10]. In the Steno-2 study, an intensive program of multifactorial risk reduction significantly lowered the rate of microvascular complications in which both nephropathy and retinopathy were decreased by about 50% as compared to controls [11].

Vascular Disease

Arterial hypertension is a frequent complication of congenital and developed kidney diseases such as renal dysplasia, glomerulonephritis (GN), and renal artery stenosis (RAS). Further, essential (idiopathic) hypertension and secondary nonrenal hypertension can cause arteriolar nephrosclerosis and extensive kidney damage, leading to renal insufficiency. Fundus examination is a simple method of evaluating the effect of arterial hypertension on the blood vessels. Hyperlipidemia and other lipid metabolism disturbances occur frequently in patients with chronic renal insufficiency, and they too contribute to the atherosclerotic complications in the microvasculature of the eye and elsewhere in the body.

Systemic diseases associated with microangiopathy, vasculitis, or diffuse intravascular coagulation can cause both renal and ocular vascular lesions. Most prominent among these diseases is diabetes, with its tendency to cause diabetic nephropathy and retinopathy. Serious vascular damage can be caused by lupus erythematodes, sarcoidosis, periarteritis nodosa, Wegener's disease, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome. In these conditions, the clinical picture is often dominated by renal insufficiency and a marked decrease in visual acuity.

Hypertensive Retinopathy

Arterial hypertension (AHT) and renal disease are closely linked. AHT can occur in acute renal conditions such as acute poststreptococcal glomerulonephritis (PSGN), Henoch-Schönlein purpura (HSP), hemolytic uremic syndrome (HUS), and acute urinary tract obstruction. It is also a frequent complication of long-term renal conditions such as chronic pyelonephritis and reflux nephropathy, chronic glomerulonephritis, renal dysplasia, and polycystic kidney disease. Renovascular abnormalities such as renal artery stenosis or occlusion also lead to AHT, due to disturbances in the renin-angiotensin system. Lastly, AHT can occur postoperatively after kidney transplantation.

Due to the vastly improved treatment of kidney disease and its associated AHT, ophthalmologists are now less frequently confronted with patients with visual loss due to hypertensive oculopathy than they were in the past. However, ocular fundus examinations can make up a significant part of the follow-up of hypertensive patients, especially in the context of diabetic nephropathy, which is often associated with AHT.

Hypertensive retinopathy has long been recognized as a clinical entity due to its high prevalence as well as its easily visualized fundus abnormalities. AHT induces autoregulatory increases of the retinal vasculature tone, leading to vasoconstriction. This is most obvious in the precapillary arterioles. Long-standing AHT leads to sclerotic vasculature, permanent arteriolar constriction, pinched arteriovenous crossing (Gunn's crossing sign), arterial tortuosity, silver-colored artery reflexes, large-angle (omega) arterial branching, and arteriolosclerosis (Table 27.2). However, these abnormalities can also occur as simple age-related changes in normotensive patients.

There are, however, several more specific signs of AHT to be found in the retina. Retinal vascular diameter is closely linked to blood

Table 27.2 The Scheie classification of arteriosclerotic retinal vascular changes (Adapted from [155])

Stage	Characteristics
I	Widening of arteriolar reflexes
II	Arteriovenous crossing sign
III	Copper-wire arteries (copper-colored arterial reflex)
IV	Silver-wire arteries (silver-colored arterial reflex)

Table 27.3 The Keith–Wagener–Barker classification of vascular changes in hypertensive retinopathy (Adapted from [156])

Stage	Characteristics
I	Constricted and tortuous arterioles
II	Severe vascular constriction
	Gunn's crossing sign: Venous blood column is constricted by sclerotic artery
III	Retinal hemorrhages
	Hard exudates
	Cotton-wool spots
	Retinal edema
IV	Papilledema

pressure [12]. Vascular diameter increases with long-standing AHT, causing a breakdown of the blood-retina barrier. This leads to intraretinal bleeding, cotton-wool spots, retinal edema, and, in extreme cases, swelling of the optic disk. Papilledema can lead to optic nerve atrophy and long-term loss of visual acuity. The ophthalmoscopic evaluation of the retinal vasculature requires a certain degree of experience, and the evaluation is also subject to subjective interpretation (Table 27.3). Digital fundus photography can help objectify findings.

Leaking retinal vessels manifest ophthalmoscopically as edema; fluorescein angiography clearly shows leakage. Resorption of the edema frequently results hard exudates. These yellow-white deposits are the precipitates of lipid residues within the outer plexiform (Henle's) layer and consist of plasma proteins, phospholipids, cholesterol, and triglycerides. These appear primarily in a circinate pattern peripheral to areas of chronic leakage. End-stage hypertensive retinopathy can result in a macular star and/or circumpapillary hard exudates.

Ischemic damage to the retinal nerve fiber layer (RNFL) is visualized as cotton-wool spots. These appear funduscopically as puffy white patches in the inner retinal layers; FA shows a small zone of capillary dropout. Flame-shaped hemorrhages, in which the blood is trapped in the nerve fiber layer, also become visible (Fig. 27.2).

Besides hemorrhage, these signs of hypertensive retinopathy generally do not on their own cause visual loss, unless they occur within or near to the fovea. However, complications of hypertensive retinopathy include retinal artery and/or vein (Fig. 27.3) occlusions and macroaneurysms that can lead to vitreous hemorrhage or exudative lesions threatening the macula. Indeed, vascular changes due to AHT are the most common cause of retinal vein occlusion. These complications can have devastating effects on visual acuity.

Hypertensive crises, generally defined as a diastolic pressure exceeding 120 mmHg, pose a particular problem. When the perfusion pressure is sharply increased, the physiological autoregulatory mechanisms of the retinal arteries are overpowered and the blood-retina barrier can be broken, leading to hemorrhage and edema. At extreme pressures, fibrinoid necrosis of the vessel walls occurs, leading to a complete loss of tone and aneurysmal dilation.

Hypertensive choroidopathy (HC) is another, albeit less common, result of acute hypertensive crises. This occurs especially in younger patients without vascular sclerosis. For example, patients with (pre)eclampsia, connective tissue disease, kidney disease, and pheochromocytoma are potentially susceptible to HC. The acute hypertension stimulates a sympathetic response, leading to vasoconstriction with reduced choriocapillary perfusion. In contrast to the retinal vasculature, the choriocapillaris is not autoregulated. Compensatory vasoconstriction, and the fact that these vessels are thin and highly fenestrated, leads to retinal edema, subretinal fluid, and infarction of the choroid and the overlying retinal pigment epithelium (RPE). In the acute stage, these lesions leak on fluorescein angiography (FA) and indocyanine green angiography (ICGA). After blood pressure normalization

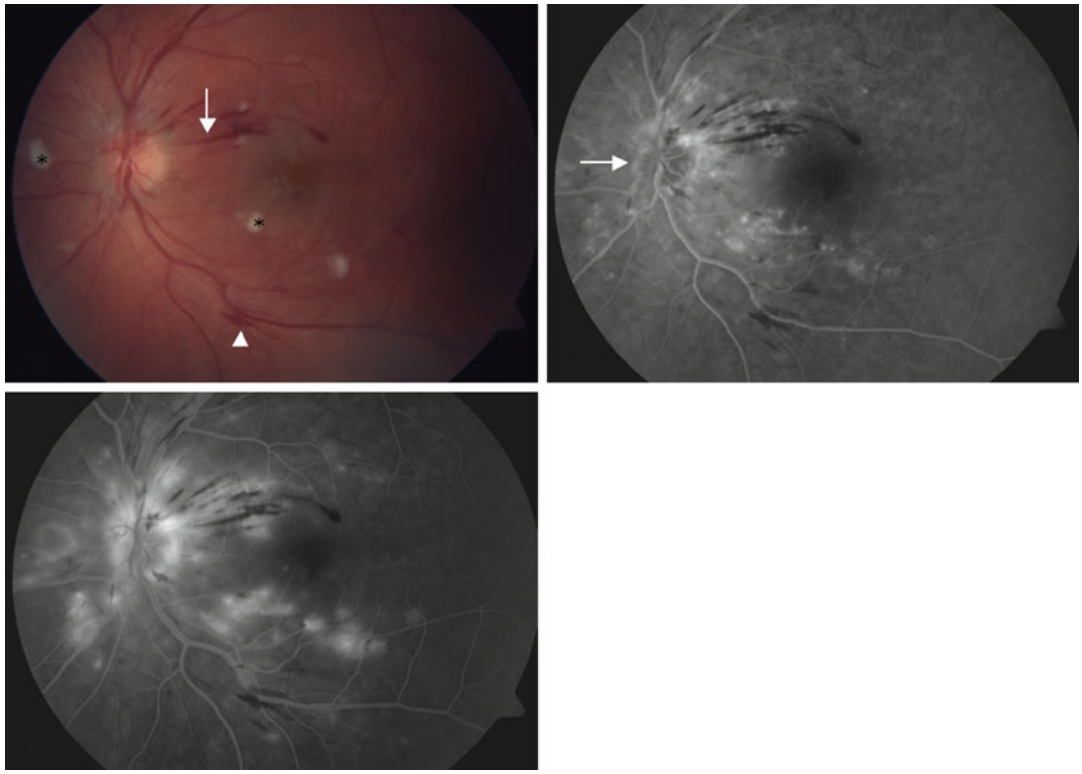

Fig. 27.2 Hypertensive retinopathy of recent onset in a 30-year-old male with typical flame-shaped hemorrhages (*arrow*) in the papillomacular region and along the inferotemporal vein (*arrowhead*), as well as several cotton-wool spots (*asterisks*). The early-phase fluorescein angiogram (**b**) shows microvascular changes with early leakage around the optic nerve head (*arrow*) and in the papillomacular region, with intensive leakage and edema in the late-phase image (**c**). The right eye had identical lesions, indicating a systemic pathology, which was an acute hypertensive crisis in this case

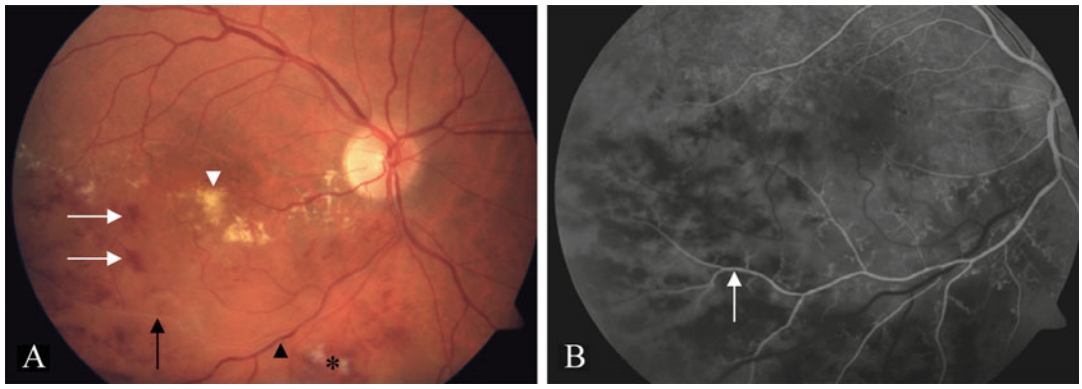

Fig. 27.3 Mixed branch arterial and venous occlusion in the inferotemporal region of the retina of the right eye. The color fundus photograph (**a**) shows nonperfusion of the artery (*black arrow*), branch venous congestion, and swelling (*black arrowhead*). Cotton-wool spots (*asterisk*) and dense hemorrhages (*white arrows*), indicative of relatively recent occlusion, are still visible. However, lipoid exudates (*white arrowhead*), located at the superior border of the occluded region, indicate that there has been edema for several months. The early-phase fluorescein angiograph (**b**) shows that while the majority of the branches of the inferotemporal artery are occluded, the artery itself (*white arrow*) is still perfused

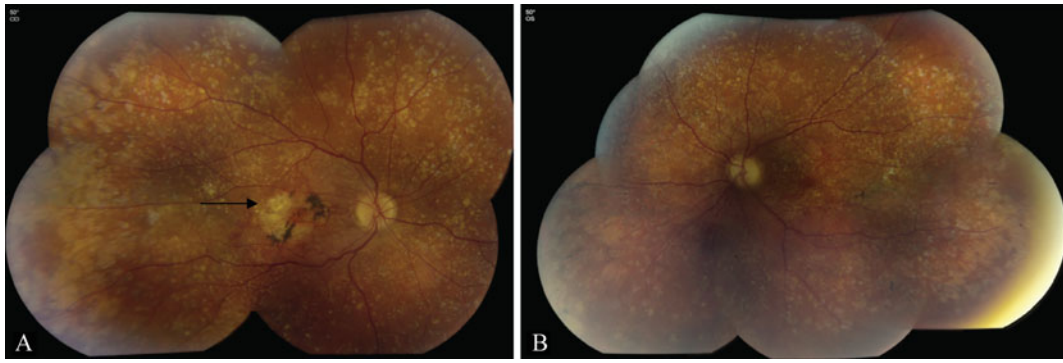

Fig. 27.4 Membranoproliferative glomerulonephritis type 2 (MPGN2; dense deposit disease): Color fundus photograph of the right eye (**a**) shows diffusely scattered drusen and retinal pigment epithelial lesions as well as an old, fibrotic, inactive subretinal membrane (*arrow*), which is responsible for markedly reduced visual acuity. The left eye (**b**) also shows MPGN2-associated drusen and a subretinal membrane with hemorrhage. This eye abruptly lost vision as a result of anterior ischemic optic neuropathy, as indicated by the pale optic disk

and regression of the hypertensive choroidopathy, specific findings include punctate beige-yellow patches of RPE necrosis or atrophy overlying the area of choroidal infarction (Elschnig spot and scars of choroidal infarct). Pigmentary changes running parallel to choroidal arteries (Siegrist's streaks) may also be present. Specific ophthalmologic interventions are not indicated. However, treatment of the underlying cause of the crisis is crucial.

Regular ophthalmoscopic examination is required to minimize the risk of complications that are generally, but not always, preventable with tight control of blood pressure. Treating the underlying disorder is crucial in hypertensive retinopathy. However, fundus changes due to arteriosclerosis are currently irreversible.

Hypertensive Optic Neuropathy

An arterial hypertensive crisis can also cause an optic neuropathy whose evolution closely parallels that of anterior ischemic optic neuropathy (AION) in the elderly population. The optic neuropathy can be the most prominent finding or can be associated with obvious signs of hypertensive retinopathy. Hypertensive optic neuropathy (HON) manifests with papillary edema and, several weeks later, atrophy of the optic nerve head (Fig. 27.4). HON leads to sudden visual loss. While AION is predominantly a disease of the elderly, due to the inability to adjust to changes in perfusion pressure due to preexisting vascular disease, HON has been postulated to be due to a sudden relative fall in arterial pressure, leading to reduced perfusion of the optic disk, whose circulation has been compromised by long-standing hypertensive vascular disease [13]. Patients complain of loss of vision, and loss of visual field is a prominent finding.

Thrombotic Microangiopathy

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two closely related microangiopathic conditions characterized by profound thrombocytopenia and microangiopathic hemolytic anemia. The diagnostic pentad for TTP includes the following characteristics: thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms and signs, various degrees of renal function abnormalities, and fever without other explanation. HUS is distinguished from TTP by the presence of acute renal failure (ARF) in addition to the thrombocytopenia and microangiopathic hemolytic anemia common to both syndromes. Some authors consider TTP and HUS to be different clinical expressions of the same disease [14].

Plasma exchange therapy is the treatment of choice for TTP. HUS, which is most commonly triggered by a prodromal diarrheal illness caused by infection with *Escherichia coli* O157 or another Shiga toxin-producing bacterial strain, does not have a standard treatment. However, because differentiation of TTH and HUS is not always possible, empiric treatment with plasma exchange should be strongly considered if the diagnosis is uncertain. Hypertension and proteinuria are serious long-term sequelae of HUS, which can lead to the need for renal transplantation.

Thrombotic microangiopathy always involves the renal glomeruli and smaller arterial vessels of the kidney, but sometimes the extrarenal vascular beds are spared. Ocular abnormalities due to the thrombotic microangiopathy of both HUS and TTP have been extensively described. Ocular involvement during TTP occurs in 14–20% of patients [15–17], although underestimation might occur due to the presentation of the ocular manifestations during the preterminal stage of the disease [18]. The lesions can be categorized according to their being caused by specific ocular thrombotic microangiopathy lesions or their being the symptoms of the systemic disorders caused by the thrombotic microangiopathy itself [16, 19]. The first group includes choroidal bleeding, intraretinal hemorrhage, retinal detachments, papilledema, diplopia, and anisocoria [20, 21]. Anisocoria can be caused by intracranial hemorrhage [22]. An oculofundal sign suggesting systemic damage due to HUS is hypertensive retinopathy. In TTP, massive bilateral retinal and/or choroidal vascular occlusion is seen [23].

Bilateral serous retinal detachments can occur due to choroidal infarction, also due to TTP, and optic neuropathy due to HUS [24]. Reversible retinal thrombotic microangiopathy and temporary blindness have also been described [25]. Retinal intravascular thrombosis has also been shown histopathologically, with signs of ischemic retinal necrosis evident in ganglion cells. Other fundus abnormalities include soft exudates, papilledema, vitreous hemorrhage, retinal detachment, and optic nerve atrophy [26]. Cortical (central) blindness has also been described [26]. Visual problems can occasionally even be the presenting sign of TTP [27]. This is of importance, because such symptoms can be cured, even in the short term, with adequate plasmapheresis [28]. Nonfundal ocular signs include palpebral purpura or swelling, chemosis, subconjunctival bleeding, and scleral jaundice.

A short-term hypertensive crisis will not usually cause ocular lesions. However, thrombotic choriocapillary microangiopathy can lead to serous retinal detachment, especially if arterial hypertension is also present. In this case, sudden loss of vision is the rule, although visual recovery follows treatment of the thrombotic microangiopathy.

Dysregulation of the Alternative Complement Pathway with Renal and Ocular Fundus Changes

Membranoproliferative glomerulonephritis type II (MPGN-II), also known as dense deposit disease or mesangiocapillary glomerulonephritis, is a rare kidney disorder that usually presents in early adulthood with proteinuria, hematuria, and renal impairment [29]. The disease is associated with dysregulation of the alternative complement pathway, and circulating C3 nephritic factor, causing "dense" ribbon-like immune deposits within the renal glomerular basement membrane (GBM). The cause of the systemic complement pathway activation is unknown, although the possibility of an immunogenetic link, via anti-factor B, has been suggested [30]. The disease may be associated with partial lipodystrophy, characterized by the loss of subcutaneous fat from the upper body [31]. However, partial lipodystrophy can also be associated with fundus changes in the absence of renal disease. Nearly 50% of patients with MPGN-II progress to end-stage renal disease within 10 years of disease onset [32]. Renal transplantation is frequently required [33].

Patients are initially asymptomatic, but scrutinizing the fundus leads to the discovery of small drusen. Fluorescein angiography may be required to identify these changes [34]. With time, the drusen become more numerous and there is a slow

evolution over many years to either geographic atrophy very similar to geographic atrophy in age-related macular degeneration (AMD) and/or to choroidal neovascularization (CNV) that is 100% occult or with a classic component. Complaints in advanced stages are similar to those in AMD. Fluorescein angiography of these patients with MPGN-II is characterized by the presence of numerous, small, tightly packed basal laminar drusen throughout the posterior pole. These fluoresce brightly on FA, giving a starry sky appearance (Fig. 27.4). The changes are located within Bruch's membrane, the choriocapillaris, and the RPE and are very similar to those observed in AMD. However, MPGN-II-associated drusen appear at a younger age than those seen in patients with AMD. Indeed, the drusen manifest early in the MPGN-II disease process, so that a dilated fundus exam can be useful in the initial diagnosis of MPGN-II, particularly in relatively young patients with chronic glomerulonephritis. Also, choroidal neovascular membranes similar to those found in AMD are often noted, and these are also seen much earlier than in AMD, between the ages of 25 and 35 years [35]. Central serous chorioretinopathy (CSCR), retinal pigment epithelial detachment, and mottled pigmentation are also seen. Fluorescein angiography (FA) can be used to confirm the diagnosis [36]. Because fluorescein dye is eliminated via both the liver and the kidney, FA can be safely conducted in patients with renal failure. OCT can be useful to both demonstrate and monitor structural changes in the RPE and choriocapillaris.

The presence of ophthalmoscopically visible fundus changes is related to the disease duration. However, because the extent of ocular involvement does not correlate well with the severity of renal involvement, renal physicians should be encouraged to refer all their MPGN type II patients to an ophthalmologist for a baseline visit, regardless of the disease severity. Patients can benefit from further ophthalmic explanation, and they should be advised to seek urgent help if distortion of central vision occurs, taking into account the risk of development of a choroidal neovascular membrane, a complication that is now treatable.

Developmental Anomalies of the Eye and Kidney

Papillorenal Syndrome

First described by Rieger in 1977, papillorenal syndrome (PRS), alternately known as renal-coloboma syndrome, is a distinct autosomal dominant disorder characterized by a spectrum of congenital kidney and eye abnormalities including optic nerve dysplasia, optic nerve coloboma, and optic pit. The condition results from a mutation of the PAX2 gene, a transcription factor with a critical role in embryologic development of the kidneys and optic nerves. PAX2 has been shown to determine the number of axons in mouse optic nerves [37]. It has also been suggested that PRS is a primary dysgenesis that causes vascular abnormalities predominantly affecting the eye, kidney, and urinary tract, leading to hypoplasia of these structures [38]. This distinct genetic disorder can be identified in patients with renal dysplasia through a careful eye examination, which is important, considering these patients are frequently asymptomatic upon presentation [39].

Differentiation of the PRS from other oculorenal syndromes (ORS) can be based on ocular findings, since the presence of optic nerve involvement makes the diagnosis of the PRS much more likely. The only other known ORS with both optic disk coloboma and renal disease is acro-renal ocular syndrome, in which the presence of thumb hypoplasia or polydactyly distinguishes it from PRS [40]. However, the disk anomaly is variable in the PRS, ranging from the morning glory anomaly to coloboma or optic pit. In PRS, the hereditary absence of central retinal vessels may be missed, leading to confusion with morning glory anomaly, isolated coloboma, or low-tension glaucoma. The association with renal disease will help avoid confusion with isolated coloboma or the morning glory anomaly (MGA). Further, the optic nerve anomaly is unilateral in MGA and bilateral in PRS. Optic disk excavation and superonasal visual field defects may lead the ophthalmologist to consider glaucoma. However, the visual field defects in PRS correspond to

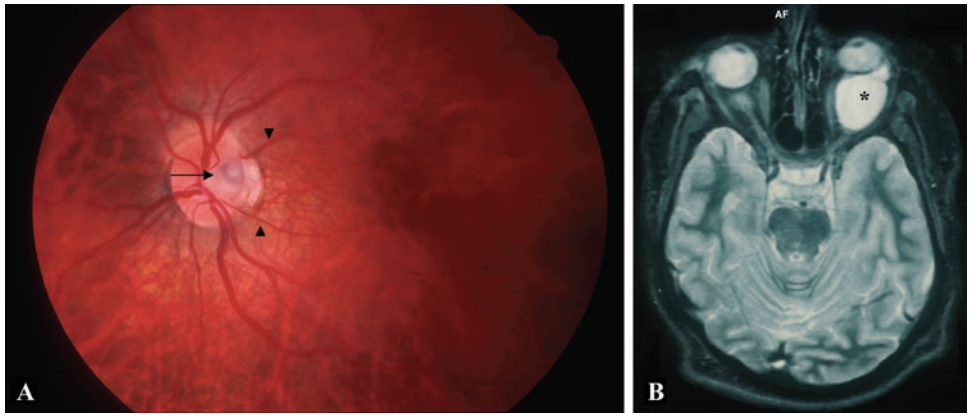

Fig. 27.5 Color fundus photograph (**a**) of a 15-year-old female patient with the PAX-2 mutation associated with papillorenal syndrome. The patient had no ocular symptoms, but screening showed an optic pit (*arrow*) and several cilioretinal vessels (*arrowheads*) in both eyes, as manifestations of optic disk dysplasia. The patient has hematuria, and the father has end-stage renal disease. The same PAX-2 mutation was identified in both father and daughter. A CT scan of another patient (**b**), a 26-year-old male with the PAX-2 mutation and bilateral ocular dysplasia. The left eye is blind and microphthalmic and has a retrobulbar cyst (*asterisk*). The right eye has severe dysplasia of the optic nerve and retina but is of a normal size. The patient's mother also has the PAX-2 mutation, but without significant loss of vision

inferotemporal areas of anomalous retinal and choroidal perfusion, and hypoplastic retina. Another clue is that multiple cilioretinal vessels, with absent or vestigial central retinal vessels, are also present (Fig. 27.5) [38].

Given the variable expression of the syndrome, a careful ophthalmologic examination is justified in all patients with an apparently isolated congenital malformation of the nephrourological system. Extreme variability can even be present within one family [41]. Alternately, renal abnormalities should be considered when atypical round optic disk colobomas are observed [42]. Upon diagnosis, first-degree relatives should undergo screening, which should also be performed on individuals with multiple cilioretinal vessels in both eyes [43]. This is of interest to the ophthalmologist because in patients with renal dysplasia, the distinct genetic disorder can be suspected by means of ocular fundus examination and confirmed with genetic tests. In patients without a known family history of the disease, the diagnosis is usually not made until kidney problems manifest. Renal hypoplasia is the most common cause of renal failure in the PRS. Vesicoureteric reflex leading to chronic pyelonephritis is a less common cause. Clinical diagnosis requires optic disk examination.

Defective Biosynthesis of Collagen Type IV: Alport Syndrome

Alport syndrome (AS) is a hereditary disorder caused by mutations in the biosynthesis genes of type IV collagen. This collagen subtype is a crucial structural component of the basement membrane in the glomerulus, retina, lens capsule, and cochlea [44–47]. The lesions correspond to the anatomic locations at which collagen IV is crucial to basement membrane structure. Originally termed hereditary familial congenital hemorrhagic nephritis, the disease is characterized by a progressive nephropathy leading to end-stage renal disease in all affected males and many affected females. The disease is most commonly X-linked, and penetrance is variable in female carriers. It is the third-most common inherited cause of renal failure in children, after nephronophthisis and reflux nephropathy. The presenting sign of Alport syndrome is often hematuria. Sensorineural deafness occurs in 60–80% of males, and ocular lesions occur in 25–40% [48].

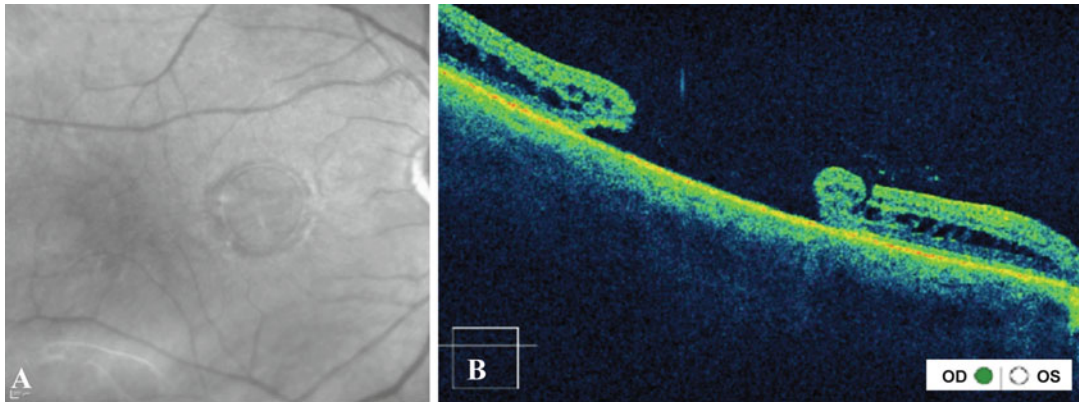

Fig. 27.6 A red-free fundus photograph (**a**) and an optical coherence tomography (OCT) (**b**) of a large, full-thickness macular hole in the right eye of a 56-year-old male patient with Alport disease. The left eye developed identical changes

Rarely, mental retardation or leiomyomatosis occurs [49].

The ocular signs are pathognomonic, consisting of retinopathy and lenticonus of the anterior lens capsule. Moreover, the corneal epithelium is fragile, leading to an increased risk of cornea erosions [50]. The characteristic dot-and-fleck retinopathy is highly specific for Alport syndrome, although an absence of retinopathy does not exclude AS. Further, it is not associated with functional impairment. Nevertheless, due to its characteristic appearance, it is very useful in the diagnosis of AS. It is present in a majority of males, in up to one third of females with X-linked disease and in up to three-quarters of patients with the less common autosomal recessive form of the disease. The lenticonus of the anterior lens capsule, indicated by the "oil droplet sign," is visible with a standard, handheld retinoscope and is also specific for Alport syndrome.

Diagnosis of Alport syndrome is not always straightforward, and it frequently depends on clinical, histopathologic, and genetic criteria. Typical clinical features and a positive family history should heighten suspicion. Clinical criteria include a positive family history of the disease, persistent (micro)hematuria, and abnormalities of the eyes and/or ears. Kidney biopsy has traditionally been the main histopathological criterion for confirming the diagnosis. However, a skin biopsy showing the absence of staining for the a5 chain of type IV collagen in the epidermal basement membrane is highly specific. This is, however, only sensitive enough to detect 80% of all cases, at best [51]. Affected patients may go unrecognized due to atypical clinical features, an unhelpful biopsy, or even lack of successful genetic testing.

Ocular features, particularly the characteristic retinopathy, can be helpful in making the diagnosis. Funduscopic examination reveals symmetric, bilateral perimacular "dot-and-fleck" retinopathy in about 40% of patients [52]. This consists of bright yellowish-white granulations surrounding the fovea. Fluorescein angiography is normal. Perimacular changes are significantly associated with earlier renal failure, and the presence of confluent lesions strengthens this association [53, 54]. The confluence of the lesions creates a polished appearance termed a "tapetal-like sheen," which extends from the perifoveal region to the outermost vascular arcades [53]. The fovea itself lacks these dots and flecks and is thus comparatively dull. The foveal region is described as looking like a "lozenge," which refers to the nonshiny appearance of a throat lozenge, or cough tablet, contrasting with the shinier perifoveal drusen. This "dull macular reflex" is best visible with red-free photography and can progress to a full-thickness macular hole (Fig. 27.6). The lozenge occurs only

in cases of central perimacular retinopathy, is diagnostic for Alport syndrome, and is significantly associated with early-onset renal failure.

Ciliopathies

The ciliopathies are systemic disorders that result in a wide range of abnormalities. This is due to the fact that cilia are common organelles present on nearly every cell in the human body, and their dysfunction can thus lead to pleiotropic disorders [55]. There are three basic categories of cilia: motile, primary, and nodal. The most well known are the motile cilia, which beat in an orchestrated wavelike fashion on the surface of epithelial cells and are involved in fluid and cell movement. Primary cilia are solitary organelles that project from the surface of cells and lack the central pair of microtubules needed to generate motile force. These cilia are involved in renal and retinal disease. A third class of cilia, nodal cilia, plays an essential role in embryology and the establishment of the left-right body axis.

Retinal and renal dysfunction is observed across a range of ciliopathies. This is due to defects in photoreceptor and renal cilia, respectively. In the retina, the primary, or sensory, cilium of photoreceptors mediates polarized trafficking of proteins for efficient phototransduction. Genetic defects in these cilia lead to retinal dysfunction. For example, retinitis pigmentosa GTPase regulator (RPGR) is a cilial-centrosomal protein mutated in over 70% of X-linked retinitis pigmentosa cases [56].

The retinal ciliopathies include selected subtypes of retinitis pigmentosa, cone dystrophy, cone-rod dystrophy, and Leber congenital amaurosis, as well as retinal degenerations associated with Bardet-Biedl syndrome, Senior-Loken syndrome, Usher syndrome, primary ciliary dyskinesia, Joubert syndrome, Laurence-Moon syndrome, McKusick-Kaufman syndrome, and Biemond syndrome. Mutations for these disorders have been found in retinitis pigmentosa-1 (RP1), retinitis pigmentosa GTPase regulator (RPGR), retinitis pigmentosa GTPase regulator interacting protein (RPGR-IP), as well as the Usher, Bardet-Biedl, and nephronophthisis genes. Other systemic disorders associated with retinal degenerations that also involve ciliary abnormalities include the Alström, Jeune, Edwards-Sethi, Ellis-van Creveld, Meckel-Gruber, orofaciodigital type 9, and Gurrieri syndromes.

Understanding these conditions as ciliopathies may help the ophthalmologist recognize associations between seemingly unrelated diseases and have a high degree of suspicion that a systemic finding may be present. Several of these diseases, such as Bardet-Biedl, Alström, and Senior-Loken syndromes, affect both the retina and the kidneys and will be discussed further.

Bardet-Biedl, Alström, and Related Syndromes

Bardet-Biedl syndrome (BBS) is an autosomal recessive ciliopathic genetic disorder characterized by six major features: retinal degeneration, renal dysfunction, central obesity, intellectual impairment, polydactyly, and hypogonadism [57]. However, the entire spectrum of abnormalities in BBS is only seen in a minority of patients. Intellectual impairment, polydactyly, and hypogonadism might be absent in female patients [58]. Nevertheless, retinal dystrophy is a consistent finding. The renal component of the disease significantly reduces patients' life expectancy, and ESRD is usually noted as the primary cause of death [59], although renal transplantation has a reasonably good outcome in BBS [60]. Histopathologically, the kidney abnormalities resemble those seen in Senior-Loken syndrome, another ciliopathic retinal-renal disorder discussed later in this chapter.

Bardet-Biedl syndrome can show a wide spectrum of retinal disease expression (Table 27.4) [61]. The retinal degeneration in BBS can be demonstrated via electroretinography (ERG) before morphological changes take place. There is progressive photoreceptor damage, leading to macular and peripheral retinal atrophy, pigment migration, vascular attenuation, and optic nerve head atrophy. The photoreceptor damage is

Table 27.4 Spectrum of retinal disease expression in Bardet-Biedl syndrome (Adapted from [63])

Severity	Characteristics
Mild	Subtle maculopathy with limited peripheral retinal dysfunction
Moderate	Pan-retinal photoreceptor dysfunction (rods > cones) with negative ERG waveform
Severe	Loss of central function with maintenance of abnormal peripheral function *or* Small central island of impaired function

morphologically similar to the degeneration observed in patients with Alström syndrome [62] and Leber congenital amaurosis [63]. It has been suggested that photoreceptor cell death might be due to an underlying defect in the function of the connecting cilium, a structure that links the inner segments to the outer segments of photoreceptors [64]. This leads to abnormal dark adaptation within the first decade of life. However, visual loss is limited during this first decade and generally manifests clinically in the second decade.

Morphologically, the posterior pole is characterized by bull's eye maculopathy. Peripherally, morphological signs of retinitis pigmentosa develop, with bony spicules appearing in the midperiphery. The pathology consists of primary degeneration of photoreceptors and secondary involvement of the other retinal layers, including the RPE, has been suggested. Overlapping oculorenal syndromes include Biedmond II syndrome, which is identical to BBS syndrome but also has an associated iris coloboma, and Alström syndrome, which is associated with diabetes mellitus and deafness but lacks polydactyly. The ocular abnormalities in Alström syndrome manifest earlier in life than they do in BBS. In Alström syndrome, retinitis pigmentosa with severe visual disability has been reported within the first year of life [65].

The retinal dystrophy is progressive and shows variable severity. To date, 12 BBS genes have been identified, with *BBS1* and *BBS10* being the most common [64]. All patients with the *BBS1* mutation show some degree of maculopathy, whereas those patients carrying *BBS10* mutations had more severely reduced VA and smaller visual fields than those with *BBS1* [66]. However, it seems that all patients with mutations in *BBS1* have some degree of maculopathy [66]. Optical coherence topography shows a disrupted inner and outer photoreceptor segment layer and a thinned RPE [66].

Senior-Loken Syndrome and Related Syndromes with Nephronophthisis

Nephronophthisis is an autosomal recessive, chronic tubulointerstitial nephropathy (*–phthisis*; wasting away), and it is the most common genetic cause of ESRD in children and adolescents [67]. It can occur in combination with tapetoretinal degeneration, in which case it is referred to as Senior-Loken syndrome (SLS), or in combination with other systemic abnormalities with or without retinal degeneration. SLS accounts for approximately 15% of nephronophthisis cases when a retinopathy and family history suggestive of autosomal recessive inheritance are seen [68]. When nephronophthisis is associated with tapetoretinal degeneration, cone-shaped epiphyses, and cerebellar ataxia, it is referred to as Mainzer-Saldino syndrome. The Boichis syndrome is the association of nephronophthisis with liver fibrosis, and it may occur in combination with deafness, cerebellar ataxia, and tapetoretinal degeneration [69]. Nephronophthisis and retinal degeneration have also been reported in association with asphyxiating thoracic dystrophy (Jeune syndrome) and with mitochondrial cytopathy and features of Kearns-Sayre syndrome.

Senior-Loken syndrome (SLS) is a rare autosomal recessive disorder characterized by the combination of familial juvenile nephronophthisis and tapetoretinal degeneration similar to Leber amaurosis, with or without mental retardation. First described in 1961 by Senior et al. [70] and Loken et al. [71] as an association of tapetoretinal degeneration with familial juvenile nephronophthisis, this syndrome is occasionally referred to as renal-retinal syndrome, juvenile nephronophthisis with Leber amaurosis, and renal dysplasia and retinal aplasia [72]. SLS is a

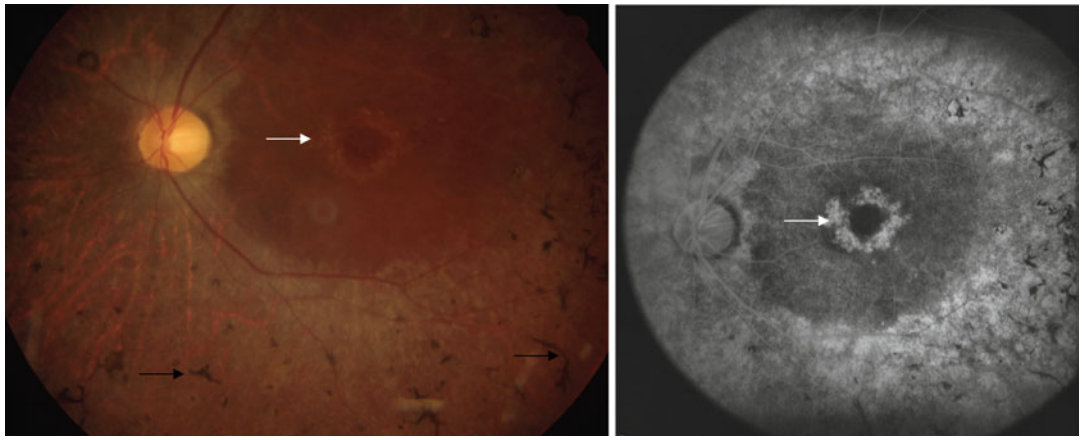

Fig. 27.7 Senior-Loken syndrome: Both the color photograph (**a**) and the early-phase fluorescein angiograph show an atrophic "bull's eye" macular lesion (*white arrows*) and peripheral retinitis pigmentosa, as evidenced by retinal atrophy with bone spicules (*black arrows*). This patient had very poor vision and end-stage renal disease

ciliopathy. In the retina, the outer segments of photoreceptor cells, which are in fact specialized sensory cilia, are affected. In the kidney, the primary apical cilia are affected. SLS is caused by a genetic defect of the nephronophthisis (NPHP) gene.

The retinopathy in SLS is variable and may be a form of severe infantile onset retinal dystrophy [73, 74], as a Leber congenital amaurosis type of abnormality [75] or as what appears as a typical retinitis pigmentosa [76]. The retinal degeneration tends to be severe, with poor visual acuities on the order of 20/200–20/400. Fundus abnormalities such as peripheral bone spicule formation, arteriolar narrowing, and optic disk pallor often appear later in the disease process (Fig. 27.7). Associated ocular findings include nystagmus, poor pupillary reflexes, retinal mottling, and high myopia. The ERG is often extinguished early in the disease. Visual field testing usually shows severe annular constriction of the visual fields [77].

A recent report of retinal imaging of a patient with SLS and poor vision focus emphasized the photoreceptors' cilia appearance in the macula [78]. Fundus autofluorescence showed diffuse spots of decreased autofluorescence in the midperiphery and a perifoveal ring of increased autofluorescence, suggesting a bull's eye maculopathy. The inner-outer photoreceptor segment junction in the central macula, corresponding to the area inside of the ring of increased autofluorescence, was barely detectable on high-resolution optical coherence tomography. This syndrome highlights the need for all children with a retinal dystrophy to have assessments of both their renal function and hearing.

Other Rare Metabolic Diseases

Congenital Disorders of Glycosylation (CDG)

The congenital disorders of glycosylation (CDG), previously known as the carbohydrate-deficient glycoprotein syndromes, are a group of rare inherited multisystem disorders resulting from genetic defects in protein glycosylation. These patients present in infancy. Although several genotypes exist, of which CDG-Ia has been most frequently described, common features of all CDG subtypes include moderate to severe neurological impairment, variable dysmorphic features, and variable involvement of other organs. Neurological disturbances frequently dominate the clinical picture and are characterized by psychomotor retardation,

hypotony, and ataxia. Patients may thus be very difficult to examine ophthalmologically.

Besides the central nervous system, the liver, kidney, pericardium, subcutis, kidney, and eyes can be involved. Ophthalmic findings involving both the anterior and posterior segment of the eye are frequent in CDG syndrome. Reported anomalies have included delayed visual maturation, strabismus, saccadic eye pursuits, retinal degeneration, and electrophysiological abnormalities [79–85]. In a more recent study, a majority (78%) of the patients with CDG-Ia was myopic, and a small minority was hypermetropic [86]. This study found the myopia to be progressive, at the rate of 0.8 diopters per year. Congenital esotropia and delayed visual maturation were consistent findings. Although some children might develop good visual acuity, the majority has low vision or is legally blind. Pallor of the optic disk is noted in about 20%, and electroretinography shows reduced rod responses, while cone responses are only slightly reduced. In the ocular fundus, attenuated retinal vessels may be observed in approximately half of the patients, indicative in this case of tapetoretinal degeneration.

It is recommended that patients be seen annually by an ophthalmologist, refracted regularly, and have glasses prescribed if myopia develops. Retinal function should also be examined regularly in order to document progression of the tapetoretinal degeneration [87].

Cystinosis

Cystinosis is a rare autosomal recessive disorder of lysosomal cystine transport characterized by intracellular accumulation of cystine, the disulfide of the amino acid cysteine [88, 89]. The accumulation is caused by a mutation of the CTNS gene, leading to defective or absent cystinosin [90], the membrane protein responsible for transporting cystine out of the cellular lysosome [91]. Crystal formation and organ damage ensue. In patients with cystinosis, different CTNS mutations produce different phenotypes. Although all nucleated cells in the body of affected patients carry the genetic defect, the kidney and the eye are particularly vulnerable to this pathology and are the first to manifest symptoms. Other organs that can be affected are the pancreas, thyroid, brain, and muscle. The subsequent late systemic complications include short stature, diabetes mellitus, hypothyroidism, cerebral calcifications, dysphagia, and distal myopathy [92, 93].

Based on the patient's age at onset, as well as the severity of the symptoms, several phenotypes have been described. Classification is based on the presence of kidney dysfunction (nephropathic cystinosis) or lack thereof (nonnephropathic cystinosis). Nephropathic cystinosis can be further divided into infantile (classic) and intermediate (juvenile-onset or adolescent). Nonnephropathic cystinosis, previously known as benign or adult-type cystinosis, is now referred to as ocular cystinosis, although nephropathic cystinosis is also characterized by ocular manifestations.

Infantile nephropathic cystinosis is both the most common and the most severe phenotype of cystinosis. These young patients present with growth retardation and Fanconi syndrome, a disorder of renal tubular function, during the first year of life. Untreated cases progress to end-stage renal disease (ESRD) later in the first decade of life [89, 94].

Corneal crystal deposits are so prominent and typical that early diagnosis can frequently be made before the manifestation of nephropathy [95]. Diagnosis is confirmed via conjunctival, bone marrow, or kidney biopsy, or via leukocyte cystine assay, in which detection of a 50–100-fold increase in the free cystine levels in polymorphonuclear leukocytes is observed. Leukocyte cystine assay is particularly useful in suspected children under 20 months who have a negative ocular examination. The diagnosis can also be made prenatally by means of a chorionic villi biopsy.

The ocular manifestations are highly characteristic, and their recognition can make a substantial contribution to the timely diagnosis of the disease. The most obvious sign is the formation of crystals in the cornea, visible on standard slit-lamp biomicroscopy. These crystals appear at approximately 1 year of age, and they progressively increase in density [96]. They are present throughout the corneal epithelium and the entire stroma.

Patients often present with photophobia. The differential diagnosis should include multiple myeloma, which can also present with corneal crystals and photophobia, albeit rarely [97]. However, in multiple myeloma, the crystals are limited to the epithelium and superficial stromal layers. Besides cystinosis and multiple myeloma, the differential diagnosis includes Bietti crystalline corneal and retinal dystrophy, Schnyder crystalline corneal dystrophy, Meesmann corneal dystrophy, Fabry disease, and reaction to certain drugs, such as amiodarone [97]. Measurement of the leukocyte cysteine, as well as the fact that the corneal crystals of cystinosis cause intense discomfort, can help distinguish between cystinosis and the other disorders.

Deposits in cystinosis are also present in other ocular structures, such as the conjunctiva, anterior chamber, iris, ciliary body, choroid, fundus, and optic nerve [98]. However, these are less frequent. Whereas corneal crystals are present in approximately 90% of patients, fundus abnormalities, such as retinal, subretinal, retinal pigment epithelial, and/or choroidal changes, may only be visible in about 30–50% [99–101]. Retinal manifestations can vary. The most common fundus finding is peripheral RPE hypopigmentation with pigmentary stippling or mottling, present in approximately 60% and noted as early as 6 months [102]. Also possible is the combination of peripheral hypopigmentation and macular pigmentary changes, or a fundus resembling that seen in retinitis pigmentosa, with bone spicules and pigment clumps. Rare manifestations are severe chorioretinal atrophy, submacular neovascular membranes, and perimacular RPE atrophy [102]. Deep yellow crystals throughout the posterior pole as well as diffuse pigmentary changes without crystals have been described. Retinal crystals are present in approximately 10% [102]. The fundus appearance has been alternately described as "fine scintillating refractile bodies" scattered throughout the posterior pole in the RPE or choroid [103] and as simply yellow crystalline choroidal material [100]. Retinopathy without crystal deposition has also been described. In this case, it is confined to the RPE, with areas of hypertrophy, depigmentation, and atrophy [104]. As patients grow older, the effects of the retinal degeneration become more apparent. These effects include nyctalopia, color vision problems, constricted visual fields, and decreased cone and rod function on ERG [105].

The cause of the retinal degeneration is unknown. Histopathological study has revealed diffuse RPE cell degeneration associated with the presence of intracellular crystals [106], which are located in the RPE and choroid [107–109]. Cellular apoptosis might also be responsible [89, 110].

Systemic treatment of the disease focuses on depletion of intracellular cystine using oral cysteamine, which improves the export of cystine from lysosomes and prevents progression of the disease [111]. However, early initiation of treatment is crucial, as cysteamine treatment may not reverse renal pathology [112]. Dialysis and/or renal transplantation is performed in case of ESRD, and chronic cystine depletion therapy is maintained post-transplantation.

Corneal deposits are not affected by oral cysteamine therapy, so cysteamine is administered topically (0.5% cysteamine eyedrops) [113]. This removes the corneal crystals and improves the associated photophobia and recurrent corneal erosions [114–116]. However, strict compliance with 6-hourly dosing is needed for proper cystine depletion [100]. Topical therapy has been shown to decrease retinal cystine infiltration [117]. The frequency of cystinotic retinopathy has been shown to correlate positively with time off cysteamine therapy and negatively with time on cysteamine therapy [118]. Oral cysteamine therapy should begin as early as possible and should not be stopped even after renal transplantation.

Fabry Disease

Fabry disease (FD), also known as angiokeratoma corporis diffusum or α-galactosidase deficiency, is an X-linked, hereditary, lysosomal storage disease caused by deficiency of the enzyme α-galactosidase A. This enzyme deficiency results in the systemic accumulation of the glycosphingolipid globotriaosylceramide (GL-3) in nearly every body tissue. Clinically, the disease is characterized

by progressive renal impairment, chronic pain and acroparesthesia, gastrointestinal disturbances, cutaneous angiokeratomas (small bluish-black, nonblanching telangiectasias), cardiomyopathy, and stroke. Diagnosis is confirmed by detection of decreased levels of α-galactosidase A in the plasma or in PMNs. Without treatment, the disease is fatal. The possibility of life-saving treatment has heightened the importance of early diagnosis so that treatment can be initiated before organs become irreversibly damaged. Treatment currently consists of intravenous enzyme replacement therapy with recombinant α-galactosidase A.

The ocular manifestations frequently present early in the disease process and can be detected upon routine ophthalmic exam. They include cornea verticillata (whorl-like radial lines emanating from a single vortex and potentially covering the entire cornea), conjunctival vessel tortuosity and aneurysmal dilation, lens opacities (posterior lens cataract), and retinochoroidal vessel abnormalities. The fundus abnormalities include retinal vessel tortuosity, irregular venous dilations, vascular sheathing, vascular occlusions, and retinal and preretinal bleeding. Characteristically, there are also anterior snowflake cataracts and, in males and carrier females, posterior lens posterior spoke-like cataracts.

Retinal vascular tortuosity is the most common retinal finding in FD, found in 77% of males and 19% of females, with the earliest reported presentation at age 13 in girls and age 11 in boys [119]. The arterioles are most commonly involved, although the venous side of the retinal circulation is involved in advanced cases. Venules assume a corkscrew appearance, and venous aneurysmal dilatation occurs. Although the ovular lesions do not typically affect the vision, both arterial and venous occlusions have been described [120, 121]. Delayed flow on FA is common in both male and female patients [117]. Indeed, FD is in fact a vasculopathy, and the diagnosis should be considered when a young patient presents with a central retinal artery occlusion [120, 122, 123]. Rarer findings include optic atrophy [123], central retinal vein occlusion [121, 124], and ischemic optic neuropathy [125]. A large minority of FD patients (44% in one study) have an enlarged blind spot on visual field testing (20° horizontally and 25° vertically), although neither dyschromatopsia nor an afferent papillary defect is present in FD [126].

Delays in diagnosis of Fabry disease are unfortunately common. Indeed, the average age at diagnosis is 29 [127, 128], and patients frequently see several specialists before the correct diagnosis is made. Ophthalmologists have the opportunity to make a timely diagnosis, before the disease is well advanced.

The Zellweger Syndrome Spectrum and Other Peroxisomal Diseases

Defects in PEX genes impair peroxisome assembly and many metabolic pathways in the peroxisome, providing the biochemical and molecular bases of the peroxisome biogenesis disorders (PBD). The Zellweger syndrome spectrum, which represents the major type of PBD, includes three phenotypes that were identified and described before the biochemical and molecular bases of these disorders had been fully determined. They include Zellweger syndrome, the most severe; neonatal adrenoleukodystrophy; and infantile Refsum disease, the least severe.

Previously referred to as cerebrohepatorenal syndrome, Zellweger syndrome is an autosomal recessive disease whose pathogenesis derives from the defective assembly of peroxisomes. It is considered the prototypical peroxisomal biogenesis disorder, and it is also the most lethal. In other peroxisomal disorders, such as X-linked adrenoleukodystrophy (described later; not to be confused with neonatal adrenoleukodystrophy) and primary hyperoxaluria type 1 (described earlier in this chapter), the metabolic abnormality is generally limited to a single peroxisomal enzyme. However, in Zellweger syndrome, as in the two other phenotypes included in the spectrum, all peroxisomes are defective.

The problem lies in the abnormal β-oxidation of several very-long-chain fatty acids. This leads to anomalous lipid metabolism and very low levels of docosahexaenoic acid (DHA), which is considered to be the most important polyunsaturated fatty

acid in the brain and retina. DHA is present in high concentrations in the brain synapses [129] and rod outer segments [130], and retinal DHA is essential for photoreceptor integrity and function [131–133].

Zellweger syndrome manifests in the neonatal period with a characteristic facies, including hypoplastic supraorbital ridges and a low and broad nasal bridge, and abnormalities of the kidneys, eyes, liver, cartilage, and central nervous system (CNS). Severe CNS abnormalities such as infantile hypotonia and seizures occur, presumably the result of neuronal migration defects and dysmyelination. Patients with Zellweger syndrome usually die within the first year of life. However, Zellweger syndrome is at the severe end of a phenotypic spectrum of Zellweger-like syndromes that may present later in childhood and even in adult life [134]. The milder variants of Zellweger syndrome share the same clinical and biochemical picture, although with lesser severity.

Ophthalmic manifestations of Zellweger syndrome comprise both dysgenetic and degenerative components. These include corneal opacification, cataract, glaucoma, pigmentary retinopathy, tapetoretinal degeneration, and optic atrophy [133]. Posterior segment abnormalities appear to result from a rapidly progressive retinal dystrophy with loss of photoreceptors and atrophy of the RPE. This leads to retinal vessel narrowing, macular abnormalities, and retinitis pigmentosa. Ganglion cell loss and optic nerve atrophy or hypoplasia can occur, as can graying of the optic nerve head and retinal depigmentation [135]. The ERG is flat and the evoked potentials are asymmetric. In the milder forms of the disease, optic nerve atrophy, retinitis pigmentosa, and a flat ERG have been described [136].

Treatment of the disorder consists of DHA ethyl ester supplementation, which is intended to correct the DHA deficiency in the brain and retina [137]. This treatment must be initiated as early as possible. Prenatal diagnosis is possible, and carriers can be identified by the characteristic curvilinear cortical lens opacities, which are visible with maximal pupillary dilation [138].

Peroxisomal Diseases: X-Linked Adrenoleukodystrophy

X-linked adrenoleukodystrophy is the most common peroxisomal disorder. The classic clinical picture is one of a male of approximately 10 years old who presents with hyperactive behavior, psychomotor abnormalities, and vision loss. Very-long-chain fatty acids are increased in the serum, leading to demyelination due to the lipotoxicity-induced neuroinflammation. Optic nerve atrophy and a normal retina are seen. Visual loss is due to cortical blindness and may be the presenting or predominant feature of the disease. Treatment consists of corticosteroids and dietary fatty acid restriction.

Peroxisomal Diseases: Refsum Disease

In classical Refsum disease (heredopathia atactica polyneuritiformis; not to be confused with infantile Refsum disease), the metabolism of phytanic acid is disturbed. This leads to chronic polyneuropathy, cerebellar ataxia, and cardiomyopathy. Ophthalmic abnormalities include cataract, retinitis pigmentosa, and optic nerve atrophy. Loss of visual acuity, as well as loss of visual field due to retinitis pigmentosa, usually precedes the biochemical diagnosis by several years [139]. A phytol-free diet can limit or even prevent the neurological damage in case of early diagnosis and initiation of diet.

Neoplastic Diseases with Kidney and Ocular Involvement

von Hippel-Lindau Disease

von Hippel-Lindau disease (VHL) is a rare, familial, autosomal dominant cancer predisposition syndrome caused by germline mutations in the VHL gene. The loss of function of the corresponding tumor suppressor protein results in the development of highly vascular tumors, both benign and malignant. The disease is

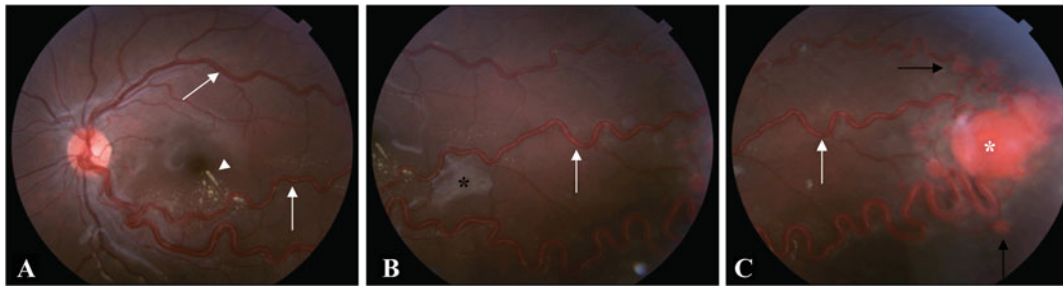

Fig. 27.8 Retinal capillary hemangioblastomas in von Hippel-Lindau disease. Tortuous, dilated feeder vessels (*arrows*) traverse from the posterior pole (**a**) via the midperiphery (**b**) to the hemangioblastomas, which are located in the peripheral retina (**c**). In this case, there is one large hemangioblastoma (*white asterisk*) and several smaller ones (*black arrows*). Lipoid exudates (*white arrowhead*) inferior to the macula and fibrosis (*black asterisk*) are also visible. The retinal capillary hemangioblastomas may remain asymptomatic for years, and spontaneous regression is possible. However, progressive visual impairment is the rule, and patients frequently present with decreased visual acuity due to exudation or tractional effects on the adjacent retina. Hemorrhage and secondary retinal detachment can also occur

characterized by multisystemic tumors. These include renal cell carcinoma, retinal and central nervous system hemangioblastomas, pancreatic neuroendocrine tumors, neuroendocrine tumors of the adrenal glands, and tumors in the liver and on the broad ligament. Although the penetrance of the disease as a whole is near complete [140], the risk of each particular tumor depends on the patient's age and the type of tumor. The cumulative risk of developing retinal capillary hemangioma (RCH), cerebellar hemangioblastoma, and renal cell carcinoma is 44%, 38%, and 5%, respectively, at 30 years and 84%, 70%, and 69% at 60 years [141]. Patients thus most typically present first with an RCH, which can be both bilateral and multifocal [142–144]. Although the RCH is not present in every patient with VHL, it is among the core diagnostic criteria of the disease [145].

The RCHs are found either peripherally or in the juxtapapillary retina. On funduscopy, the retinal lesion is yellow-orange and is well circumscribed, with a dilated feeder artery and a tortuous draining vein (Fig. 27.8). In some cases, a vascular proliferation consisting of fine, superficial, juxtapapillary vessels is noted [146]. These can be associated with fibrovascular proliferation and epiretinal membrane formation. The RCH may remain asymptomatic for years, and spontaneous regression is possible. However, progressive visual impairment is the rule, and patients will frequently present with decreased visual acuity due to exudation or tractional effects on the adjacent retina [147]. Hemorrhage and secondary retinal detachment can also occur [148]. Visual prognosis is markedly improved by early detection and treatment, which typically involves the destruction of the tumor by laser photocoagulation, cryotherapy, photodynamic therapy, and radiation, or, rarely, surgical excision [149, 150]. Treatment is only effective in early stages, before the RCH has become too large or has caused secondary complications.

Discovery of an RCH should prompt a systemic evaluation and search for associated VHL manifestations. These tumors may occur years after the diagnosis of the RCH. It is thus imperative that these patients be followed regularly, with thorough assessment of those organ systems typically involved in VHL (kidney, adrenals, CNS). Lifelong ophthalmologic follow-up is recommended. Because of the disease's autosomal dominant inheritance, family members should also be screened. This should include neurological, medical, and ophthalmologic screening as well as computed tomography (CT) scan of the abdomen, brain, and upper cervical spinal cord; ultrasound of the kidneys, liver, and pancreas; and measurement of the catecholamine levels via serologic or urinary samples.

Light Chain Deposition Disease

Various lymphoplasmacytic disorders such as lymphoma, multiple myeloma, and Waldenström's macroglobulinemia are associated with the overproduction and systemic extracellular deposition of monoclonal immunoglobulin light chains. These light chains can deposit in tissues and cause two separate conditions: AL amyloidosis and light chain deposition disease (LCDD). The condition depends on the conformation of the light chain (LC) deposits. Whereas AL amyloid results from the conversion of monoclonal light chains into twisted β-pleated sheets, in (LCDD), the light chains fail to assume a β-pleated sheet configuration. Under electron microscopy, AL amyloid has a fibrillar appearance, while LCDD deposits are granular.

The clinical manifestations of LCDD depend on which tissues are involved in the LC deposition and the consequent organ dysfunction. Because the LCs are filtered by glomeruli, reabsorbed by the proximal tubules, and degraded in tubular cells, the kidney is an obvious target for LC deposition and the ensuing damage. Kidney disease manifests in the form of renal insufficiency in nearly all patients, and it rapidly proceeds to uremia despite early and aggressive treatment [151]. Transplantation is frequently required, and patient survival was poor until recently [152]. Diagnosis of the underlying lymphoproliferative disease is usually made first; LCDD is diagnosed via renal biopsy, which shows the classic picture of nodular sclerosing glomerulopathy in approximately 50% of cases [153].

Ocular pathology in LCDD is caused by the deposition of LCs in the uvea, including the ciliary body, pars plana, and choroid. The iris seems to be spared. Ocular involvement was first reported in 1995 in a postmortem oculopathologic case report that demonstrated dense deposits in the choroid and in Bruch's membrane [154]. The deposits form a PAS-positive layer beneath the RPE, closely resembling those of Kimmelstiel-Wilson disease in the kidney. In vivo visual impairment and fundus changes have been reported in a case series [155]. Patients with long-standing LCDD can present with night blindness, poor dark adaptation, metamorphopsia, and/or decreased visual acuity. Fundus examination reveals serous and serohemorrhagic retinal pigment epithelium (RPE) detachments, multiple tears, and diffuse degeneration of the RPE, as well as progressive fibrotic changes (Fig. 27.9).

Neither choroidal neovascularization nor other choroidal or retinal vascular abnormalities are present. ICGA shows normal retinal and choroidal perfusion and no choroidal neovascularization. An unusually dark choroid is observed under the areas of massive RPE detachment. The electroretinogram of these long-standing cases of LCDD is severely affected or almost entirely

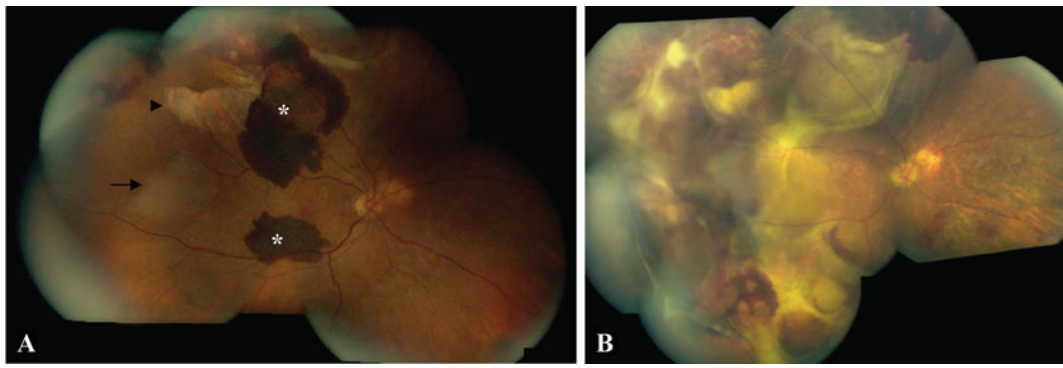

Fig. 27.9 Light chain deposition disease: A patient presented with a several-year history of poor vision in the left eye and recent loss of vision in the right eye. Color fundus photography of the right eye (**a**) showed a recent tear (*arrow*) and an older tear (*arrowhead*) of the retinal pigment epithelium as well as extensive hemorrhages (*asterisks*) in the right eye. Extensive fibrosis and progressive devastation of the posterior pole were observed at 13 months after initial presentation (**b**)

flat. Autofluorescence showed numerous large, very dark atrophic areas and diffuse RPE abnormalities.

It has been proposed that the progressive LC deposition in choroid and Bruch's membrane leads to dysfunction of the RPE pump function, causing a flow disturbance between choroid and retina and subsequent RPE detachments and tears and progressive retinal malfunction [156]. Visual function slowly deteriorates in cases with long follow-up, combining reduction of the visual field and loss of visual acuity. We assume that the long-term visual prognosis of all patients with LCDD is guarded, taking into account that renal function replacement and pharmacological treatment have considerably prolonged life in these patients.

Controversies and Perspectives

In 1836, Bright described amaurosis in end-stage renal disease. After the introduction of the ophthalmoscope by von Helmholtz in 1951, Liebreich reported in 1859 albuminuric retinitis or Bright's disease. In 1860, von Graefe and Schweigger suggested that ocular lesions could be caused by generalized disorders of the vascular system and that in these conditions the kidneys could be affected as well. In 1914, Volhard and Fahr attributed the retinopathy in patients with nephritis to arterial hypertension. Later reports stressed that renal failure can induce arterial hypertension. Today, arterial hypertension is still a very common and important cause of morbidity and mortality. Severe hypertensive retinopathy is at present rare, but hypertension-induced sclerosis is a major cause of retinal vascular accidents and macular edema with visual loss. The other major cause of ocular and kidney disease of modern times is diabetic microangiopathy, with retinopathy and nephropathy requiring optimal lifelong treatment to avoid high morbidity and mortality. In other systemic diseases, such as thrombotic thrombocytopenic purpura, dense deposit disease, and light chain deposition disease, the high vulnerability of the retina and kidney is evident.

Developmental anomalies of kidneys and eyes were previously described as papillorenal syndrome, and familiar occurrence was recognized, with an autosomal dominant pattern of inheritance. At present, genetic testing is available to screen for an underlying PAX 2 mutation.

Intense genetic and biochemical research has resulted in the identification of a wide spectrum of multisystem diseases with a specific metabolic or structural defect. Some of these diseases predominantly affect kidneys and eyes. For example, Alport syndrome is a hereditary disorder caused by mutations in the biosynthesis of type IV collagen. This collagen subtype is a crucial structural component of the basement membrane in the glomerulus, retina, lens capsule, and cochlea. A second example is the cancer predisposition syndrome von Hippel-Lindau disease, which confers a strong predisposition for renal cancer and for neurological and ocular problems caused by angiomas. In suspected persons and family members of patients with von Hippel-Lindau disease, genetic testing is highly recommended, as carriers of the disease have to be examined on a regular basis and treatment must be considered.

In conclusion, oculorenal syndromes represent a heterogeneous group of malformations and systemic diseases with particular and unusual ocular and renal features. Historically, these syndromes were classified according to their Mendelian pattern of inheritance or according to related diseases without Mendelian inheritance. In this chapter, we classified the diseases based on the actual understanding of the disorders.

Focal Points

- The kidney and eye are closely linked in many diseases, both common and rare. Developmental problems of kidney and eyes can share a common genetic underground. An example is the PAX2 mutation, inherited as an autosomal dominant disease with extremely variable expression. Patients can present with a blind, microphthalmic eye and end-stage renal disease requiring renal function replacement, while family members with the same

genetic defect may have minor changes such as an optic pit or a small kidney without functional abnormalities.

- Patients with the cancer predisposition syndrome von Hippel-Lindau are at risk for renal cancer and for development of angiomas with neurological and ocular complications. Genetic screening is recommended for suspected persons and for direct family members of patients with von Hippel-Lindau.
- Metabolic defects can induce renal and ocular changes and malfunction, and in some of these diseases, an underlying genetic defect has been identified. An example is cystinosis, a rare autosomal recessive disorder caused by the mutation of the CTNS gene, leading to defective transport of cystine out of the cellular lysosome. The kidney and the cornea are particularly vulnerable to the ensuing crystal formation. Renal insufficiency, photophobia, and poor vision are frequent complications.
- The most common metabolic disease affecting eye and kidney is diabetes mellitus, in which patients develop microvascular changes in the retinal and capillary beds leading to microalbuminuria and renal failure and to macular edema and proliferative diabetic retinopathy.
- Alport syndrome is an example of a structural defect responsible for combined renal and ocular disease. The disorder is caused by mutations in the biosynthesis genes of type IV collagen, a crucial component of the basement membrane in the glomerulus, retina, lens capsule, and cochlea. Affected patients suffer from renal failure, deafness, and ocular changes with maculopathy, lenticonus, and fragile cornea.
- The ciliopathies are a group of recently identified disease entities with cilial malfunction. Cilia are common organelles present on nearly every cell in the human body and important in embryogenesis (nodal cilia), fluid and cell movement (motile cilia), and visual and renal function (primary cilia). In the retina, the primary, or sensory, cilium of photoreceptors mediates polarizing trafficking of proteins for efficient phototransduction. Genetic defects in these cilia lead to retinal dysfunction. Retinal and renal dysfunction is observed across a range of ciliopathies. An example is Senior-Loken syndrome. In the kidney, the primary apical cilia are affected, and in the retina, the outer segments of photoreceptor cells are affected, which are specialized sensory cilia. Manifestations of disease are nephronophthisis with renal dysfunction and retinal dystrophy.
- Arterial hypertension can occur in acute renal conditions and is a frequent complication in long-term renal conditions. The repercussions in the ocular fundus are well known. Due to improved treatment of arterial hypertension and kidney disease, severe hypertensive retinopathy is now less frequently observed than in the past. However, long-standing arterial hypertension, together with aging, leads to sclerotic vasculature and to ocular and nonocular vascular accidents, which are very common problems today.
- Systemic diseases associated with microangiopathy, vasculitis, or diffuse intravascular coagulation can cause both renal and ocular vascular lesions. In lupus erythematosus, sarcoidosis, periarteritis nodosa, Wegener's disease, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome, the clinical picture is often dominated by renal insufficiency and a marked decrease in visual acuity.
- Dysregulation of the alternative complement pathway is present in dense deposit disease, combining membranoproliferative glomerulonephritis type 2, partial lipodystrophy, and AMD-like fundus changes.

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Index

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