Retina Atlas

Series Editors: Sandeep Saxena · Richard F. Spaide · Eric H. Souied · Timothy Y.Y. Lai

Inflammatory and Infectious Ocular Disorders

Hyeong Gon Yu
Editor

Springer

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Series Editors

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About the Editor

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Acute Posterior Multifocal Placoid Pigment Epitheliopathy

1

Dae Joong Ma

Introduction

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is a rare inflammatory eye disease affecting the outer retina, retinal pigment epithelium (RPE), and choriocapillaris in mostly otherwise healthy adults between the ages of 20 and 50 years. It shows no clear gender preference. APMPPE was first described by Gass in 1968 in a series of three young female patients who presented with multiple large plaque-like lesions at the level of the RPE associated with temporary bilateral visual loss (Gass 1968). APMPPE is considered one of the "placoid diseases" together with serpiginous choroiditis (SC), relentless placoid chorioretinitis, and persistent placoid maculopathy due to the "placoid" nature of the lesions and similarities on fluorescein angiography (FA) and indocyanine green angiography (ICGA) findings (Mirza and Jampol 2012).

Etiopathogenesis

The etiology and pathogenesis of APMPPE is uncertain. It is currently believed to be an inflammation of the outer retina and RPE (Gass 1968) or secondary to a hypersensitivity-induced obstructive vasculitis, resulting in ischemic injury of the overlying RPE and photoreceptor (Heiferman et al. 2017).

Clinical Features

A history of an antecedent viral or flu-like illness or recent vaccination was reported in over one third of patients (Gass 1968; Holt et al. 1976). Patients manifest with a sudden onset of visual blurring, scotoma, metamorphopsia, or photopsias (Fiore et al. 2009). Initial visual acuity is 20/25 or worse in 76.6% of eyes and 20/40 or worse in 58.3% but rarely worse than 20/400 (Fiore et al. 2009; Smith et al. 1978). The disease usually shows a bilateral involvement at presentation or sequential involvement with an interval of days to weeks. Anterior segments may have no or mild non-granulomatous inflammation (1+ to 2+) (Lowes 1977; Alvi and Fishman 1995). The vitreous may also show a mild to moderate inflammation.

The acute presentation is multiple, round, and confluent creamy gray-white plaques, typically 1- to 2-disc areas in size (Figs. 1.1a, b and 1.2a). The lesions are typically bilateral and normally confined to the posterior to the equator. Active lesions can develop and evolve over the course of several weeks, and lesions of various stages may appear simultaneously (Figs. 1.1c, d and 1.2b, c). After acute stage, the lesions typically resolve centrally resulting in hypopigmentation. Later, lesions develop mild pigment mottling and pigment condensation. Finally, coarse pigment clumping increases over several months (Figs. 1.1e, f and 1.2d).

Atypical APMPPE with localized serous retinal detachments have been reported, which resembles Vogt–Koyanagi–Harada disease (Birnbaum et al. 2010; Garg and Jampol 2004). The occurrence of choroidal neovascularization (CNV) (Fig. 1.3) (Bowie et al. 2005), optic disc edema (Abu El-Asrar and Aljazairy 2002; Frohman et al. 1987), subhyaloid hemorrhage (De Souza et al. 1999), retinal vasculitis (De Souza et al. 1999; Abu El-Asrar and Aljazairy 2002; Thomas et al. 2012), or retinal vein occlusion has also been reported (Abu El-Asrar and Aljazairy 2002; De Souza et al. 1999).

In the acute stage of the disease, the active cream-colored lesions block the choroidal fluorescence during the early phases of FA (Fig. 1.4b). Irregular staining was observed in the lesions that had previously blocked fluorescence in the later phase of FA (Fig. 1.4c). In the late or resolved stage of the disease, the mottled RPE demonstrate window defects without leakage.

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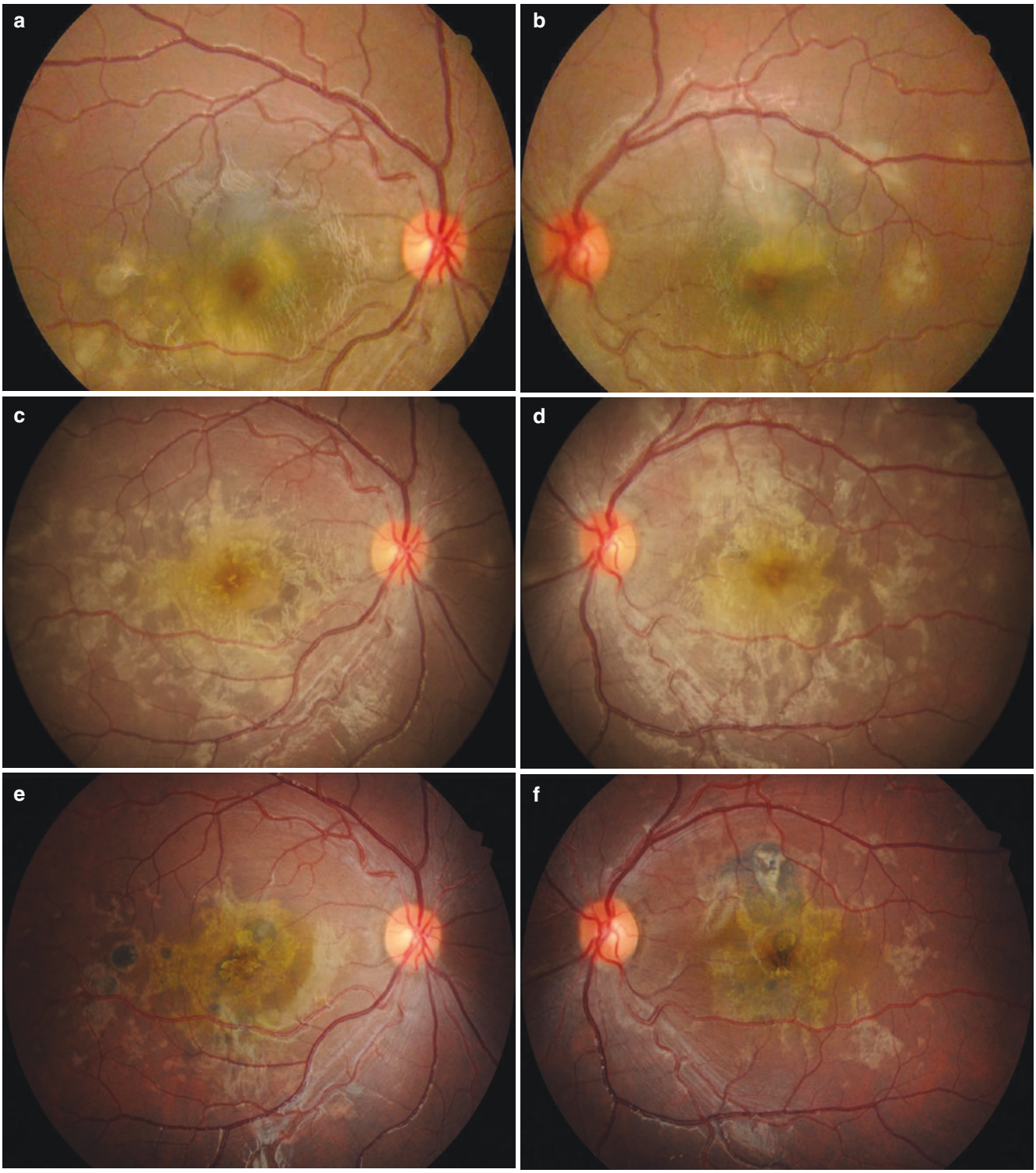

Fig. 1.1 Color fundus photography of a 29-year-old male. (**a**, **b**) Initial presentation. (**c**, **d**) Two weeks. (**e**, **f**) Sixteen months after initial presentation

In ICGA, acute lesions show hypocyanescence in the early phase (Fig. 1.4d) and become more defined in shape in the late phase (Fig. 1.4e). These hypocyanescent lesions are numerous than the lesions observed on funduscopy and FA. Unlike FA, deep choroidal vessels are visible within the active lesion during early phase of ICGA and no hypercyanescence develops in the late phase. These findings support the hypothesis that the active APMPPE lesions result

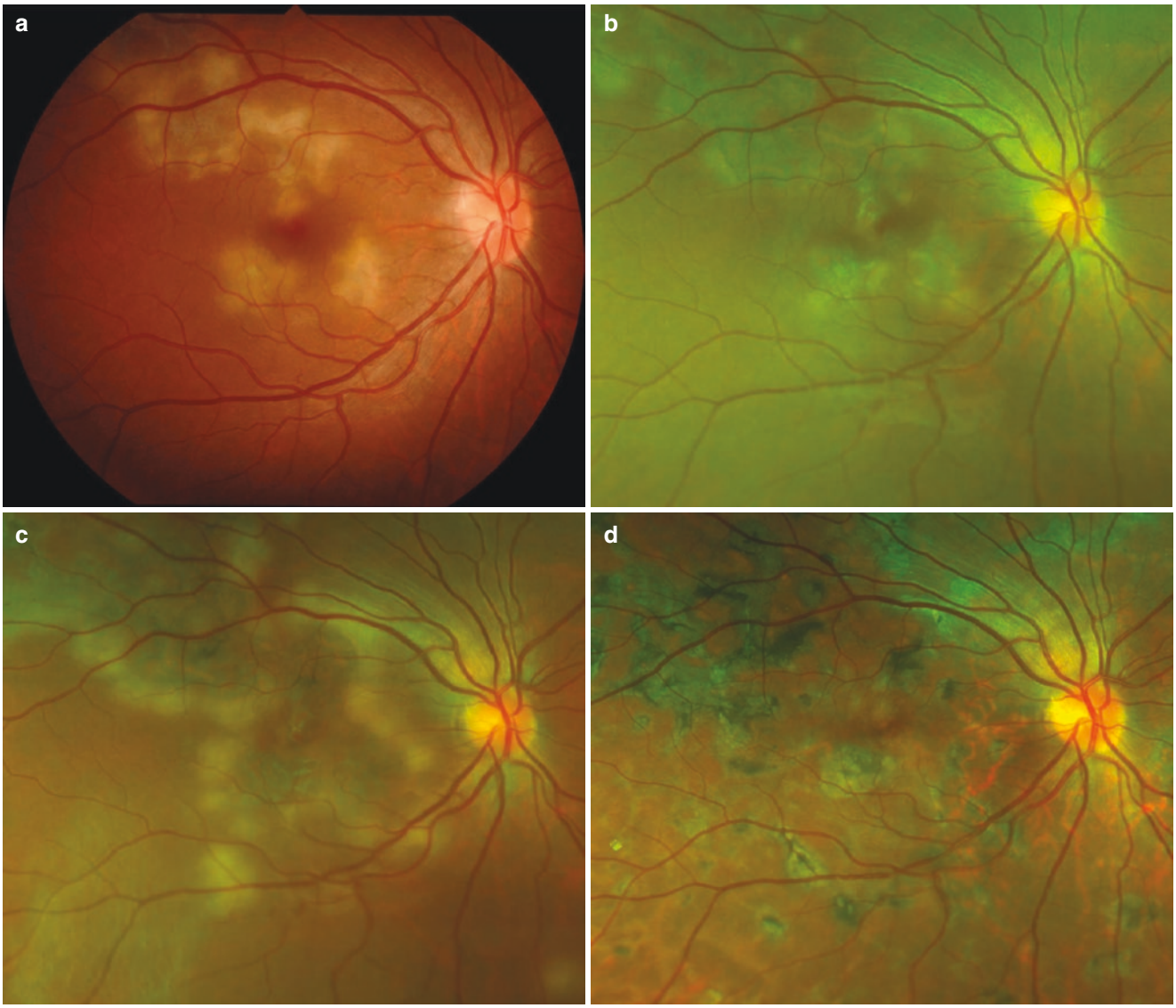

Fig. 1.2 Color fundus photography of a 33-year-old female. (**a**) Initial presentation. (**b**, **c**) One and 4 weeks after initial presentation. Fresh lesions and lesions at various stages are observed simultaneously. (**d**) Six months after initial presentation, hypopigmentation with coarse pigment clumping has developed

from the choriocapillaris nonperfusion presumably due to inflammation (Hedges et al. 1979). The hypocyanescence becomes less defined and smaller in the late or resolved stage of the disease, as disappearance of the outer retina or RPE swelling, which support the alternative hypothesis suggesting the primary inflammation of the outer retina and RPE (Gass 1968).

Spectral-domain optical coherence tomography (SD-OCT) reveals disruption of the outer retina early in the disease (Fig. 1.5, white arrow). As the lesions heal, RPE disruption occurs (Fig. 1.5, arrow head). Fluid associated with the placoid lesions has also shown in some patients, which is speculated as an intraretinal fluid accumulation rather than an exudative retinal detachment (Garg and Jampol 2004; Montero et al. 2011). Recent studies with optical coherence tomography angiography revealed choriocapillaris flow abnormalities extending beyond the SD-OCT lesions in acute APMPPE and reversible choroidal hypoperfusion in healed APMPPE lesions (Kinouchi et al. 2017; Burke et al. 2017). These findings suggest that the decreased blood flow consistent with choriocapillaris results in an ischemic RPE insult, rather than primary inflammatory change in RPE (Heiferman et al. 2017).

Spaide reported that the early hypofluorescent areas observed on FA did not match up precisely with the RPE changes on fundus autofluorescence (FAF), which suggests that the presence of choriocapillaris perfusion defects (Spaide 2006). Meanwhile, the staining of the lesion in the late phase FA matched the lesions observed on FAF in shape and size.

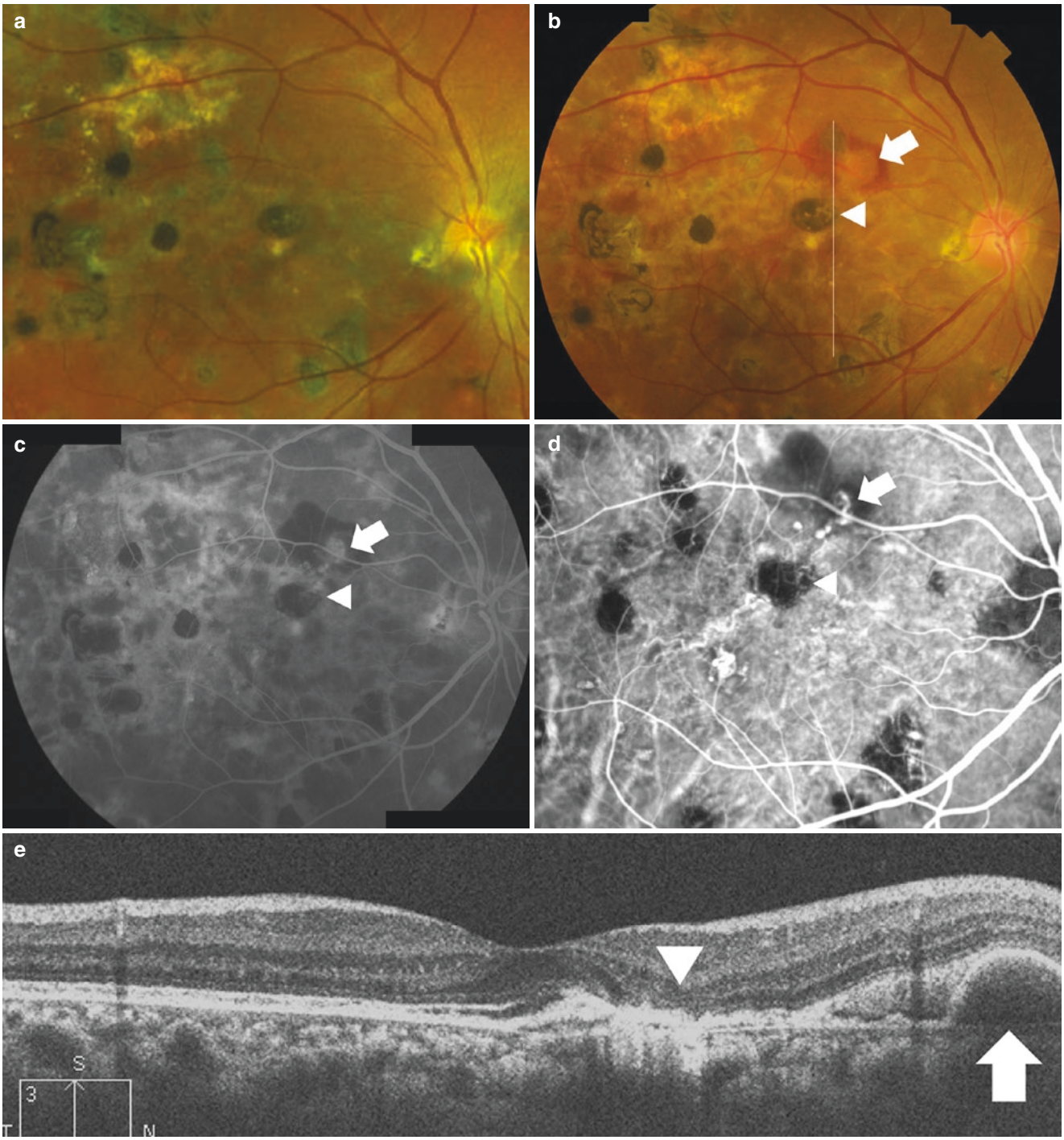

Fig. 1.3 Development of choroidal neovascularization (CNV). (**a**) Healed acute posterior multifocal placoid pigment epitheliopathy lesion of a 65-year-old female. (**b**) Five months later, subretinal hemorrhage (SRH) and pigment epithelial detachment (PED) were developed (white arrow). (**c**, **d**) In contrast to healed hypofluorescent and hypocyanescent lesion (arrow head), new hyperfluorescent and hypercyanescent CNV was observed (white arrow). (**e**) Optical coherence tomography shows the healed lesion with the outer retina disruption (arrow head) and new CNV lesion with SRH and PED (white arrow)

These findings also support that the hypothesis that the RPE abnormalities resulted from the choroidal abnormalities (Spaide 2006). As resolving, the placoid lesions contracts centripetally and develop pigmented core with a depigmented halo. On FAF, these lesions are observed as intense hyperautofluorescence surrounded by hypoautofluorescence. These autofluorescence changes follow the clinical appearance (Spaide 2006).

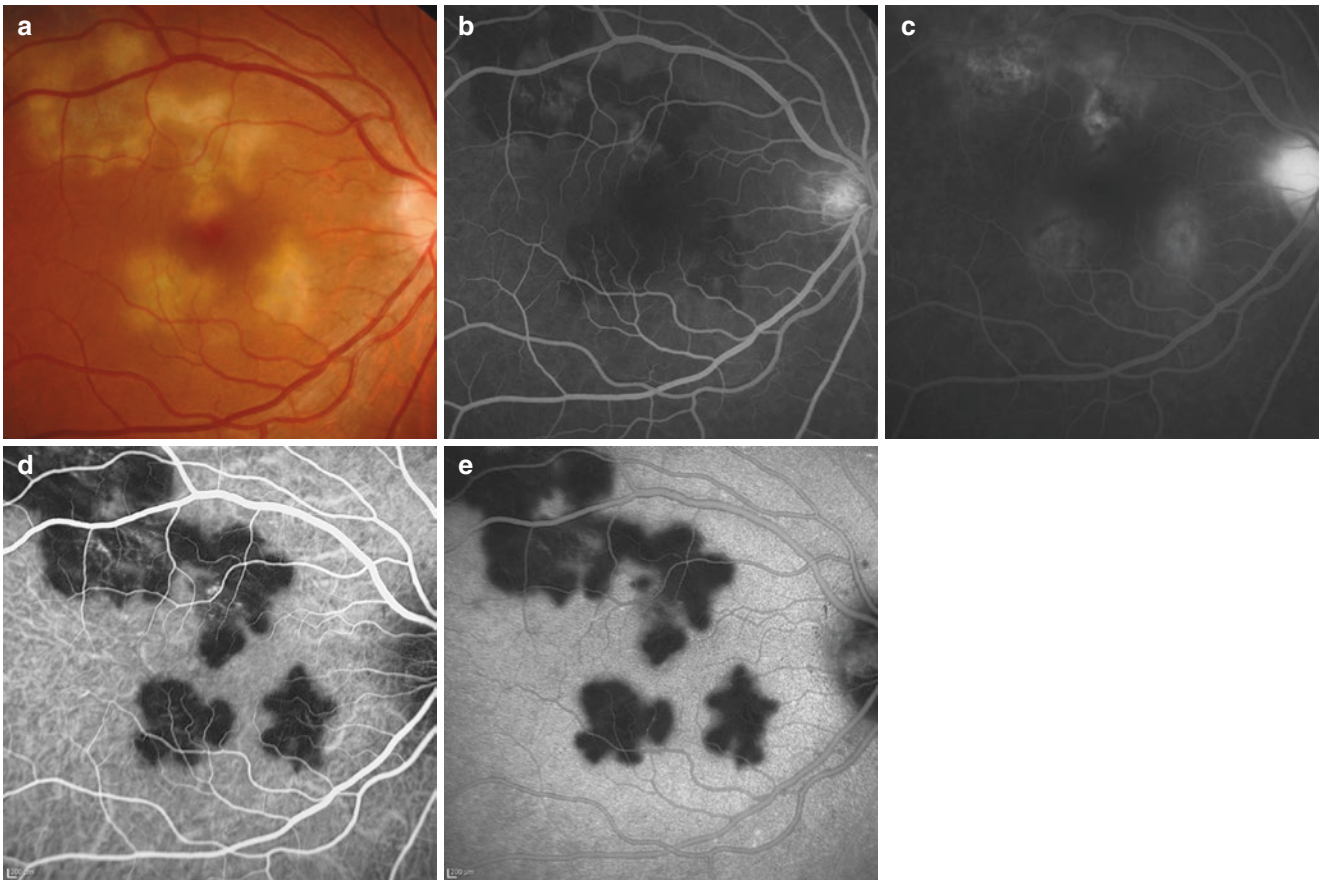

Fig. 1.4 Fluorescein angiography (FA) and indocyanine green angiography (ICGA) of the patient in Fig. 1.2. (**b**) Early phase FA shows hypofluorescence at the placoid lesions observed in the color fundus photography (**a**). (**c**) Late phase FA shows hyperfluorescence with irregular staining in the placoid lesions. (**d**, **e**) Early and late phase ICGA shows hypocyanescence which are greater than the extent of placoid lesions observed in color fundus photograph and FA

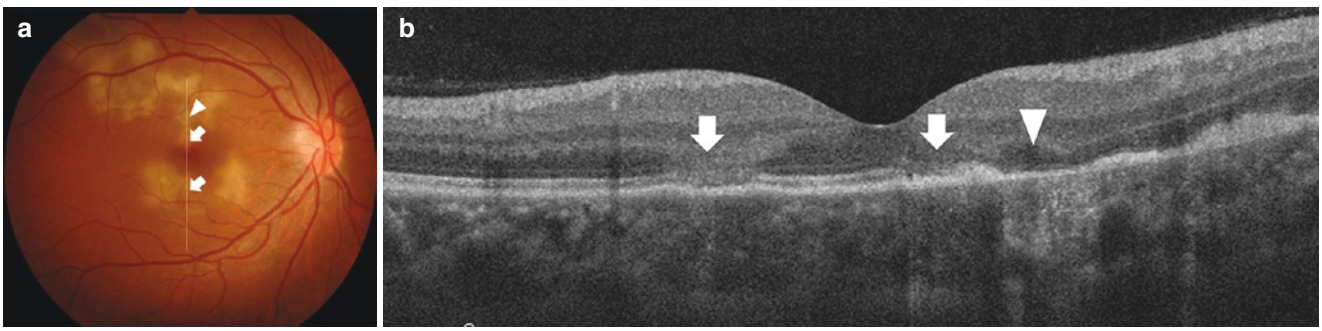

Fig. 1.5 Optical coherence tomography shows disruption of the outer retina (white arrow) and retinal pigment epithelium disruption (arrow head) at the placoid lesion

Differential Diagnosis

Diagnosis of APMPPE can be challenging because several diseases of different etiologies can also present with the similar clinical signs. The most challenging differential diagnosis might be SC, but clinical differentials do exist. SC usually starts from the optic disc and progresses in a serpentine fashion, while APMPPE lesions are always around the macula (Sudharshan et al. 2010; Annamalai et al. 2012). Scar formation is more prominent in SC and is not a characteristic feature in APMPPE. It can take up to a few years to develop signs in the fellow eye after unilateral involvement of SC lesion, while APMPPE is usually symmetrical in presentation (Annamalai et al. 2012).

Because of considerable overlap between APMPPE and SC, a term "Ampiginous choroiditis" has been used (Nussenblatt et al. 1996). However, some authors differentiate ampiginous choroiditis from SC and APMPPE based on the following points. Ampiginous choroiditis has smaller lesion than SC and APMPPE, approximately ½ disc area. Unlike SC, ampiginous choroiditis usually occurs in the mid-periphery and periphery, and the posterior pole may be involved later. Ampiginous choroiditis lesions are recurrent unlike APMPPE, and the active lesions show central hypofluorescence with hyperfluorescent margins in FA in contrast to the blocked fluorescence observed in APMPPE (Jyotirmay et al. 2010).

Management

In contrast to the previous reports with a good visual prognosis and a benign course (Gass 1968; Williams and Mieler 1989; Fitzpatrick and Robertson 1973), recent studies reported limited visual recovery in some patients (Wolf et al. 1991; Vianna et al. 1993; Fiore et al. 2009). The visual prognosis strongly depends on the presence of the foveal involvement at the initial presentation. Approximately 60% of the eyes have residual symptoms at the final visit (Fiore et al. 2009).

There is no definite guideline for the treatment of acute APMPPE. While some studies showed benefits of systemic corticosteroids (Deutman et al. 1972; Kirkham et al. 1972), others reported no change in prognosis despite treatment (Gass 1968; Annesley et al. 1973; Fitzpatrick and Robertson 1973). Some authors support the use of corticosteroids when there is macular involvement or central nervous system involvement (O'Halloran et al. 2001; Birnbaum et al. 2010; Brezin et al. 1995). El-Markaby and colleagues reported that the use of tumor necrosis factor blockers in severe cases of APMPPE resulted in significant visual improvement without recurrence (El-Markaby et al. 2012). In case of CNV development, anti-vascular endothelial growth factor agents have been found to be useful in treatment (Mavrakanas et al. 2010; Battaglia Parodi et al. 2010).

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Serpiginous Choroiditis

2

Narsing A. Rao and Julie You Kwon

Introduction

Serpiginous choroiditis (SC) is a rare, progressive, recurrent, idiopathic posterior choroidal inflammatory disease affecting retinal pigment epithelium (RPE), choriocapillaris, and choroid. It is characterized by a geographic pattern of choroiditis that typically extends from the peripapillary area in a serpentine, pseudopodial fashion. It was first described by Hutchinson who noted a pattern of choroidal inflammation that appeared progressive with active borders in otherwise healthy patients or in patients with tuberculosis or syphilis (Hutchinson 1900). In 1970, Gass coined the entity *serpiginous choroiditis*, because of its wavy margins at the borders and recurrent choroidal inflammation that spread in a centrifugal fashion (Gass 1970).

Serpiginous choroiditis is characterized by a geographic pattern of grayish yellow discoloration representing juxtapapillary choroidal inflammation that extends in serpentine manner (Fig. 2.1). In literature, this entity has been previously described as peripapillary chorioretinitis (Gass 1997), helicoid peripapillary choroidal degeneration (Franceschetti 1962), geographic choroiditis, geographic choroidopathy (Hamilton and Bird 1974), and geographic helicoid peripapillary choroidopathy (Schatz et al. 1974).

Classic serpiginous choroiditis can be subdivided into either juxtapapillary serpiginous or macular serpiginous choroiditis, depending on the main area of geographic lesion. Infectious choroiditis from *Mycobacterium tuberculosis*, herpesvirus, or *Treponema pallidum* can mimic serpiginous choroiditis, and these infectious choroiditis are known as serpiginous-like and multifocal serpiginoid choroiditis (Nazari Khanamiri and Rao 2013). This chapter will focus on the classic serpiginous choroiditis.

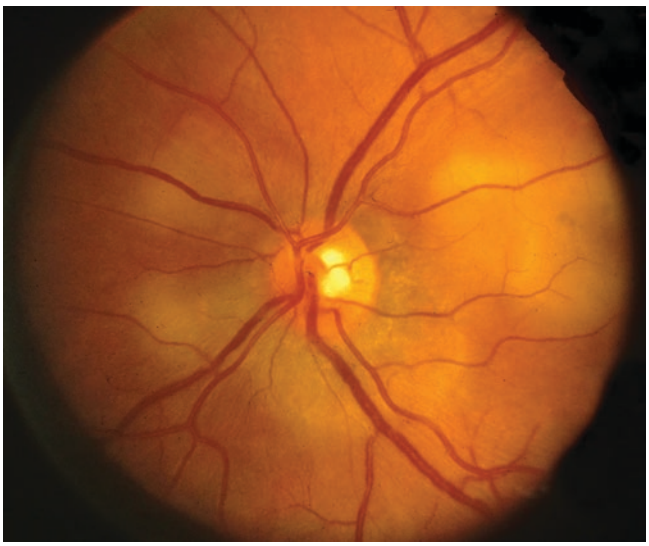

Fig. 2.1 Fundus findings of serpiginous choroiditis in active phase. Note the creamy yellow lesions emanating from peripapillary choroid

Epidemiology and Clinical Features

The prevalence of SC is rare, and reported cases in literature ranges from 0% to 5.4% of posterior uveitis with the highest reported cases in India. (Biswas et al. 1996; McCannel et al. 1996; Nazari Khanamiri and Rao 2013) SC has been traditionally reported as a disease of otherwise healthy Caucasians; the high reported percentage of cases in India may represent the tuberculosis variant of multifocal serpiginous choroiditis. Patients with SC are usually otherwise healthy, middle-aged, in fifth to sixth decade, although the age range can vary widely from 11 to 70 years (Abrez et al. 2007; Nazari

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Khanamiri and Rao 2013). There is a slight gender predilection for males (Abrez et al. 2007).

Serpiginous choroiditis is typically bilateral, but patients may present asymmetrically. Patients may complain of blurred vision or small central or paracentral scotoma. They may be asymptomatic before foveal involvement. The average time between presentation in one eye and onset in the other eye may be up to 5 years (Chisholm et al. 1976).

On clinical exam, serpiginous choroiditis is predominantly a posterior uveitis with minimal to no anterior chamber inflammation; vitritis may be present in about 30% of the cases, and it is mild (Mirza and Jampol 2006). The creamy-white lesions emanate in pseudopodial fashion from the optic nerve. Disease activity is confined to the leading edge of the lesion and may be associated with shallow subretinal fluid and/or vascular sheathing. It shows choriocapillaris and RPE atrophy and subretinal fibrosis (Fig. 2.2). RPE hyperpigmentation is present at the periphery of the lesions. New lesions occur on the border of old scars (Fig. 2.3). Vision may be severely affected if choroidal neovascularization in macula occurs, which can happen in up to 25% of cases (Christmas et al. 2002; Jampol et al. 1979; Laatikainen and Erkkila 1981). Final visual outcome can range from 20/200 to count fingers.

In about one third of patients, patients may present with creamy yellow lesions solely in the macula, termed macular serpiginous choroiditis (Fig. 2.4) (Hardy and Schatz 1987; Mansour et al. 1988). Choroidal neovascularization develops more frequently and earlier in the course of the disease, thereby carries a poorer prognosis.

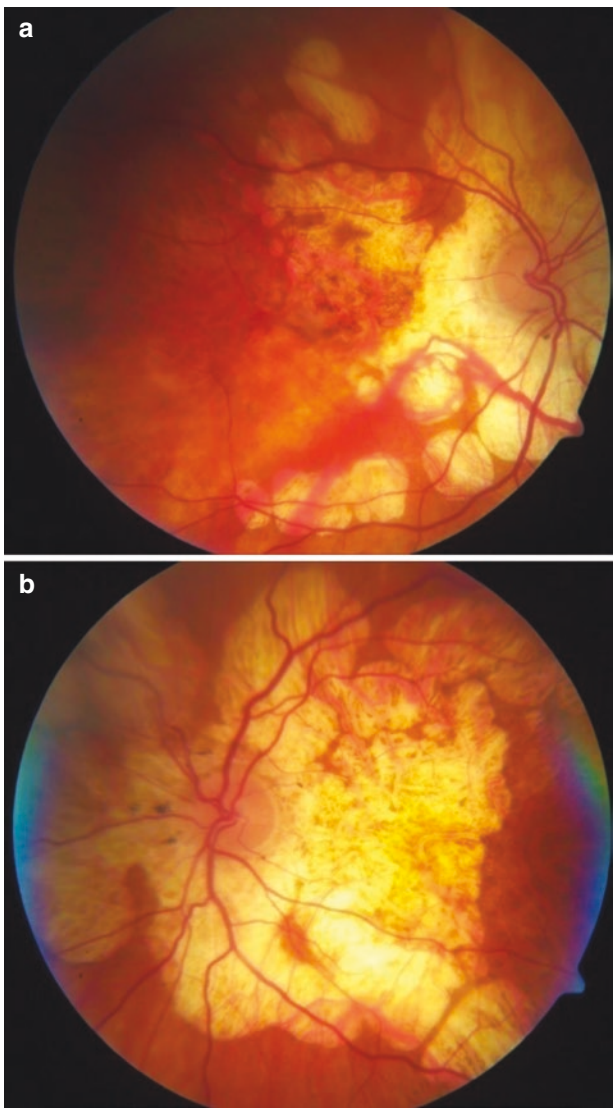


Fig. 2.2 Color fundus photograph shows right (**a**) and left (**b**) eyes with classic juxtapapillary serpiginous choroiditis in chronic phase emanation from peripapillary choroid and RPE damage affecting the macula

Pathogenesis

The etiology of serpiginous choroiditis is unknown; possible etiologies may be autoimmune, infectious, vascular, or degenerative (Mirza and Jampol 2006). There is no consistent HLA association with SC, although there appears to be a higher frequency of HLA-B7, HLA-A2, HLA-B8, and HLA-Dw3 (Laatikainen and Erkkila 1981). Broekhuyse and colleagues also found an immune response to retinal S antigen but not to opsin, in SC (Broekhuyse et al. 1988). Given that clinical and imaging studies localize the inflammatory disease of SC to choroid and RPE, the sensitivity to retinal S antigen may be a secondary effect due to extensive damage of retina by serpiginous choroiditis. In histopathology of serpiginous lesion, there is extensive loss of RPE with loss of overlying retina and monocular cell infiltrate in choriocapillaris (Wu et al. 1989). SC responds remarkably well to anti-inflammatory effects of steroids and immune-suppressive therapy. It has been hypothesized that SC is an autoimmune and organ-specific disease of the eye (Nazari Khanamiri and Rao 2013).

Imaging and Ancillary Diagnostic Tools

Fluorescein and indocyanine green angiography support the diagnosis and management of SC. Progression can be followed with fundus autofluorescence imaging. Choroidal neovascularization, RPE changes, and atrophy can be followed with optical coherence tomography (OCT). Newer studies like microperimetry and optical coherence tomography angiography (OCT-A) are gaining importance in the management of the disease.

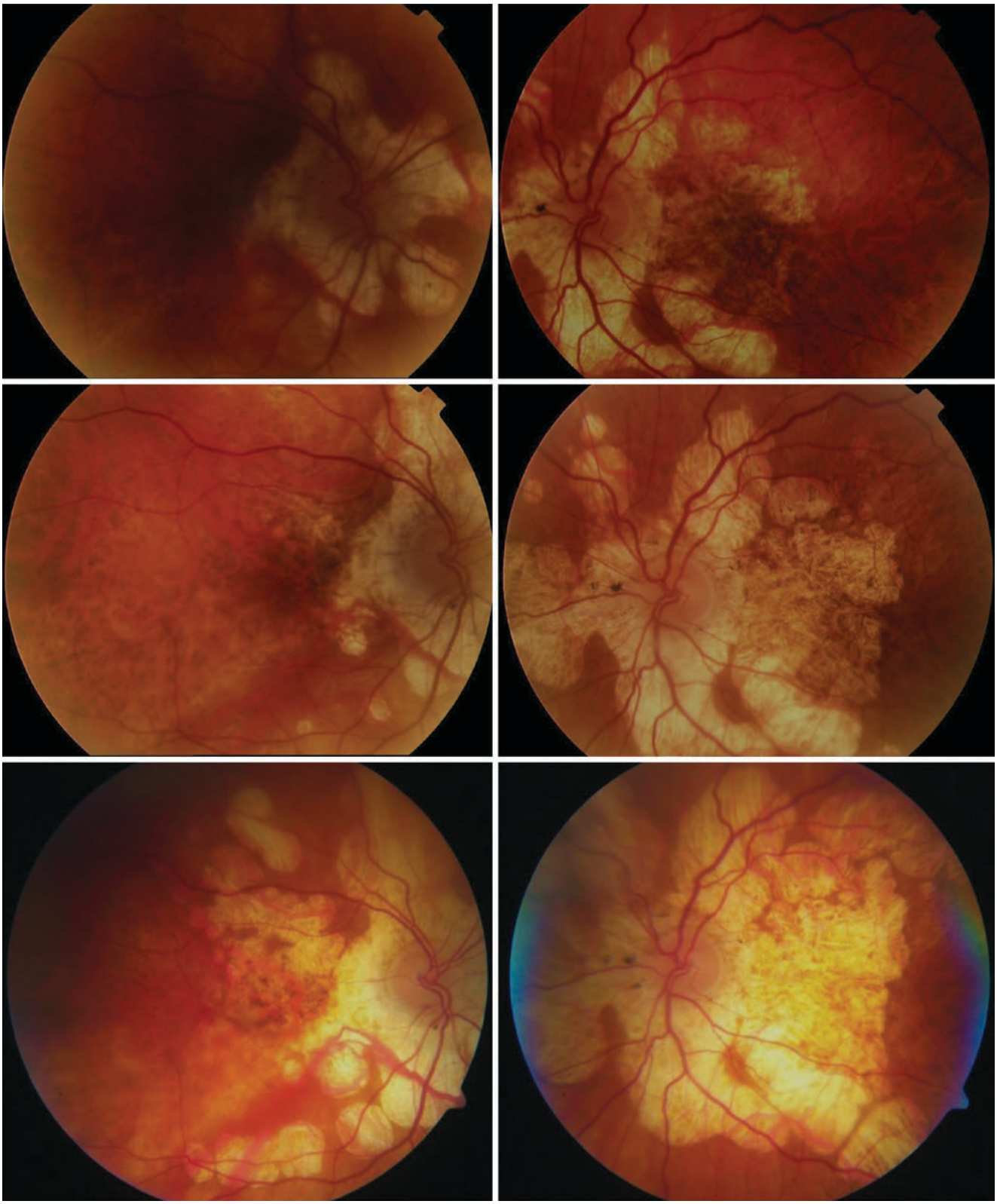


Fig. 2.3 Progression of serpiginous choroiditis in a 76-year-old Caucasian woman from December 2001 (top), March 2004 (middle), to April 2008 (bottom). The choroiditis extends in a juxtapapillary fashion, extending from the leading edge of a lesion. This patient has been reported in part in cited references (Nazari Khanamiri and Rao 2013 with permission)

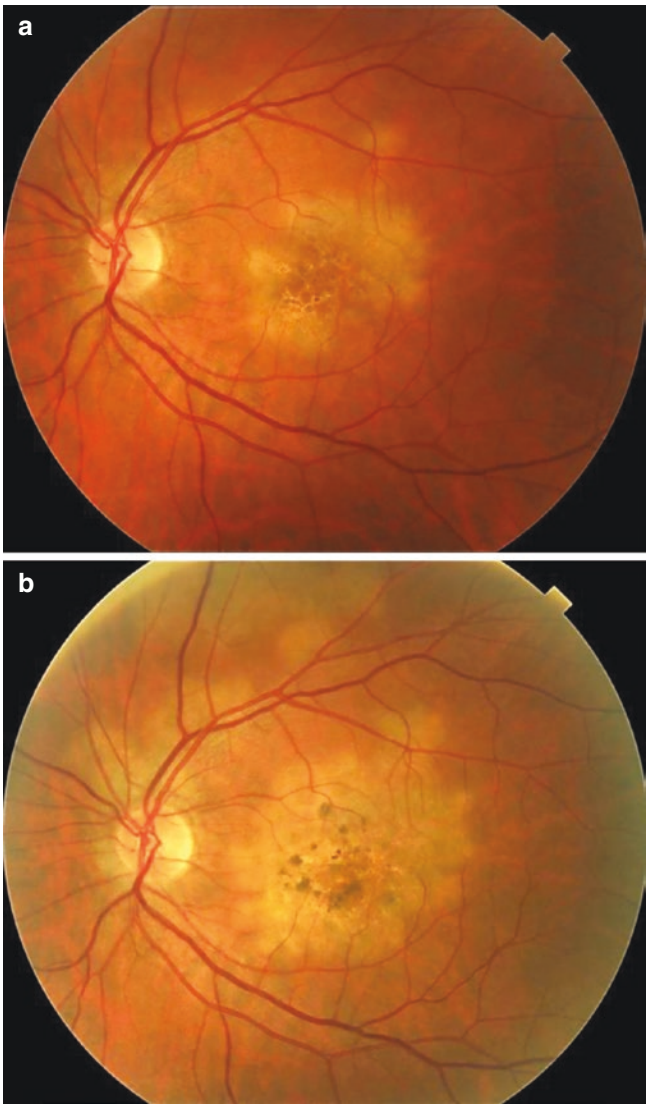


Fig. 2.4 (**a**) Macular variant of serpiginous choroiditis with the yellow, creamy lesions clustered in jigsaw-like pattern in the macula. (**b**) Fundus of the same patient in chronic phase. Note the RPE atrophy clustered around the macula in chronic phase

Fluorescein Angiography

Fluorescein angiography shows classic blockage of choroidal flush in early phase, early hypofluorescence (Fig. 2.5), and late hyperfluorescence of active lesion. Early hypofluorescence may be secondary to inflammatory occlusion of choriocapillaris or blocked fluorescence by retinal pigment epithelium edema (Quillen and Blodi 2002; Mirza and Jampol 2006). Active SC

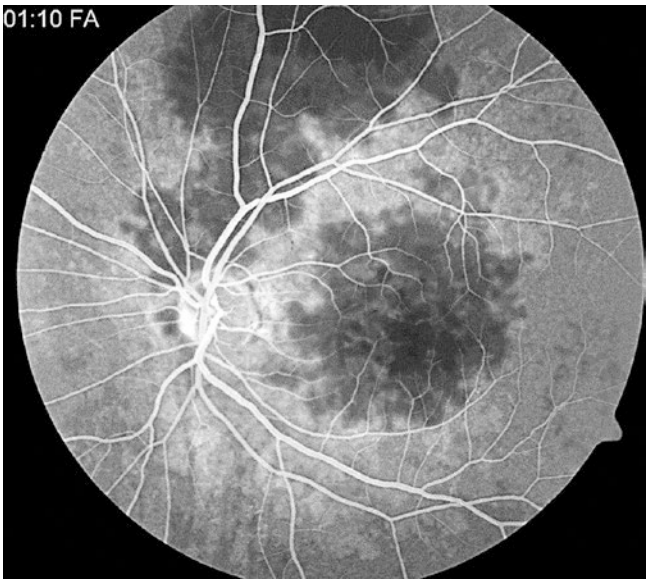


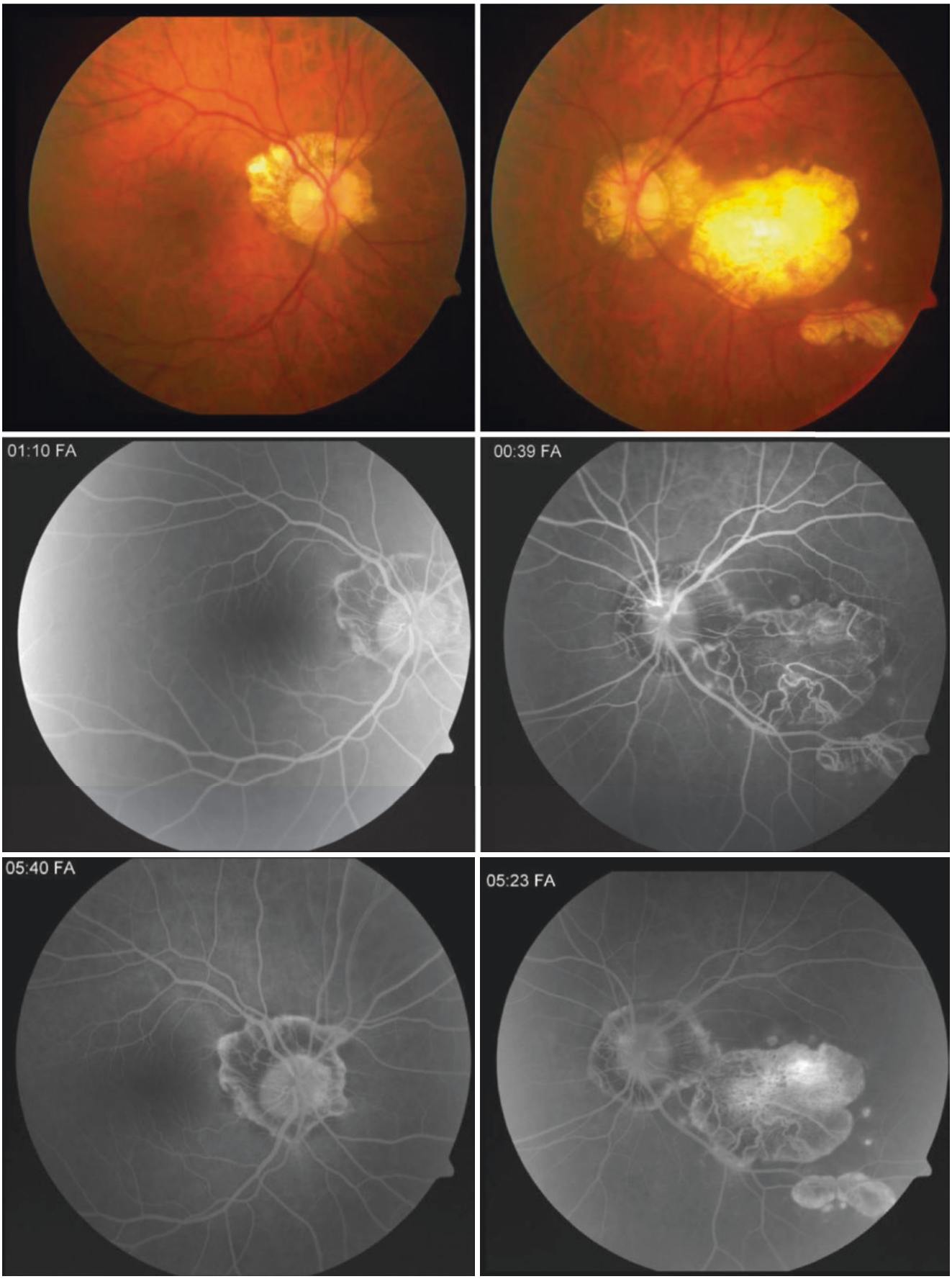
Fig. 2.5 Fluorescein angiography of early phase demonstrating hypofluorescent, ill-defined lesions in the macula and superior to optic disc

appears as hypofluorescent patches with poorly, ill-defined hyperfluorescence of outer borders of serpiginous lesions (Fig. 2.6). The fluorescein angiogram is characteristic and has been described as "fingers" of affected tissue because the hyperfluorescence occurs at the edge of the lesion and spreads inward (Mirza and Jampol 2006). In late phases of FA, active lesions appear as uniform or spotty hyperfluorescence from leaking large choroidal vessels (Nazari Khanamiri and Rao 2013). Atrophic lesions show diffuse loss of pigment, choroidal vessels, late staining on fluorescein angiography (Fig. 2.7).

Indocyanine Green Angiography

ICGA allows for better staging and identification of active lesions in SC lesions (Giovannini et al. 1996). SC lesions on ICGA can be classified into four phases: subclinical or choroidal phase, active phase, sub-healing phase, and inactive healed phase (Giovannini et al. 1996). In subclinical or choroidal phase, ICGA demonstrates hypofluorescent areas consistent with choriocapillary nonperfusion; there is usually a normal FA and fundus exam (Giovannini et al. 1996). In active phase, there is evidence of choroiditis with overlying yellow-white retinal lesions. The ICGA may show early and late hypofluorescent patch with faint borders that appear larger than the corresponding FA lesions; margins of those borders may become hyperfluorescent in late

Fig. 2.6 Fluorescein angiography of a 65-year-old Caucasian female with serpiginous choroiditis affecting the macula. Right eye vision is 20/30, left eye is count fingers at 4 ft. Top fundus photo of right eye (left panel) shows peripapillary atrophy superiorly. Fluorescein angiography in early phase (middle left) shows RPE atrophy and late phase shows hyperfluorescent staining around the edge of the lesion (bottom left). Left eye (right panel) fundus photo shows peripapillary lesion with large macular lesion extending from the peripapillary lesion. Early phase (middle right) of fluorescein angiography shows some blockage, and late phase (bottom right) shows hyperfluorescence especially at the superotemporal edge of the lesion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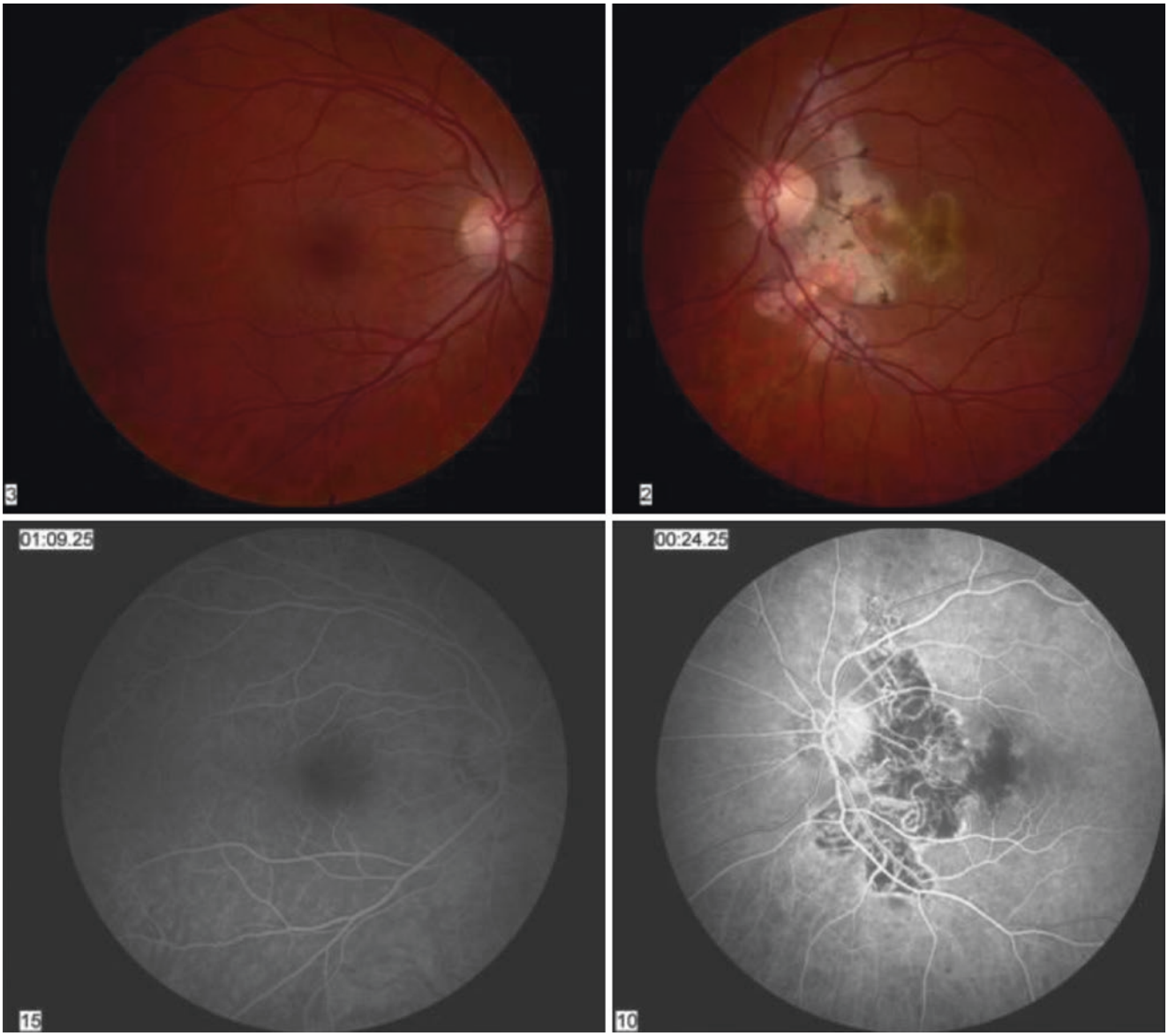

Fig. 2.7 Fundus photograph of a 42-year-old Caucasian woman with serpiginous choroiditis primarily in the left eye. Fluorescein angiography shows late phase reactivation in fovea in left eye. Vision in left eye had acutely decreased to 5/200. In fluorescein angiography, active choroiditis appears as a hypofluorescent patch with progressive marginal hyperfluorescence from leaking vessels; healed lesions are surrounded by hyperfluorescent staining. Also note that the RPE and choriocapillaris atrophy allow for visualization of medium to large choroidal vessels. (images courtesy of Dr. Kumar Rao, MD, St. Louis, MO) and published in part in reference cited (Nazari Khanamiri and Rao 2013 with permission)

phases (Giovannini et al. 1996). In sub-healing phase, ICGA may demonstrate late hyperfluorescent lesions which are consistent with altered choroidal permeability and persistent inflammation in what appears to be a quiescent, healed lesion on FA (Giovannini et al. 1996). Inactive healed lesions appear to be well-defined hypofluorescent lesions on ICGA.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a noninvasive imaging modality that can be used to assess any evidence of choroidal neovascularization, RPE atrophy, epiretinal membrane, cystoid macular edema, and subretinal fibrosis and fluid. Spectral domain OCT demonstrates retinal atrophy with loss and disruption of photoreceptor layers (Fig. 2.8) (Punjabi et al. 2008). In active SC, OCT demonstrates outer retinal and choriocapillaris hyper-reflectivity and may be associated with subretinal fluid overlying area of choroiditis (Gallagher et al. 2007). Healed serpiginous lesions may also show outer retina hyper-reflectivity but appear more granular and nonuniform and originates from RPE proliferation and migration (Nazari Khanamiri and Rao 2013). RPE may be thinned and atrophic, and

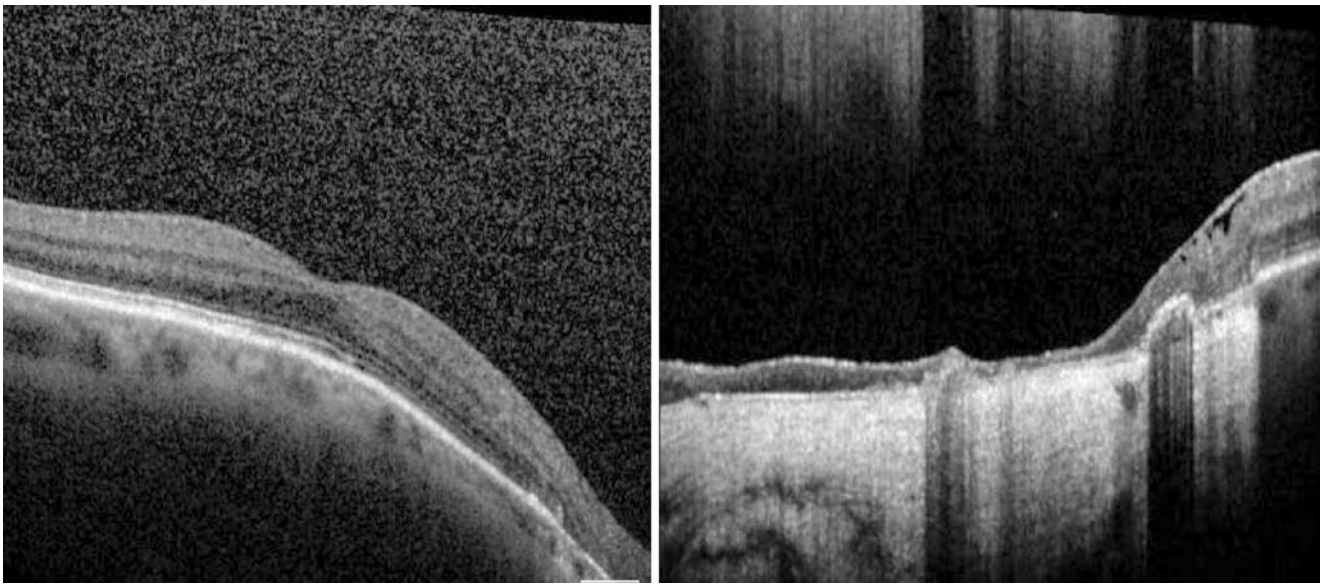

Fig. 2.8 Optical coherence tomography of the same patient in Fig. 2.7. Left image shows OCT of right eye, with loss of outer retina structures and RPE atrophy nasal to macula (in the peripapillary region). Right image shows OCT of left eye, showing diffuse chorioretinal atrophy and retinal atrophy and epiretinal membrane

intraretinal cystic changes may be present. OCT is an important tool in managing disease progression, response to therapy, and assessing vision-threatening choroid neovascularization.

Fundus Autofluorescence (FAF)

Fundus autofluorescence is a noninvasive imaging modality that can be used to monitor progression of serpiginous choroiditis. Auto-fluorescence occurs due to lipofuscin accumulated within the RPE cells and can be used as a marker of RPE health. FAF can detect early damage to RPE episodes and can be used to monitor acute and chronic episodes of SC (Arantes et al. 2011). In acute phase of SC, fundus autofluorescence may show hypoautofluorescence due to outer retina edema masking normal RPE autofluorescence. Then, active lesion may show hyperautofluoresence due to the accumulation of lipofuscin in the stressed RPE. As the serpiginous lesion heals, the lesion shifts from hyper- to hypoautofluorescence due to atrophy and RPE loss (Fig. 2.9).

Management

Management of serpiginous choroiditis is based on the level of inflammation, degree of foveal involvement and side effects, and tolerability of various agents. While SC is presumed to be autoimmune, systemic and ocular infection must be ruled out. The most recent consensus panel of uveitis experts recommend combined systemic corticosteroids with immunosuppressive agents, with local therapy when needed (Jabs et al. 2000). Given presumed autoimmune pathogenesis of SC and usually bilateral nature of the disease, the main acute phase is treated with high-dose systemic steroids. Long-term management to prevent recurrence depends on immunomodulatory agents. Some patients may require intravitreal anti-vascular endothelial growth factor therapy for choroidal neovascularization in fovea. Because the condition is so rare and because of lack of randomized control studies, there is limited consensus on initial and maintenance dose of immunomodulatory agent or duration of treatment.

Prompt treatment with high-dose prednisone (60–80 mg oral prednisone or intravenous pulse methyl prednisone) can limit choroiditis progression. Initial response to high-dose prednisone is evident within the first 36 h and takes about 2–8 weeks for complete resolution. Once acute choroiditis is controlled, prednisone should be tapered over the course of 1–3 months. There are complications of long-term corticosteroid use. In conjunction with prednisone therapy, immunomodulatory therapy can be used to decrease recurrence and acuity of choroiditis. Immunosuppressive agents used in SC management include T-cell inhibitors like cyclosporine, antimetabolite like azathioprine and mycophenolate, alkylating agents like cyclosporine and chlorambucil, and biologic agents such as interferon alpha-2a.

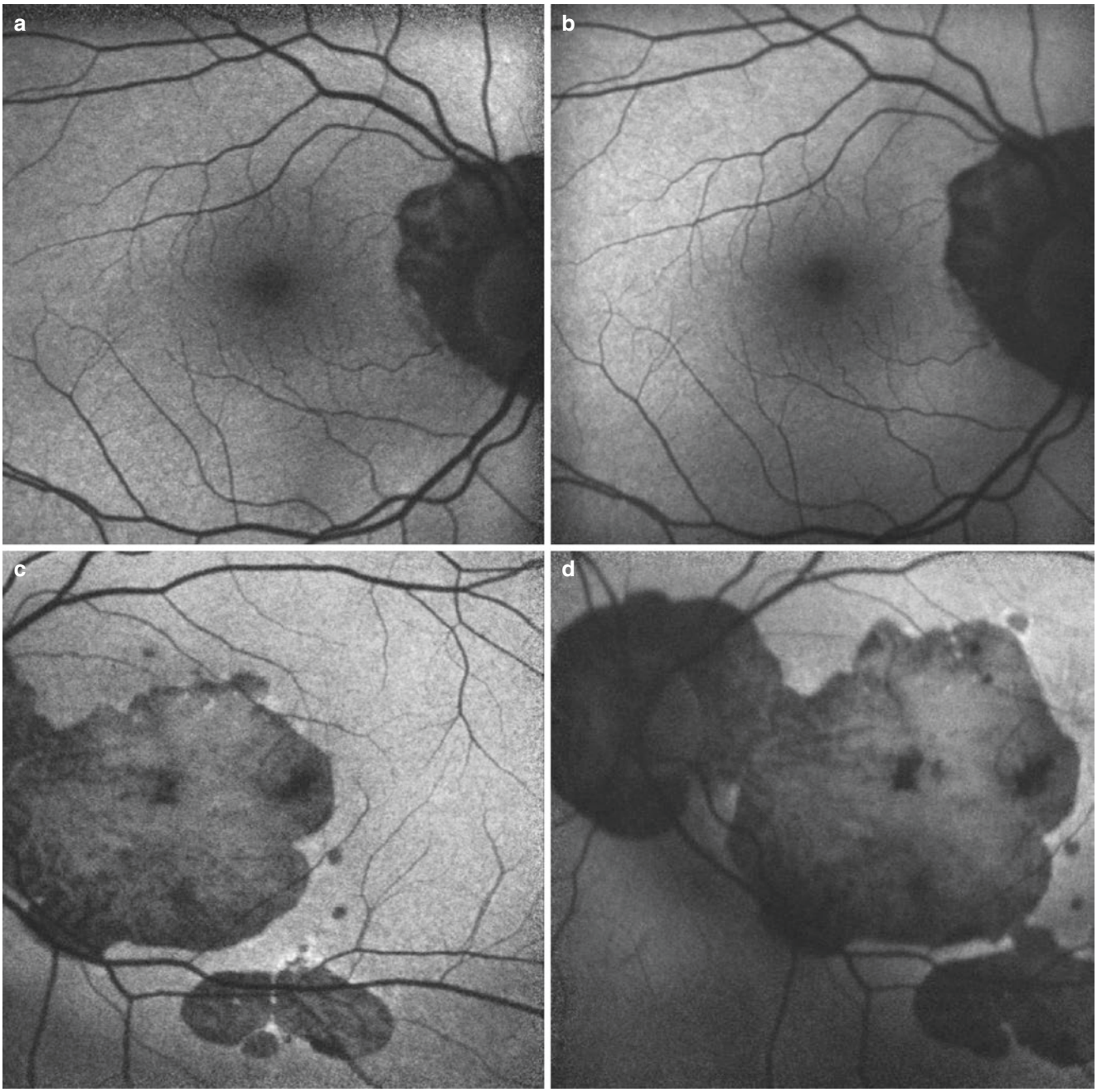

Fig. 2.9 Fundus autofluorescence of the patient in Fig. 2.6 in July 2013 (**a**, **b**) and April 2017 (**c**, **d**). There has been an interval increase of RPE atrophy as can be easily seen by increased size of the hypoautofluorescence in the right eye (peripapillary) and in the extension of the contiguous lesions in the macula to inferotemporal lesion in the left eye

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Punctate Inner Choroidopathy

3

Hyeong Gon Yu and Dae Joong Ma

Introduction

Punctate inner choroidopathy (PIC) is a relatively uncommon idiopathic inflammatory multifocal chorioretinopathy, which occurs at the level of the outer retina, retinal pigment epithelium (RPE), and inner choroid. PIC was first described in 1984 by Watzke and colleagues in a series of 10 young myopic women who presented with blurred central vision, photopsia, and paracentral scotomas (Watzke et al. 1984). PIC is considered one of the "white dot syndromes" and is reported as having a considerable overlap with acute zonal occult outer retinopathy (Gass 2003; Ahnood et al. 2017; Francis et al. 2005). The development of various imaging modalities has led to a better understanding of PIC, but whether PIC is truly a separate disease entity or simply a subset of the so-called PIC/MCP spectrum is still controversial (Jampol and Becker 2003; Spaide et al. 2013).

PIC is a dynamic disease with variable courses and presents as various clinical manifestations. Diagnosis and monitoring of patients with PIC are facilitated by current imaging modalities, especially optical coherence tomography (OCT) and fundus autofluorescence (FAF).

Etiopathogenesis

The etiology and pathogenesis of PIC are poorly understood. It is proposed to be an autoimmune disease that arises in the context of polygenic susceptibility triggered by an environmental stimulus, such as infection, immunization, or stress (Ahnood et al. 2017).

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Clinical Features

According to a survey of 77 individuals with PIC, the presenting symptoms included scotoma (91%), blurred vision (86%), photopsia (73%), floaters (69%), photophobia (69%), metamorphopsia (65%), and peripheral vision loss (26%) (Gerstenblith et al. 2007). The occurrence of scotomata was generally unilateral (86%). Waxing and waning of symptoms before commencing treatment were reported in 32% of patients. Most patients present with unilateral symptoms. However, the condition is commonly bilateral; the original study showed that 80% of patients had bilateral disease (Watzke et al. 1984), but more recent studies showed that the occurrence of bilateral disease ranged from 49% to 58% (Zhang et al. 2011; Essex et al. 2010; Watzke et al. 1984).

Patients with PIC present with variable visual acuity (VA) scores; however, their VA is often good. Essex and colleagues reported visual outcomes in a cohort of 74 eyes with PIC lesions; of these, 66% had a VA score of 20/50 and 15% had a VA score of <20/200 (Essex et al. 2007). Variable VA may reflect the variable location of inflammatory lesions or their sequelae. Leung and colleagues reported an incidence rate of 0.06/eye-year for a VA of 20/50 or worse and 0.01/eye-year for a VA of 20/200 or worse in the study cohort (Leung et al. 2010).

PIC is distinguished from multiple choroiditis and panuveitis (MCP) by the lack of intraocular inflammation and the absence of cells in the anterior chamber and vitreous cavity on slit-lamp biomicroscopy (Watzke et al. 1984; Kedhar et al. 2007; Amer and Lois 2011). Moreover, fundus examination reveals 12–25 well-defined gray or yellow round opaque lesions, which are typically smaller (about 100–300 μm in diameter) than the lesions observed in patients with MCP. These lesions are normally confined to the posterior pole but sparing the peripapillary region and distributed randomly or occasionally in a linear pattern (Fig. 3.1) (Watzke et al. 1984). These inflammatory lesions may be associated with an overlying neurosensory detachment and usually evolve into atrophic chorioretinal scars, but some lesions dis-

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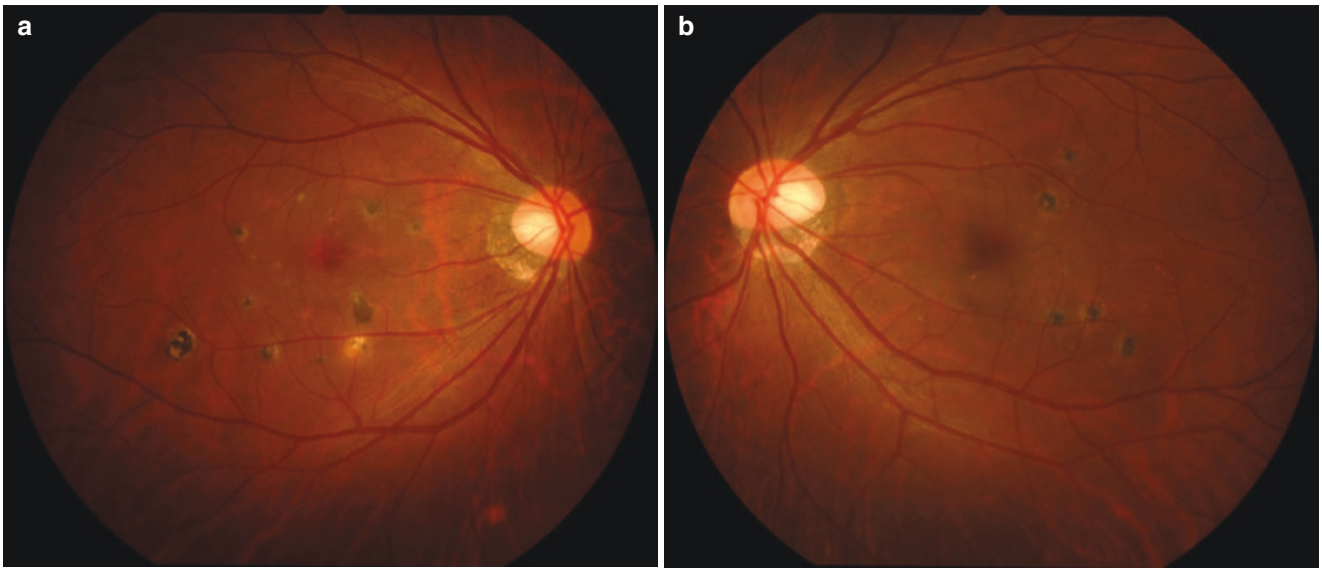

Fig. 3.1 Color fundus photography of a 37-year-old, Asian, myopic woman, right (**a**) and left (**b**) eyes, demonstrating characteristic features of punctate inner choroidopathy

appear without sequelae. Some scars become more pigmented and distinct after 2–3 years and can resemble the punched-out lesions of presumed ocular histoplasmosis syndrome. Subretinal fibrosis and choroidal neovascularization (CNV) are the two important complications that may significantly affect the patients' vision. The risk of CNV in patients with PIC varies significantly between studies, but more recent studies have reported low rates of CNV. Essex and colleagues reported that CNV occurred in 22% of patients after a mean follow-up of 4.5 years in a cohort of 74 eyes with no CNV at baseline (Essex et al. 2010). Leung and colleagues reported an incidence of 0.02/eye-year for new CNV and 0.04/eye-year for recurrence of CNV in the study cohort; however, patients with PIC-related CNV showed better VA scores (≥20/40 in 43% of eyes) as compared to that in patients with age-related macular degeneration-related CNV (Leung et al. 2010). Pathology findings indicated that PIC-related CNV grew in the subretinal space, anterior to the RPE (type 2 CNV) (Olsen et al. 1996). Over time, the new vessels developed connections to form larger neovascular complexes with multiple feeder vessels. The following fibrotic response resulted in subretinal fibrosis with dumbbell-shaped pattern. A study has shown that subretinal fibrosis is relatively common, with occurrence in at least one eye in 56% of patients (Gerstenblith et al. 2007). Both subretinal fibrosis and CNV occurred in the early phase of the disease.

Watzke and colleagues reported that the lesions were hyperfluorescent in the early arterial phase of fluorescein angiography (FA) and exhibited staining in the arteriovenous phase (Watzke et al. 1984). More lesions appearing as tiny hyperfluorescent lesions that scattered in the posterior pole are observed using FA compared to clinical fundus examination. Areas of hyperfluorescence correspond to the lesions regardless of the presence of CNV and persist through the early and late venous phase; nevertheless, some lesions may demonstrate blocked fluorescence in the arterial phase. On the other hand, the presence of CNV is characterized by hyperfluorescence in the early phase and leakage in the late phase (Fig. 3.2) (Olsen et al. 1996). Leakage of fluorescein into a serous neurosensory retinal detachment is also possible (Watzke et al. 1984). In later stages of disease, punctate window defects are seen as the RPE atrophies.

Indocyanine green angiography (ICGA) can detect many more lesions, which appear as hypofluorescent areas in both early and late phases; as in the case of other white dot syndromes, these hypofluorescent areas correspond to the choroidal lesions that represent localized areas of hypoperfusion (Levy et al. 2005).

Several choroidal vessels revealed localized hyperfluorescent points close to the vessel wall/border, which indicates the presence of associated vasculitis. Larger choroidal vessels crossed these hypofluorescence areas, which suggest that the vasculitis is limited to smaller choroidal vessels and the choriocapillaris (Tiffin et al. 1996).

Spectral-domain optical coherence tomography (SD-OCT) reveals RPE elevation that fluctuates with disease activity and sub-RPE hyperreflective signals with intact Bruch's membrane (BM) (Fig. 3.3). Photoreceptor-associated bands are not visible during the active phase but are readily detected when lesions are clinically stable. This finding may aid in monitoring the clinical course in patients with PIC (Channa et al. 2012).

Zhang and colleagues suggest that five stages (I–V) of choroidal vasculitis may occur during the evolution of PIC lesions and show that OCT findings vary depending on the

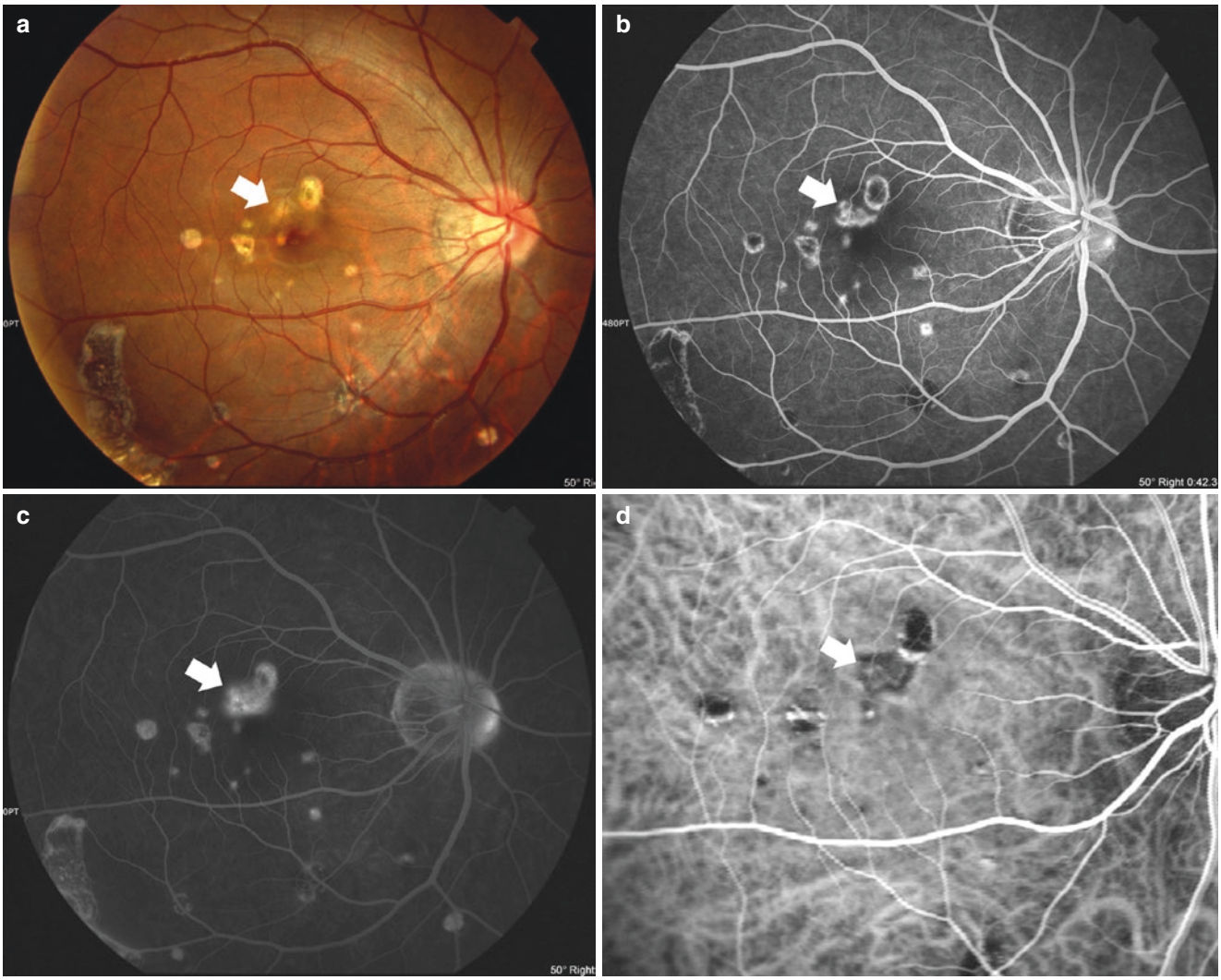

Fig. 3.2 (**a**) Fundus photo of the right eye of a 35-year-old woman. Early (**b**) and late (**c**) fluorescein angiography shows increasing fluorescence of the inactive lesions (staining) and leakage from the active choroidal neovascularization (CNV) (arrow). (**d**) Indocyanine green angiography shows a corresponding CNV lesion

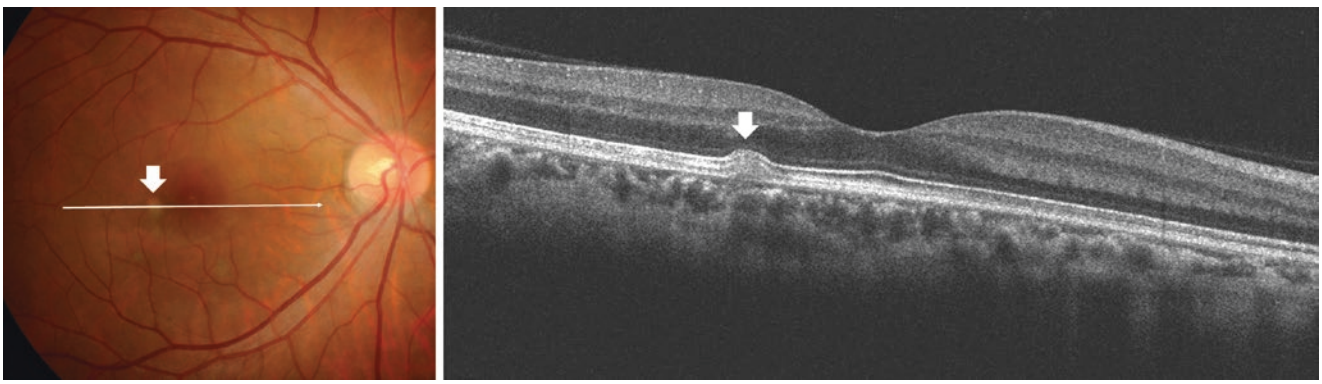

Fig. 3.3 Optical coherence tomography shows a hyperreflective lesion in the outer retina corresponding to the acute lesion (arrow)

stage (Zhang et al. 2011, 2013). In stage I, "presumed choroidal vasculitis," there is minimal irregularity in the outer nuclear layer because the involved level is confined to the inner choroid. In stage II, "obliteration of choriocapillaris," the lesion is represented by a focal hyperreflective elevation of the RPE with corresponding disruption of the photorecep-

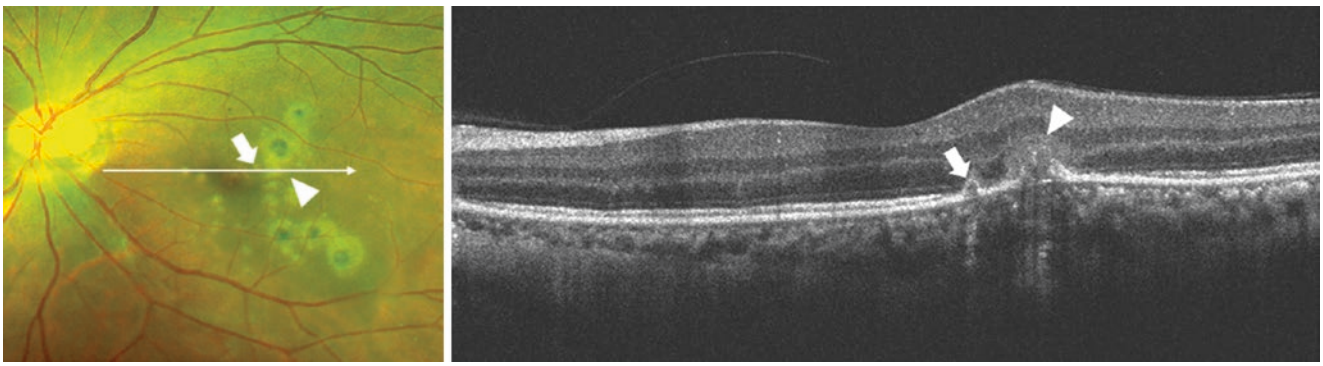

Fig. 3.4 Optical coherence tomography shows a cross-sectional image of two active punctate inner choroidopathy lesions. The arrow shows a focal elevation of retinal pigment epithelium (RPE) with a corresponding ellipsoid zone disruption (stage II). The arrowhead shows a nodule with moderate reflectivity, breaks through the RPE, and then sprouts toward and replaces the photoreceptor layer until it reaches and domes the outer plexiform layer (stage III). The RPE relics and Bruch's membrane at the break gradually disappear, uncovering the choroidal part of the nodule

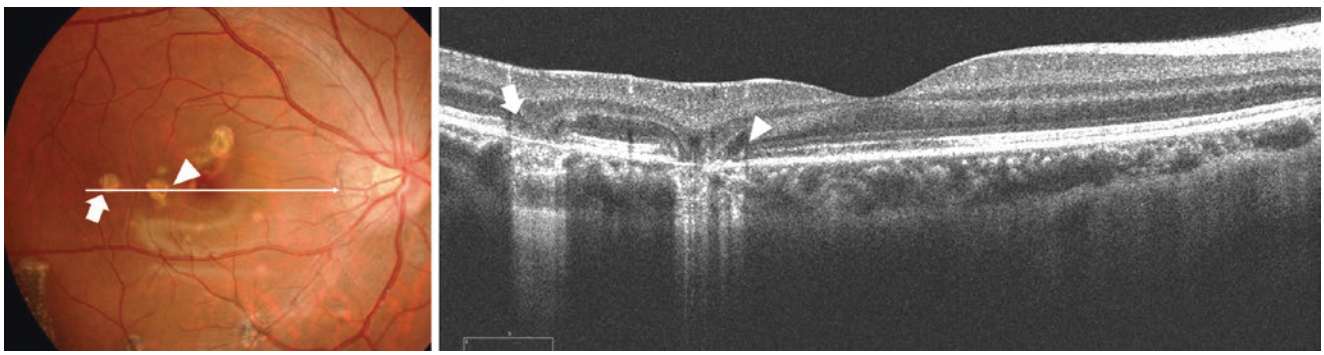

Fig. 3.5 Optical coherence tomography shows nodules regressing from the apex toward the choroid, followed by an incarcerated herniation of the outer plexiform layer and inner retina (with a V-shaped appearance) through the break in the retinal pigment epithelium and Bruch's membrane (arrow and arrowhead, stage IV)

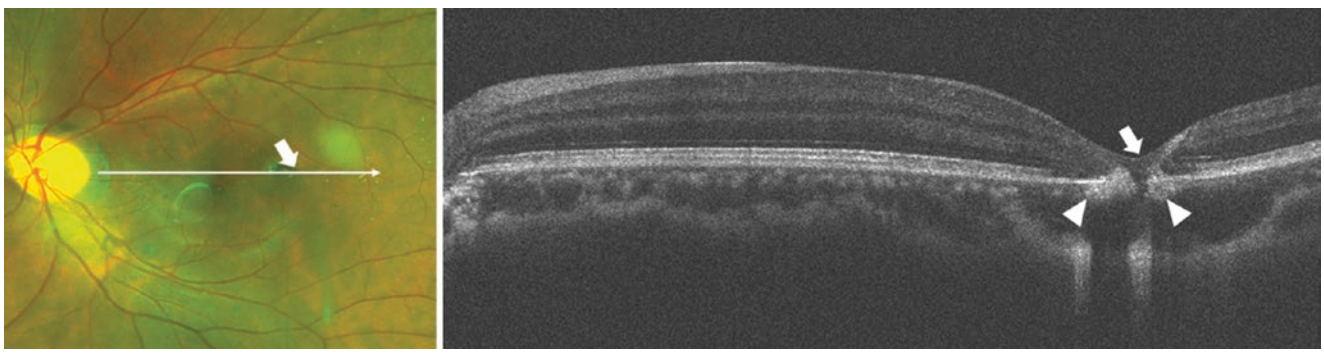

Fig. 3.6 Optical coherence tomography shows that the photoreceptor layer around the lesion is gradually lost with the sagging of the outer plexiform layer (OPL) and inner retina (arrow) (stage V). Meanwhile, retinal pigment epithelium (RPE) proliferation (with posterior shadowing, arrowheads) repairs the RPE break and relieves the retinal hernia, making the OPL outline reappear

tor ellipsoid zone (Fig. 3.4). In stage III, "inflammatory infiltration," the nodular lesions with moderate reflectivity break through the RPE, forming a hump-shaped lesion beneath the outer plexiform layer. This may be associated with subsequent disruption of BM and involvement of the outer retina (Fig. 3.4). In stage IV, "atrophy," lesions regress in a retrograde manner with tissue loss from the photoreceptor layer and inner choroid. This results in a V-shaped herniation of the outer plexiform layer and inner retina into the choroid (Fig. 3.5). In stage V, "progressive atrophy and pigmentation," there is loss of photoreceptors around the lesion. This is often seen as extensive attenuation of the external limiting membrane, photoreceptor ellipsoid zone, and interdigitation zone, adjacent to the PIC lesions (Fig. 3.6).

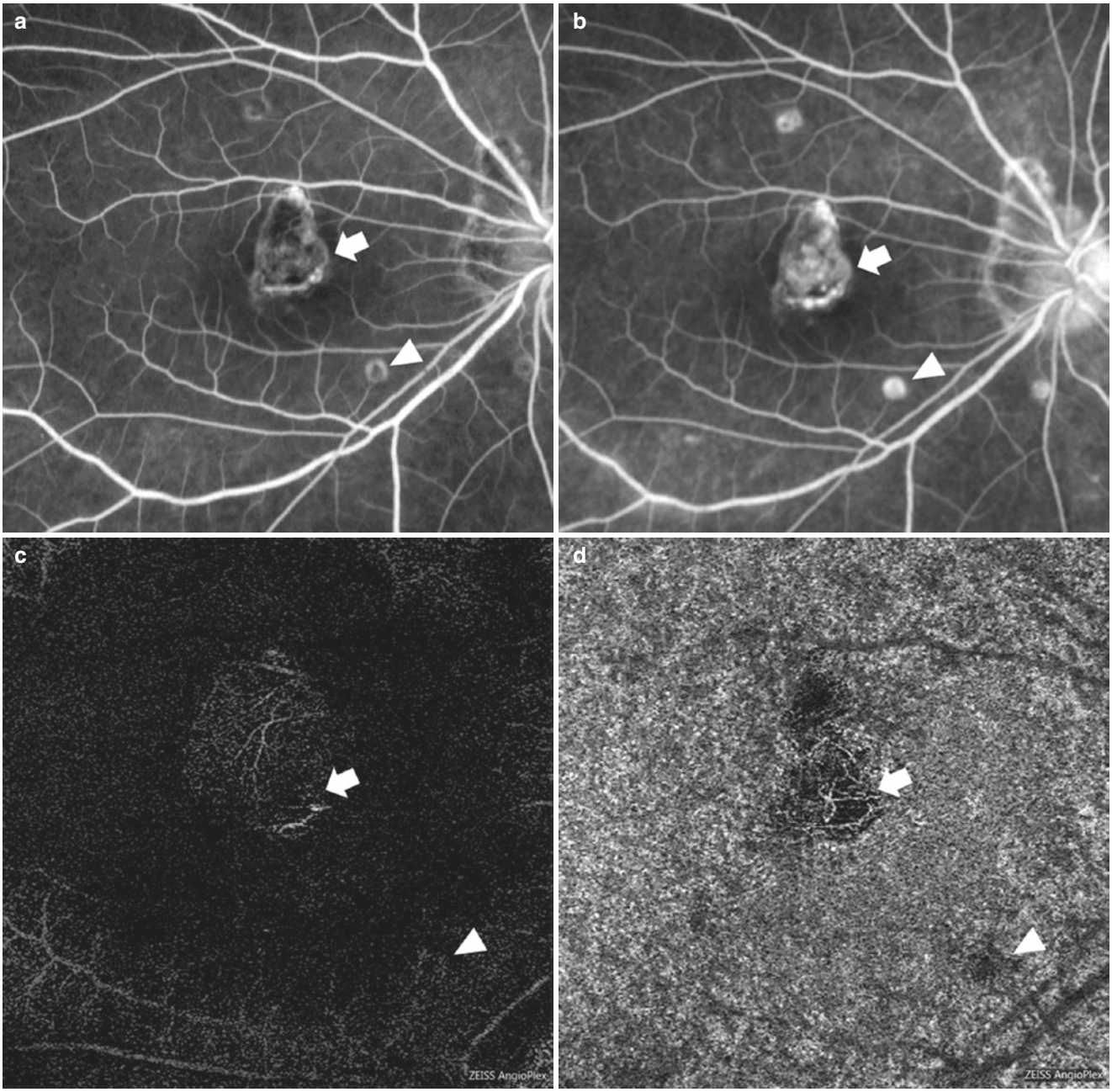

Fig. 3.7 Fluorescein angiography shows hyperfluorescence at all punctate inner choroidopathy (PIC) lesions (arrow and arrowhead) in early (**a**) and late phases (**b**). A 6 mm × 6 mm optical coherence tomography angiography of the outer retina (**c**) and choroidal capillaries (**d**) in two PIC lesions. Arrow indicates abnormal flow, whereas arrowhead indicates no apparent flow

Spaide and colleagues reported that acute lesions appeared as nodular collections under RPE and ruptured into the outer retina with outpouring of infiltrate (Spaide et al. 2013). They point out that the differentiation between active inflammatory lesions and CNV may not be possible even with multimodal imaging, because both can cause infiltrative lesions with breakdown in the blood–retina barrier. However, the use of OCT angiography (OCTA) to evaluate PIC lesions may enable differentiation between active inflammatory lesions and CNV, even in patients in whom FFA was inconclusive (Fig. 3.7) (Levison et al. 2017).

In a study using enhanced depth imaging (EDI)-OCT, about 20% of clinically inactive PIC patients showed localized RPE elevation with an underlying hyporeflective space, which has been previously described as a sign of activity (Levison et al. 2017). The authors suggested that this may represent subclinical PIC. Choroidal thickness can be used to monitor the stage of disease activity. Choroidal thickness

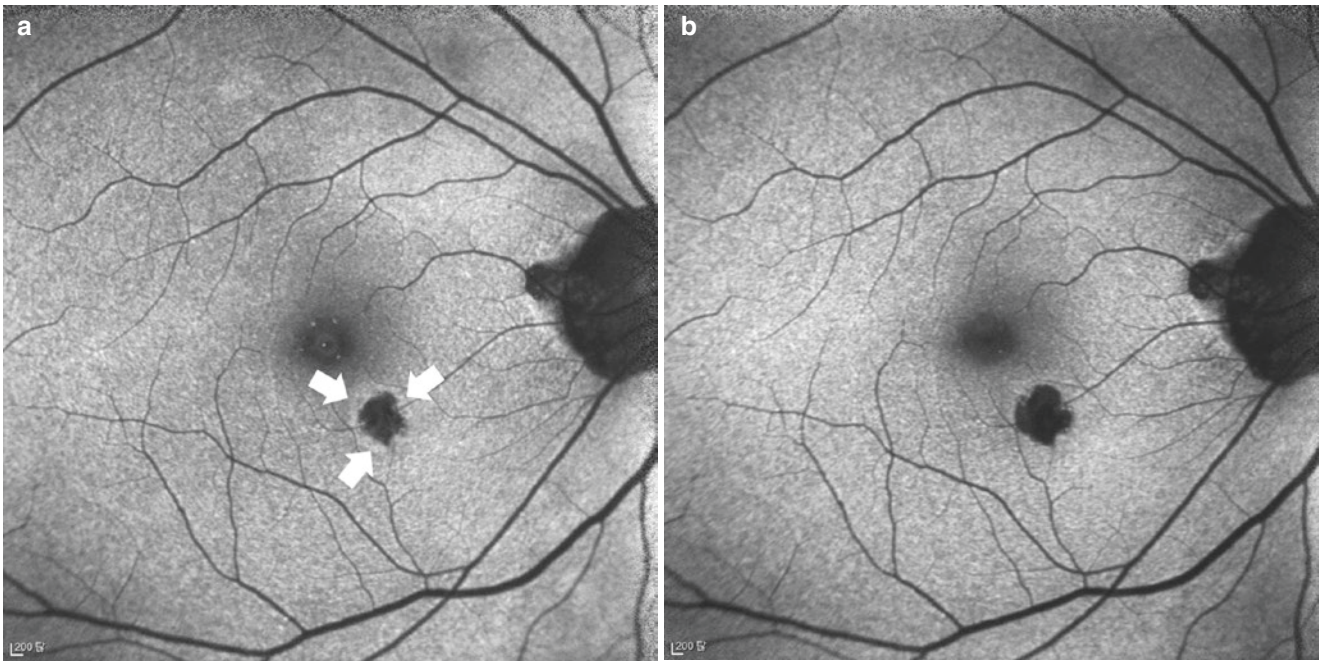

Fig. 3.8 (**a**) Fundus autofluorescence image of a 45-year-old woman taken at the time of acute symptom demonstrates the hypoautofluorescent punctate inner choroidopathy lesion with a surrounding zone of hyperautofluorescence (arrows). (**b**) Eight months later, when the patient was asymptomatic, the disease was considered quiescent. The hypoautofluorescent punctate lesion has enlarged and the hyperautofluorescence surrounding zone has disappeared

increases throughout the active phase, then significantly decreases at later stages due to atrophy of outer retinal layers, reaching a lower minimum level than that attained during the early stages of the disease (Zhang et al. 2013). The use of serial quantitative assessment of retinal thickness maps on SD-OCT for detecting flare-up of PIC lesions and monitoring treatment response has also been described (Madhusudhan et al. 2016).

Fundus autofluorescence (FAF) imaging can distinguish between the different phases of PIC lesions (Arcinue et al. 2015). Active lesions demonstrated hypoautofluorescent spots with hyperautofluorescent margins (Fig. 3.8). This hyperautofluorescent margin resulted from the gradual loss of the photoreceptors around the active lesions with intact RPE. Both subclinical lesions and atrophic lesions appeared hypoautofluorescent, but the subclinical lesions appeared more distinctive on near-infrared FAF imaging than on blue FAF imaging. The hypoautofluorescence of subclinical lesions was the result of small clusters of damaged RPE cells overlying focal chorioretinal lesions, whereas the hypoautofluorescence of atrophic lesions was the result of a lack of RPE cells carrying fluorophores. The progression of PIC can be predicted noninvasively using FAF, which reflects the progression of RPE atrophy (Hua et al. 2014). In stage II PIC lesions, defined by Zhang and colleagues as focal elevation of the RPE and corresponding disruption of EZ (Zhang et al. 2011, 2013), the mean progression rate of RPE atrophy was 3.735 mm^2/year, which was greater than that of laser scars in patients with nonproliferative diabetic retinopathy cases (0.127 mm^2/year).

Management

The management of PIC is challenging due to the variability in disease severity and the cause of vision loss between patients or even in the same patient at different time points. Intervention is generally indicated to treat new or active inflammatory lesions, particularly those threatening the fovea or secondary CNV. The condition of the fellow eye should also be considered while formulating treatment strategies. Treatment options include local and systemic corticosteroids, systemic immunomodulatory drugs, intravitreal anti-vascular endothelial growth factory (VEGF), photodynamic therapy (PDT), argon laser, submacular surgery, and combination therapy.

Observation

No treatment is advised for the majority of patients without evidence of CNV or inflammatory lesions very close to fixation, especially those who show a self-limiting course with good visual prognosis (Amer and Lois 2011). Essex and colleagues reported that 66% of eyes with PIC lesions but no CNV at baseline remained unchanged without new PIC

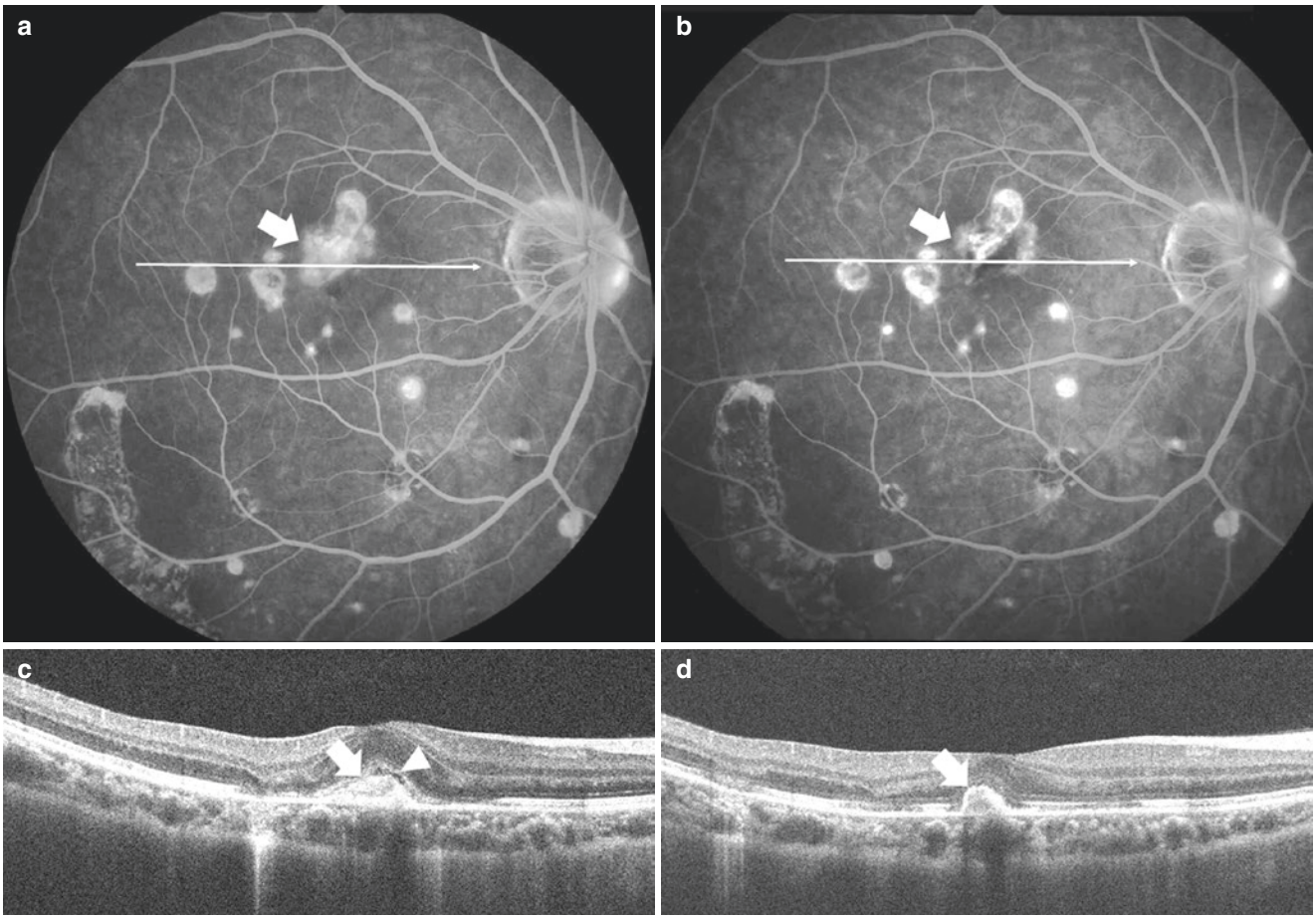

Fig. 3.9 Optical coherence tomography images of the 35-year-old woman described in Fig. 3.2. (**a**, **c**) Before treatment, active choroidal neovascularization (CNV, arrow) and subretinal fluid (SRF, arrowhead) are seen. (**b**, **d**) After intravitreal bevacizumab injection, regressed CNV (arrowhead) and complete resolution of SRF is observed

lesions or CNV lesions during a mean follow-up of 4.5 years (Essex et al. 2010). In this patient cohort, VA was also well preserved, with a mean VA of 0.11 logMAR to 0.09 logMAR.

Medical Therapy

***Corticosteroids*:** Systemic or local (periocular or intravitreal) administration of corticosteroids is thought to effectively inhibit the critical immune and inflammatory pathways in PIC and PIC-associated CNV, and steroids are thought to have an antiangiogenic role (Levy et al. 2005; Flaxel et al. 1998; Brueggeman et al. 2002). In the Gerstenblith survey, 60% of PIC patients underwent treatment with systemic corticosteroids, 22% with intraocular corticosteroids, and 10% with periocular corticosteroids (Gerstenblith et al. 2007). The effectiveness of corticosteroids in controlling PIC-associated CNV was reported by several investigators (Flaxel et al. 1998; Levy et al. 2005) who postulated that the use of corticosteroids might not alter outcomes but may result in faster recovery of vision.

***Other Immunomodulatory Therapy*:** Corticosteroid-sparing immunosuppressants should be considered in patients who require maintenance doses greater than 7.5 mg of prednisolone per day or when there are specific contraindications for the ongoing corticosteroid therapy. Mycophenolate mofetil (CellCept®; Genentech, San Francisco, CA) is commonly used (Galor et al. 2008; Ehlers et al. 2011; Turkcuoglu et al. 2011), and the use of other agents such as sirolimus (rapamycin), interferon beta-1A, and thalidomide has been reported in some cases (Nussenblatt et al. 2007; Cirino et al. 2006; Ip and Gorin 1996).

Intravitreal Anti-VEGF Therapy

Several studies have evaluated the safety and efficacy of anti-VEGF therapy in CNV secondary to PIC, specifically bevacizumab (Mansour et al. 2009; Zhang et al. 2012; Chan et al. 2008) and ranibizumab (Chan et al. 2008; Rouvas et al. 2011). Most of the studies reported favorable anatomical and functional outcomes. Figure 3.9 shows a representative case with CNV secondary to PIC treated with bevacizumab.

Photodynamic Therapy

Photodynamic therapy with verteporfin (PDT) has been used as a safe treatment modality to stabilize and improve vision in PIC-associated CNV lesions (Brouzas et al. 2010; Chatterjee and Gibson 2003; Leslie et al. 2005; Lim et al. 2006; Wachtlin et al. 2003).

Laser Photocoagulation

Since the advent of PDT and anti-VEGF therapy, laser photocoagulation has been regarded as unsuitable for the centrally located macular CNV in PIC. However, it is still worth considering for extramacular lesions.

Submacular Surgery

Initial success of surgical excision of subfoveal CNV and macular translocation surgery was reported but was associated with high recurrence rates (Olsen et al. 1996; Essex et al. 2007; Ehlers et al. 2011).

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Multifocal Choroiditis and Panuveitis

4

Eun Young Choi and Min Kim

Introduction

Multifocal choroiditis and panuveitis (MCP) is an idiopathic chorioretinal inflammatory disease accompanied by prominent vitritis and anterior segment uveitis. The acute inner chorioretinal lesions subsequently evolve into pigmented scars and may lead to the development of choroidal neovascularization (CNV). In late 1973, two patients with bilateral anterior uveitis associated with a chorioretinopathy that resembled ocular histoplasmosis syndrome were reported for the first time (Nozik and Dorsch 1973). Additionally, 28 patients with anterior uveitis, vitritis, and multiple lesions at the retinal pigment epithelium (RPE) level were described (Dreyer and Gass 1984), and they coined the term MCP. Subsequently, several investigators documented clinical features of diffuse subretinal fibrosis (Doran and Hamilton 1982), multiple evanescent white dot syndrome (Jampol et al. 1984), and punctate inner choroidopathy (PIC) (Watzke et al. 1984), each of which are distinctly different clinical entities. Additionally, a characteristic inner choroidal lesion that subsequently evolves into RPE pigmentation, fibrosis, and development of CNV in the absence of anterior or vitreous inflammation was described by Morgan et al. as multifocal choroiditis (MFC) (Morgan and Schatz 1986). These diseases were previously classified as the same disease entity because of their similar clinical characteristics (Jampol et al. 1984). Later, these disorders were classified as different entities in 79 patients having enlarged blind spots with other clinical, angiographic, and electroretinographic evidence (Reddy et al. 1996).

Epidemiology

MCP occurs more frequently in women and predominantly in young and otherwise healthy people. The median age of onset is the mid-30s (Dreyer and Gass 1984; Morgan and Schatz 1986; Reddy et al. 1996). A moderate degree of myopia was present in all but one patient with MCP (Morgan and Schatz 1986). There has been no reported ethnic or genetic predisposition related to this disease. The geographic distribution of MCP is different from that of presumed ocular histoplasmosis syndrome (POHS) (Dreyer and Gass 1984), which is endemic for histoplasmosis, and MCP shows a relatively low percentage of positive responses to the histoplasmin skin test (Dreyer and Gass 1984).

Etiopathogenesis

The etiology and pathogenesis are not well known. Patients with MCP have no associated systemic disease or familial history. The hypothesis suggested that white spot syndromes occur in individuals with common non-disease-specific autoimmune susceptibility factors (Jampol and Becker 2003). Subsequently, the same group reported a high prevalence of systemic autoimmunity not only in patients with MCP but also in their relatives (Pearlman et al. 2009).

Some investigators have suggested a viral etiology. Herpes simplex type 1 was cultured in the chorioretinal specimens of a patient suspected of having bilateral MCP (Grutzmacher et al. 1983). Moreover, intraocular antibodies against varicella zoster were detected in two cases and herpes simplex virus in one case among seven patients with MCP (Frau et al. 1990). The relationship between MCP and chronic infection with the Epstein–Barr virus was also suggested by detecting viral capsid antigen IgM or antibodies to Epstein–Barr early antigens in 10 patients with MCP (Tiedeman 1987). However, the reappraisal research (Spaide et al. 1991a) failed to support this association. Histopathologic examination of MCP lesions has revealed non-granulomatous perivascular choroidal infiltrates of mixed lymphocytes, consisting mainly of B lymphocytes, in association with early CNV (Dunlop et al. 1998; Nolle and Eckardt 1993; Shimada et al. 2008). These findings were not significantly different from the findings of PIC.

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Clinical Features

Although asymmetric, MCP occurs frequently in both eyes. Bilaterality has been reported to be as low as 45% (Morgan and Schatz 1986) and as high as 79% (Reddy et al. 1996). Patients with MCP usually present with blurred or decreased central vision with scotoma. Floaters and photopsia are less common. The mean initial vision on examination of 68 eyes with MCP was 20/50 (Reddy et al. 1996), varying from 20/40 to light perception. Mild-to-moderate anterior uveitis was observed in 52% (Dreyer and Gass 1984) of patients with MCP, with the signs including anterior chamber cells and flare, non-granulomatous keratic precipitates, and posterior synechiae. Vitreous inflammation was more common, observed in 100% of eyes by the same study group (Reddy et al. 1996). In the absence of anterior uveitis and/or vitritis, it may be classified as idiopathic MFC (Fung et al. 2014), and MFC is often regarded as a spectrum of disease that is indistinguishable from PIC (Essex et al. 2013). MCP eyes have a very similar pattern of multiple choroiditis that suggests POHS (Raven et al. 2017). In the acute phase of MCP, multiple round to oval, yellow-gray lesions at the RPE levels, measuring about 50–350 μm, are scattered throughout the posterior pole and mid-periphery (Joondeph and Tessler 1990; Quillen et al. 2004) (Fig. 4.1). Occasionally, the lesions may be clustered, or they may be linearly arranged, parallel to the ora serrata, similar to the clinical findings shown in POHS (Spaide et al. 1991b) (Fig. 4.2). Exudation may develop over the areas of active lesion during the active phase. The active lesions change to round and atrophic scars, appearing as punched-out lesions with various degrees of hyperpigmentation, and the scars can enlarge in size (Raven et al. 2017) (Fig. 4.3). Peripapillary atrophy is frequently observed in MCP eyes (Fig. 4.4). Optic disc swelling and hyperemia occur not uncommonly, with prevalence up to 34% according to prospective follow-up studies (Reddy et al. 1996), but the development of optic neuropathy is not common, reported in only 11% of 122 examined MCP eyes (Kedhar et al. 2007).

Acute enlargement of the blind spot without disc swelling was described in observational studies on MCP (Khorram et al. 1991; Callanan and Gass 1992). The etiology of the blind spot enlargement is unknown. Some investigators explained that it was because the nasal retina is more involved through the medial posterior ciliary artery, as MCP develops hematogenously (Brown and Folk 1999; Hayreh 1975). Others suggested that preferential involvement of rod photoreceptors in MCP may induce a field defect around the blind spot (Curcio et al. 1990; Reddy et al. 1996).

Electroretinography (ERG) findings in MCP show diffuse involvement depending on the disease severity associated with chorioretinal involvement. Normal to borderline ERGs were noted in 41% of examined MCP eyes, while moderately to severely depressed ERGs were observed in 38%

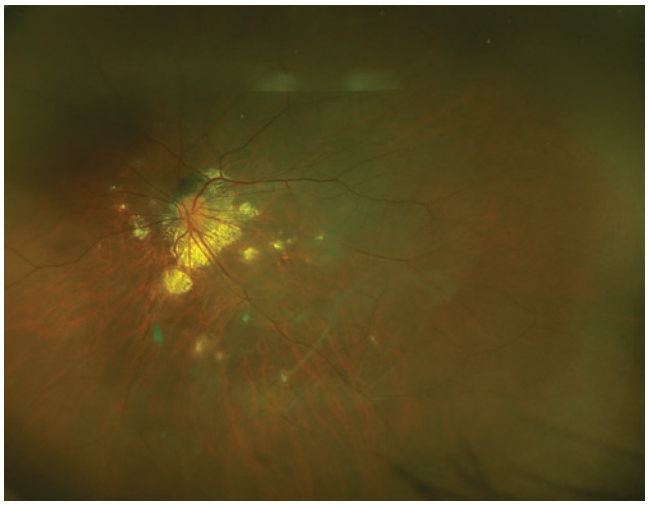

Fig. 4.1 Wide-field fundus imaging shows multiple round to oval gray-yellowish chorioretinal lesions of variable size (about 50–1000 μm) in the posterior pole and mid-periphery of the retina

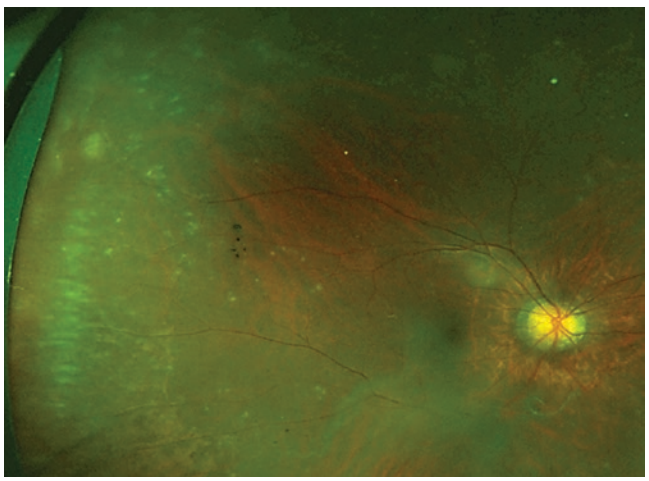

Fig. 4.2 Wide-field fundus imaging demonstrates a linear peripheral arrangement of yellow-gray spots denoting choroiditis

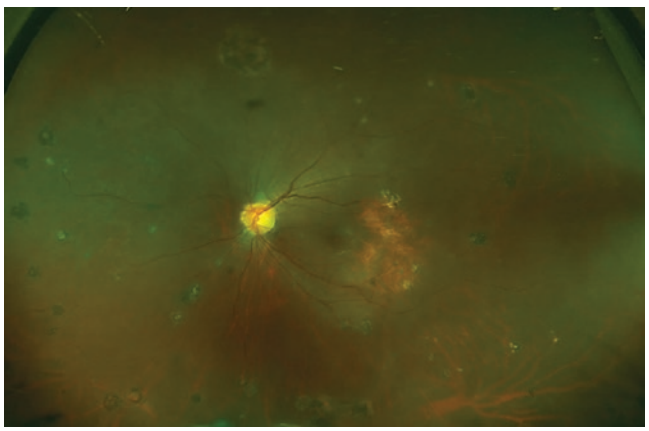

Fig. 4.3 Wide-field fundus imaging reveals multiple punched-out atrophic lesions that are indicative of choroiditis

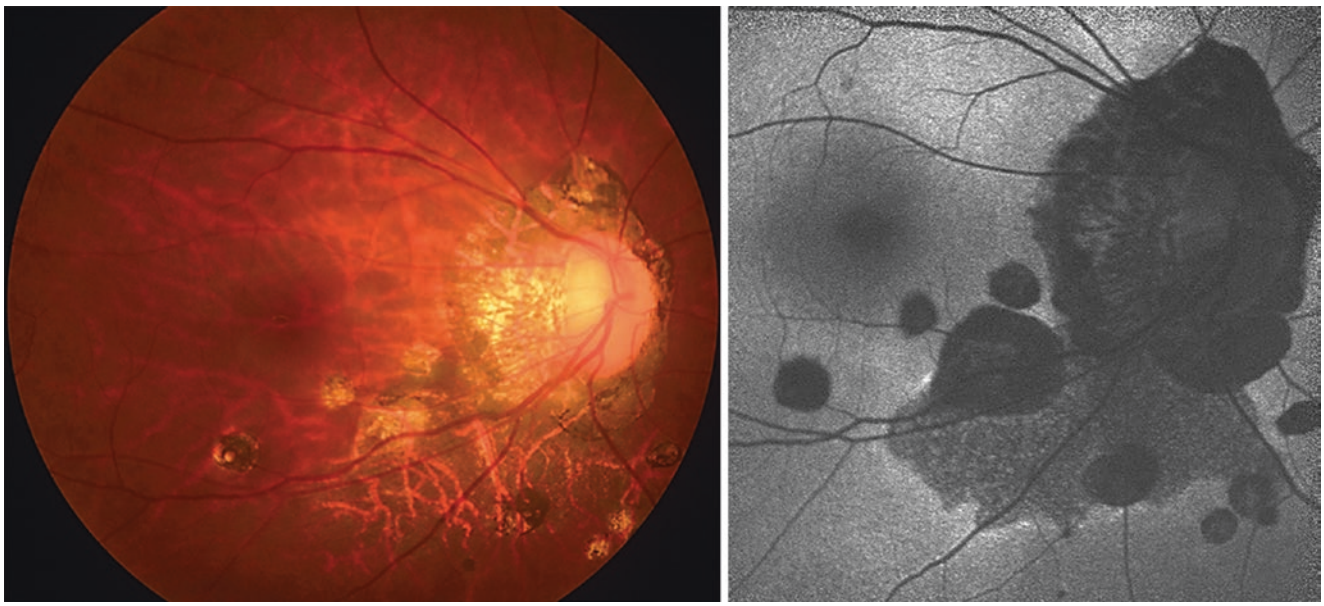

Fig. 4.4 Color fundus photography and autofluorescence imaging demonstrate extensive peripapillary atrophy

(Dreyer and Gass 1984). Abnormal ERG responses in MCP were described as rod dysfunction, prolonged cone b-wave implicit times, and poor oscillatory potentials (Reddy et al. 1996). Multifocal ERG revealed a diffuse and irreversible depression in first-order responses in MCP patients, most of which did not correspond to the scotomas on the Goldman visual field (Curcio et al. 1990).

MCP is a chronic disease that may persist for many years and typically has multiple recurrences in one or both eyes (Reddy et al. 1996; Fung et al. 2014). Reactivation of inflammation includes cellular infiltrates of the anterior chamber and vitreous, enlargement of previous lesions, and the appearance of new lesions (Reddy et al. 1996). The mean final visual acuity was 20/42 when 65 eyes with MCP were followed-up for an average of 92 months (Fung et al. 2014). The reported incidence of cystoid macular edema (CME) in MCP varies, ranging from 14% (Dreyer and Gass 1984) to more than 40% (Kedhar et al. 2007). CNV, responsible for 45% of irreversible visual loss to 20/200 or worse (Thorne et al. 2006), has been reported in 32–46% of patients with MCP (Dreyer and Gass 1984; Reddy et al. 1996; Fung et al. 2014). Epiretinal membrane (ERM), with a reported incidence of about 5% in eyes with MCP (Kedhar et al. 2007), accounted for 28% of vision loss to less than 20/50 in one study (Thorne et al. 2006).

Diagnosis

The diagnosis of MCP is usually a clinical one based on the characteristic fundus findings, and ancillary tests only help establish the diagnosis of MCP.

Fluorescein Angiography

In the acute phase, the active lesions of MCP may appear hypofluorescent on the fluorescein angiogram (FA) with staining and leakage in the late phase. The punched-out atrophic scars in the healed phase show early hyperfluorescence with fading out in the late phase as window defects (Fig. 4.5). If CNV is present, characteristic early hyperfluorescence with late leakage appears in the peripapillary or macular areas.

Indocyanine Green Angiography

Indocyanine green (ICG) angiography provides additional information not detected by fundus examination and FA alone, which helps to understand the pathophysiology of MCP, to differentiate from other inflammatory chorioretinopathies and to identify the progression and recovery of MCP. Multiple hypofluorescent spots of variable size can be found on the posterior pole on ICG angiography that are not apparent on FA or clinical examination (Slakter et al. 1997) (Fig. 4.6). These hypofluorescent lesions on ICG angiography generally represent acute or subacute disease. They are not constant, resolving spontaneously as the acute process subsides or with anti-inflammatory therapy. Visual field defects and corresponding areas of hypofluorescence on the ICG study were found in the same study group (Slakter et al. 1997). In seven eyes showing enlarged blind spots on visual field testing, ICG angiography showed confluent hypofluorescence surrounding the optic nerve (Slakter et al. 1997). The authors described that the hypofluorescent lesions in

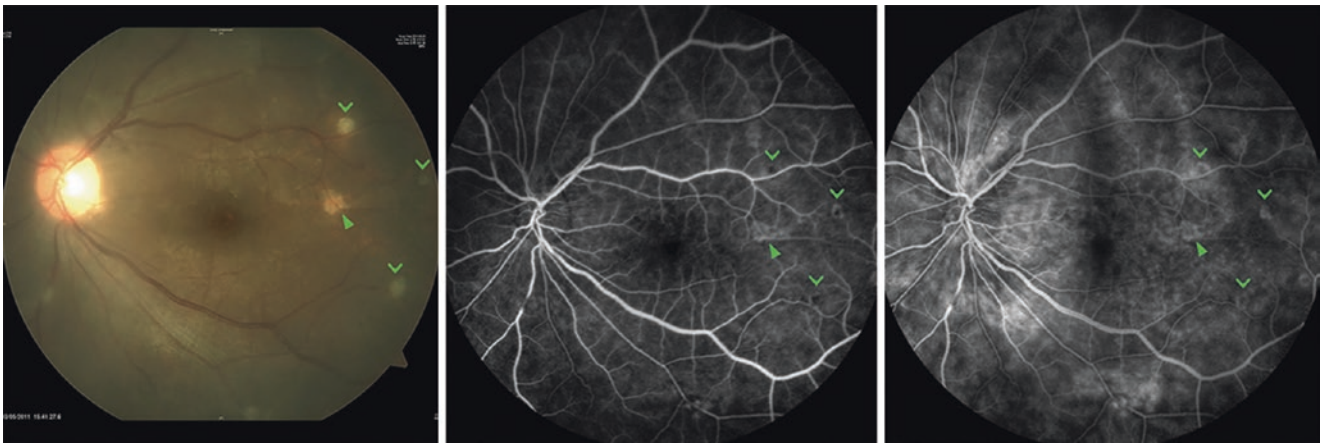

Fig. 4.5 Color fundus photo (left) and fluorescein angiogram of the early (middle) and late (right) phases show multifocal chorioretinal lesions in the different stages. The active lesions (three arrowheads) appear with decreased fluorescence in the early phase and fluorescence staining in the late phase. Early hyperfluorescence with fading out in the late phase is observed in the atrophic lesion (filled triangle)

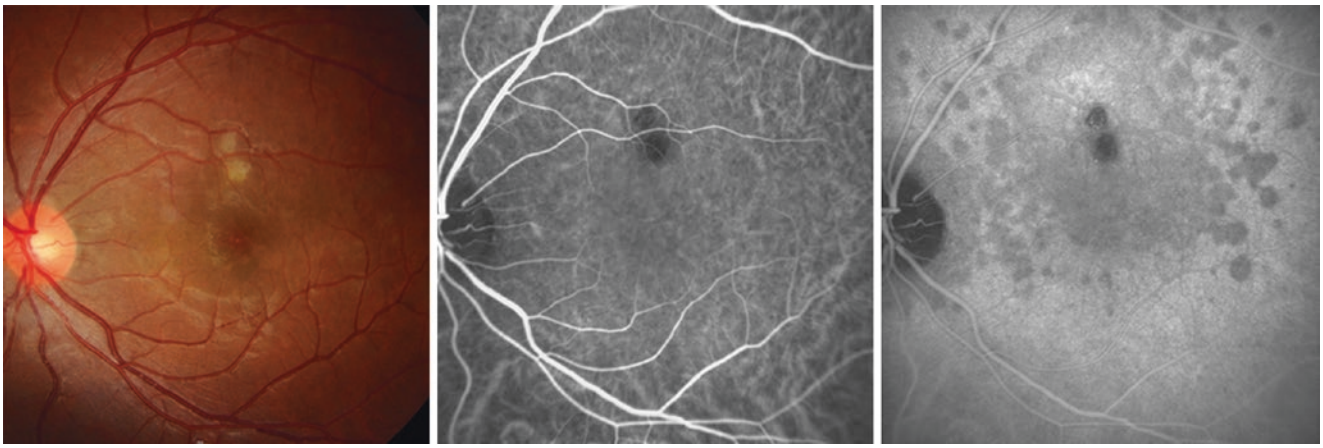

Fig. 4.6 Early phase indocyanine green angiogram (middle) demonstrates focal hypofluorescent spots which are also visible in the color fundus photograph (left). Late phase indocyanine green study (right) shows a large number of hypofluorescent spots of variable size throughout the posterior pole. These lesions are not apparent on the fundus photo

MCP may be the result of focal collections of inflammatory cells or debris at the level of the choriocapillaris producing "blocked fluorescence" or in the middle layer of the choroid causing a "space occupying effect." Underlying perfusion abnormalities of the choroid and choriocapillaris have been suggested as another potential pathophysiology of the hypofluorescent lesions seen on ICG angiography.

Fundus Autofluorescence

Two major types of hypoautofluorescence have been identified. Chorioretinal hypoautofluorescent spots greater than 125 μm were usually observed corresponding to the area of a punched-out scar visible by color fundus photography (Haen and Spaide 2008) (Fig. 4.7). Autofluorescence imaging also demonstrates hypoautofluorescent lesions measuring less than 125 μm that were typically not visible by color fundus photography (Haen and Spaide 2008) (Fig. 4.8). Subsequently, in another study of 16 MCP eyes, 12 eyes predominantly presented with punctate hypoautofluorescent spots corresponding to multiple areas of chorioretinal atrophy (Yeh et al. 2010). Macular hyperautofluorescence may be observed in the area of active chorioretinitis (Fig. 4.8), which also correlated with complete resolution with immunosuppressive therapy.

Optical Coherence Tomography

Optical coherence tomography (OCT) is useful not only in the evaluation of chorioretinal lesions in the macula but also in the detection of CME and CNV lesions. Thinning of the retina with disruption of the photoreceptor inner and outer segment junction was described mainly in the macular lesions and in the peripapillary atrophic scars of MCP by

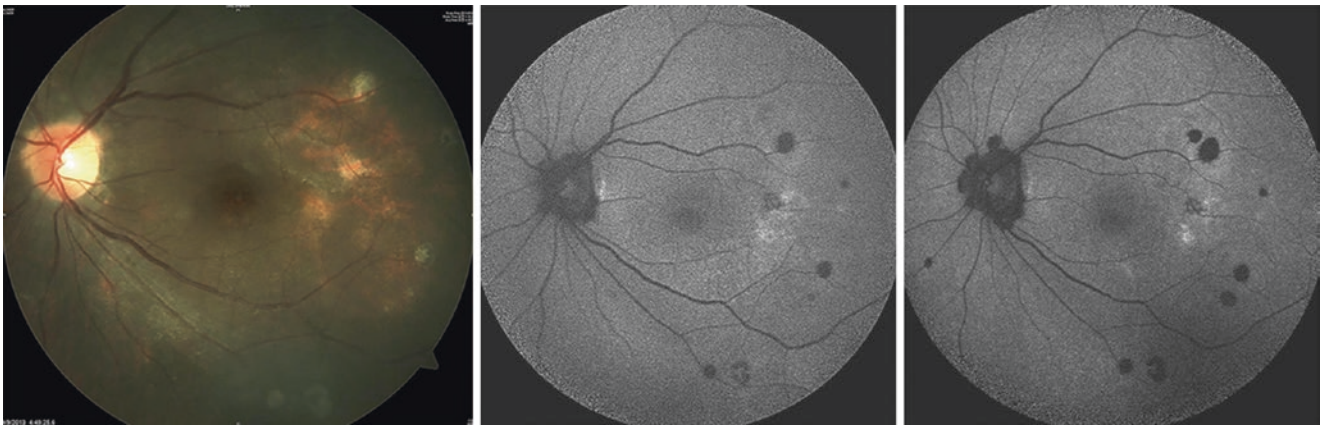

Fig. 4.7 Autofluorescence imaging (middle) at the initial visit shows multiple small hypoautofluorescent lesions in the posterior pole that correspond to the subretinal yellowish to creamy lesions on the color fundus photograph (left). Over the course of 3 years, enlargement of the size and increase in the number of hypoautofluorescent spots can be seen (right)

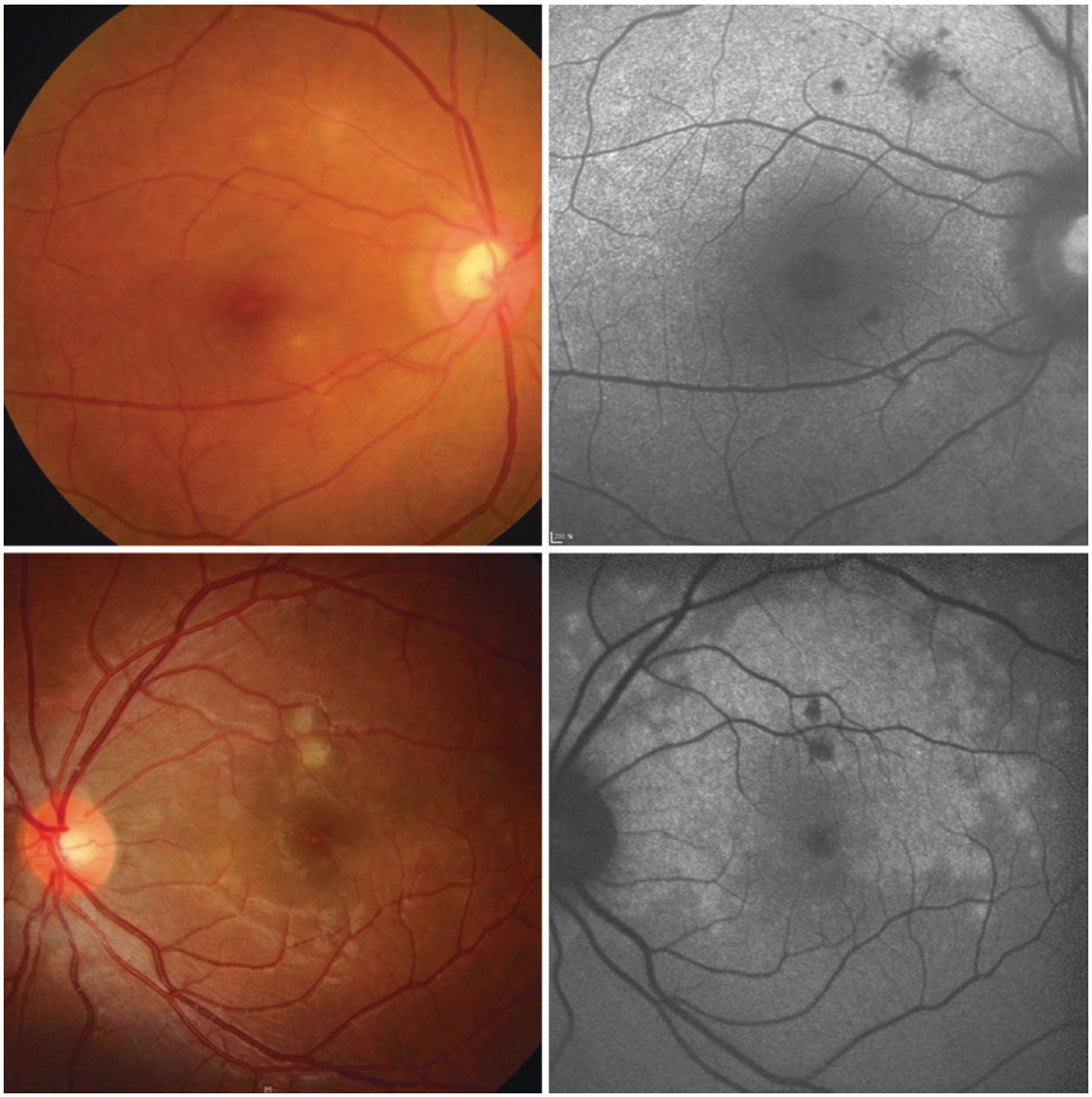

Fig. 4.8 Autofluorescence photography (upper right) demonstrates multiple tiny hypoautofluorescent spots which are not well visualized in color fundus photography (upper left). Autofluorescence photography (lower right) shows macular hyperautofluorescence, indicative of active chorioretinitis in the posterior pole that is also not revealed on color fundus photography (lower left)

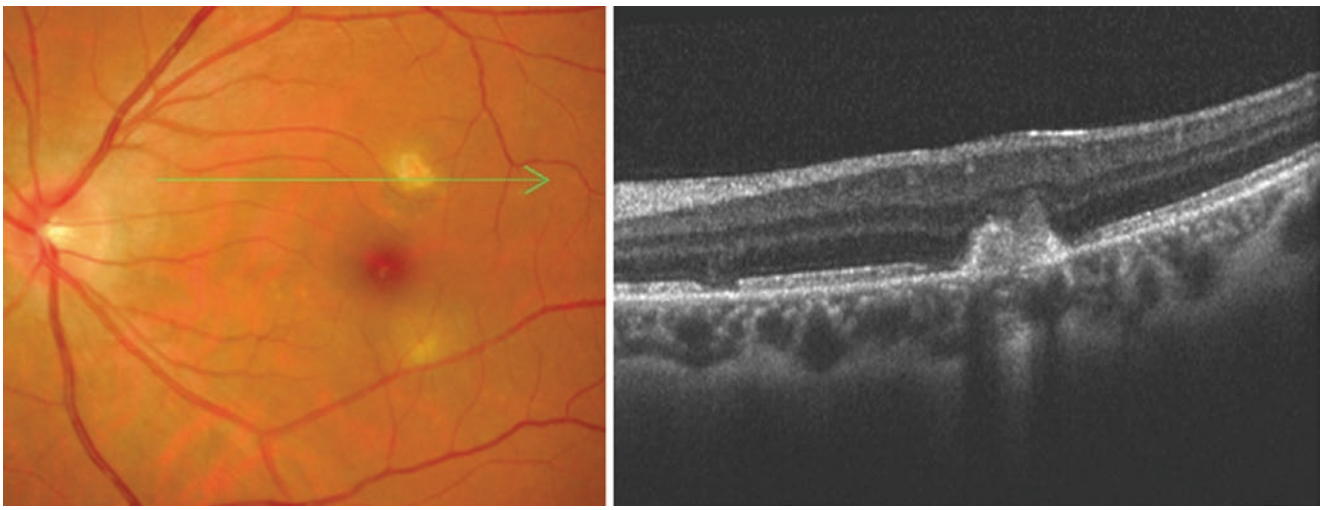

Fig. 4.9 Spectral-domain optical coherence tomography shows drusen-like subretinal accumulation of hyperreflective inflammatory lesion during the acute stage with disruption of the outer nuclear layer and the photoreceptor inner and outer segment junction

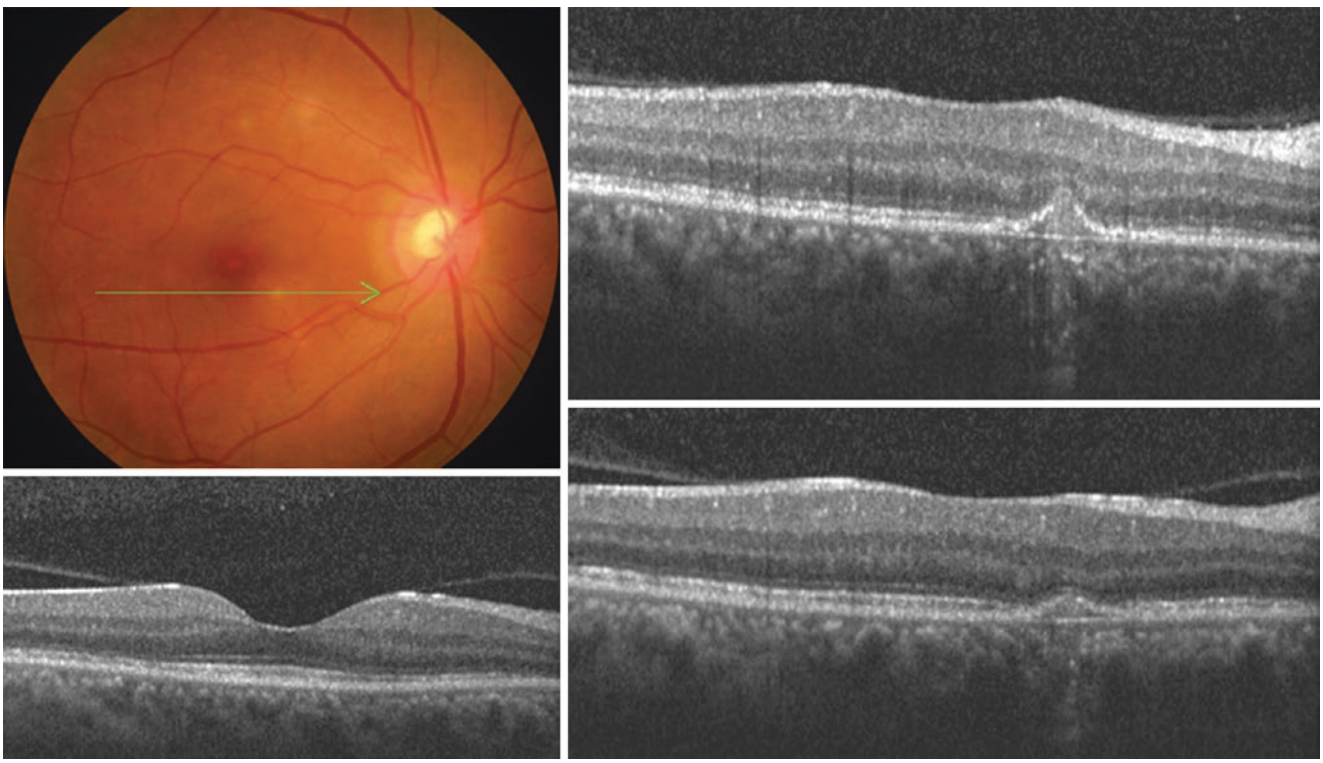

Fig. 4.10 On spectral-domain optical coherence tomography (OCT), the acute lesion initially appears as a "volcano eruption"-like subretinal infiltration (upper row), with remarkable resolution after oral steroid therapy (lower right). OCT image through the fovea also reveals the presence of inflammatory cells in the posterior vitreous (lower left)

several authors (Spaide et al. 2008; Yasuno et al. 2009). Drusen-like accumulation at the sub-RPE layer and inflammatory cells in the posterior vitreous can also be found in the acute lesions of MCP (Vance et al. 2011) (Fig. 4.9). The sub-RPE lesion may sometimes have a vertically elevated "volcano eruption-like" appearance on OCT, which can decrease in size in response to anti-inflammatory therapy (Fig. 4.10). OCT also allows visualization of inflammatory cells in the posterior vitreous. The choroidal pathologies were visualized by the development of high-penetration OCT. Localized thinning of the choroid, occlusion of the choroidal vessels, and localized hyper-reflectivity were noted in MCP lesions, accounting for hyper-pigmentation of the choroid (Yasuno et al. 2009) (Fig. 4.11). It can be difficult to distinguish the

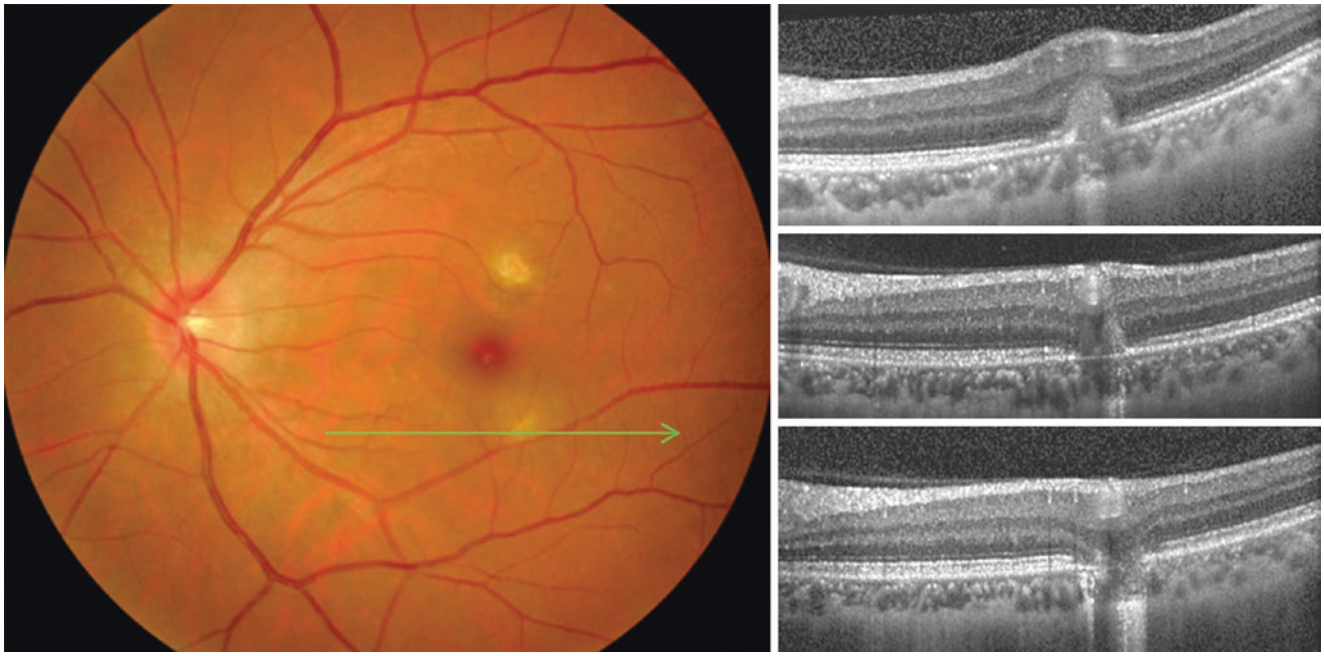

Fig. 4.11 Sequential spectral-domain optical coherence tomography of 1-year interval shows the chronic changes of a lesion. With the resolution of subretinal inflammatory material accumulation, the disruption of the outer retinal layer progresses (top and middle, right), and afterwards, localized atrophic changes to the choroid with an increase in hyper-reflectivity is observed (bottom, right)

acute lesions of chorioretinitis from inflammatory CNV based on clinical examination and FA. However, CNV demonstrates characteristic OCT features, such as a sub-RPE component infiltrating the outer retinal layer and associated fluid exudation, not so commonly seen with inflammatory lesions (Amer et al. 2015)

Optical Coherence Tomography Angiography

In addition to OCT, optical coherence tomography angiography (OCT-A) is a promising tool in detecting inflammatory CNV and in differentiating it from inflammatory lesions of MCP. OCT-A flow signatures consistent with neovascularization can be identified mixed in subretinal and sub-RPE layers (Zahid et al. 2017) (Fig. 4.12). Lesions with no definitive signs of FA leakage were frequently found to have neovascularization using OCT-A. OCT-A showed an increase in the hyporeflective ring around the CNV and in the hyper-reflectivity of the CNV vessels themselves after anti-vascular endothelial growth factor (VEGF) therapy (Levison et al. 2017).

Management

Steroids and Immunomodulatory Therapy

The use of systemic or periocular corticosteroids can be effective in controlling intraocular inflammation in patients with MCP. An improvement of visual acuity in MCP eyes had been reported previously (Dreyer and Gass 1984; Morgan and Schatz 1986), and it was more significant in those associated with CME (Cantrill and Folk 1986; Nussenblatt et al. 1996). However, there have been serial reports that the therapeutic effect of corticosteroids in MCP is temporary and limited in the acute phase (Nolle et al. 1998). In those studies, most patients with MCP eventually had visual deterioration due to CNV development during corticosteroid therapy (Cantrill and Folk 1986; Brown et al. 1996).

Since MCP is chronic and recurrent in nature, long-term immunomodulatory therapy may be a more effective alternative treatment modality in MCP. The immunomodulatory agents for MCP include immunosuppressive agents such as methotrexate, azathioprine, cyclosporine, cyclophosphamide, chlorambucil, tacrolimus, leflunomide, mycophenolate mofetil, infliximab, adalimumab, and etanercept. A retrospective case series report of 19 patients with MCP revealed that immunomodulatory therapy effectively controlled inflammation and preserved vision without any significant drug-related complications (Michel et al. 2002). In a retrospective cohort study of 122 MCP eyes, immunomodulatory therapy significantly reduced the risk of developing posterior pole complications such as CME, ERM, and CNV by 83% (Thorne et al. 2006). In a paper outlining immunosuppressive treatment guidelines for ocular inflammatory disease suggested by 12 uveitis specialists, MCP was cited as an entity that frequently requires immunomodulatory therapy at some point in its disease course (Jabs et al. 2000).

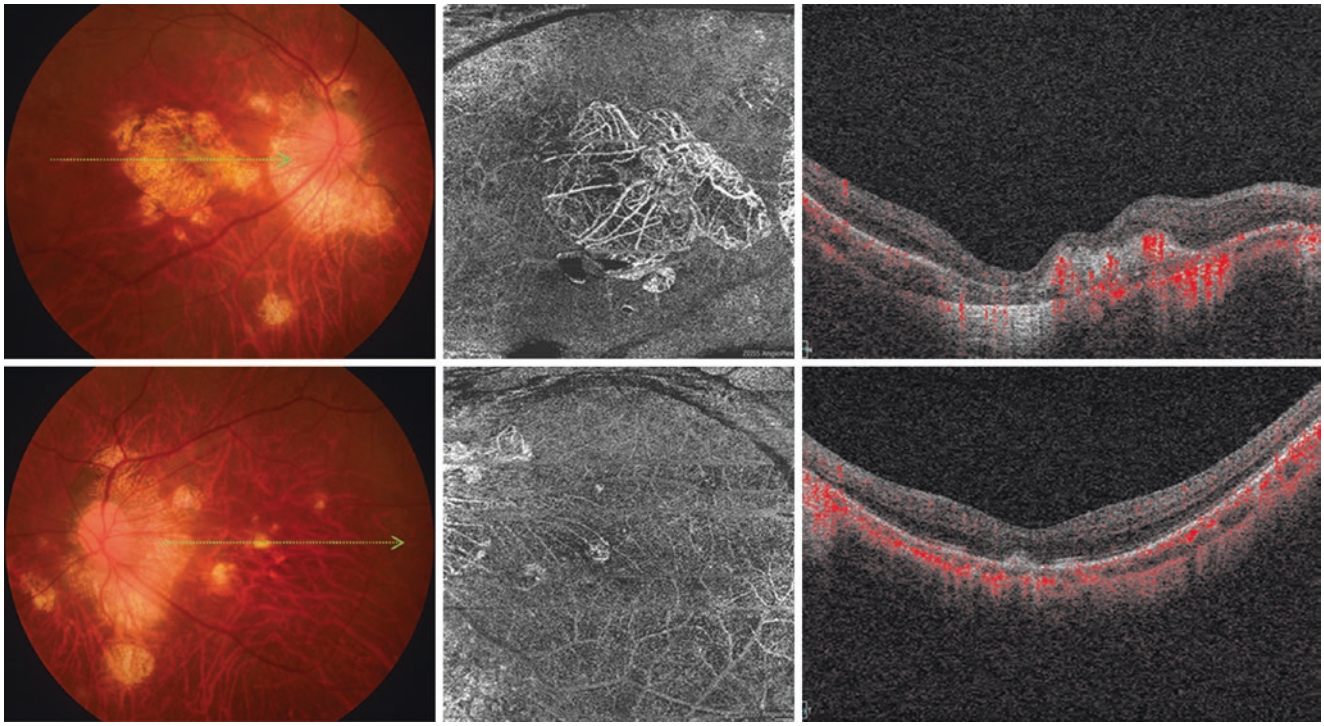

Fig. 4.12 Color fundus photograph demonstrates a large patchy chorioretinal atrophy at macula with subretinal grayish membrane involving the fovea and peripapillary atrophy (upper left). Optical coherence tomography angiography (OCT-A) through this lesion reveals the presence of choroidal neovascularization (CNV) with an area of active vascular flow in the subretinal hyperreflective material (upper right). In an eye with active multifocal choroiditis and panuveitis without CNV (lower left), no blood flow signal was detected on the OCT-A image of the active inflammatory chorioretinal lesion (lower right)

Treatment of Choroidal Neovascularization

Choroidal neovascularization is the most common posterior pole complication of MCP (Dreyer and Gass 1984; Morgan and Schatz 1986; Brown et al. 1996), accounting for the major cause of vision impairment, up to 45% of vision loss to worse than 20/200 (Thorne et al. 2006). The treatment modalities in the management of CNV due to MCP are very similar to the methods used for exudative age-related macular disease treatment. Several investigators reported that sustained visual improvement was achieved by intravitreal injections of anti-VEGF agents in CNV associated with MCP (Fine et al. 2009; Chang et al. 2008). In those retrospective studies, the mean number of intravitreal injections was 1.6 and 3.4 per year. Photodynamic therapy has also proven effective in preserving visual acuity in CNV due to MCP (Parodi et al. 2004; Brown et al. 2009).

The efficacy and safety of laser photocoagulation for the treatment of CNV secondary to MCP have not been extensively studied. In four cases, extrafoveal and juxtafoveal CNVs arising due to MCP were significantly regressed with sparing of central vision (Brown et al. 1996), but subfoveal CNV lesions should not be treated with laser. Intravitreal methotrexate for the treatment of CNV in MCP was reported in one case report as being effective for preserving vision and preventing flare for over 20 months of treatment (Mateo-Montoya et al. 2013).

Submacular surgery for CNV associated with MCP was widely studied before the development of antiangiogenic drugs; however, because of the high incidence of adverse events in the perioperative period and the lack of significant visual benefit to the patients, its role was extremely limited in the treatment of CNV complicating MCP (Hawkins et al. 2004; Giansanti et al. 2009).

Pars Plana Vitrectomy

There has been no randomized controlled study on the efficacy of pars plana vitrectomy in the treatment of general or MCP-related uveitis. In a case series of nine patients having medically refractory MCP, pars plana vitrectomy did not result in any meaningful therapeutic effect (Nolle and Eckardt 1993).

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Multiple Evanescent White Dot Syndrome

5

Ji Eun Lee

Introduction

Multiple evanescent white dot syndrome (MEWDS) is an acute multifocal outer retinopathy manifesting multiple white dots at the level of the outer retina or retinal pigment epithelium (RPE) (Jampol et al. 1984). Usually young adults are affected unilaterally. Epidemiologic data show a female predominance having the peak incidence in late 20s, although age spans teens to 60s.

The cause of MEWDS is still unknown. There are several entities having similar clinical features; acute idiopathic blind spot enlargement (AIBSE), punctate inner choroidopathy (PIC), multifocal choroiditis, and acute zonal occult outer retinopathy (AZOOR). These may develop concurrently in each eye of one patient, or sequentially in one eye. Gass suggested the term of AZOOR complex representing a spectrum of a single disease or viral infection. However, no virus has been reported to be isolated reproducibly in patients with this group of diseases. Increased serum immunoglobulin level and the high frequency of a specific HLA haplotype support an association of immunologic mechanism (Desarnaulds et al. 1996). Preceding flu-like symptoms propose a viral infection as an environmental trigger.

MEWDS has an excellent prognosis and does not require treatment typically. Systemic steroid may be helpful to hasten recovery of vision and fundus findings.

Clinical Features

Clinical Symptoms

Patients usually complain of blurred vision of acute onset in one eye. Sometimes they report transient photopsia or a temporal scotoma corresponding to enlarged blind spot. Flu-like illness may precede in one third of cases. Presenting visual acuity may vary 20/300 to 20/20.

Fundus Findings

The most typical features are numerous small ill-defined white spots with a diameter about 100–200 μm at the level of deep retina or RPE (Fig. 5.1). They are prominent in the posterior pole having the fovea sometimes spared. The white spots are resolved completely after several weeks to months. Fine granularity of the fovea is the classic appearance (Fig. 5.2), which may be the only presentation of the fundus (Shelsta et al. 2011). After resolution of fundus findings, it is challenging to differentiate MEWDS from AZOOR or AIBSE. Striking features of late indocyanine green angiography (ICGA) and patch defects of the photoreceptor layer shown in en face optical coherence tomography (OCT) are useful to confirm the diagnosis (Fig. 5.3). Vitritis, retinal venous sheathing, and optic disc swelling are often observed. Rarely, a progressive geographic depigmentation or choroidal neovascularization (CNV) have been reported.

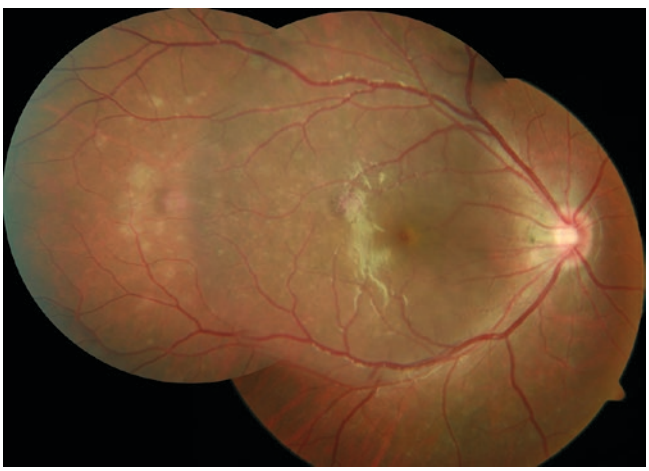

Fig. 5.1 Color fundus photograph shows numerous small white spots scattered in the posterior pole

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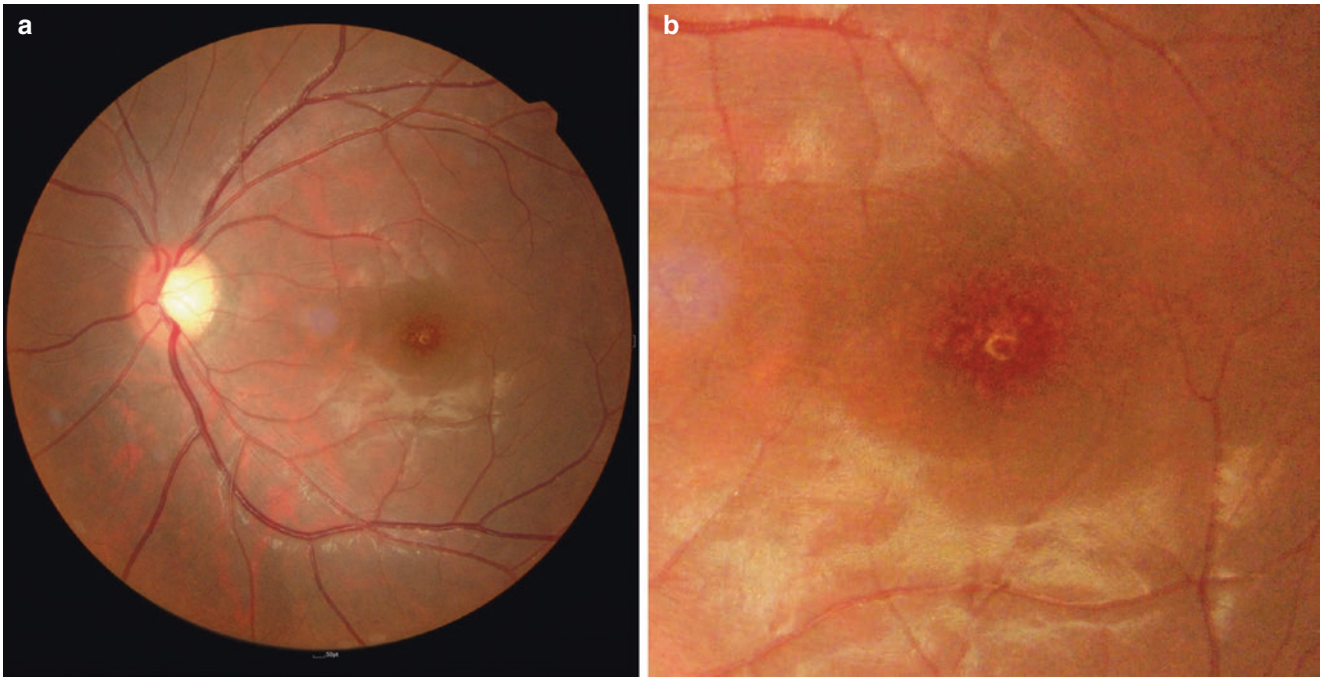

Fig. 5.2 Fundus photograph shows no white spots (**a**) but fine granularity of the fovea (**b**)

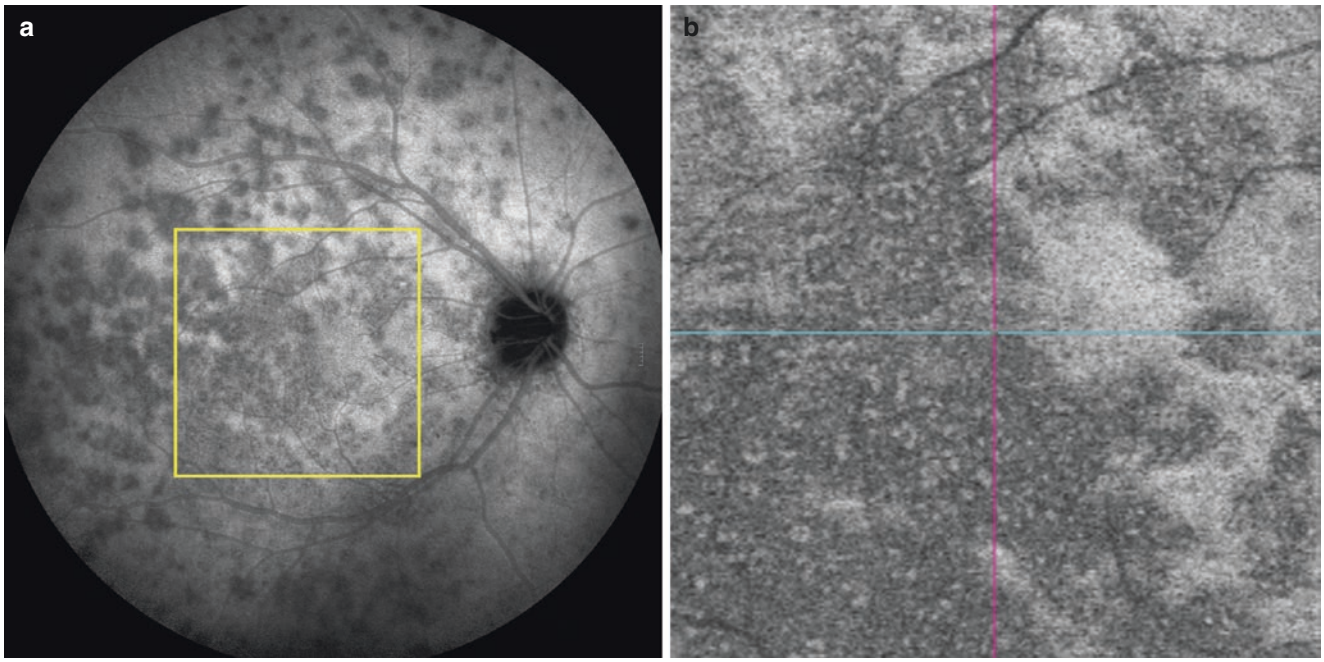

Fig. 5.3 Late phase indocyanine green angiography (**a**) of Fig. 5.1 case demonstrates multiple hypofluorescence spots, which are more discrete than fundus findings and correspond to hyporeflectivity seen in en face optical coherence tomography image at the ellipsoid zone level (**b**)

Angiography

Fluorescein angiography (FA) demonstrates early and late hyperfluorescence of the white dots. Early diffuse leakage of patchy appearance leaves late staining at the level of the deep retina (Fig. 5.4). Other less frequent findings include papillary leakage and focal retinal vascular stain. After resolution of fundus appearance, FA findings become normal soon, although subtle increased transmission may remain in the macula corresponding to the white dots or foveal granularity.

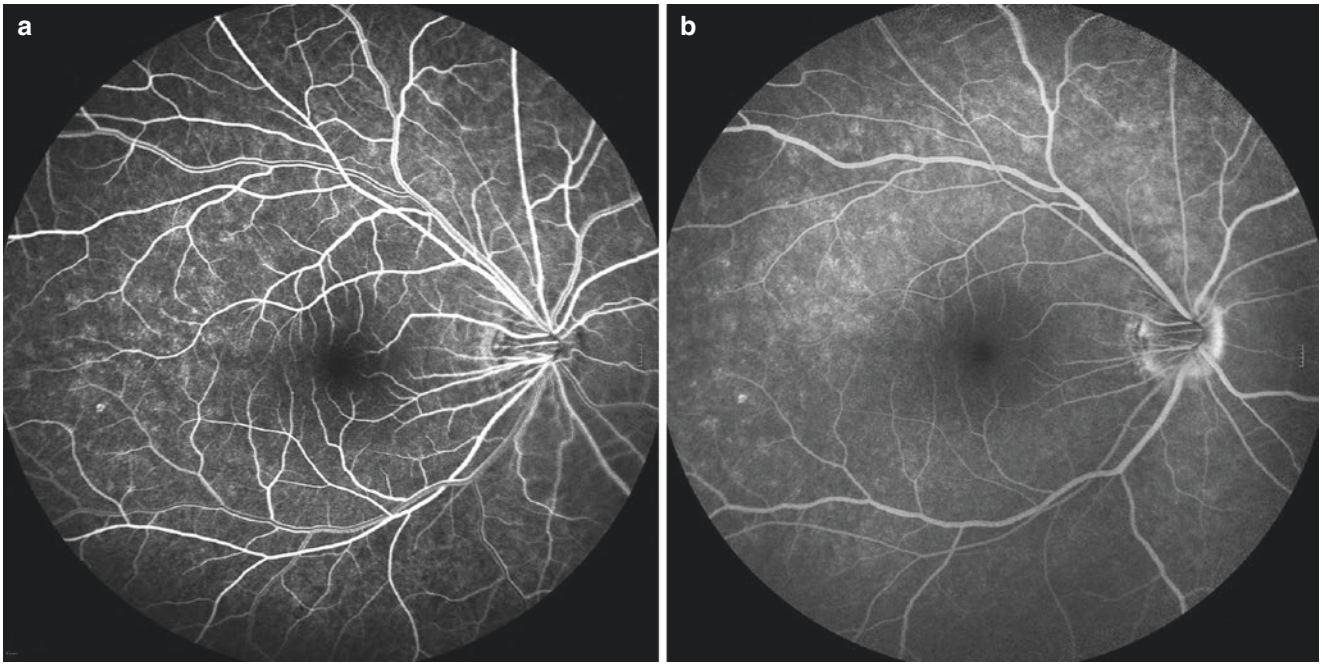

Fig. 5.4 Fluorescein angiography of Fig. 5.1 case. Leakage in the early phase (**a**) and staining in the late phase (**b**) are observed as patchy hyperfluorescence

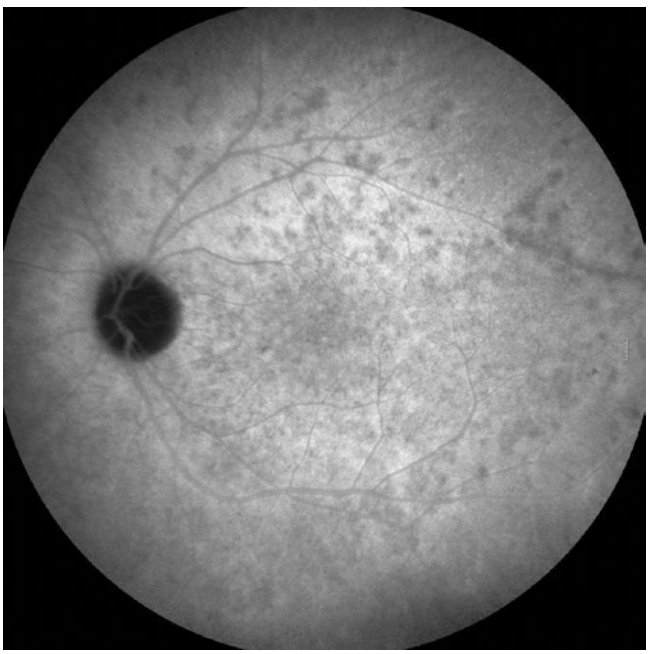

Fig. 5.5 Late phase indocyanine green angiography of Fig. 5.2 case revealed multiple hypofluorescence spots which were not observed in fundus examination

ICGA shows normal large choroidal vessels in the early phase, and patchy hypofluorescent spots are numerous and distinct than the white dots seen clinically in the late phase (Fig. 5.5) (Ie et al. 1994). These spots represent effects of the RPE and photoreceptors on the choriocapillaris, rather than primary disturbance of the choroidal circulation. The abnormal findings of ICGA persist much longer than the clinical symptoms or fundus abnormalities, but disappear gradually (Tsukamoto et al. 1999).

Optical Coherence Tomography

Spectral-domain OCT revealed disturbance in the ellipsoid zone (EZ, synonym of the IS-OS junction) corresponding to the white dots observed in fundus photography or angiography (Sikorski et al. 2008). Reflectivity of the underlying choroid increases, and the choroid has a trend of transient thickening in the acute phase. The EZ defect can be restored, but persists longer than fundus findings. It is observed best in en face imaging as a multiple spot or plaque of hyporeflectivity, which is helpful to diagnose without ICG angiography (Fig. 5.6).

Visual Field

Although visual field may be normal, various abnormalities can also be seen including a generalized depression, cecocentral, or arcuate scotoma in addition to the classical finding of an enlarged blind spot (Fig. 5.7) (Nakao and Isashiki 1986). These abnormalities usually persist longer than fundus lesions.

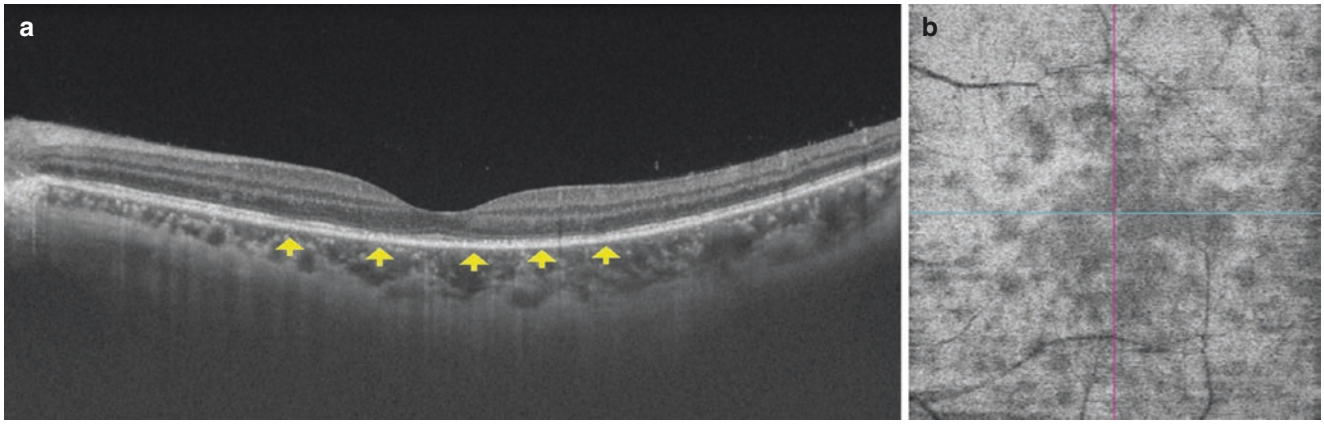

Fig. 5.6 Optical coherence tomography (OCT) shows multifocal attenuated signals from the ellipsoid zone (EZ) in the B-scan (**a**). The signal defects are identified more clearly in the en face OCT image at the level of the EZ (**b**)

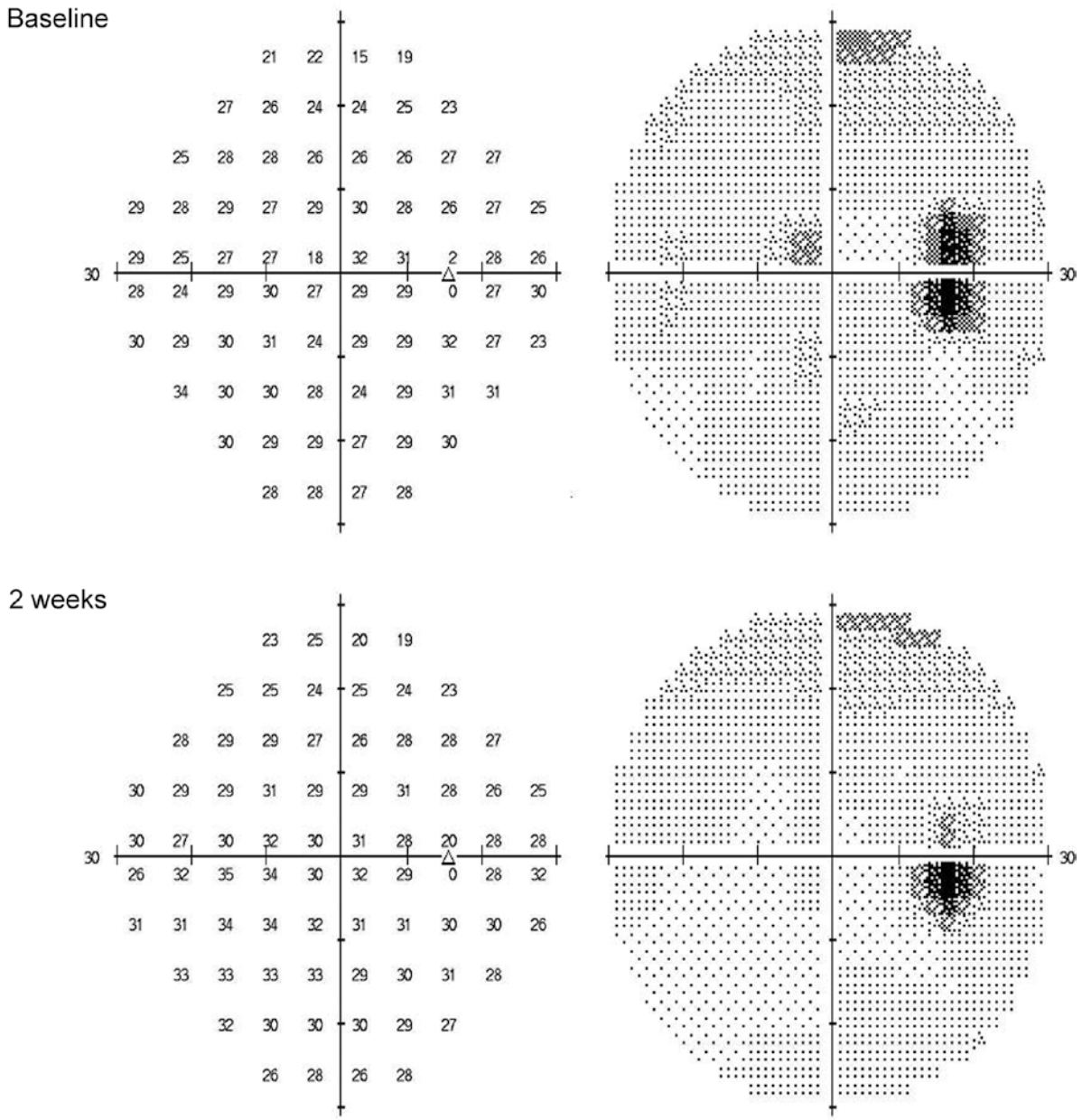

Fig. 5.7 Visual field of Fig. 5.1 case. Central scotoma and enlarged blind spot noted at baseline improved 2 weeks later

Management and Course

MEWDS has the excellent natural course, and no treatment is required (Fig. 5.8). Systemic steroid may be prescribed for hastening visual recovery with no supporting evidence. In case of complicated choroidal new vessels, anti-VEGF therapy resulted in a successful regression (Rouvas et al. 2007).

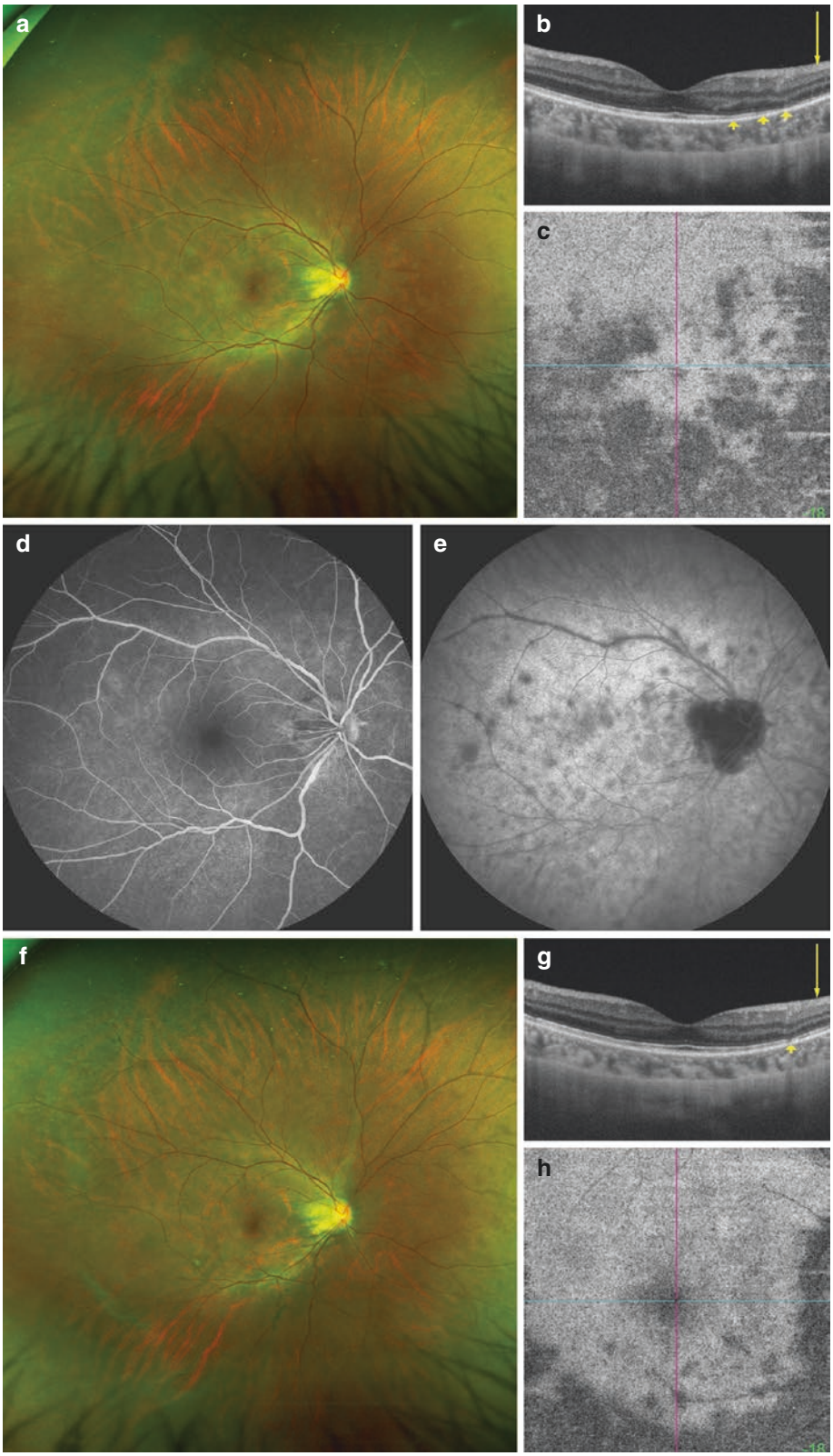

Fig. 5.8 Multiple evanescent white dot syndrome in a 35-year-old woman. (**a**) At baseline, numerous white spots are noted mainly in the posterior pole. (**b**, **c**) Defects in the ellipsoid zone (EZ) are depicted in B-scan and en face image of optical coherence tomography (OCT). (**d**) Patchy hyperfluorescence and focal vascular leakage is seen in the late phase of fluorescein angiography. (**e**) Hypofluorescent spots are numerous and distinct in the late phase of indocyanine green angiography. The fovea center was spared and visual acuity was 20/20. (**f**–**h**) One month later, fundus lesions resolved completely, but EZ defects are still noted in B-scan and en face OCT images

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Acute Zonal Occult Outer Retinopathy

6

Wataru Saito and Susumu Ishida

Introduction

Acute zonal occult outer retinopathy (AZOOR) is an idiopathic clinical entity with acute zonal impairment of the outer retina, which initially shows no funduscopic abnormalities. AZOOR was first described by Gass in 1993 (Gass 1993) and is characterized by an acute onset of scotomata, often with photopsia in one or both eyes, minimal funduscopic changes (Fig. 6.1), and functional and morphological impairments of the outer retina detected by electroretinography (ERG) and spectral-domain optical coherence tomography (SD-OCT) (Gass et al. 2002; Saito et al. 2015). The retinal sites affected by AZOOR often develop zonal atrophy of the retinal pigment epithelium (RPE), which is a characteristic feature in the convalescent stage of AZOOR (Fig. 6.2).

Gass reported that chorioretinal diseases such as multiple evanescent white dot syndrome (MEWDS) sometimes shared clinical features in common with AZOOR (Gass 1993; Holz et al. 1994). Therefore, Gass hypothesized that the etiologies of MEWDS, punctate inner choroidopathy (PIC), acute macular neuroretinopathy (AMN), and multifocal choroiditis and panuveitis were the same as that of AZOOR, and these conditions could be classified as subtypes of AZOOR (AZOOR complex), even though they presented with funduscopic abnormalities (Gass 1993, 2003). Similarly, acute annular outer retinopathy, which involves a thin gray-circular ring lesion, is also classified as a subtype of AZOOR because, apart from the gray ring lesion, it also has AZOOR-like features (Gass and Stern 1995).

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Diagnostic Criteria

In 2002, Gass described diagnostic criteria of AZOOR as follows (Gass et al. 2002): acute visual field or vision loss usually with concurrent photopsia, one or more visual field defect regions that could not be explained by funduscopic examination or fluorescein angiography (FA), and decreased amplitude on ERG. ERG is an important tool for the diagnosis of AZOOR because it can detect functional loss of the photoreceptor. Multifocal ERG is especially useful because it can focally detect depressed amplitudes in the AZOOR-affected area (Arai et al. 1998).

In 2007, Li reported that SD-OCT revealed loss or discontinuity of the ellipsoid zone (EZ) corresponding to the AZOOR lesion sites (Li and Kishi 2007). Since then, SD-OCT evidence of outer retinal morphological abnormalities has become an important tool for the diagnosis of AZOOR (Spaide et al. 2008). Thus, it is important to verify morphological and functional photoreceptor impairments

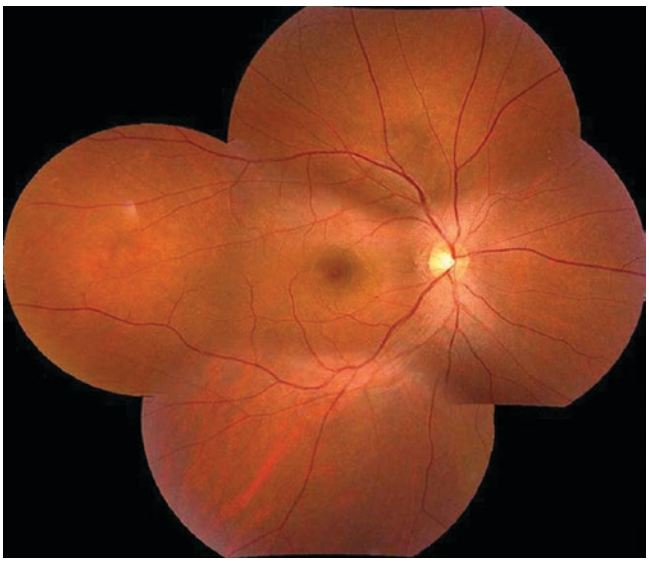

Fig. 6.1 Fundus photograph shows no abnormalities of the retina at the initial visit. The patient's best-corrected visual acuity (BCVA) is 0.4

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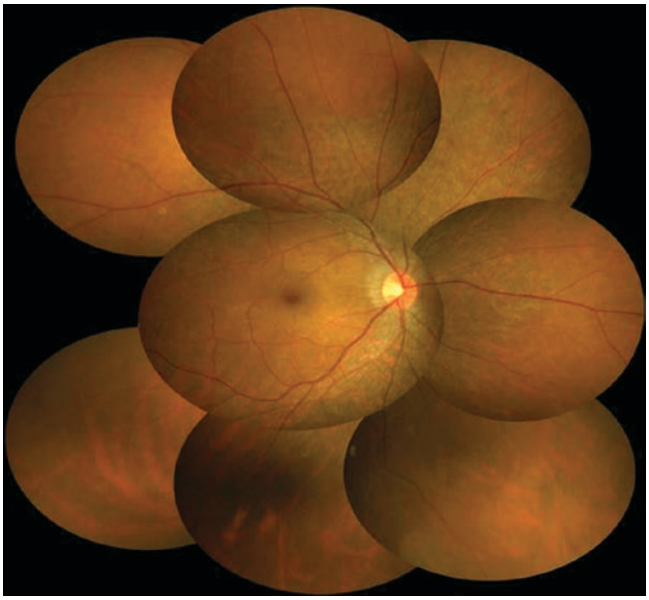

Fig. 6.2 In the same eye as that shown in Fig. 6.1, zonal atrophy of the retinal pigment epithelium gradually appeared corresponding with the affected retinal site. The BCVA recovered to 1.0 after the administration of systemic corticosteroid therapy

via both SD-OCT and ERG to obtain a diagnosis of AZOOR and to rule out other diseases, such as infectious chorioretinitis (e.g., syphilis and tuberculosis) and cancer-associated retinopathy.

Etiopathogenesis

The mechanism that causes photoreceptor impairments in AZOOR remains unclear. Approximately 30% of patients with AZOOR have systemic autoimmune diseases (Gass et al. 2002; Hintzen and van den Born 2006). Systemic corticosteroid therapy appears to be effective for patients with AZOOR (Saito et al. 2014, 2015; Kitakawa et al. 2012; Chen et al. 2015). These observations suggest that AZOOR has an autoimmune/inflammatory mechanism. At present, two opinions on the etiology of AZOOR are under consideration. One is the anti-retinal antibodies (ARAs) theory because recent studies have reported that serum ARAs are high in patients with AZOOR (Tagami et al. 2014; Qian et al. 2017). However, ARAs might be secondarily produced following retinal impairment caused by AZOOR (Forooghian 2017), because there is no evidence of an association between ARAs and the pathogenesis of AZOOR.

The other theory pertains to choroidal impairment because the photoreceptors receive a supply of oxygen and nutrition from the choriocapillaris. In patients with AZOOR, macular choroidal blood flow velocity is increased, and choroidal thickness decreased when visual function and outer retinal morphology improved (Saito et al. 2014; Hashimoto et al. 2017). This circulatory and morphological pattern is consistent with that of choroiditis, for example, Vogt–Koyanagi–Harada disease and serpiginous choroiditis (Hirooka et al. 2015; Takahashi et al. 2014). Moreover, other AZOOR complex diseases, MEWDS, PIC, and AMN show the same pattern (Hashimoto et al. 2015, 2016, 2019; Hirooka et al. 2014a, b). Therefore, these results suggest that inflammatory choroidal circulatory impairment is involved in the common pathogenesis among AZOOR complex diseases including AZOOR. However, these observations might be secondary to damaged photoreceptors (Fagan 2014). Thus, further studies are needed to verify whether either of the two AZOOR theories is correct.

Clinical Features

Patient Demographics

AZOOR predominantly affects myopic young or middle-aged females. The median age of onset is approximately 35 years, and 70–80% of patients are females (Gass et al. 2002; Saito et al. 2015). Among Japanese AZOOR patients, 46% have myopia of more than−6 diopters (Saito et al. 2015). In Caucasian patients, approximately 60% initially have unilateral involvement, but this proportion eventually decreases to 30% (Gass et al. 2002). In Japanese patients, the frequency of unilaterality at the final visit appears to be lower than in Caucasian patients (Saito et al. 2015). Patients with AZOOR may have an antecedent flu-like illness.

Symptoms and Ocular Findings

Patients with AZOOR have an acute onset of one or more zones of visual field defect with or without loss of visual acuity. Moreover, they often complain of photopsia such as flickering and whirling within the regions of the visual field defect, which is a characteristic of AZOOR. Relative afferent pupillary defect is present in 24% of the affected eyes (Gass et al. 2002), and patients with this finding may often be misdiagnosed with retrobulbar optic neuritis. Inflammatory cells are not present in the anterior chamber but may be present in the anterior vitreous. The presence of vitreous cells is associated with large visual field defects at the initial visit (Gass et al. 2002; Saito et al. 2015). In most cases, the initial appearance detected by funduscopic examination is normal (Fig. 6.1). Abnormal findings such as a few punctate atrophic scars, which are unrelated to the AZOOR-affected sites, may be present. A white demarcation line at the margin of the lesions and retinal vascular changes such as perivascular sheathing may also be observed (Gass et al. 2002; Mrejen

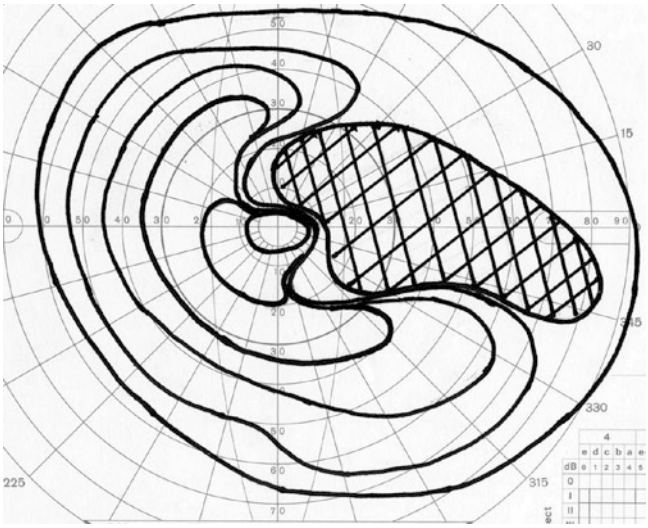

Fig. 6.3 Goldmann perimetry shows a large enlargement of the blind spot. The BCVA is 1.0

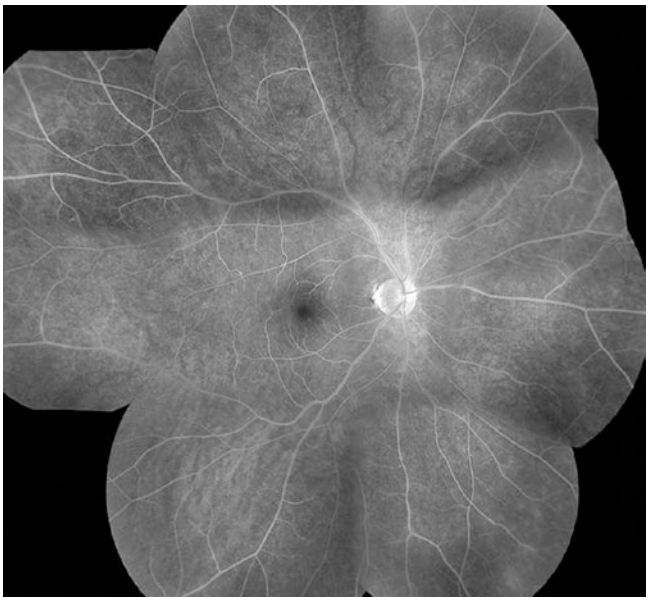

Fig. 6.4 Fluorescein angiography in the acute stage (same eye as that in Fig. 6.1) appears normal, except for retinal vasculitis

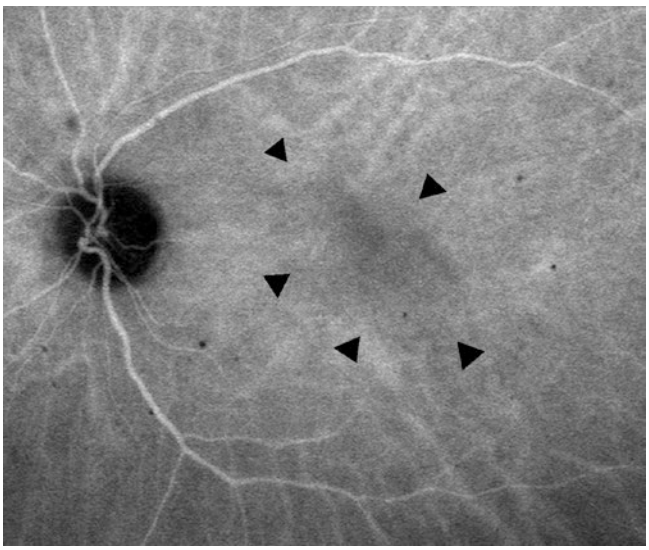

Fig. 6.5 Indocyanine green angiography in the late phase shows macular geographic hypofluorescence (arrowheads) in an eye with a central scotoma

et al. 2014). The affected retinal area later develops a zonal area of RPE degeneration in cases with no or little improvement of visual function (Fig. 6.2). This appears to occur more frequently in Caucasian patients than in Japanese patients (48% vs. 10%) (Gass et al. 2002; Saito et al. 2015). On perimetry tests, an enlargement of the blind spot is commonly detected, often with sparing of central sensitivity (Fig. 6.3) (Gass et al. 2002; Saito et al. 2015). In addition, various scotomata, such as central scotoma, ring scotoma, arcuate scotoma, and hemianopia may be present.

Fundus Angiography

In most cases, fluorescein angiography reveals no abnormalities in the acute stage of AZOOR. In some cases, retinal vasculitis or staining of the optic disc will be present (Fig. 6.4). In the convalescent stage, a window defect is observed corresponding to RPE atrophy. On indocyanine green angiography, abnormal findings such as hypofluorescence in areas related or unrelated to the lesions (Fig. 6.5), diffuse choroidal hyperfluorescence in the middle or late phases, and hyperfluorescence along with large choroidal vessels have been previously reported (Saito et al. 2007, 2015; Monson and Smith 2011).

Optical Coherence Tomography

In the acute stage of AZOOR, SD-OCT shows loss or discontinuity of the EZ and interdigitation zone (IZ) corresponding to the AZOOR lesion sites (Fig. 6.6a) (Li and Kishi 2007; Spaide et al. 2008). In milder cases, only the IZ will be absent and the EZ will remain intact (Tsunoda et al. 2011). Abnormalities of the EZ and IZ improve or recover in some patients whose visual function improves (Fig. 6.6b) (Chai et al. 2011; So et al. 2011; Saito et al. 2014, 2015; Matsui et al. 2014). In contrast, impairments of the EZ may not improve or only improve slightly, often with retinal thinning, in patients whose visual function does not improve. The presence or absence of abnormalities of the outer nuclear layer at the acute stage may determine whether visual field defects in AZOOR patients will improve (Matsui et al. 2014).

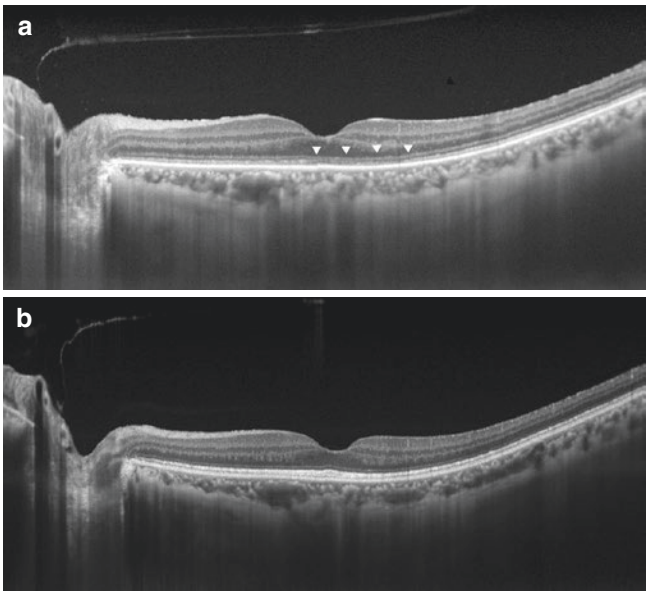

Fig. 6.6 (**a**) Enhanced depth imaging optical coherence tomography demonstrates loss of the ellipsoid zone and interdigitation zone at the macula (arrowheads) in an eye with central scotoma. The patient's BCVA is 0.1. (**b**) Macular ellipsoid zone and interdigitation zone were restored together with spontaneous improvement of visual function. The BCVA returned to 1.0

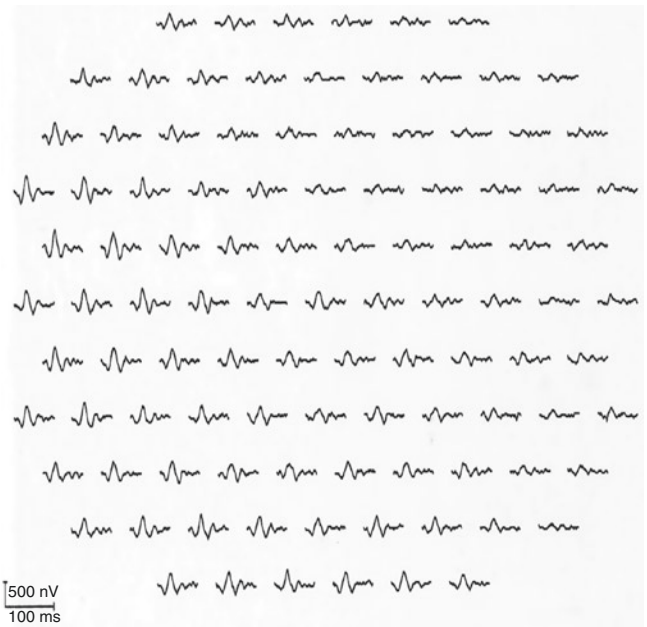

Fig. 6.7 In the eye shown in Fig. 6.3, multifocal electroretinography reveals decreased responses corresponding to retinal sites with visual field defects

Electroretinogram

The rod–cone mixed maximum response on full-field ERG shows a reduction of the a-wave and b-wave in eyes with AZOOR, depending on the extent of impairment of the photoreceptors, which suggests that photoreceptors become dysfunctional as well as impairments of the inner retinal layers in AZOOR (Jacobson et al. 1995; Francis et al. 2005). However, we often encounter AZOOR cases with normal amplitudes of the a-wave when the affected area is small. In such cases, multifocal ERG is very useful for the diagnosis of AZOOR, because it can detect decreased focal cone responses corresponding to the AZOOR lesion sites (Fig. 6.7) (Arai et al. 1998). Both cone and rod responses on full-field ERG may be decreased in more severe cases, while only cone responses may be decreased in milder cases (Kuniyoshi et al. 2014). The implicit time of 30-Hz flicker response is delayed, and the electrooculography light rise is reduced (Francis et al. 2005).

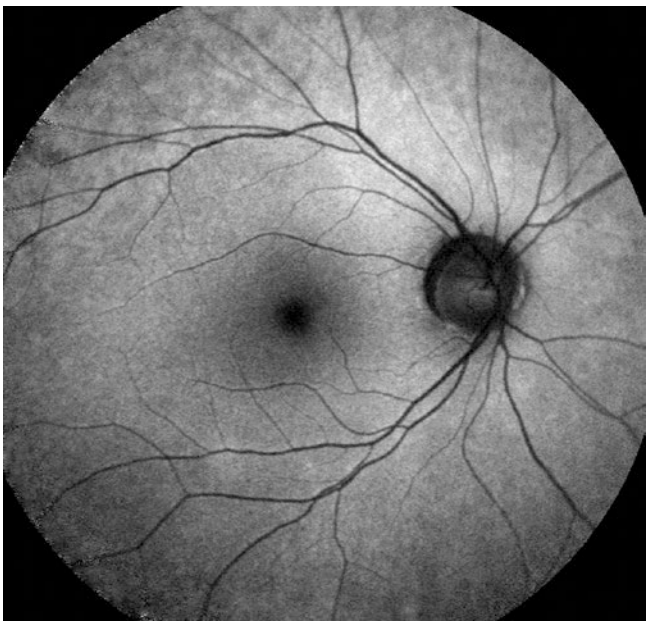

Fig. 6.8 Fundus autofluorescence shows hyper-autofluorescence corresponding to the retinal sites with visual field defects in the acute stage of a patient with AZOOR

Other Examinations

Fundus autofluorescence (FAF) initially shows patchy or geographic hyper-autofluorescence corresponding to the AZOOR-retinal lesion sites, which may disappear if visual function improves (Fig. 6.8) (Mrejen et al. 2014). When the affected area later develops retinal degeneration, it may show hypo- or hyper-autofluorescence in accordance with the degree of RPE impairment (Fig. 6.9) (Fujiwara et al. 2010). Thus, FAF is a useful tool for observing the lesion area in cases of AZOOR. On laser speckle flowgraphy, which examines blood flow velocity noninvasively and quantitatively, choroidal blood flow velocity at the lesion increases with

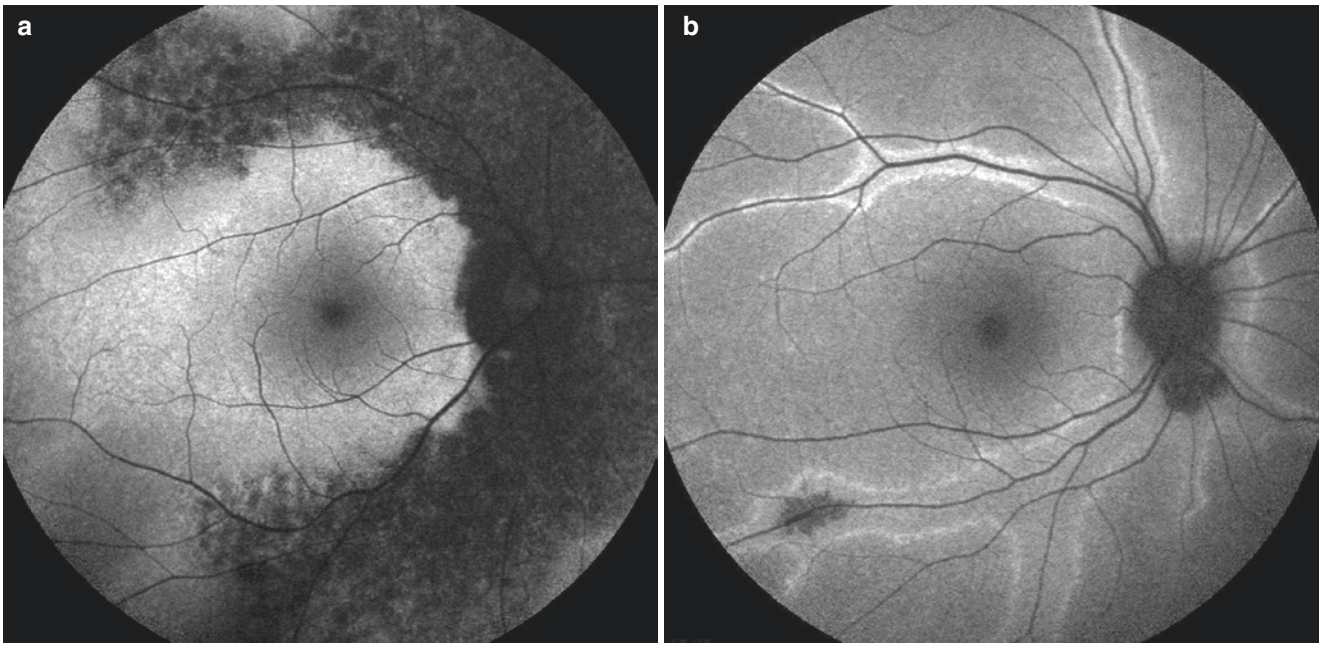

Fig. 6.9 In two patients at the convalescent stage, fundus autofluorescence clearly shows hypo- (**a**) or hyper-autofluorescence (**b**) matching the zonal atrophy or dysfunctional site of the retinal pigment epithelium (**a**: same eye as that in Fig. 6.1)

regression of the disease, suggesting that LSFG is a useful tool for evaluating the activity of AZOOR (Saito et al. 2014). Adaptive optics scanning laser ophthalmoscopy has demonstrated fewer cone photoreceptor cells as well as morphological abnormalities, which may be restored with the regression of AZOOR (Nakao et al. 2015).

Management

Strategies for the management of AZOOR have not yet been determined. The natural progress and visual prognosis in patients with AZOOR appears to be different between Caucasian and Asian patients. In Caucasian patients, the visual field impairment ceased to develop in 80% of patients during a 6-month follow-up period after the initial visit, while it partially improved in only 20% of patients (Gass et al. 2002). At the final visit, the logMAR value of the BCVA was less than 0.1 in 70% and 1.0 or more in 27% of patients. These observations suggest that Caucasian patients do not necessarily have a good prognosis. On the other hand, approximately 70% of Japanese patients showed improved visual function during the 6-month follow-up period from baseline (Saito et al. 2015). The final logMAR BCVA was 0.0 or less in 92% of patients and more than 1.0 in only 4%, suggesting that Japanese patients have better visual prognosis. Therefore, observation of the changes in visual function with no treatment may be recommended, particularly in Asian patients with AZOOR whose central vision is intact.

Established treatment methods for AZOOR patients with progressive visual impairments have not yet been determined. Several reports have suggested the efficacy of systemic corticosteroid therapy for these patients (Saito et al. 2007, 2014, 2015, Kitakawa et al. 2012; Chen et al. 2015). Systemic corticosteroid therapy with sufficient duration and dose after the initial treatment (e.g., steroid pulse therapy) leads to significant improvements of the BCVA and sensitivity on perimetry in Japanese patients experiencing progressive visual impairment (Saito et al. 2015). Adalimumab appears to be effective in a case with AZOOR and resistance to systemic corticosteroid therapy (Neri et al. 2014). Future prospective studies with large numbers of patients are needed to verify the efficacy of systemic corticosteroid therapy.

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Birdshot Chorioretinopathy

7

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Introduction

Birdshot chorioretinopathy (BSCR) is a rare, bilateral, posterior uveitis with a chronic course. BSCR has a very strong association with HLA-A29, with approximately 96% of patients testing positive (Shah et al. 2005). The first report of BSCR has been credited to Franceschetti and Babel in 1949, who described a patient with multiple hypopigmented choroidal lesions as having "chorioretinopathy with candle wax spots" (Franceschetti and Babel 1949). Ryan and Maumenee coined the name "birdshot retinochoroidopathy" in their 1980 case series of 13 patients. The clinical findings in their patients included creamy chorioretinal lesions, macular edema, disc edema, and vitreous debris with minimal anterior segment inflammation (Ryan and Maumenee 1980). In 1981, Gass further characterized the syndrome, but chose the name "vitiliginous chorioretinitis," due to the similarity of the fundus findings in the skin of patients with vitiligo. This description of BSCR also recognized the development of nyctalopia, dyschromatopsia, and electroretinographic abnormalities as the disease progressed (Gass 1981). Consensus criteria for the definition of BSCR have been developed (Table 7.1), which closely resemble the clinical findings noted in these early studies (Levinson et al. 2004). Since the first comprehensive descriptions in the early 1980s, many advances have been made in our understanding of the genetics, pathogenesis, and treatment of BSCR. This chapter summarizes our current understanding of BSCR, with a focus on the role of fundus examination and chorioretinal imaging techniques to diagnose BSCR, assess disease activity, and monitor progression.

Table 7.1 Birdshot chorioretinopathy diagnostic criteria (adapted from Levinson et al. (2004))

Birdshot chorioretinopathy diagnostic criteria	
Required characteristics	• Bilateral disease
	• Three or more peripapillary birdshot lesions in one eye
	• No or minimal anterior segment inflammation
	• Low-grade vitreous haze
Supportive findings	• HLA-A29 positivity
	• Retinal vasculitis
	• Cystoid macular edema
Exclusion criteria	• Keratic precipitates
	• Posterior synechiae
	• Presence of other infectious, inflammatory, or neoplastic disease causing choroidal lesions

Epidemiology and Demographics

Although there have been no large studies to determine the prevalence of BSCR in the general population, it is certainly a rare disease. In the United States and Europe, BSCR comprises 0.5–1.5% of the cases seen in uveitis practices and 6.0–7.9% of posterior uveitis cases. By extrapolating from the overall prevalence of uveitis in the general population (38–115 cases/100,000 persons), Minos and colleagues arrived at an estimated prevalence of 0.2–1.7 cases/100,000 persons (Vadot et al. 1984; Gritz and Wong 2004; Minos et al. 2016). They further postulated that the true prevalence is at the lower end of the range because the referral centers conducting the studies likely have an overrepresentation of rare uveitis syndromes (Minos et al. 2016).

The onset of BSCR occurs most commonly in middle age. In a comprehensive review of 52 published studies, Shah and colleagues determined that 53 years (standard deviation ±9.4 years) was the mean age of onset (Shah et al. 2005). Although it is rare in childhood, cases have been reported in the teenage years (Pivetti-Pezzi 1996). Most of the larger case series report a slight female predominance.

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There are also substantial differences in prevalence by race, with Caucasian patients representing nearly all of the reported cases of BSCR (Shah et al. 2005). However, individual cases of BSCR have been reported in black and Hispanic patients, and a case series of patients has been reported in Japan (Saito et al. 2002; Baddar and Goldstein 2016; Knezevic et al. 2016). No cases have been reported from South Asia. Although some of the racial predilection may be due to HLA-A29 prevalence by race, this alone cannot completely explain the difference, as is discussed in the next section.

Genetics and Pathophysiology

Approximately 96% of BSCR patients are HLA-A29 positive, which is the strongest known association of an HLA allele with any disease. The association is so strong that other diagnoses should be considered if a patient is HLA-A29 negative (Brézin et al. 2011). However, the exact role of HLA-A29 in the pathogenesis remains unclear. Some of the controversy over the role of HLA-A29 comes from its racial distribution. The two main subtypes of the HLA-A29 allele, HLA-A∗29:01 and HLA-A∗29:02, have both been associated with BSCR. However, the vast majority of reported HLA-A29-positive BSCR patients have the HLA-A∗29:02 allele (Levinson et al. 2004; Brézin et al. 2011). The frequency of HLA-A∗29:02 in the United States is greatest in the Caucasian population at 4.34% and lowest in Asians at 0.1%. However, the frequency in African-Americans and Hispanics is 3.57% and 4.20%, respectively. Although the low frequency of HLA-A29 in Asians may be a protective factor, the frequency in Hispanics and African-Americans is similar overall to Caucasians. Unknown protective factors present in Hispanics and African-Americans, or unknown risk factors in Caucasians, are likely to explain the difference in BSCR prevalence despite similar HLA-A29 frequencies (Brézin et al. 2011).

Mice engineered to express a human HLA-A29 transgene derived from a patient affected by BSCR spontaneously develop a posterior uveitis similar to BSCR, providing the best evidence of a direct role for HLA-A29 in BSCR pathogenesis (Szpak et al. 2001). HLA-A29 codes for a major histocompatibility complex class 1 (MHC-I) protein, whose function is to present antigens to CD8 T cells. A recent genome-wide association study has also linked endoplasmic reticulum aminopeptidase 2 (ERAP2) with BSCR. ERAP2 is an enzyme that processes antigens for presentation by MHC-I molecules, which raises the interesting hypothesis that ERAP2 antigen processing in conjunction with HLA-A29 presentation may be sequential steps in the development of autoimmunity in BSCR patients (Kuiper et al. 2014b). Although more than 100 endogenous HLA-A29 ligands have been identified, none have been directly linked with BSCR (Boisgerault et al. 1996).

Consistent with the strong HLA-A29 association, T cells also appear to play an important role in BSCR pathogenesis. Histopathologic studies of enucleated BSCR eyes demonstrate choroidal lesions in which T cells predominate (Pulido et al. 2012). Vitreous samples from BSCR eyes are rich in T cells that react to retinal and choroidal extracts, and aqueous samples are rich in interleukin-17 (IL-17), a T-cell cytokine (Kuiper et al. 2011; 2014a).

Clinical Findings

Symptoms

Patients with BSCR often present with complaints of decreased vision while maintaining good central acuity on formal testing. In many cases, the mild symptoms in the early stages of disease can lead to a delay in diagnosis. In their comprehensive review, Shah and colleagues found the following visual complaints among a group of symptomatic BSCR patients: blurry vision (88%), floaters (43%), nyctalopia (18%), and dyschromatopsia (9%). At the time of initial presentation, 62% of patients had visual acuity better than 20/40 in both eyes and 76% had acuity better than 20/40 in at least one eye. Even among the small subset of patients with 20/20 acuity in both eyes, the vast majority complained of blurriness or floaters (Shah et al. 2005). Formal testing of color vision demonstrates defects in the majority of patients, most commonly in the blue-yellow axis (Gasch et al. 1999). The course of BSCR has been described as chronic and insidious, with gradual decline in visual function, although recent studies have found that long-term stability can be achieved with chronic immunosuppression (Shah et al. 2005; Tomkins-Netzer et al. 2014). Pain, photophobia, and conjunctival injection are atypical and suggest another underlying etiology of the posterior segment findings (Shah et al. 2005; Minos et al. 2016).

Clinical Signs and Exam Findings

Anterior examination generally demonstrates a quiet anterior chamber, although low-grade cell may be present. Flare, keratic precipitates, and posterior synechiae are not typically seen.

The diagnosis of BSCR is made primarily on the basis of the fundus examination, and the most recent diagnostic criteria, defined in 2006, are summarized in Table 7.1. Early in the disease course, there may be no apparent fundus abnormalities, as development of chorioretinal lesions often lags

behind symptom onset by several years (Godel et al. 1989). The classic finding in BSCR is birdshot lesions, which are creamy, ovoid choroidal lesions that are one eighth to one half disc diameter in size (Fig. 7.1). Birdshot lesions are often oriented with their long axis perpendicular to the disc and appear to radiate toward the periphery (Priem and Oosterhuis 1988). Lesions are typically concentrated near the optic disc and in the inferior and nasal quadrants (Fig. 7.1a). With time, the lesions may coalesce to form linear patterns or to create the appearance of peripapillary atrophy (Fig. 7.1b, c) (Ryan and Maumenee 1980; Gass 1981; Priem and Oosterhuis 1988). Eventually, the lesions may develop hyperpigmentation or become well-demarcated areas of atrophy. Other common findings are cystoid macular edema and epiretinal membranes. Retinal and choroidal neovascularization have also been reported (Priem and Oosterhuis 1988).

Examination of the vitreous frequently demonstrates anterior vitreous cells and vitreous haze. Snowballs and snowbanks are typically absent in BSCR patients. Retinal vasculitis is present with active disease and most commonly presents with phlebitis, which is characterized by venous beading and irregular venous caliber. With time, the arterioles become attenuated. Vessel sheathing is uncommon but may be present (Ryan and Maumenee 1980; Priem and Oosterhuis 1988). Examination of the optic disc may demonstrate edema, or in late stages, pallor (Priem and Oosterhuis 1988). Although the fundus exam is key to making the diagnosis of BSCR, additional imaging modalities are useful in confirming the diagnosis in uncertain cases and for monitoring disease activity.

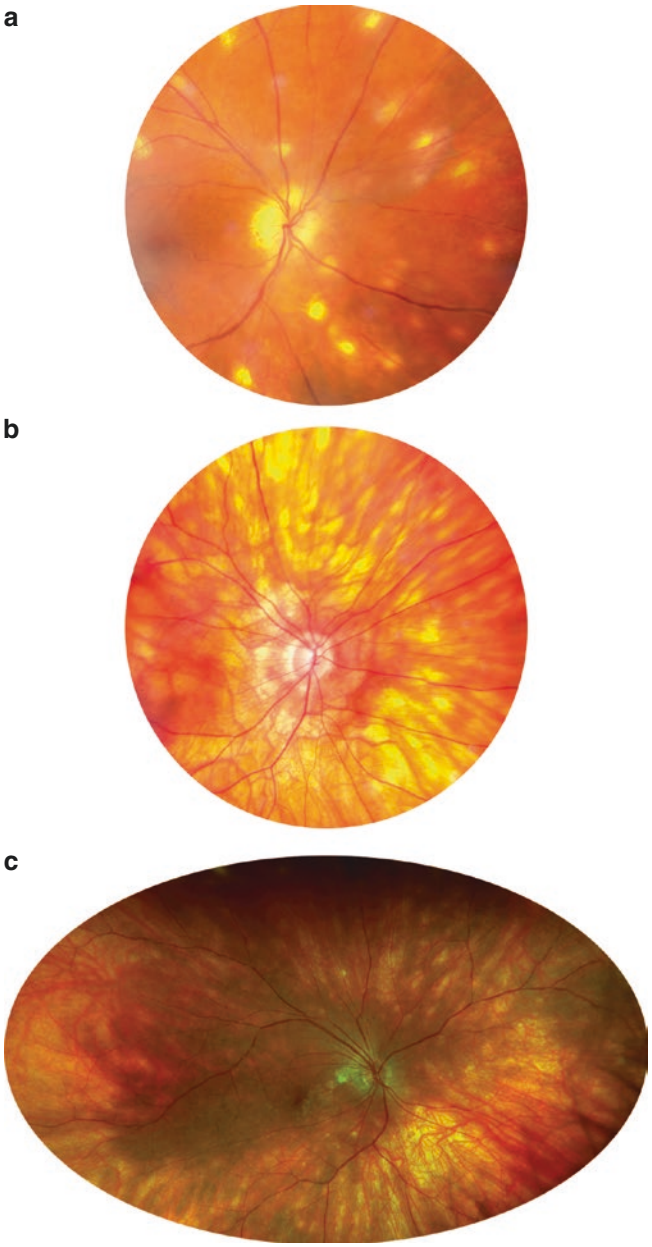

Fig. 7.1 (**a**) Fundus photograph of a 62-year-old female taken 6 years after her initial diagnosis with BSCR demonstrates discrete, round to ovoid birdshot lesions concentrated inferonasally to the disc. Also note attenuation of the arterioles and the irregular venous caliber. (**b**) Fundus photograph of a 53-year-old female taken 6 years after her initial diagnosis. The birdshot lesions appear as more elongated or linear areas of hypopigmentation. The patient also has a large area of peripapillary atrophy, which can result from coalesced birdshot lesions near the optic disc. (**c**) Optos 200Tx image from a 72-year-old female taken approximately 3 years after the onset of her symptoms. Her lesions are concentrated nasally and appear to radiate from the optic disc. Some lesions coalesce into linear areas of hypopigmentation

Imaging

Fluorescein Angiography (FA)

Fluorescein angiography is a very versatile technique for diagnosing and monitoring BSCR, as it facilitates evaluation of most of the affected structures. BSCR patients frequently develop macular edema, which often has a petalloid appearance on FA. The retinal vasculitis, characterized by vascular leakage, arteriole attenuation, and irregular venous caliber, is also best evaluated by FA, since it may be subtle or undetectable on clinical exam. The optic disc may also demonstrate hyperfluorescence or leakage (Fig. 7.2). Although it is uncommon, choroidal neovascularization may occur in BSCR and is readily detected by FA (Priem and Oosterhuis 1988; Howe et al. 1997).

Detection of the birdshot lesions is often easier on clinical exam than by FA, since the lesions demonstrate subtle and variable staining patterns. In early phases of the angiogram, the birdshot lesions may demonstrate hyper- or hypofluorescence (Fig. 7.3a, b). In late phases, the lesions usually demonstrate mild to moderate hyperfluorescence (Gass 1981; Priem and Oosterhuis 1988).

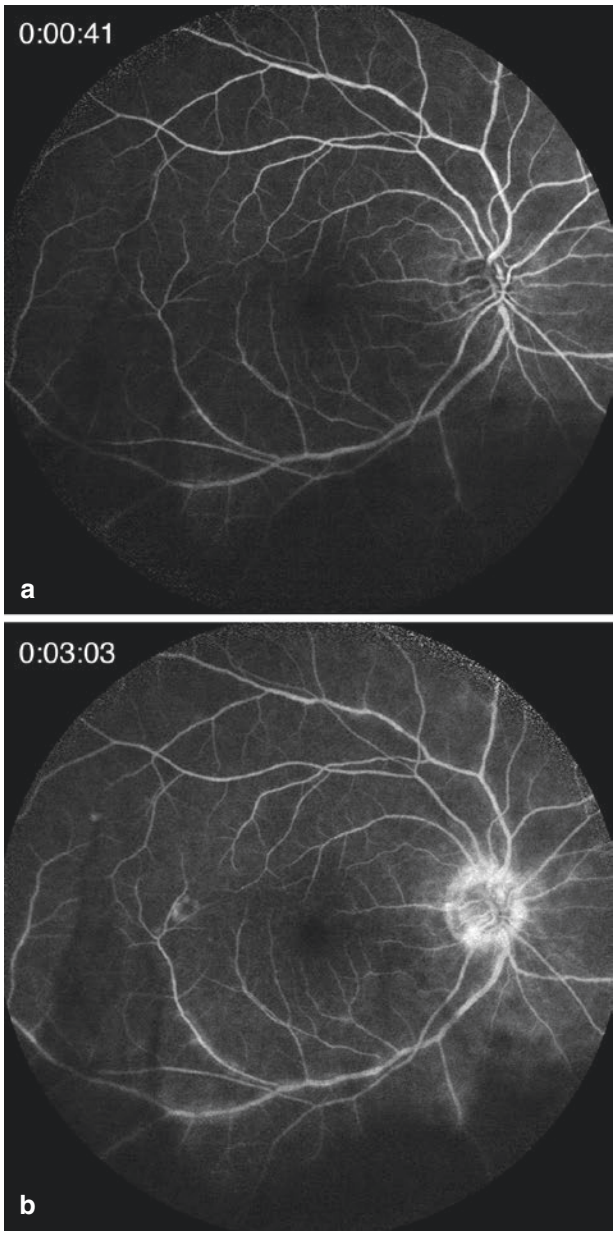

Fig. 7.2 Representative fluorescein angiogram images from a patient with active disease. (**a**) Venous beading and irregular caliber seen along the superotemporal arcades in early venous phase. (**b**) In this mid phase image, there is extensive vascular leakage, mostly from the veins. Disc leakage is also seen. No birdshot lesions are seen in these images

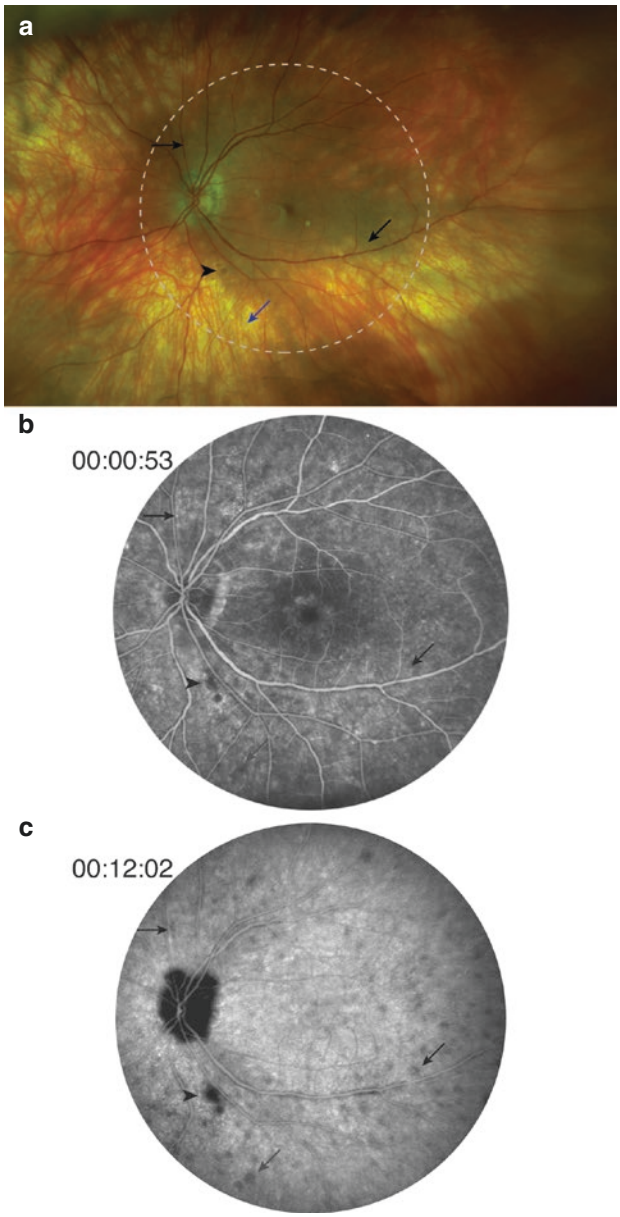

Fig. 7.3 (**a**) Optos 200Tx image demonstrating subtle, hypopigmented birdshot lesions that are apparent in both the nasal and temporal periphery. Gray circle indicates the approximate area imaged in (**b**) and (**c**). (**b**) Venous phase fluorescein angiogram image with extensive venous beading. (**c**) Late phase indocyanine green angiogram image. Black arrows denote birdshot lesions with a subtle hypopigmented appearance on the Optos image, subtle hyperfluorescence on fluorescein angiography, and hypocyanescence on ICG. Blue arrows indicate a lesion with hypofluorescence on FA. Many of the lesions seen on the Optos and ICG images are isofluorescent or not readily apparent on FA. The black arrowheads indicate a retinal hemorrhage with associated blockage on the FA and ICG images

Indocyanine Green (ICG) Angiography

ICG angiography can facilitate the evaluation of birdshot lesions, since the lesions are often more apparent on ICG than they are on clinical exam. Early stage lesions are typically round, hypocyanescent, and located near large choroidal vessels. They are more apparent in the intermediate and late phase ICG images (Figs. 7.3c and 7.4) (Fardeau et al. 1999). Two hypotheses proposed for the hypocyanescent appearance are blockage by the lymphocytic infiltrates and choroidal non-perfusion in the area of the lesions (Howe et al. 1997). Lesions that are mature or atrophic have an isocyanescent appearance. In active or progressive disease, the lesions will become larger or numerous, whereas the lesions can shrink or disappear entirely during remission (Fig. 7.5). In active disease, the ICG angiogram may show late diffuse hypercyanescence or indistinct choroidal vessels (Fardeau et al. 1999).

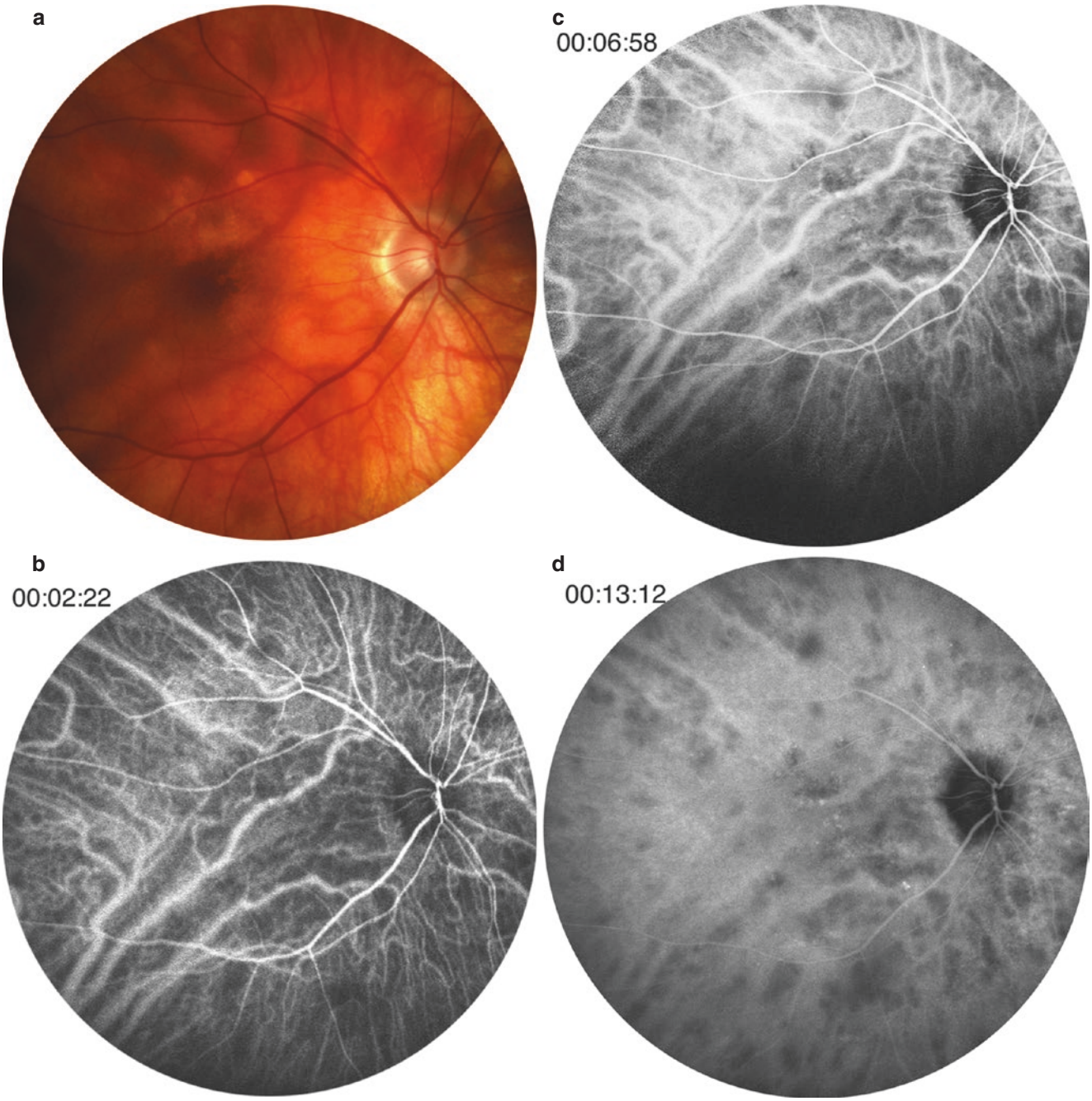

Fig. 7.4 (**a**) Color fundus photo of a patient with subtle birdshot lesions. (**b**) Early, (**c**) middle, and (**d**) late phase ICG images from the same eye. The birdshot lesions are not apparent on the early phase image. Subtle areas of hypocyanescence are seen in the mid phase image, but many distinct lesions are present in the late phase image

Fundus Autofluorescence (FAF)

Retinal pigment epithelium changes in BSCR can be followed with FAF. Birdshot lesions may demonstrate hypoautofluorescence, especially as they become more atrophic. In patients with lightly pigmented fundi, FAF can be useful to localize the lesions. Hypoautofluorescence may develop along the retinal vasculature (Giuliari et al. 2009).

Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCT-A)

There are several well-defined OCT abnormalities in BSCR. Cystoid macular edema is common in BSCR, and OCT is an excellent tool for monitoring the response to treatment (Fig. 7.6a). Ellipsoid zone disruption is common, even

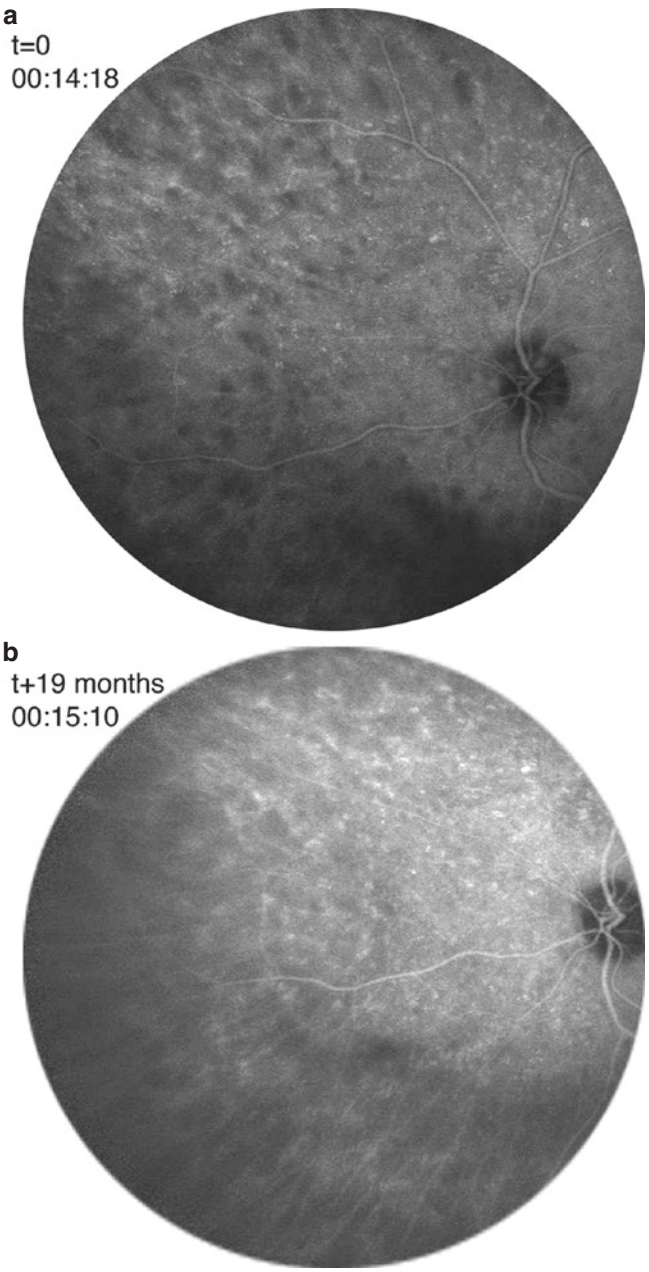

Fig. 7.5 Resolution of birdshot lesions. (**a**) Late phase ICG image at initial presentation of a patient reporting photopsias and floaters for 3 months, which demonstrates many hypocyanescent birdshot lesions. The patient also had marked phlebitis at this time (Fig. 7.2). Treatment with mycophenolate mofetil and prednisone was initiated, but inflammation worsened whenever the steroids were tapered necessitating a switch to infliximab with improvement in vasculitis (not shown) and haze. (**b**) ICG image of the same eye 19 months after the initial presentation and 6 months after initiation of infliximab demonstrating a marked decrease in birdshot lesions

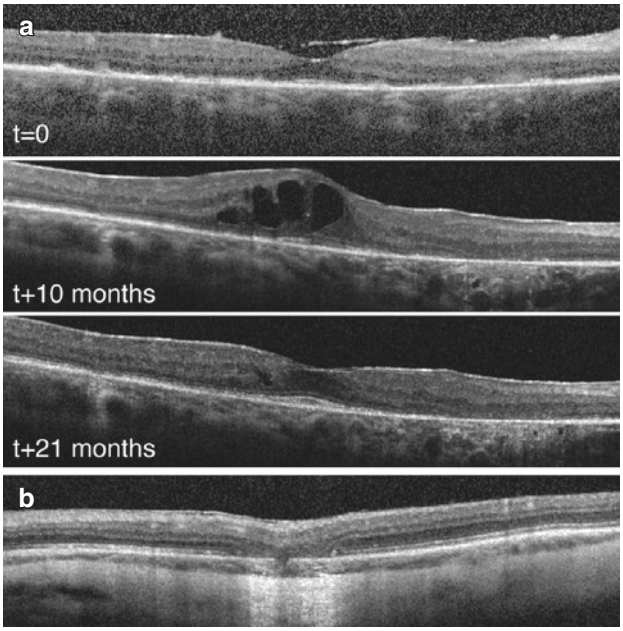

Fig. 7.6 (**a**) Series of OCT images from the same patient. The top ($t = 0$) image was taken at the time of initial presentation. The patient complained of floaters and decreased vision for 2 weeks prior to this evaluation. The OCT demonstrates an epiretinal membrane and ellipsoid disruption. She started on oral prednisone and mycophenolate mofetil. The patient developed cystoid macular edema (t + 10 months) that eventually improved and stabilized (t + 21 months) with an intravitreal dexamethasone implant (Ozurdex). (**b**) OCT image of the left eye of a 61-year-old patient, taken 14 years after the initial diagnosis. This image is superior to the fovea and demonstrates focal atrophic scarring with otherwise well-preserved retinal architecture. There is choroidal thinning and a mild epiretinal membrane

in patients with inactive disease. Epiretinal membranes and areas of retinal atrophy can also be assessed with OCT (Fig. 7.6). A few studies of enhanced depth imaging have found choroidal abnormalities, but they are not yet well-established disease markers. Boni and colleagues found hyporeflective choroidal lesions in many patients, which correlated with disease duration and the presence of vitreous haze. Some, but not all, birdshot lesions noted on color photography were associated with choroidal lesions on OCT (Böni et al. 2016). Birnbaum and colleagues found that the presence of suprachoroidal fluid correlated with the presence of vasculitis and vitreous haze and suggested its potential use in monitoring disease activity (Birnbaum et al. 2014). Only a few small studies regarding the OCTA findings in BSCR have been published. The largest study to date analyzed 37 BSCR eyes and found decreased capillary density without a change in the size of the foveal avascular zone (Fig. 7.7) (Roberts et al. 2018). Another report found increased intercapillary space, telangiectasias, and capillary loops (de Carlo et al. 2015).

Functional Testing

In addition to imaging, other modalities used to monitor BSCR progression include visual field testing and electroretinogram (ERG). Visual field testing has been used to monitor

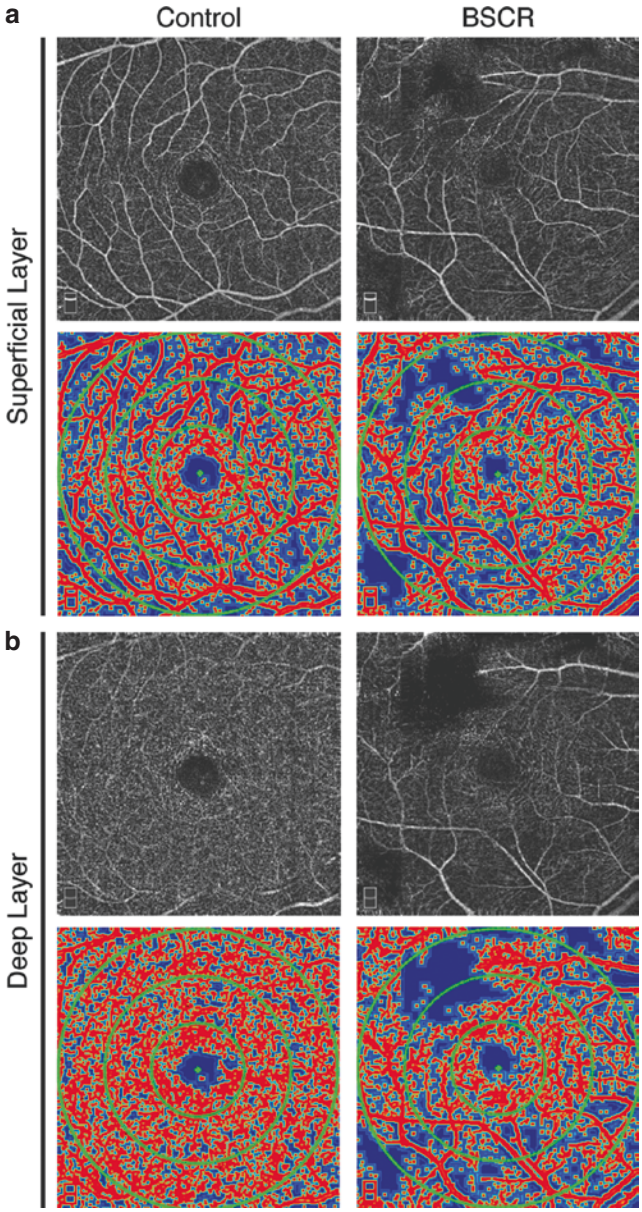

Fig. 7.7 Optical coherence tomography angiography images were acquired from a healthy control and a BSCR patient using an Optovue Angiovue (Fremont, CA). Images of the (**a**) superficial and (**b**) deep capillary layers are shown. An algorithm used to measure vessel density was used to generate the false color images below, which show capillary density in red. This BSCR patient has decreased superficial and deep capillary density

BSCR progression and response to treatment. Patients who are treated with immunosuppressive medications have improvements in their visual fields (Thorne et al. 2008; Shao et al. 2014). Electroretinography (ERG) is also a well-established modality to monitor progression in BSCR. In full-field ERG, the prolongation of the 30 Hz flicker implicit time is the most sensitive measure of damage by BSCR, and it can improve with treatment (Holder et al. 2005). In a small retrospective study, an abnormal 30 Hz flicker prior to tapering systemic immunosuppression correlated with recurrence of inflammation during the subsequent year (Zacks et al. 2002). Depression of both the photopic and scotopic b-wave amplitudes has been reported across many studies (Tzekov and Madow 2015).

Treatment

Many agents have been used to treat BSCR, but there are no randomized controlled trials to definitively prove the efficacy of these treatments. Oral corticosteroids are the most commonly used treatment. While oral corticosteroids have demonstrated efficacy in controlling the acute inflammation in BSCR, they do not appear to adequately control chronic inflammation with about one third of eyes experiencing a decline in vision with oral corticosteroids over long follow-up periods (Shah et al. 2005). Many authors have advocated for the early introduction of steroid sparing immunosuppressive therapy to limit steroid side effects and to better preserve visual function (Kiss et al. 2005; Becker et al. 2005; Menezo and Taylor 2014; Knecht et al. 2014).

Cyclosporin A has been used as a first-line option because it targets T cells, which appear to play a central role in BSCR pathogenesis. Other groups have demonstrated success using antimetabolite agents, such as mycophenolate mofetil, azathioprine, and methotrexate (Kiss et al. 2005; Goldberg et al. 2014; Doycheva et al. 2015). Monotherapy has been successful with all of these agents, although combination with corticosteroids or other steroid-sparing agents is necessary in many cases (Goldberg et al. 2014; Doycheva et al. 2015). Biologic agents have been used successfully to treat BSCR, and the TNF-α inhibitors are the most widely studied among this group. In a retrospective case series of 22 patients who had failed other immunosuppressive strategies, 93% of patients treated with infliximab achieved remission after 1 year of treatment (Artornsombudh et al. 2013). Other biologics, such as adalimumab, have been used to treat BSCR, but they have only been reported as small case series (Menezo and Taylor 2014; Shao et al. 2014).

Local corticosteroid therapy has also been used to manage BSCR. Periocular triamcinolone and intravitreal triamcinolone have both demonstrated efficacy in treating posterior uveitis (Menezo and Taylor 2014). Corticosteroid implants, including the dexamethasone implant (Ozurdex, Allergan) and fluocinolone acetonide implant (Retisert, Bausch and Lomb), are effective in treating noninfectious posterior uveitis, and they have been employed to treat BSCR (Lowder et al. 2011; Burkholder et al. 2013; Menezo and Taylor 2014). The corticosteroid implant has demonstrated good control of inflammation in BSCR, but it was associated with high rates of cataract and glaucoma that required additional surgical interventions (Burkholder et al. 2013).

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Sympathetic Ophthalmia

8

Cindy Ung and Lucy H. Young

Introduction

Sympathetic ophthalmia is a rare, bilateral, diffuse granulomatous form of uveitis that occurs after either surgical or accidental trauma to the uvea of one eye, usually 3 months after injury. The eye sustaining the injury is the "exciting" eye, and the fellow eye is the "sympathizing" eye. Sympathetic ophthalmia has potentially devastating visual consequences if treatment is delayed or inadequate.

The incidence of sympathetic ophthalmia has greatly decreased during the last 30 years as a result of improvements in modern surgical and medical treatments. The only prospective study on the incidence of sympathetic ophthalmia was performed on a small population in UK and Ireland, which shows an incidence of 0.03 per 100,000 people (Kilmartin et al. 2000a). Historically, accidental penetrating trauma was the most common cause of sympathetic ophthalmia, but now surgical trauma, particularly vitreoretinal surgery or secondary operations on predamaged eyes with fresh intraocular hemorrhages, is considered the major risk factor (Chan et al. 1995; Kilmartin et al. 2000a, b; Su and Chee 2006). The current sympathetic ophthalmia risk following vitrectomy might be nearly twice that after external retinal detachment repair and more than twice that of the previously reported 0.06% sympathetic ophthalmia risk after vitrectomy (Gass 1982). Sympathetic ophthalmia can also occur without penetrating eye trauma and has been reported following intravitreal injection (Brouzas et al. 2009), fungal keratitis (Guerriero et al. 2011; Buller et al. 2006), irradiation of choroidal melanoma (Brour et al. 2012), plaque brachytherapy (Ahmad et al. 2007), and laser cyclotherapies (Edwards et al. 2014).

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Pathogenesis

The exact pathogenesis of sympathetic ophthalmia is still unknown. The eye possesses inherent immune privilege with the presence of a blood–retinal barrier at the level of the retinal vascular endothelium and the retinal pigment epithelium (RPE) and the lack of a recognizable lymphatic drainage pathway. The most favored theory is an autoimmune process to an intraocular antigen incited by the breakdown of this blood–retinal barrier and access to the conjunctival lymphatic drainage following a penetrating injury. Rao and coauthors suggested that a wound with uveal prolapse may permit sequestered ocular antigens to sensitize the host and abrogate tolerance to these antigens, resulting in an immunopathologic response and intraocular inflammation (Power and Foster 1995; Rao et al. 1983; Sharp et al. 1984). Evidence for the precise autoantigen responsible in sympathetic ophthalmia is still inconclusive, as retinal S-antigen, melanin-associated antigens, and antigens derived from the RPE and choroid have all been implicated (Marak 1979; Rao et al. 1983; Wong et al. 1971).

Clinical Features

The diagnosis of sympathetic ophthalmia is based on the patient's history and clinical examination. The clinical presentation is variable, and the onset of inflammation in the sympathizing eye is quite often insidious. The time from surgery or trauma to onset of sympathetic ophthalmia has been reported from 5 days to 50 years, with approximately 80% of patients developing symptoms within 3 months and 90% within 1 year (Lubin et al. 1980).

The inflammatory response seen in the anterior chamber is granulomatous with mutton-fat keratic precipitates on the corneal endothelium and findings of an acute anterior uveitis. In the posterior segment, there may be nummular, depigmented, chorioretinitis spots known as Dalen-Fuchs nodules, papillitis, serous retinal detachment, choroiditis, and vitritis

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(Castiblanco and Adelman 2009) (Fig. 8.1). Dalen-Fuchs nodules are frequently located in the midperiphery of the fundus between Bruch's membrane and the retinal pigment epithelium and may not be present in 30–50% of cases (Kilmartin et al. 2000b).

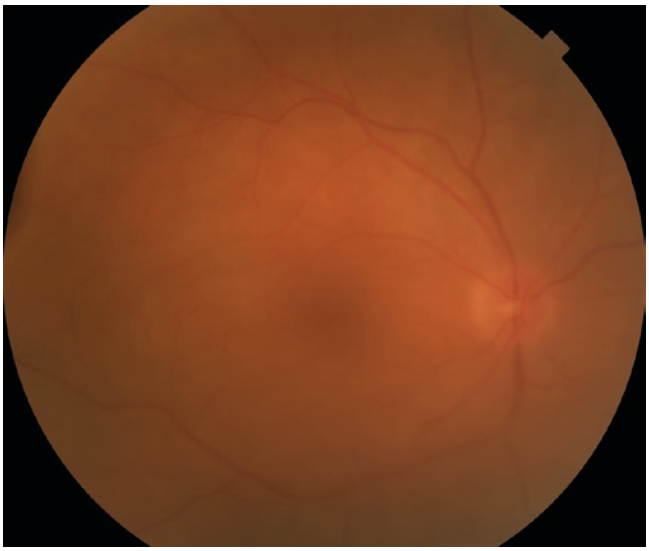

Fig. 8.1 Panuveitis with mild choroidal folds in the right eye of an 81-year-old man, 6 months after vitrectomy and intravitreal antibiotics for endophthalmitis in the left eye following a complicated cataract surgery. He noted gradual loss of vision for a week. Visual acuity was 20/50 in the right eye and light perception in the left eye. Visualization of the fundus was hazy due to 2+ keratic precipitates, anterior chamber inflammation, and mild vitritis. Note edematous and hyperemic disc and multiple light yellow lesions at the level of the retinal pigment epithelium. (Courtesy of Dr. Demetrios Vavvas)

Imaging

Fluorescein angiography (FA) is also useful in evaluating posterior segment involvement. In the acute phase of sympathetic ophthalmia, the FA typically demonstrates multiple hyperfluorescent sites of leakage at the level of the retinal pigment epithelium in the early phase followed by pooling of fluorescein dye in the detached areas (Fig. 8.2). In severe cases, these foci may consolidate with pooling of dye beneath the areas of exudative neurosensory detachment (Castiblanco and Adelman 2012). Dalen-Fuchs nodules may be hyper- or hypofluorescent depending on the integrity of the overlying RPE (Chang and Young 2011). The optic nerve may also demonstrate leakage in the later stages (Fig. 8.3). Optical coherence tomography (OCT) is helpful in demonstrating choroidal thickening in the posterior pole with or without exudative retinal detachment (Fig. 8.4).

Indocyanine green angiography (ICGA) is a useful diagnostic adjunct to confirm diagnosis and monitor response to therapy (Moshfeghi et al. 2005). Two patterns have been described. Hypofluorescence during the intermediate and late phase may correlate with chorioretinal atrophy. When there is active choroiditis, ICGA shows multiple hypocyanescent areas during the intermediate phase and not in in the late phase (Bernasconi et al. 1998). These are believed to represent focal, choroidal, inflammatory infiltrates (Fig. 8.5). B-scan ultrasonography can also be used to reveal choroidal thickening (Fig. 8.6).

Autofluorescence is a noninvasive imaging modality that can be useful in patients with sympathetic ophthalmia. Speckled areas of hypoautofluorescence resembling leopard spots can be seen in previous areas of exudative detachment. Over time, depigmentation of the RPE can occur (Fig. 8.7).

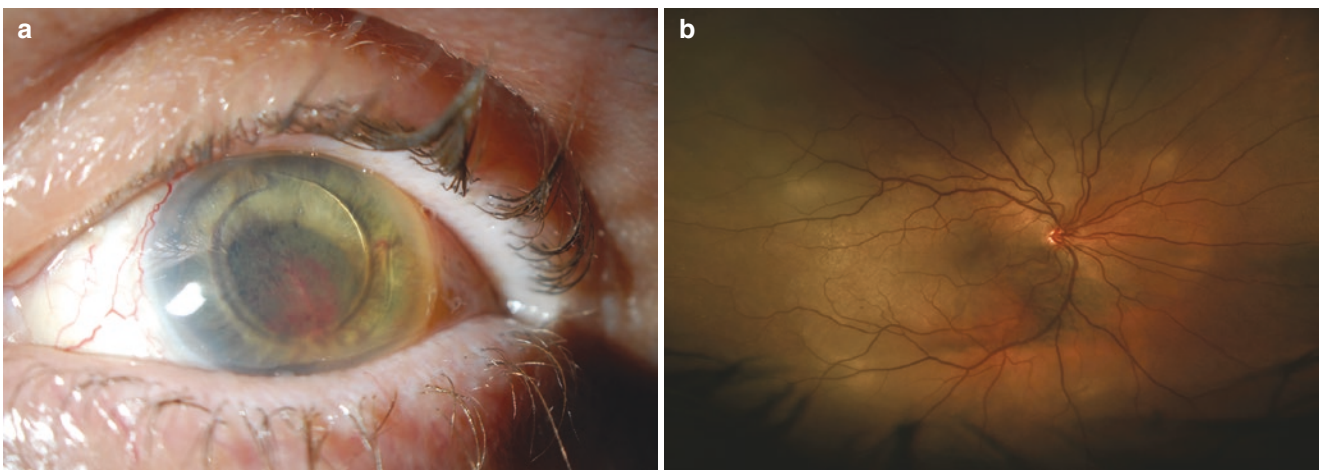

Fig. 8.2 Panuveitis with exudative retinal detachment in the right eye of a 54-year-old man, 6 months after surgical repair of zone 3 ruptured globe followed shortly by two vitreoretinal procedures for retinal detachment associated with giant tear. Visual acuity was 20/400 in the right eye and light perception in the left eye. (**a**) The left eye is pre-phthisical. (**b**) Note shallow exudative retinal detachment throughout the posterior pole extending to mid-periphery. (**c**, **d**) Fluorescein angiography shows multiple pinpoint areas of leakage in the early phase followed by increasing pooling of the dye in the detached areas

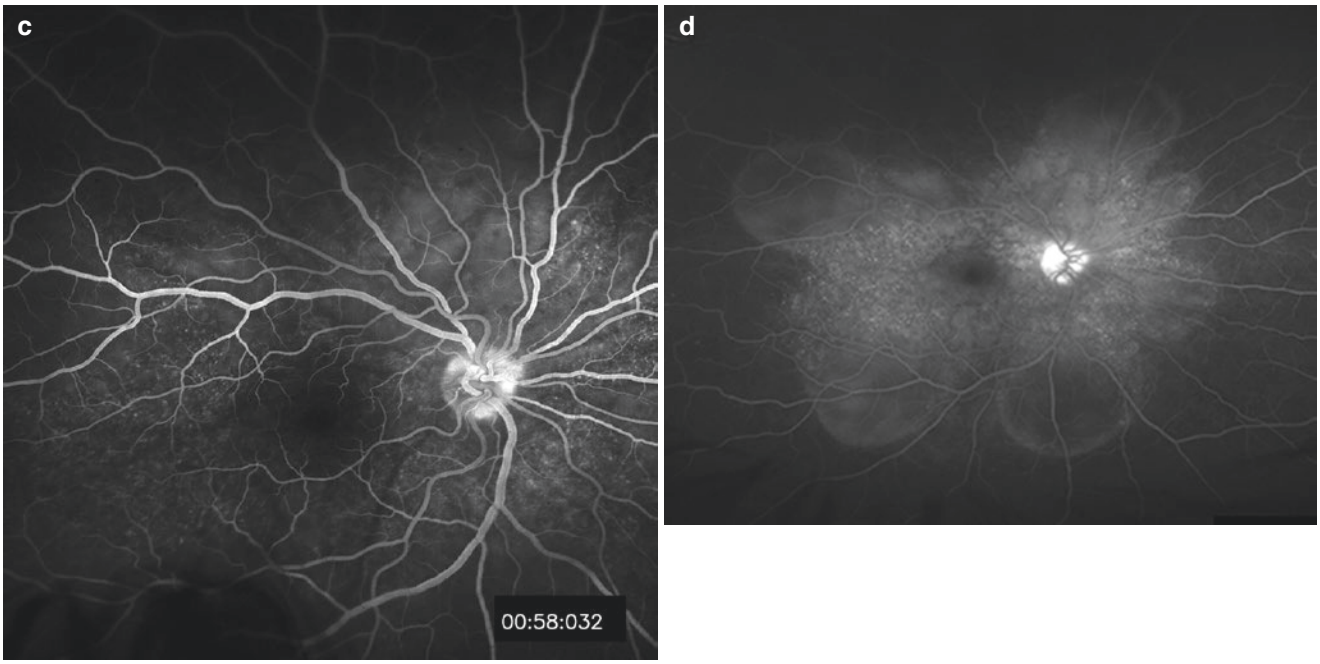

Fig. 8.2 (continued)

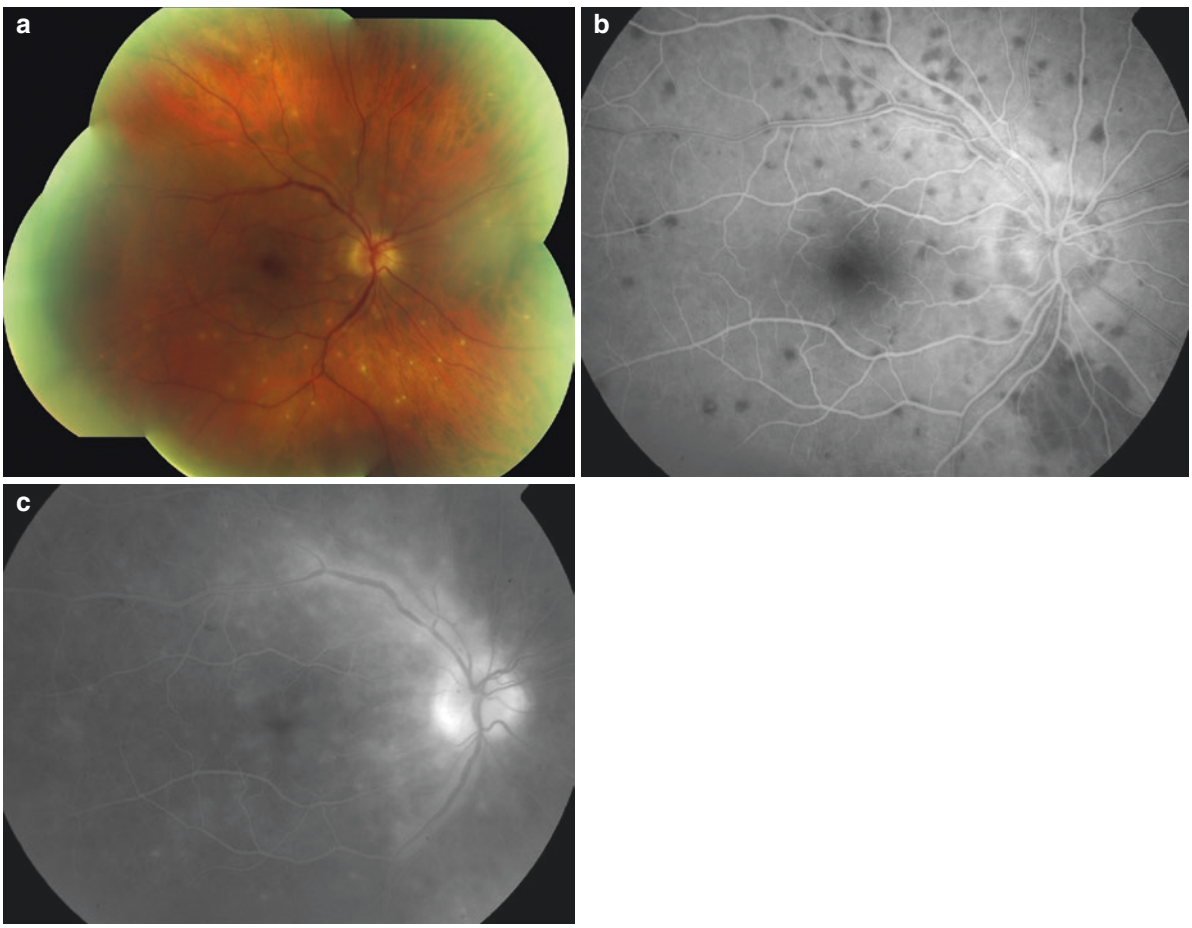

Fig. 8.3 Posterior uveitis in the right eye of a 69-year-old man, 9 months after surgical repair of a ruptured globe of the left eye. He noted blurry vision and floaters for few days. Visual acuity was 20/20 in the right eye and no light perception in the left eye. (**a**) Note multiple creamy yellow chorioretinal lesions around the hyperemic and edematous optic disc. (**b**) These hypopigmented spots are multifocal choroidal granulomas which obstruct the choriocapillaris and appear nonfluorescent early on fluorescein angiography. (**c**) Later angiograms show staining of these lesions, low-grade vasculitis, and papillitis. Multiple atrophic spots developed throughout the fundus 5 years after management with prednisone and immunotherapy. Visual acuity was 20/30-2. (Courtesy of Dr. George Papaliodis)

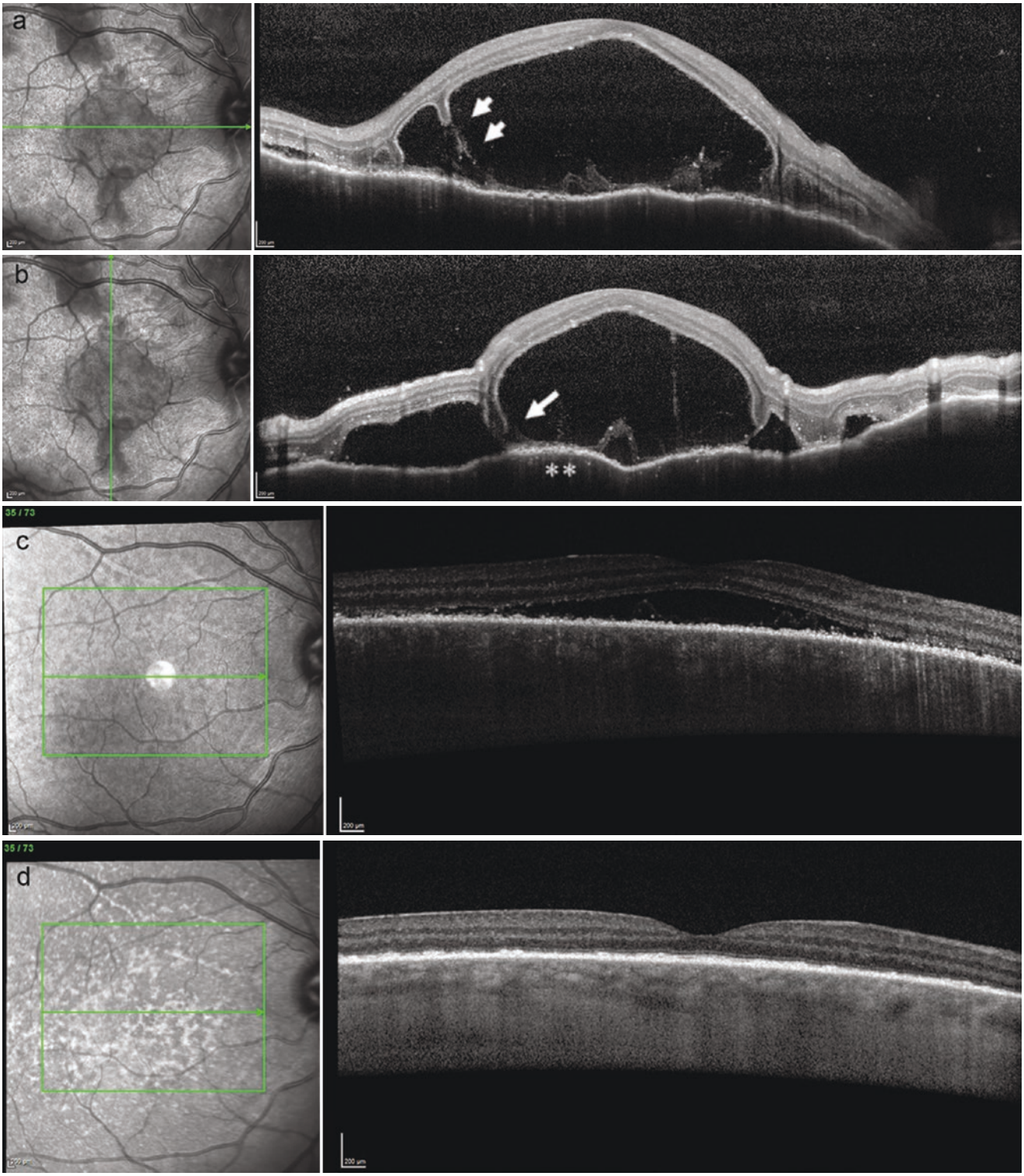

Fig. 8.4 Optical coherence tomography (OCT) images of the right eye. (**a**) OCT horizontal scan image shows a serous retinal detachment with subretinal septa and reflective dots consistent with fibrin in the subretinal fluid (SRF). The subretinal septa cross the detachment dividing it into pockets (arrows). (**b**) OCT vertical scan image shows thick choroid with loss of physiologic vascular pattern (white asterisks) and subretinal choroidal folds. (**c**) OCT shows reduced SRF after two doses of IV solumedrol. (**d**) OCT shows resolved SRF and improved choroidal vascular pattern 10 days after steroid pulse therapy

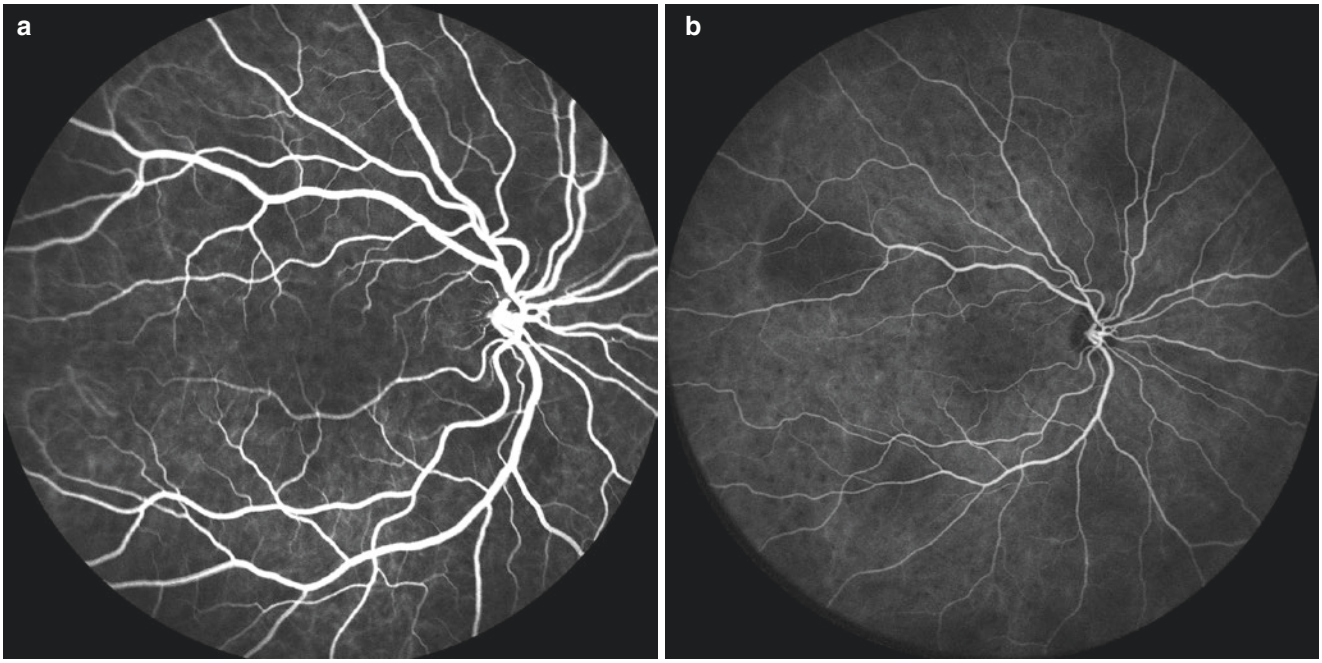

Fig. 8.5 Indocyanine angiography (ICGA) shows fuzziness of stromal vessels and multiple hypocyanescent spots (early phase, **a**) remaining up to the late angiographic phase (**b**) indicating full thickness choroidal granulomas

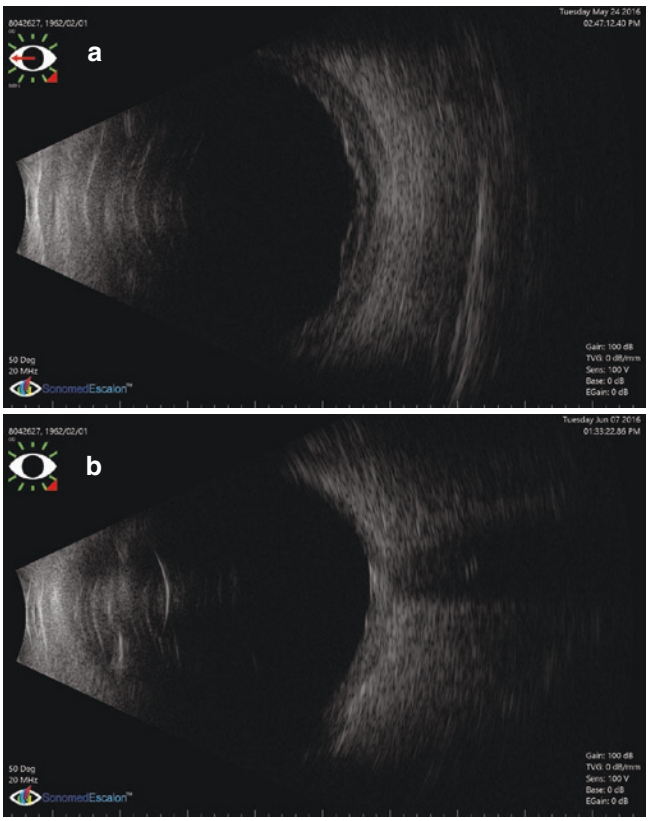

Fig. 8.6 B-scan ultrasonography of the right eye shows choroidal thickening posteriorly with an overlying membranous interface corresponding to the exudative retinal detachment (**a**) and 10 days after IV solumedrol, the choroidal layer remains thickened but the exudative retinal detachment is resolved (**b**)

Differential

Other causes of bilateral granulomatous inflammation include Vogt–Koyanagi–Harada syndrome (VKH), sarcoidosis, phacoanaphylactic uveitis, chronic idiopathic uveitis, infectious granulomatous uveitis (bacterial and fungal) such as that occurs in tuberculosis and syphilis, and intraocular lymphoma. VKH in particular can have a similar presentation to sympathetic ophthalmia and may have Dalen-Fuchs nodules. These patients with VKH do not have a history of ocular injury and have systemic manifestations of VKH such as deafness, poliosis, and vitiligo.

Although there are no specific laboratory studies to establish the diagnosis of sympathetic ophthalmia, it is important to rule out the presence of other diseases with focused clinical studies. These include PPD skin testing, chest radiography, measurement of serum angiotensin-converting enzyme, lysozyme, RPR and FTA-Abs, and possibly lumbar puncture.

Prevention and Management

Surgical Treatment

The classic teaching has been that enucleation within 14 days after ocular injury protects the second eye from the development of sympathetic ophthalmia (Albert and Diaz-Rohena 1989). The protective role of enucleation has been largely

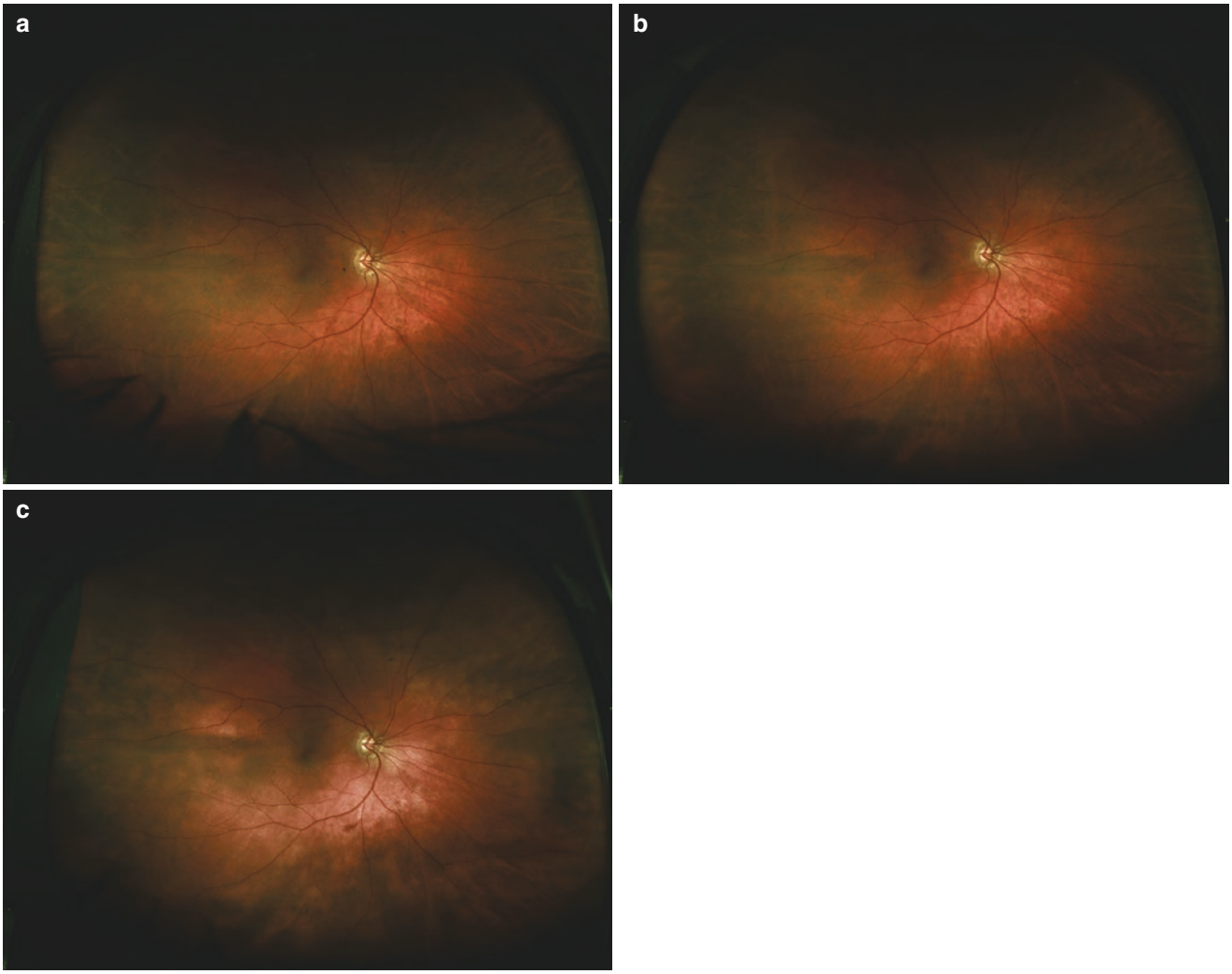

Fig. 8.7 (**a**–**c**) Color fundus photographs over a year period revealing depigmentation of the RPE

unproven and generally discouraged unless open globe repair is deemed impossible at the time of injury (Manandhar 2011).

Controversy still exists regarding enucleation of the exciting eye once sympathetic ophthalmia has commenced. Although Lubin et al. published data that early enucleation of the exciting eye after the onset of sympathetic ophthalmia yields better vision in the sympathizing eye (Lubin et al. 1980), this has not been supported by more recent studies (Reynard et al. 1983). Enucleation should not be performed in the exciting eye with vision because not uncommonly, the exciting eye may be the one with the better vision (Moshfeghi et al. 2000; Gasch et al. 2000).

Medical Treatment

Immunosuppressive therapy is the mainstay of treatment. The initial approach, in most cases, should be with corticosteroids. Systemic corticosteroids are recommended on a daily basis, beginning with a high dose of a short-acting agent (1.0–1.5 mg/kg/day prednisone). If the disease is severe, intravenous pulse steroid therapy (1.0 g/day × 3 days) followed by oral prednisone can be considered (Hebestreit et al. 1997). Therapeutic efficacy should be evaluated at 3 months. If corticosteroid therapy is effective, then a slow taper should be initiated (Table 8.1).

Patients who become resistant to corticosteroids or develop side effects may be candidates for therapy with other immunosuppressive agents such as chlorambucil, cyclophosphamide, azathioprine, or cyclosporine. Cyclosporine has been used at 5 mg/kg/day, tapering to a maintenance dose of 1 mg/kg/day with regular monitoring of blood pressure and renal function. Azathioprine, at a dose of 50 mg three times a day, has also been used effectively in combination with low-dose corticosteroids with blood count monitoring (Hakin et al. 1992). Mycophenolate dosage has been 1 g b.i.d. Chlorambucil has a risk of infertility and secondary

Table 8.1 Treatment for sympathetic ophthalmia

Initial therapy
High-dose corticosteroid (prednisone 1–2 mg/kg/day) for 3 months
If severe, IV solumedrol 1 g/day for 3 days followed by oral prednisone
If no response/side effects
Cyclosporine 5 mg/kg/day with 1 mg/kg/day taper
Azathioprine 50 mg three times a day
Mycophenolate 1 g twice a day
Chlorambucil 2 mg/day

malignancies and should be reserved for elderly patients who have failed other options. Collaborative management with an internist, rheumatologist or hematologist is advisable.

Early diagnosis and initiation of treatment can yield good visual results (Kilmartin et al. 2000a). Chan and associates reported 16 of 32 patients achieving 20/40 or better vision after immunosuppressive treatment for sympathetic ophthalmia (Chan et al. 1995).

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Vogt–Koyanagi–Harada Disease

9

Peizeng Yang and Zi Ye

Introduction

Vogt–Koyanagi–Harada (VKH) disease is an autoimmune disorder characterized by bilateral granulomatous panuveitis frequently associated with multiple extraocular findings such as vitiligo, poliosis, dysacusis, alopecia, and neurological involvement. In 1906, Vogt reported a patient with nontraumatic uveitis associated with poliosis. Bilateral idiopathic uveitis patients with poliosis, vitiligo, dysacousia, and alopecia were subsequently reported by Koyanagi in 1929. Because of the uniformity of these findings, disease reported by Vogt and Koyanagi was identified as one uveitis entity and named as Vogt–Koyanagi syndrome. In 1926, a disease characterized by cerebrospinal fluid (CSF) change and retinal detachment was reported by Harada as a separate uveitis entity. Subsequently, more and more studies suggested that Vogt–Koyanagi syndrome and Harada disease are the different manifestations in different stages of the same disease. In a study on 410 Chinese VKH patients, we revealed that Harada disease is the early manifestation, whereas Vogt–Koyanagi syndrome is the feature in recurrent stage (Yang et al. 2007).

VKH disease commonly affects young and middle-age adults, and the predominant age of disease onset is 20–50 years. It has no gender predilection, although several studies show that female is more likely to be affected. VKH disease primarily occurred in pigmented races, such as Asians and native Americans. It has rarely been reported in European populations (Du et al. 2016).

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Etiopathogenesis

Although exact pathogenesis of VKH disease remains uncertain, microbial infection, autoimmune response, and genetic susceptibility have been thought to play a role in the development of this disease. As the meningeal manifestations such as headache, fever, and meningismus are observed prior to the uveitis attack, microbial infection is considered as a triggering factor in VKH disease. Earlier studies have detected the Epstein–Barr virus (EBV) DNA in CSF and vitreous from patients with VKH disease. However, these findings are not confirmed by subsequent studies. Sugita et al. find that peptides derived from cytomegalovirus envelope glycoprotein H (CMV-egH$_{290\text{-}302}$) and from tyrosinase have a high homology of amino acid sequence and that the T-cell clones established from VKH patients can recognize CMV-egH$_{290\text{-}302}$ as well as tyrosinase peptides (Sugita et al. 2007). A hypothesis that immune cells may recognize and attack the host proteins as exogenous antigens because of the similarity of genome sequence has been proposed. Other evidences supporting this hypothesis are that the expression of some pattern recognition receptors (PRRs, which could recognize microbial products and then trigger the immune response), TLR3, TLR4, NOD1, and NOD2, is significantly increased in active VKH patients.

An autoimmune response directed against melanin-associated antigen, interphotoreceptor retinoid binding protein, and retinal S-antigen has been observed in VKH disease. Increasing number of studies provide evidences that T-cell subsets, including Th17, Th1, and Treg cells, together with their functional cytokines IL-17, IFN-γ, IL-10, and TGF-β play an important role in the initiation and maintenance of the autoimmune response (Chi et al. 2007; Du et al. 2016). Significantly higher expression of IL-17 and IFN-γ and increased percentage of Th17 and Th1 cells are observed in active VKH patients. Treg cells, which possess immune regulatory properties, show functional impairment and

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quantitative reduction in active VKH patients. Other immune cells such as macrophage and dendritic cells (DCs) also contribute to the development of VKH disease. They can produce IL-23 and IL-12, which in turn stimulate Th17 and Th1 cell polarization and promote IL-17 and IFN-γ production. In addition, a network of cytokines, chemokines, cell receptors, as well as other factors also contribute to the development of VKH disease through modulating IL-23/IL-17 pathway. Higher expression of leptin, osteopontin (OPN), IL-7, and IL-21 and lower expression of 1,25-dihydroxyvitamin D3, liver X receptor, IL-27, IL-25, and IL-37 are detected in active VKH patients. This disturbed expression of these molecules may collectively result in the activation of IL-23/IL-17 pathway and in turn lead to the development of VKH disease.

Human leukocyte antigens DR4 (HLA-DR4) and DRw53 (HLA-DRw53) have been shown to be strongly associated with VKH disease in different ethnic populations. Other HLA antigens including DQw3, B54, DQ4, DR1, DRB1∗0405, DQA1∗0301, and DQB1∗0401 are also identified as susceptible genetic factors for this disease. Genome-wide association studies (GWAS) on Chinese VKH patients confirm the strong association of HLA-DRB1/DQA1 loci with this disease. Additionally, two new non-HLA loci including IL23R-C1orf141 and ADO-ZNF365-C1orf141 are identified as VKH disease-susceptibility loci (Hou et al. 2014). Studies in different populations identified that single-nucleotide polymorphisms of CTLA-4, SUMO4, PTPN22, IFN-γ, IL-17, IL-12B, TLR9, TNIP1, NLRP1, OPN, miR-146a, and DHCR7 confer susceptibility to this disease. In addition, copy number variations (CNVs) of some immune-related genes including complement 4 (C4), C3, IL-17F, IL-23A, and FAS are also found to be associated with VKH disease.

Taken together, a hypothesis can be that environmental factor such as a virus infection may induce an immune response to the antigens as stated above in a currently unknown way in the individuals with a constellation of risk genetic factors, therefore subsequently leading to the development of VKH disease.

Clinical Features

Various manifestations can be observed in different stages of VKH disease. Moorthy et al. classified this disease into four stages according to the manifestations during the course of the disease: prodromal stage, acute uveitis stage, chronic convalescent stage, and chronic recurrent stage (Moorthy et al. 1995) (Table 9.1). Another phasing system is also proposed based on our study on 410 Chinese VKH patients (Yang et al. 2007). This system also consists of four stages: prodromal stage, posterior uveitis stage, anterior uveal involvement stage, and recurrent granulomatous anterior uveitis stage (Table 9.2). Both systems are generally similar, but our system more highlights the evolutionary process during the course. For instance, the disease begins with diffuse choroiditis, progresses to a non-granulomatous anterior uveitis, and finally becomes a granulomatous panuveitis with striking anterior segment involvement unless appropriate treatments are instituted.

Table 9.1 Classification systems developed for VKH disease by Moorthy et al. (1995)

Stages	Clinical features
Prodromal stage	Headache, fever, meningismus, hearing loss, tinnitus, stiffness of neck and back
Acute uveitis stage	Sudden bilateral blurring and decrease of vision, choroiditis, multiple neuroepithelium detachment, exudative retinal detachment, optic disc edema or hyperemia, acute intraocular pressure (IOP) (occasionally), granulomatous anterior uveitis (occasionally)
Chronic convalescent stage	"Sunset glow" fundus, Dalen-Fuchs nodules, Sugiura's sign, vitiligo
Chronic recurrent stage	Recurrent granulomatous anterior uveitis, Koeppe and Busacca nodules, rare active posterior uveitis, poor response to corticosteroid, intraocular complications

Table 9.2 Classification systems developed for VKH disease by Yang et al. (2007)

Stages	Clinical features
Prodromal stage (about 1 or 2 week before uveitis attack)	Headache, fever, meningismus, hearing loss, tinnitus, stiffness of neck and back
Posterior uveitis stage (about 2 weeks after uveitis attack)	Choroiditis, exudative retinal detachment, optic disc edema or hyperemia, acute IOP (occasionally)
Anterior uveal involvement stage (from 2 weeks to 2 months after uveitis attack)	Active posterior uveitis, non-granulomatous anterior uveitis
Recurrent granulomatous anterior uveitis stage (more than 2 months after uveitis attack)	"Sunset glow" fundus, Dalen-Fuchs nodules, migration of RPE, recurrent granulomatous, Koeppe and Busacca nodules, intraocular complications

Prodromal Stage

The prodromal stage refers to 1 or 2 weeks before uveitis attack and is characterized by meningismus, hearing loss, tinnitus, and abnormal sensitivity to touch of the hair. CSF pleocytosis can be observed in this stage.

Posterior Uveitis Stage

The posterior uveitis stage refers to within 2 weeks after uveitis attack. Sudden bilateral blurring and decrease of vision

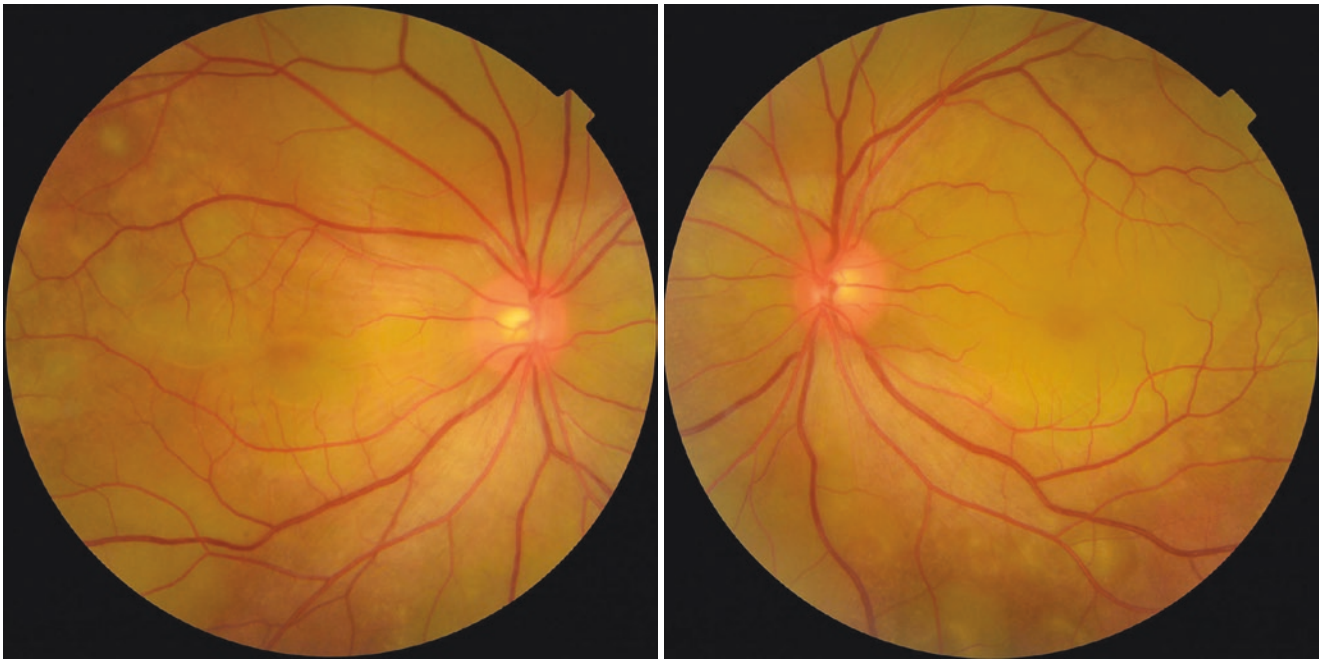

Fig. 9.1 Multiple exudative retinal detachment and optic disc swelling in a patient with VKH disease at posterior uveitis stage

are the most common symptoms. The majority of patients present with decreased vision simultaneously in both eyes. In the remaining patients, the interval between uveitis onsets of both eyes is usually from 1 to 2 weeks. Diffuse choroiditis is the characteristic finding. Most patients present with exudative retinal detachment and optic disc swelling (Fig. 9.1). No anterior reaction is observed in this stage. Fundus fluorescein angiography (FFA) shows numerous punctate hyperfluorescent dots in the early phase and subretinal dye pooling in the late phase (Fig. 9.2a). Optic disc staining is also a common finding. Indocyanine green angiography (ICGA) typically shows multiple hypofluorescent dots and dark areas corresponding to serous retinal detachment (Fig. 9.2b). Exudative retinal detachment disclosed with optical coherence tomography (OCT) is a rule in this stage (Fig. 9.2c). Tinnitus, hearing loss, and meningismus may be still present in this stage.

Anterior Uveal Involvement Stage

The anterior uveal involvement stage usually begins from 2 weeks after the uveitis attack. This stage usually lasts for 1.5 months. In this stage, choroiditis is still observed in most patients. A mild to moderate anterior uveitis characterized by flare and cells in the anterior chamber and dust-keratic precipitates (KP) is the prominent manifestation. Granulomatous anterior uveitis is very rarely seen in this stage. Mild vitreous inflammatory reaction and optic disc swelling are also noted. Tinnitus and hearing loss are the most common extraocular symptoms, and integumentary changes including poliosis, alopecia, and vitiligo are observed in some patients in this stage (Fig. 9.3).

Recurrent Granulomatous Anterior Uveitis Stage

Without appropriate and prompt treatment, VKH patients may eventually develop recurrent chronic granulomatous anterior uveitis. During this stage, active choroiditis normally resolves and "sunset glow" fundus ensues as a result of depigmentation of the retinal pigment epithelium (RPE) cells and the choroid (Fig. 9.4). In some patients, the sclera tissue can be observed because of severe depigmentation of the choroid (Fig. 9.5). Dalen-Fuchs nodules, which manifest as small, round to oval active lesions in the midperiphery of the fundus, chorioretinal atrophy, and migration of RPE cells are the other common findings in the posterior segment (Fig. 9.4). Anterior uveitis is a very striking feature and typically presents with mutton fat KP, Koeppe nodules, Busacca nodules, and significant anterior chamber reaction (Fig. 9.6). Window defects due to RPE cell damages and blockade of fluorescence arising from migration of retinal RPE cells are common FFA findings. Ultrasound biomicroscopy may show the cells in the anterior chamber as thickened and swollen ciliary body as well as ciliochoroidal detachment in patients in this stage (Fig. 9.7). Ocular complications including cataract, secondary glaucoma, subretinal fibrosis, and choroidal neovascularization are observed in this stage. Poliosis, alopecia, and vitiligo are common extraocular findings.

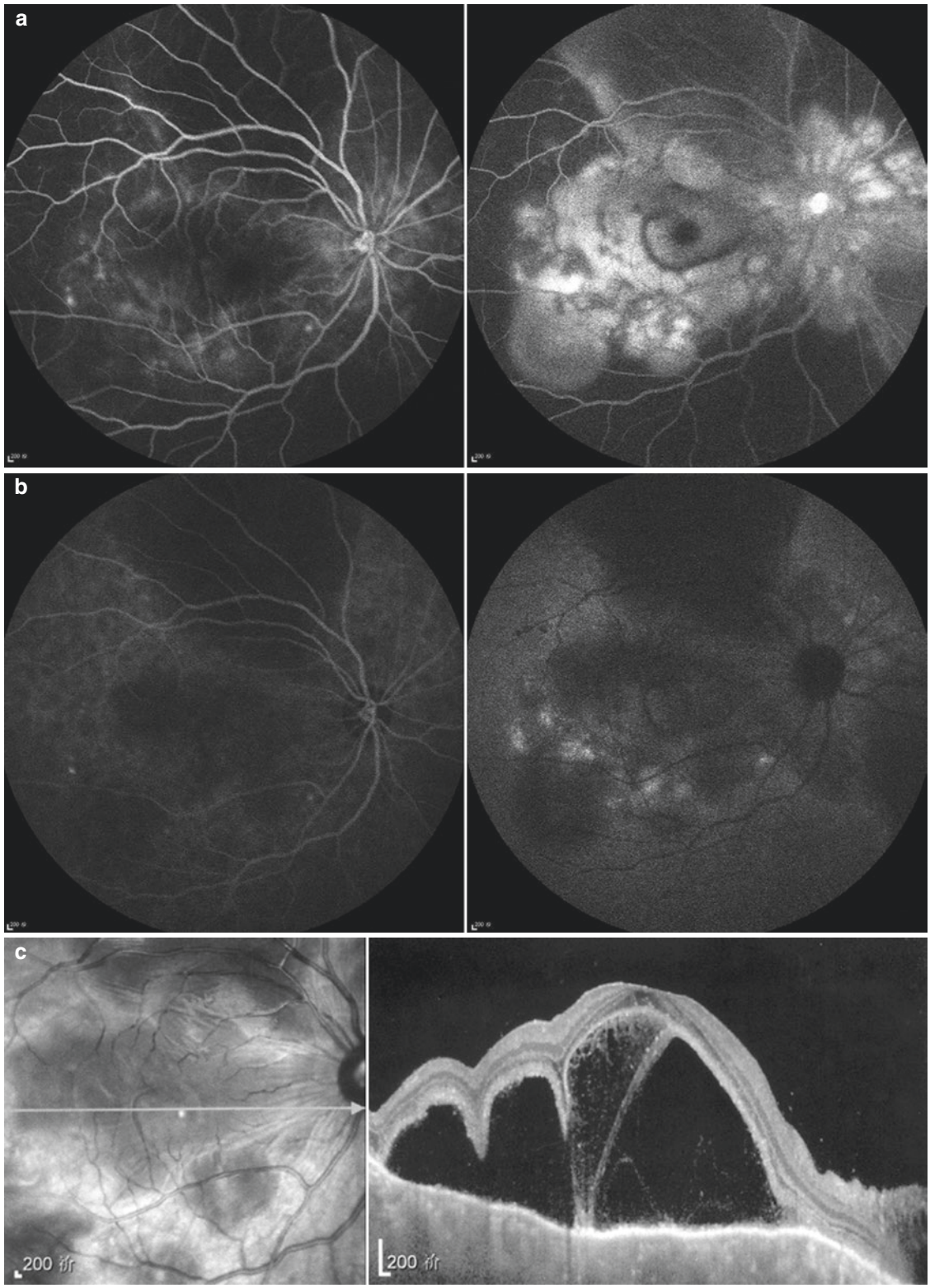

Fig. 9.2 FFA, ICGA, and OCT examination of a patient with VKH disease at posterior uveitis stage. (**a**) FFA shows punctate hyperfluorescent dots in the early stage and subretinal dye pooling in the late stage. (**b**) ICGA shows multiple hypofluorescent dots and dark areas corresponding to serous retinal detachment. (**c**) OCT shows serous retinal detachment. (**d**–**f**) The aforementioned alterations resolved at 1 month following treatment

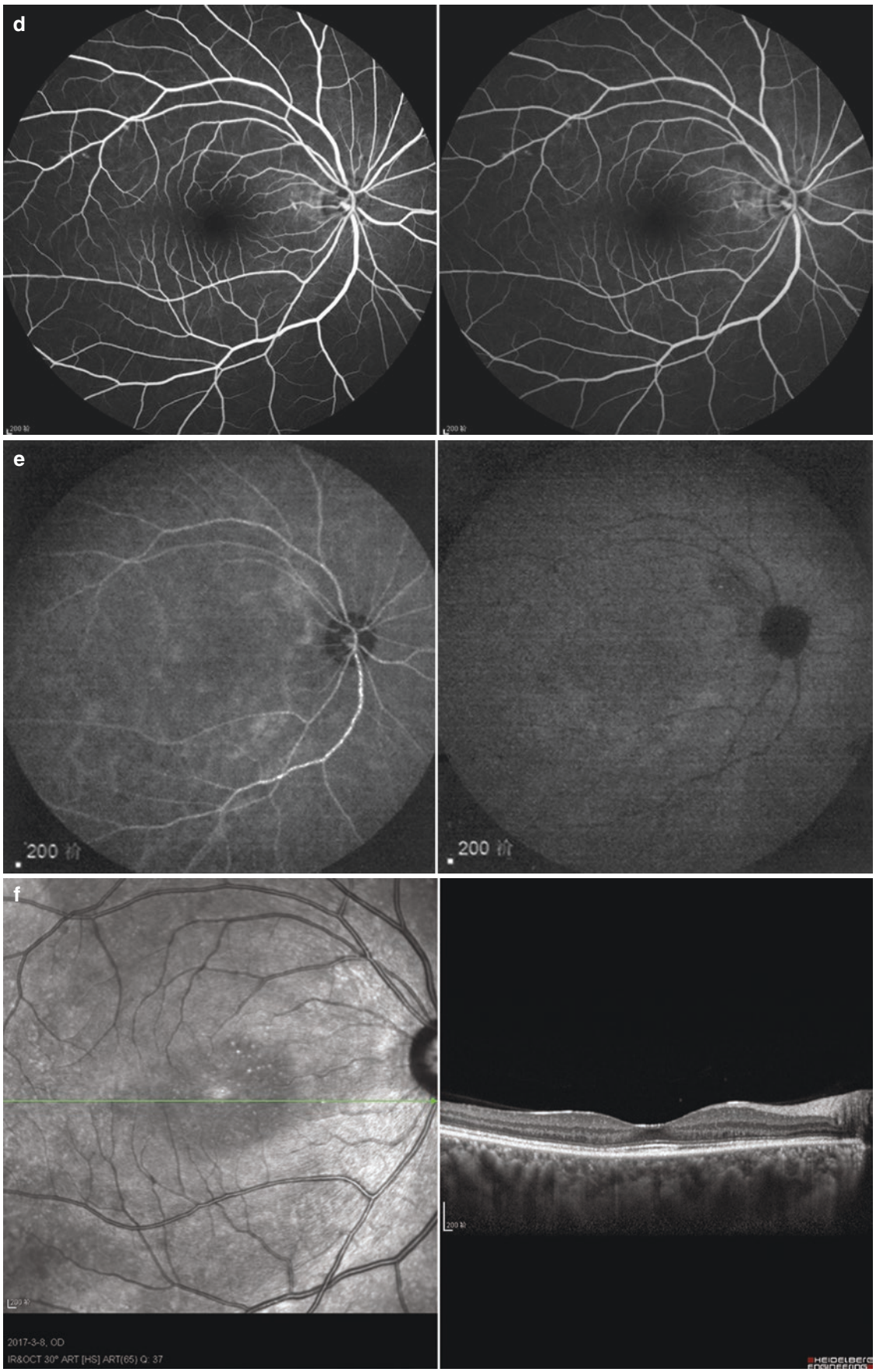

Fig. 9.2 (continued)

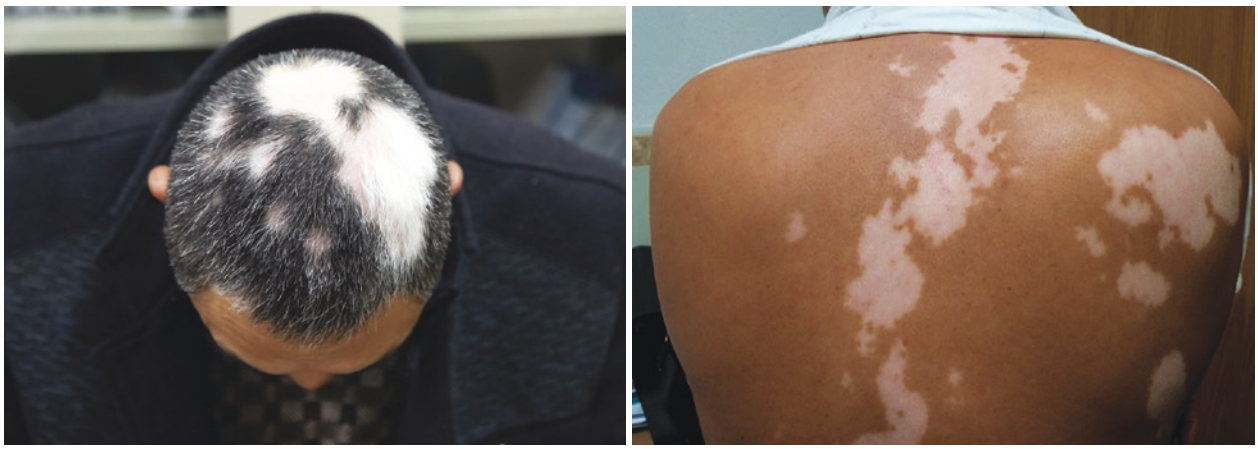

Fig. 9.3 Poliosis, alopecia, and vitiligo observed in VKH patients

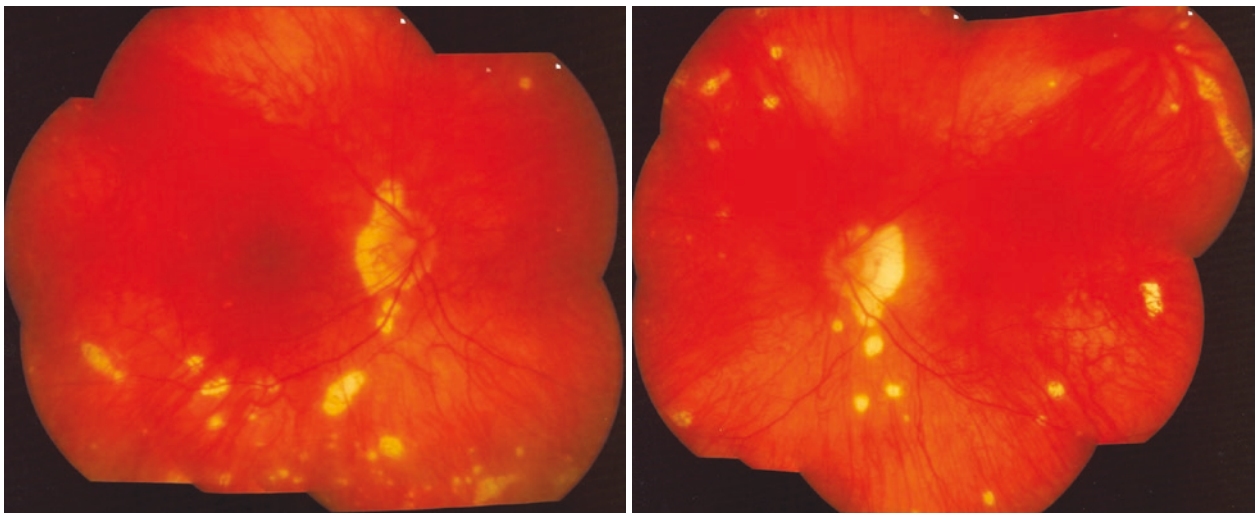

Fig. 9.4 Sunset glow fundus and multiple Dalen-Fuchs nodules observed in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

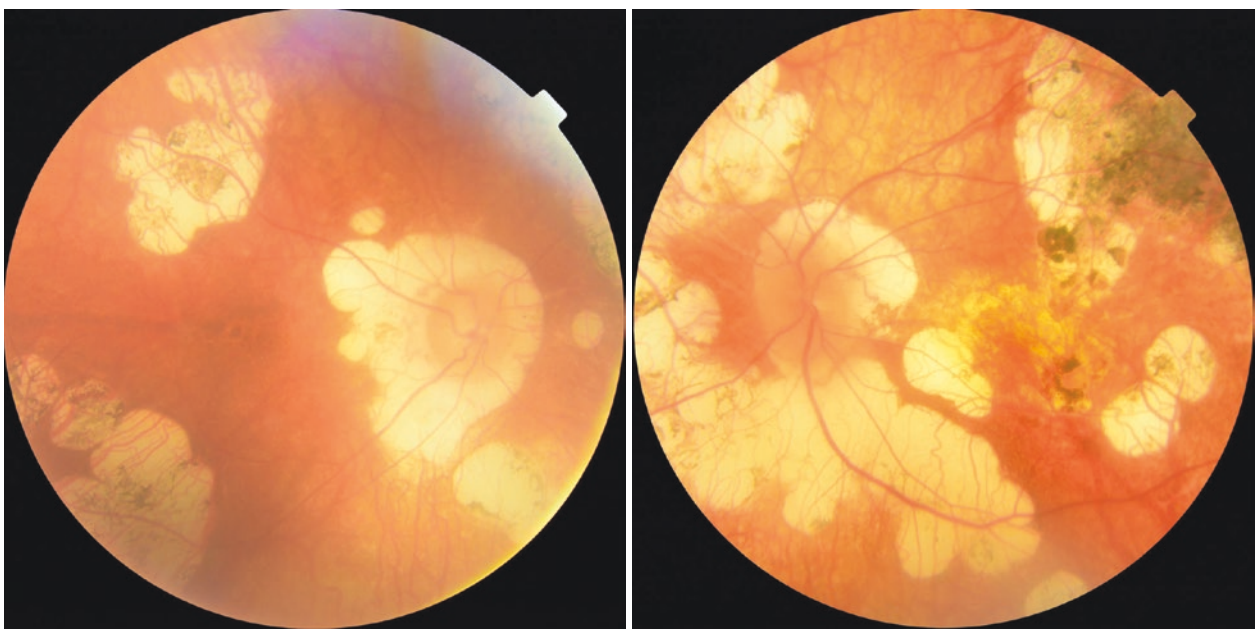

Fig. 9.5 Confluent chorioretinal atrophies and irregular hyperpigmentation observed in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

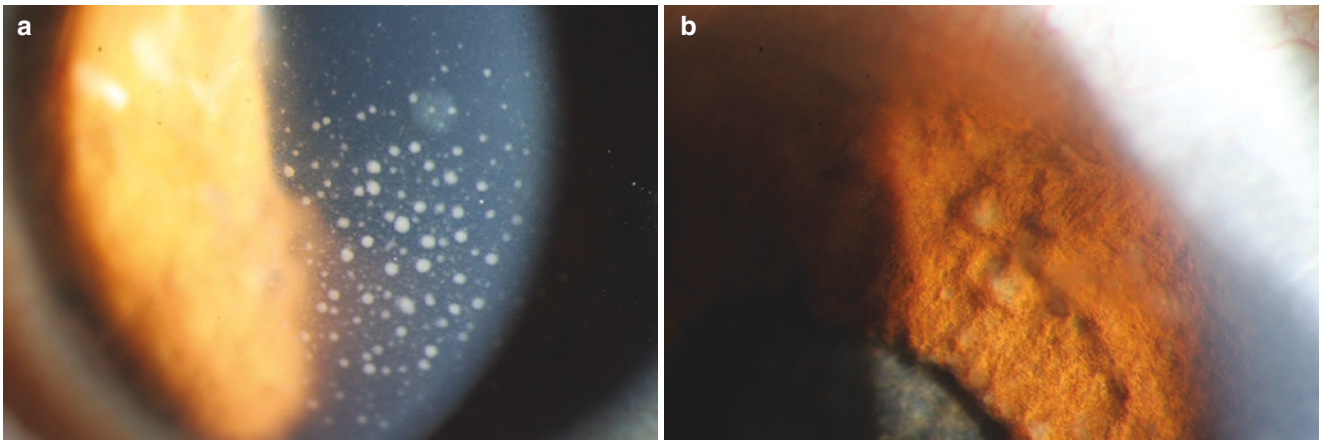

Fig. 9.6 Mutton fat keratic precipitate (**a**) and Busacca nodules (**b**) observed in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

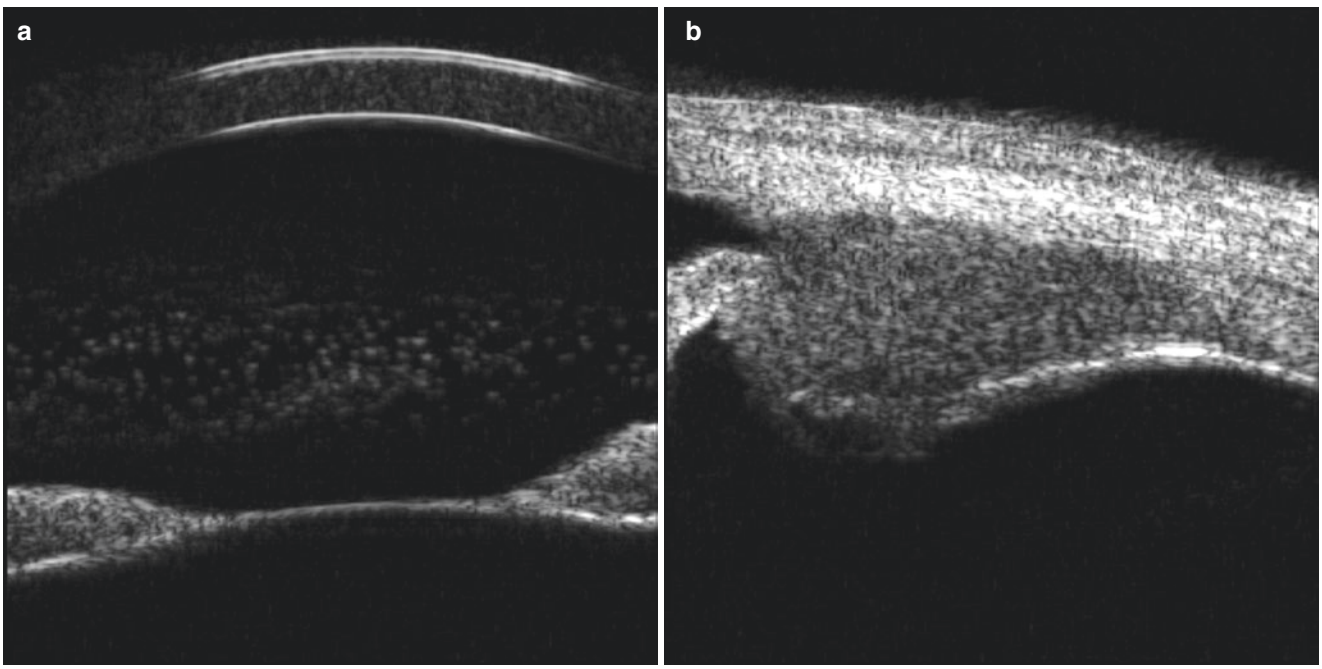

Fig. 9.7 Inflammatory cells in the anterior chamber (**a**) and swollen ciliary body (**b**) disclosed by ultrasound biomicroscopy in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

Diagnostic Criteria

Several diagnostic criteria for VKH disease have been proposed during the last decades. Currently, the most widely used criteria are the revised diagnostic criteria endorsed by the International Nomenclature Committee on nomenclature (Read et al. 2001) (Table 9.3). These criteria include the different manifestations during the disease process and classify VKH disease into three categories: complete VKH disease, incomplete VKH disease, and probable VKH disease. Although the diagnostic criteria are highly sensitive and specific, they define the disease without extraocular manifestations only as "probable VKH disease." It seems not to be scientific enough since some patients present with the typical intraocular signs such as "sunset glow" fundus and Dalen-Fuchs nodules with a typical evolutionary process. Adequate treatment in early stage can influence the long-term clinical manifestations of VKH disease and support the diagnosis. An effort is being made by us to develop novel criteria based on a large number of Chinese VKH patients and is expected to be used clinically in the future.

Table 9.3 Revised diagnostic criteria endorsed by the International Nomenclature Committee on nomenclature (Read et al. 2001)

Complete VKH 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 or
(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, pooling within subretinal fluid, and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography and
(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 or
(b) Sugiura's sign
(3) Other ocular signs
(a) Nummular chorioretinal depigmented scars or
(b) Retinal pigment epithelium clumping and/or migration or
(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 the definition of meningismus, however) or
b. Tinnitus or
c. Cerebrospinal fluid pleocytosis
5. Integumentary finding (not preceding the onset of central nervous system or ocular disease)
a. Alopecia or
b. Poliosis or
c. Vitiligo
Incomplete Vogt–Koyanagi–Harada disease (criteria 1–3 and either 4 or 5 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis and
2. No clinical or laboratory evidence suggestive of other ocular disease entities and
3. Bilateral ocular involvement
4. Neurologic/auditory findings; as defined for complete Vogt–Koyanagi–Harada disease above or
5. Integumentary findings; as defined for complete Vogt–Koyanagi–Harada disease above
Probable Vogt–Koyanagi–Harada disease (isolated ocular disease; criteria 1–3 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 as defined for complete Vogt–Koyanagi–Harada disease above

Management

Prompt and adequate management of VKH disease can halt the disease in early stage and improve the visual prognosis. Systemic treatment with corticosteroids and other immunosuppressive drugs such as cyclosporine A (CsA), cyclophosphamide, methotrexate, azathioprine, and chlorambucil has achieved a good result in most patients. Recently, some biologic agents are employed in the management of recalcitrant VKH disease and show a positive result.

Corticosteroids

System corticosteroids are considered as the first choice in the treatment of VKH disease. The reported initial dose of corticosteroids is usually 1–1.5 mg/kg/day followed by gradual tapering (Hayasaka et al. 1982; Moorthy et al. 1995; Rubsamen and Gass 1991; Yang et al. 2007). Higher dose or even intravenous pulse therapy has been recommended by some authors for severe cases. However, high-dose of corticosteroids may virtually cause severe side effects. Recently, we developed the

therapeutic regimens using a relatively lower dose of corticosteroids mostly in conjunction with immunosuppressive agents (see below) for the treatment of VKH disease. The initial dose of corticosteroids is 0.6–0.8 mg/kg/day of prednisone for patients in early stage and 0.4–0.6 mg/kg/day for patients in late stage. Systemic corticosteroid is gradually tapered to a maintenance dose, 15–20 mg/day, over 4–6 months with the subsidence of the intraocular inflammation. Treatment with this maintenance dose usually lasts for another 4–6 months followed by gradual tapering to final cessation. For patients with marked retinal detachment, posterior sub-Tenon's injection of triamcinolone acetonide (20 mg) is used as an adjunct to systemic corticosteroids. For patients with anterior chamber reaction, corticosteroid eye drops and cycloplegic agents are indicated to control the anterior segment inflammation. A study based on 998 Chinese VKH patients shows that these therapeutic regimens can effectively control the intraocular inflammation in 98% of these patients (Fig. 9.2d–f). Up to 80% of these patients achieve a final vision ≥20/40.

Immunosuppressive Agents

Immunosuppressive agents are required for patients who are resistant to corticosteroids or who do not tolerate the side effects of corticosteroids. Furthermore, they are also recommended for patients with recurrent anterior uveitis. CsA is one of the most commonly used immunosuppressive agents. Previous studies show that CsA is a better glucocorticoid-sparing agent as compared to azathioprine (Cuchacovich et al. 2010). In our clinic, we usually commence the treatment with an initial dose of 2–4 mg/kg/day for 5–6 months. If the initial dose is more than 2 mg/kg/day, it is gradually tapered to the maintenance dose of 2 mg/kg/day. Other agents including cyclophosphamide, methotrexate, azathioprine, and chlorambucil are also advocated in the treatment of this disease in the context of the individual conditions. A beneficial result has been observed in most patients treated with various immunosuppressive agents.

Biological Agents

Biological agents such as infliximab, adalimumab, and rituximab have been successfully used in patients with refractory VKH disease. Prospective randomized clinical trials on a large number of patients are needed to optimize the use of these agents in the treatment of VKH disease.

Complication Management

Surgery therapy is necessary for complicated cataract and should be performed after intraocular inflammation is completely controlled (Moorthy et al. 1994). For secondary glaucoma, anti-glaucoma medications show a good result in most patients. Surgery intervention is indicated if complete posterior synechia or widespread anterior synechia is present or the patients fail to respond to medication treatment. Photocoagulation, intravitreal injection of anti-VEGF agents, as well as surgical excision has been used in patients with subretinal fibrosis or choroidal neovascularization.

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Intermediate Uveitis

10

Pınar Ç. Özdal and Ilknur Tugal-Tutkun

Introduction

Anatomically, the term *intermediate uveitis* (IU) refers to the subset of uveitis where the vitreous is the major site of the inflammation, and the presence of peripheral vascular sheathing and macular edema do not change the classification. The IU may or may not be associated with infection or systemic disease, whereas the term *pars planitis* has been recommended for a particular subset of IU associated with snowbank and snowball formation in the absence of an infectious or systemic disease (Jabs et al. 2005).

Epidemiology and Etiology

The incidence and prevalence of IU show great variability according to geographic, genetic, and referral patterns of the patients. It is the least common anatomic type of uveitis in most of the series and accounts for 0.9–16% of all uveitis patients (Jones 2015; Nakahara et al. 2017; Silpa-archa et al. 2015; Singh et al. 2004; Yalçındağ et al. 2018). However, pars planitis is an important cause of pediatric uveitis and constitutes 5–26.7% of uveitis in this age group (Ozdal et al. 2015; Yalçındağ et al. 2018).

The IU may be associated with infectious diseases such as tuberculosis, leprosy, Lyme disease, syphilis, toxocariasis, Whipple's disease, Epstein–Barr virus infection, and noninfectious systemic diseases such as multiple sclerosis (MS), sarcoidosis, thyroid disease, and inflammatory bowel disease. The IU cases not associated with infectious or systemic diseases are considered as idiopathic. In a recent study including both pediatric and adult patients, idiopathic IU has been reported in 59% (Ness et al. 2017). Association with systemic diseases is extremely rare, and IU is almost always idiopathic in the pediatric population (Tugal-Tutkun 2011).

Besides systemic disease associations, the presence of HLA-DR15 and HLA-A28 in patients with IU and the presence of HLA-DR2, -DR15, -B51, and DRB1∗0802 in patients with pars planitis suggest an immunogenetic predisposition and autoimmune process in its pathogenesis. Patients with IU who are positive for HLA-DR15 were reported to have systemic findings of other HLA-DR15-related disorders such MS, optic neuritis, and narcolepsy, suggesting a common genetic background (Arellanes-Garcia et al. 2008; Babu and Rathinam 2010; Bonfioli et al. 2005; Ness et al. 2017; Ozdal et al. 2015; Raja et al. 1999).

Although affecting all age groups, IU is mostly seen in young adults within the third and fourth decades (Babu and Rathinam 2010; Bonfioli et al. 2005). Pars planitis, however, predominantly affects children between 6 and 10 years of age and adolescents (Ozdal et al. 2015). The disease has no definite gender predilection. In studies comparing childhood-onset and adulthood-onset cases, boys constituted the majority of childhood cases, while women made up most of the adult cases (Heinz et al. 2014; Paroli et al. 2014).

Clinical Features

Floaters and blurred vision are the most common symptoms at presentation. Other less common symptoms include pain, photophobia, and red eye. Severe cases may present with significant visual loss due to macular edema or aggregation of floaters in the vitreous. The disease may also be asymptomatic and diagnosed incidentally during routine eye examination, especially in young children (Babu and Rathinam 2010; Donaldson et al. 2007; Paroli et al. 2011). Young children may even present with strabismus secondary to the development of amblyopia or complications which cause leukocoria (Fig. 10.1) (Paroli et al. 2011; Tugal-Tutkun 2011).

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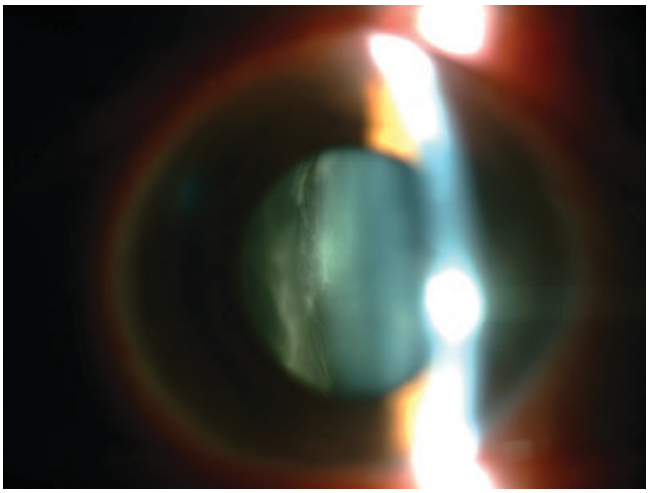

Fig. 10.1 Slit lamp photograph shows dense vitreous condensation causing leukocoria

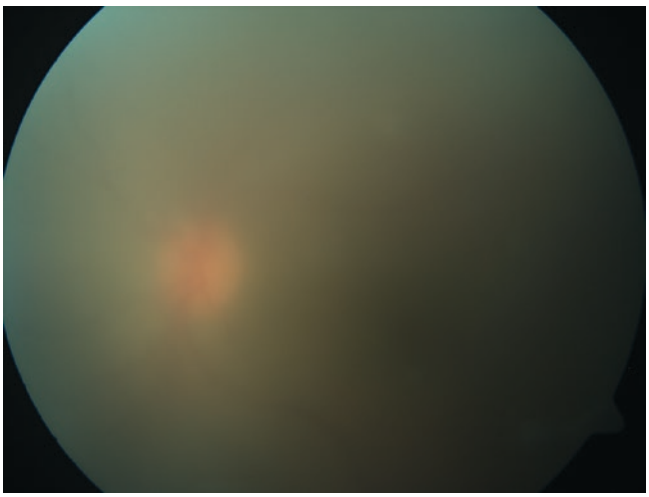

Fig. 10.3 Fundus photograph shows severe vitreous haze associated with intermediate uveitis

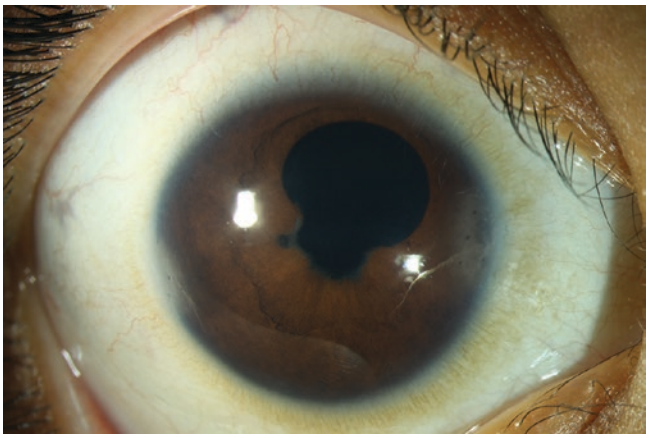

Fig. 10.2 Slit lamp photograph shows posterior synechiae particularly involving the inferior iris and a band keratopathy in a child with pars planitis

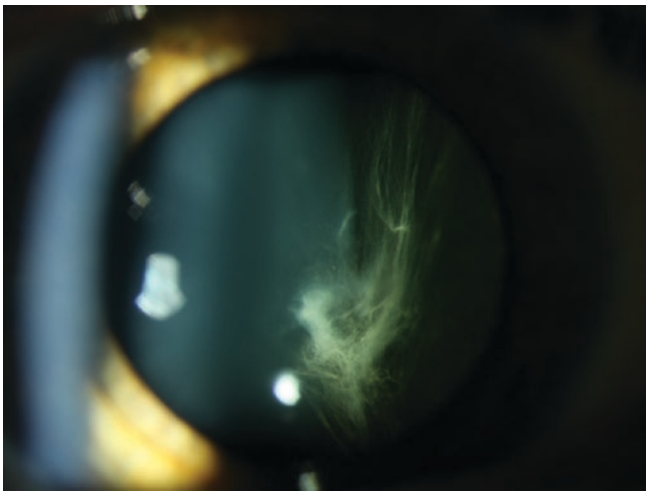

Fig. 10.4 Slit lamp photograph shows severe vitritis and condensation of the anterior vitreous which is visible in the pupillary area

IU, especially pars planitis, affects both eyes in most of the patients. However, an asymmetric involvement with few vitreous cells in the less affected eye may be seen (Ozdal et al. 2015; Tugal-Tutkun 2011). High rates of bilaterality, ranging between 70% and 90%, have been reported in the Western literature (Babu and Rathinam 2010).

The eye is usually quiet with mild to moderate anterior segment inflammation associated with keratic precipitates (KP) distributed mostly in the inferior part of the cornea. Peripheral corneal endotheliopathy characterized by inferior stromal edema and linearly arranged KPs on the border of edematous and normal cornea has also been reported. Posterior synechiae particularly involving the inferior iris (Fig. 10.2) may be observed especially in childhood pars planitis and usually do not occur in adulthood. In children with long-standing inflammation, a band keratopathy may develop (Bonfioli et al. 2005; Donaldson et al. 2007; Tugal-Tutkun 2011). Compared to adults, anterior segment inflammation, band keratopathy (Fig. 10.2), peripheral corneal endotheliopathy, and posterior synechiae are more frequent in children (Tugal-Tutkun 2011). The characteristic finding of IU is vitritis (Fig. 10.3) which may or may not cause vitreous haze. Vitreous inflammation may be severe and can be visible in the pupillary area at biomicroscopic examination (Fig. 10.4). Yellow-white inflammatory aggregates called as *snowballs* are usually found in the mid-vitreous and inferior peripheral vitreous (Fig. 10.5). A snowball may rarely be located on the surface of the macula. With progression, these aggregates coalesce (Fig. 10.6a, b) forming a plaque of exudates usually located inferiorly and called as *snowbank* (Fig. 10.7a, b). Snowballs and snowbank are diagnostic findings of pars planitis. Vitreous bands and vitreous condensations at the inferior peripheral retina are findings

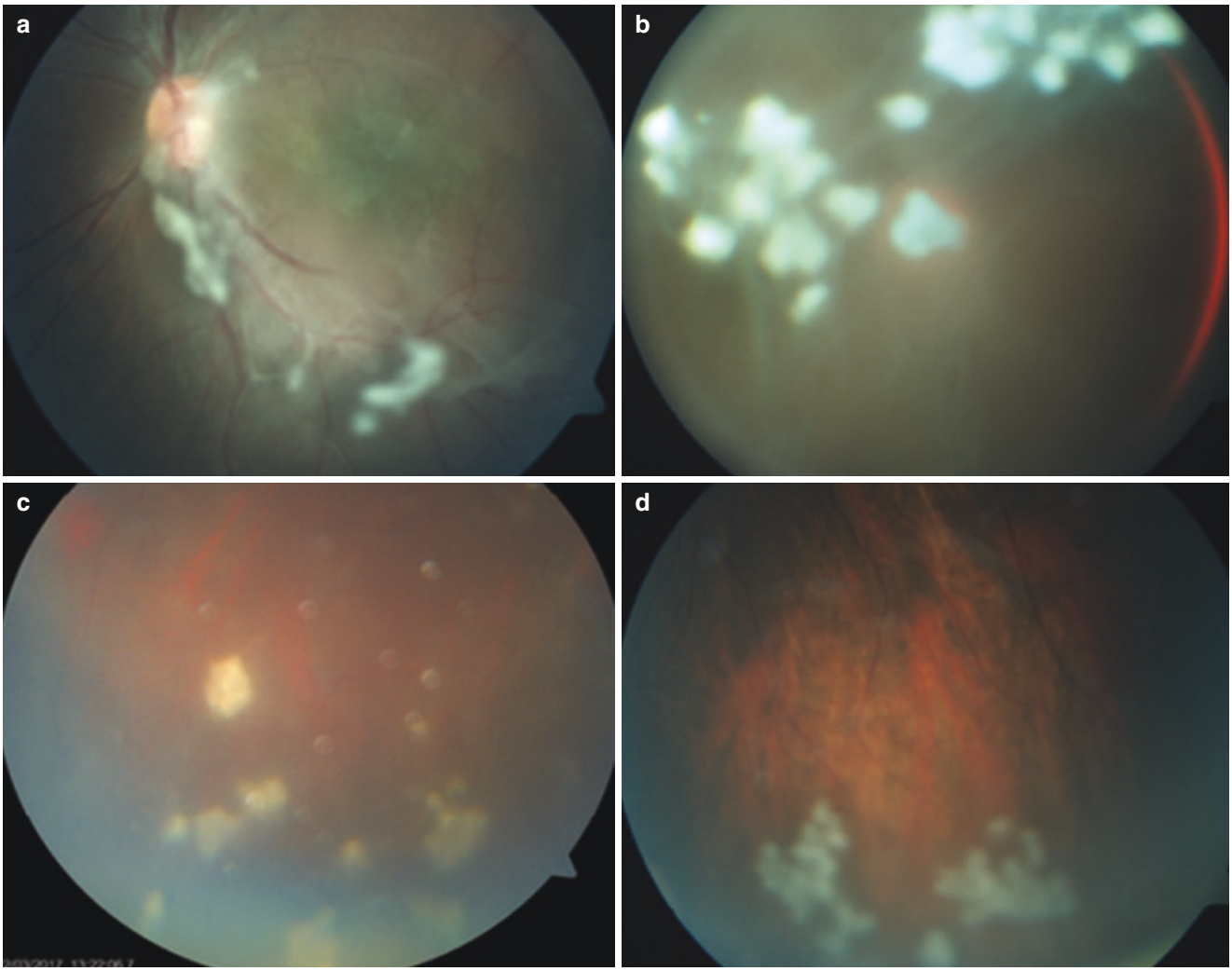

Fig. 10.5 (**a**–**d**) Fundus photographs show variable location of snowballs in patients with pars planitis

suggesting pars planitis (Fig. 10.8). Sheathing of peripheral retinal venules due to retinal vasculitis is another common clinical finding of IU (Fig. 10.9). Optic disc edema can be observed in around 70% of the cases when fluorescein angiography (FA) is performed (Arellanes-Garcia et al. 2008) (Fig. 10.10a, b).

Ocular Complications

Cystoid macular edema (CME) is the most common complication of IU and the leading cause of visual morbidity (Fig. 10.11). Chronic edema can lead to further macular complications such as scarring, epiretinal membranes, and macular hole formation (Fig. 10.12) (Bonfioli et al. 2005).

Because of the chronic and asymptomatic course, presentation with ocular complications is a prevalent condition especially among pediatric patients. The most frequent complications of pars planitis include CME, cataract, and severe vitreous opacities. Band keratopathy (Figs. 10.2 and 10.13), seclusion pupillae (Fig. 10.13), glaucoma, epiretinal membrane formation (Fig. 10.14a–d), vitreous condensation, retinal neovascularizations (Fig. 10.15a, b), vitreous hemorrhage (Fig. 10.16), retinal detachment, peripheral retinoschisis, cyclitic membranes, and amblyopia are also well-known consequences of chronic pars planitis in children (Arellanes-Garcia et al. 2008; Ness et al. 2017; Ozdal et al. 2015).

Occasionally, dense vitreous condensation appearing as leukocoria may be misdiagnosed as cataract particularly in young children. Pars planitis is the leading cause of vitreous hemorrhage in children which may be associated with neovascularization of the optic disc or the peripheral retina (Tugal-Tutkun 2011). Optic disc neovascularization is mostly due to severe intraocular inflammation. Retinal neovascularization, elsewhere or in the snowbank, and rarely peripapillary subretinal neovascularization have also been reported in pars planitis (Arellanes-Garcia et al. 2008).

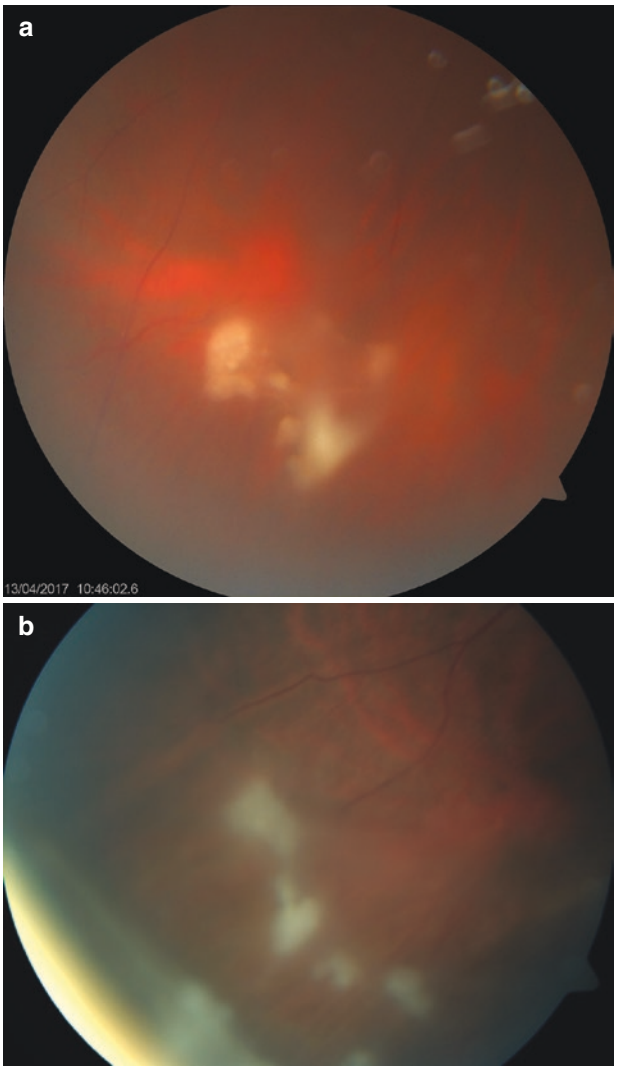

Fig. 10.6 (**a**, **b**) Fundus photographs show snowballs coalescing and making a plaque located on the inferior retina

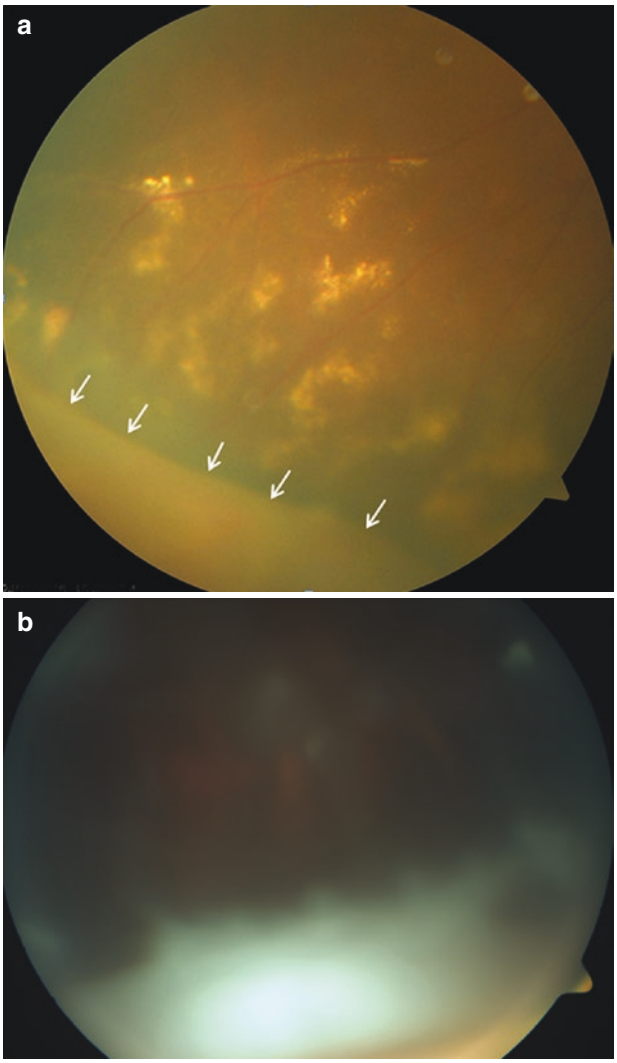

Fig. 10.7 Fundus photograph demonstrates snowbank exudates with a distinct border located inferiorly (shown with white arrows, **a**) and with irregular border located inferiorly (**b**)

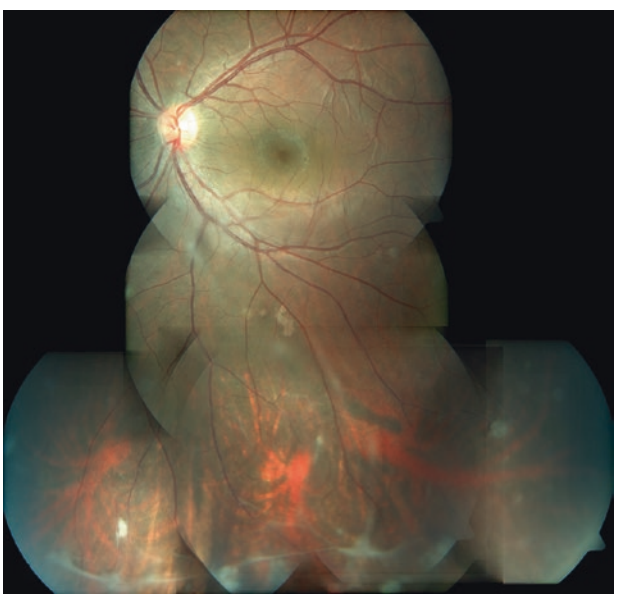

Fig. 10.8 Fundus photograph shows vitreous bands, condensations, and snowballs at the inferior retina

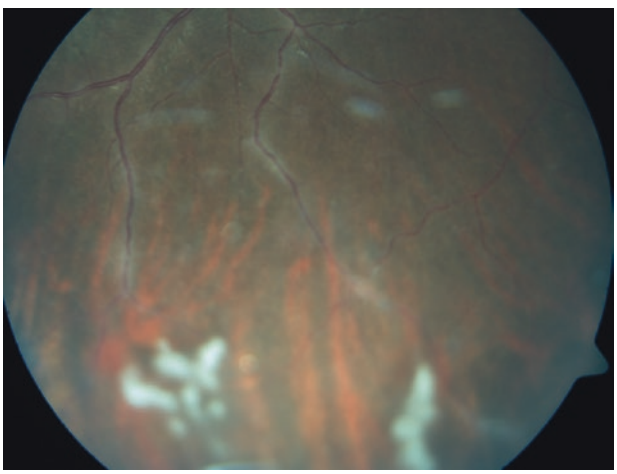

Fig. 10.9 Fundus photograph shows snowballs and vascular sheathing at the inferior retina

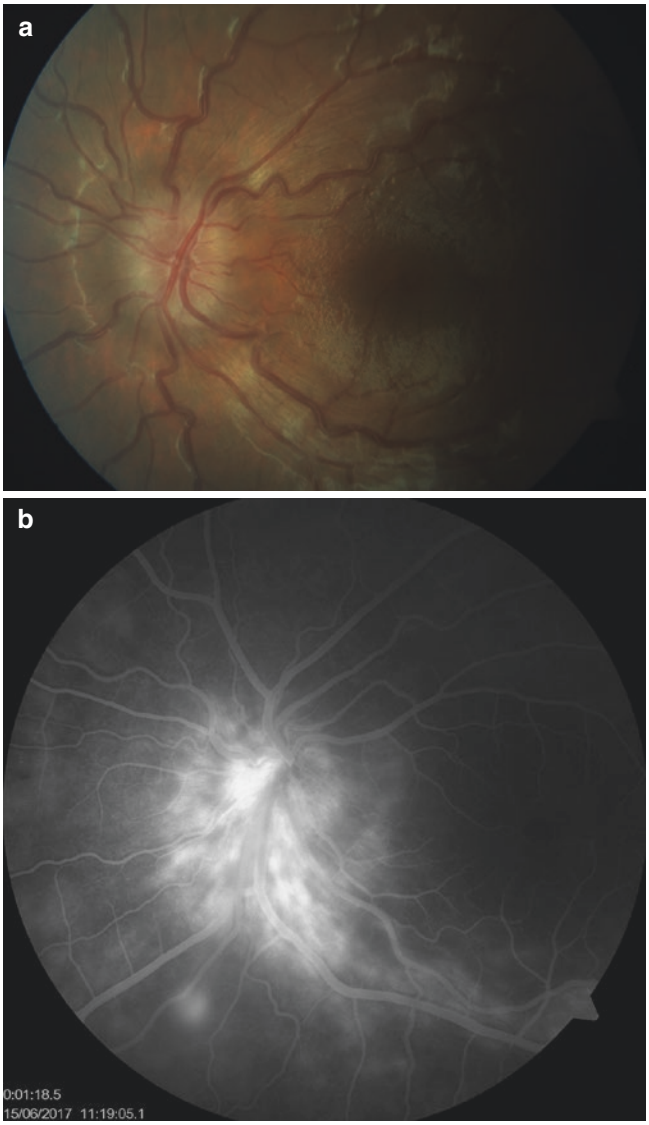

Fig. 10.10 (**a**, **b**) Fundus photographs showing optic disc edema in patients with pars planitis

Peripheral retinal traction and retinal tear may occur occasionally (Fig. 10.17a, b). Retinal detachment (tractional, rhegmatogenous, or exudative) is also a rare complication of pars planitis (Donaldson et al. 2007; Paroli et al. 2011) (Fig. 10.18). Inferior peripheral retinoschisis, however, is a more frequent complication which occurs almost exclusively in children (Tugal-Tutkun 2011) (Fig. 10.19a–d). Retinoschisis has been reported in 19% of eyes in a recent study from a tertiary referral center. It has been found to be bilateral, inferior, and adjacent to a snowbank (Malalis et al. 2017). Young children with pars planitis are at high risk of amblyopia as a consequence of band keratopathy, vitreous opacities and cataracts obscuring the visual axis, or persistent macular edema. Delayed diagnosis and treatment may result in permanent visual loss.

Diagnosis

The diagnosis of IU is based on clinical findings. Decreased and/or blurred vision, floaters in the absence of pain, redness, and photophobia are suggestive symptoms. Clinical diagnosis is based on the presence of vitreous cells, snowballs, and pars plana exudation. When ophthalmoscopy with scleral depression is not performed, inferior snowballs or snowbanks can be missed and especially pars planitis may be underdiagnosed. There is no specific diagnostic laboratory test for IU. For a diagnosis of an idiopathic IU or pars planitis, however, systemic associations and mainly infectious causes of IU need to be ruled out with a careful history, systemic evaluation, and laboratory tests.

Systemic investigations include complete blood count, serological tests for syphilis, Lyme and cat-scratch disease, serum angiotensin-converting enzyme (ACE) and lysozyme levels, chest x-ray, purified protein derivative skin test, and brain magnetic resonance imaging (MRI). Because of the significant association with MS, neuroimaging should be performed especially in adult patients, in whom systemic associations are more common. Imaging modalities such as FA, optical coherence tomography (OCT), ultrasound biomicroscopy (UBM), and ultrasonography are also helpful in confirming the diagnosis and/or showing the disease-related complications.

Fluorescein angiography is usually performed to assess the presence of CME, retinal vasculitis, neovascularizations, and retinal ischemia. Retinal vascular leakage, diffuse capillary leakage, and CME are common FA findings (Fig. 10.20a). Peripheral retinal ischemia, however, may be observed as a less frequent FA finding of the disease (Fig. 10.20b). Fluorescein angiography is also valuable in documenting the response to treatment, especially in eyes with CME and peripheral vasculitis. The OCT imaging shows disease-related macular and retinal changes and provides information regarding the reversibility of lesions. It is valuable in detecting macular edema and its sequelae such as cystoid changes, epiretinal membranes, macular hole, and atrophy. As in FA, it is beneficial in monitoring the treatment response. Ultrasonography and UBM are valuable methods providing additional information regarding the ciliary body, pars plana, and retina when visualization of the fundus is obscured due to band keratopathy, cataract, synechiae, vitreous inflammation, or hemorrhage (Babu and Rathinam 2010; Ozdal et al. 2015).

Sarcoidosis

It has been reported that IU was associated with sarcoidosis in about 10% of patients (Ness et al. 2017). Cystoid macular edema, optic disc edema, and periphlebitis are typical

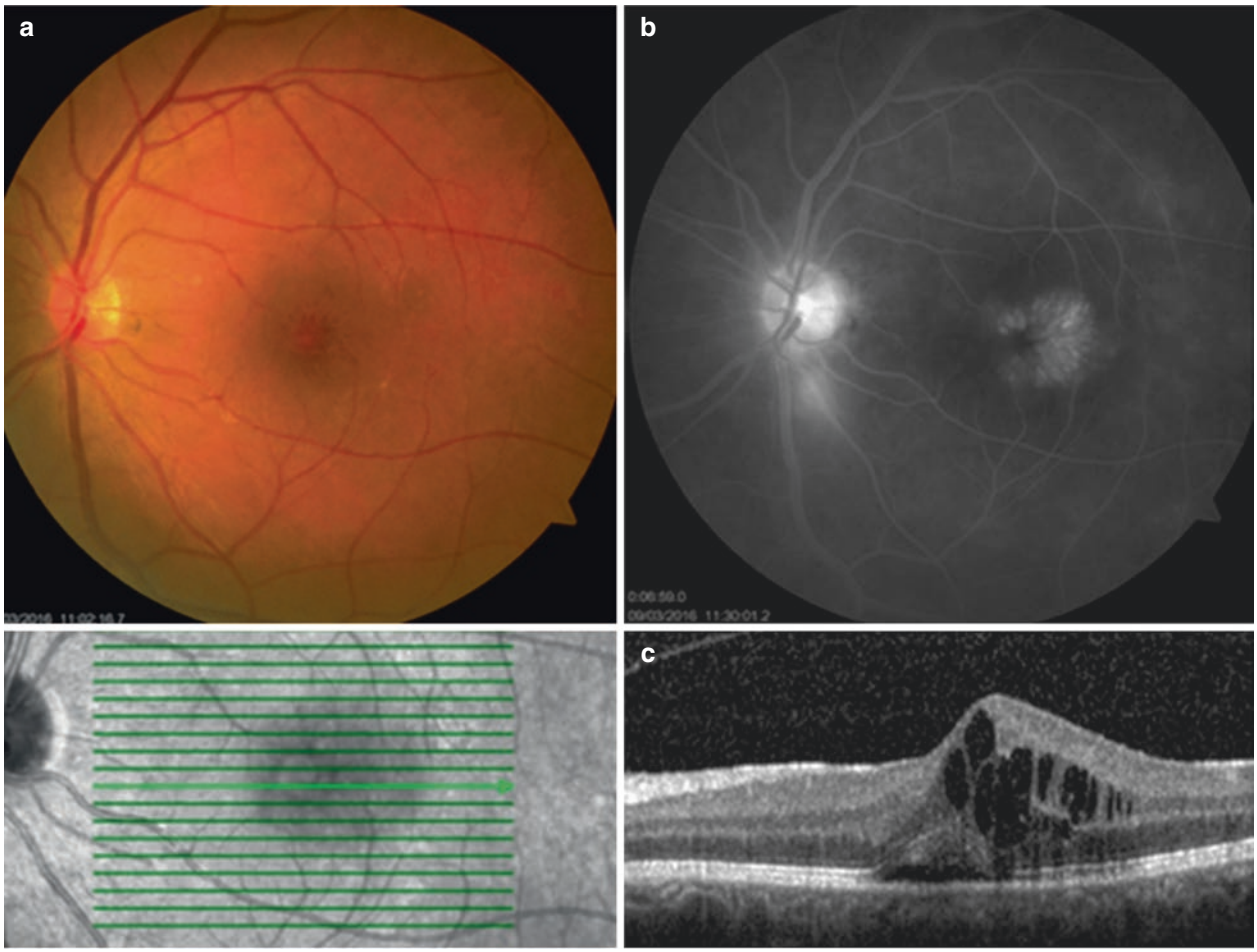

Fig. 10.11 Fundus photograph (**a**), fluorescein angiography (**b**), and optical coherence tomography (**c**) of a patient with intermediate uveitis complicated with cystoid macular edema

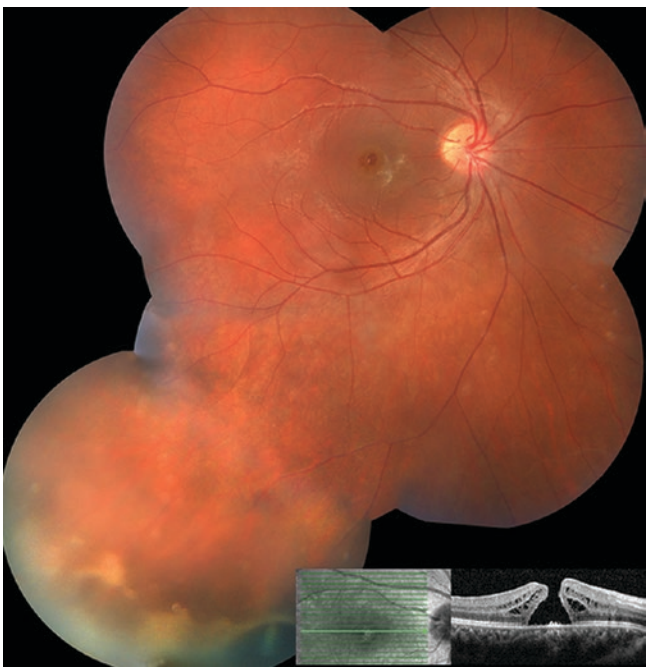

Fig. 10.12 Fundus photograph and optical coherence tomography of a patient with pars planitis complicated with the development of a macular hole

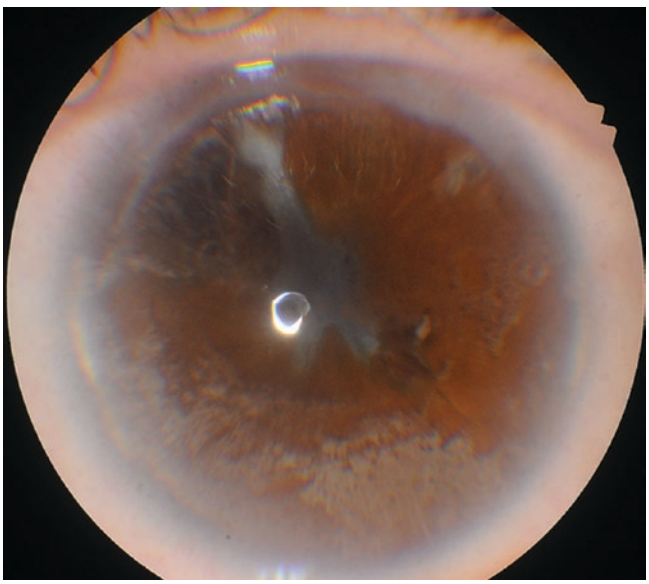

Fig. 10.13 Slit lamp photograph shows band keratopathy, seclusio pupillae, and secondary cataract associated in the more severely affected eye of a 5-year-old girl with bilateral pars planitis

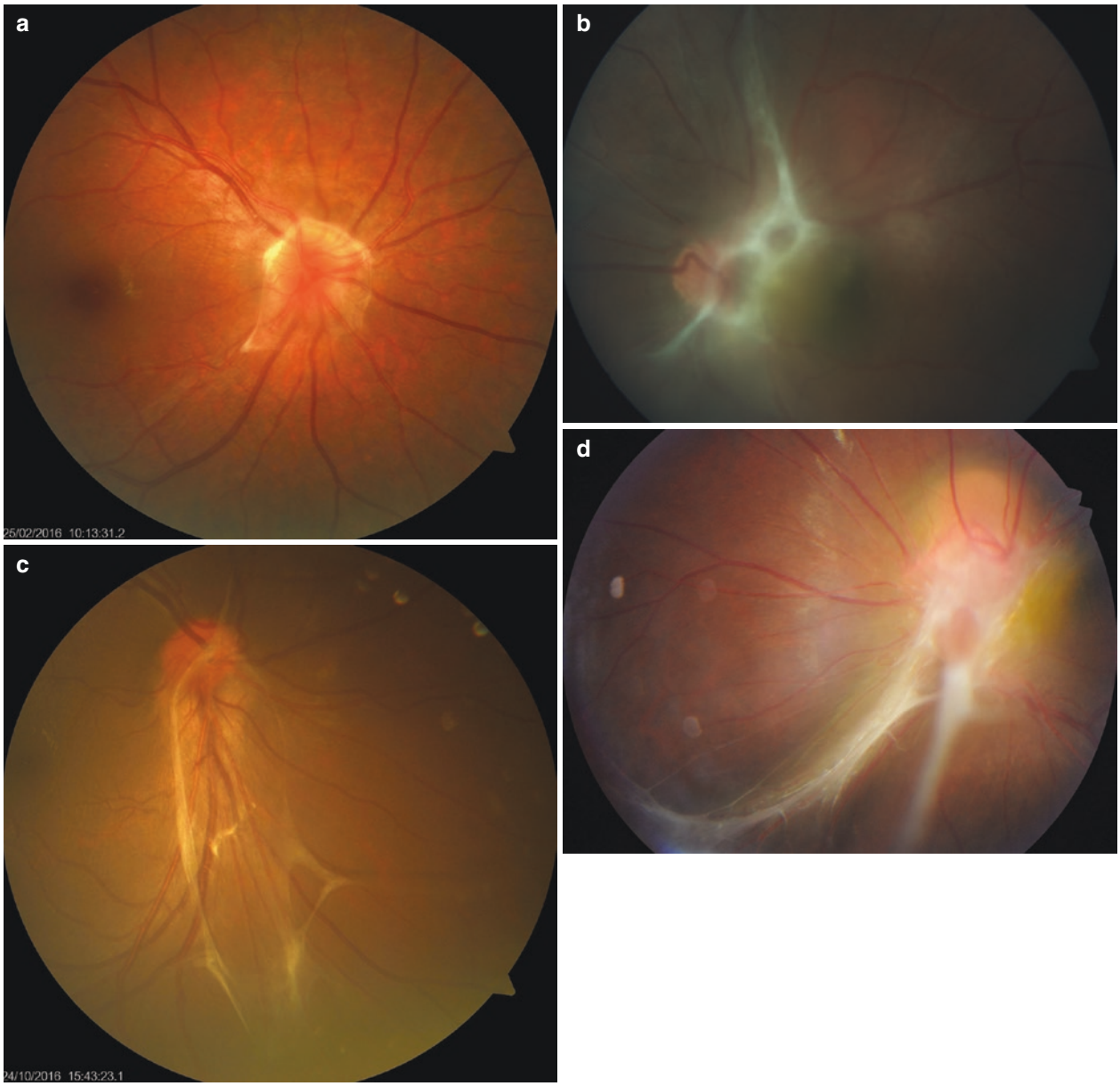

Fig. 10.14 (**a**–**d**) Fundus photographs showing various epiretinal membrane in intermediate uveitis

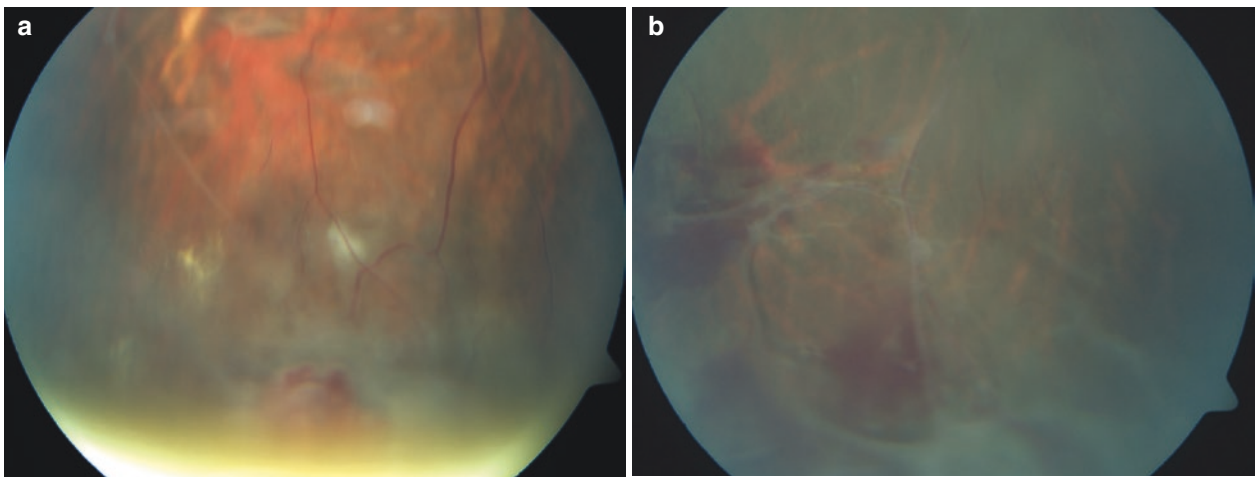

Fig. 10.15 Fundus photographs showing exudates, periphlebitis, snowballs, and neovascularization at the inferior peripheral retina (**a**) and vitreous bands and retinal hemorrhages from the neovascularizations (**b**) in pars planitis

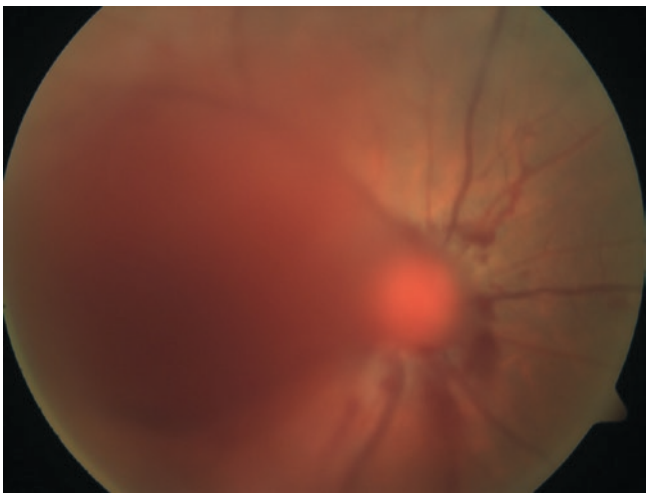

Fig. 10.16 Fundus photograph shows vitreous hemorrhage from the optic disc neovascularization

findings of sarcoidosis-associated IU (Babu and Rathinam 2010) (Fig. 10.21a, b). Pulmonary manifestations such as hilar lymphadenopathy, serum ACE and lysozyme levels, gallium scan, chest computed tomography, biopsy from conjunctival nodules or skin granuloma, bronchoalveolar lavage, and transbronchial lung biopsy are helpful in diagnosing sarcoidosis (Ozdal et al. 2015).

Multiple Sclerosis

About 20% of patients with IU have been shown to have MS. A strong association between pars planitis and MS has already been shown. Children with pars planitis may later develop MS during adolescence or in adulthood, and IU may be the first manifestation of MS (Fig. 10.22a, b). Thus, in the presence of clinical signs suggestive of MS such as prominent retinal periphlebitis with or without optic neuritis, a neurological evaluation, MRI of brain, and cerebrospinal fluid analysis should be performed (Ness et al. 2017; Raja et al. 1999). A granulomatous anterior uveitis accompanied by retinal periphlebitis is also highly suggestive of MS.

Tuberculosis

Mycobacterium tuberculosis may induce an intermediate uveitis with nonspecific clinical presentation or with clinical findings of pars planitis. A low-grade chronic inflammation, vitritis, snowball opacities, peripheral vascular sheathing, snow banking, and peripheral retinochoroidal granuloma may be observed. To make the differential diagnosis, accurate history, chest imaging, tuberculin skin test, and interferon gamma release assays are all helpful especially in

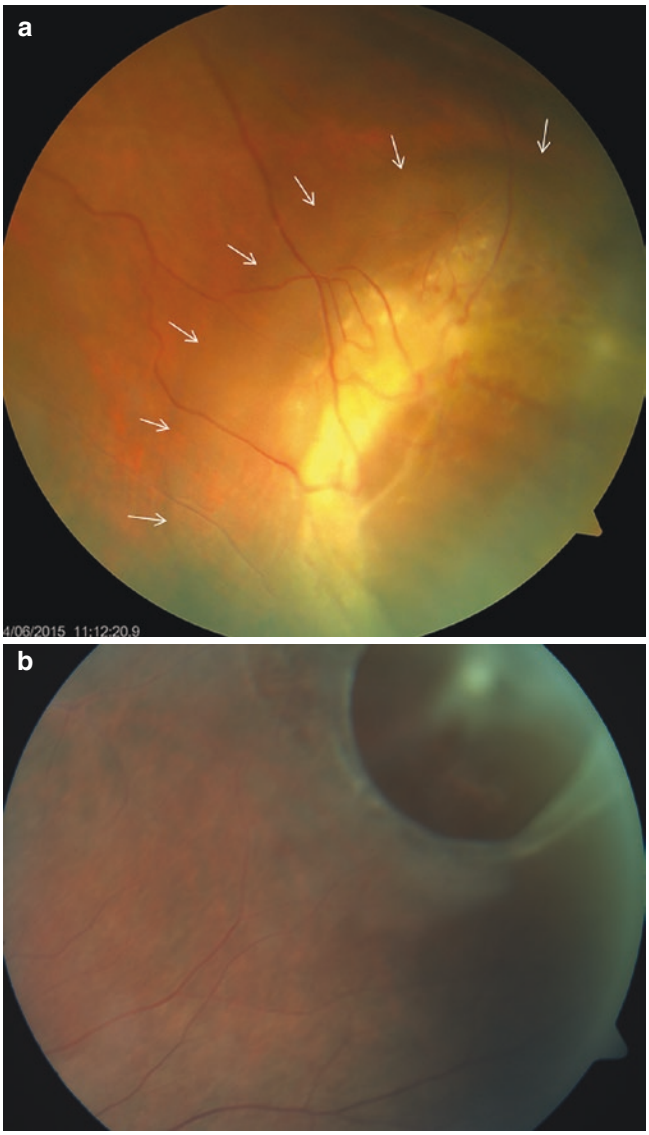

Fig. 10.17 (**a**, **b**) Fundus photographs showing retinal tear due to peripheral retinal traction and minimal subretinal fluid around the tear

patients living in endemic areas (Babu and Rathinam 2010; Gupta et al. 2015).

Syphilis

Syphilis may present with all anatomic types of uveitis. Anterior uveitis, both granulomatous and non-granulomatous, is the most common form of syphilitic uveitis. Intermediate uveitis has been observed in 10.3% of the cases (Anshu et al. 2008). Placoid retinitis, neuroretinitis, and retinal vasculitis are other common findings of syphilitic uveitis. The diagnosis of syphilis can be suggested by history and systemic and ocular examination and confirmed by serologic tests. Polymerase chain reaction (PCR) of ocular fluids may be performed when needed.

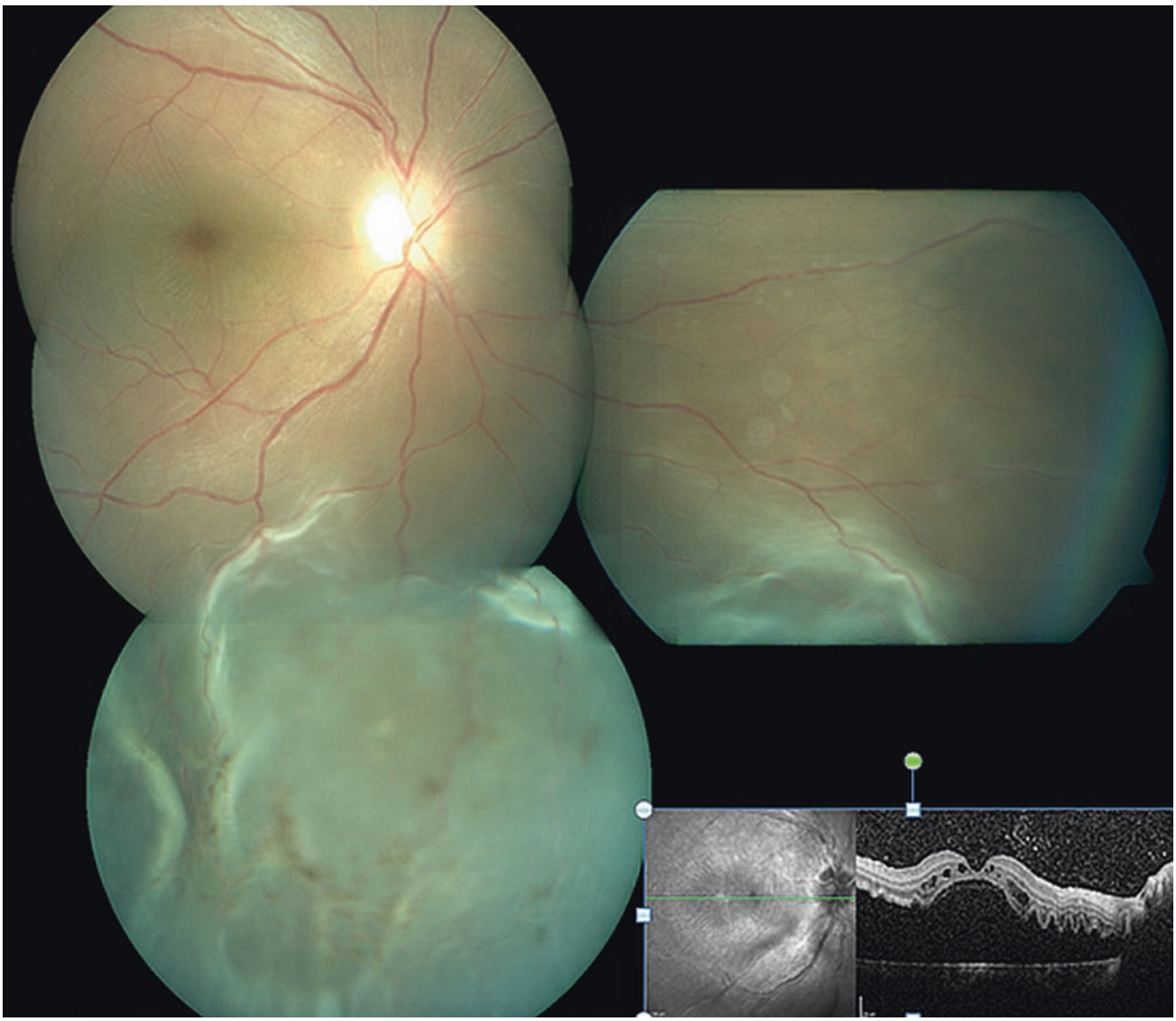

Fig. 10.18 Fundus photograph shows inferior exudative retinal detachment involving the macula. Optical coherence tomography confirms the macular detachment

Lyme Disease

Intermediate uveitis associated with Lyme disease caused by *Borrelia burgdorferi* has been reported in both adults and children (Babu and Rathinam 2010) (Fig. 10.23a–d). History of exposure to ticks, presence of rash and chronic arthritis, Lyme indirect immunofluorescence assay, and Lyme enzyme-linked immunosorbent assay are all helpful in the diagnosis (Whitcup 2010).

Other Rare Causes of Intermediate Uveitis

Serologic tests for cat-scratch disease, a gastroenterologic evaluation for inflammatory bowel disease in patients with a history of chronic or bloody diarrhea, should also be considered (Whitcup 2010). Ocular toxocariasis may present as unilateral IU and peripheral toxocara granuloma may sometimes be difficult to distinguish from snowbank of idiopathic pars planitis. Serology and UBM are valuable for the diagnosis of ocular toxocariasis (Ozdal et al. 2015).

Differential Diagnosis

In Children

As chronic anterior uveitis which is idiopathic or associated with juvenile idiopathic arthritis (JIA) has complications similar to pars planitis such as band keratopathy, posterior

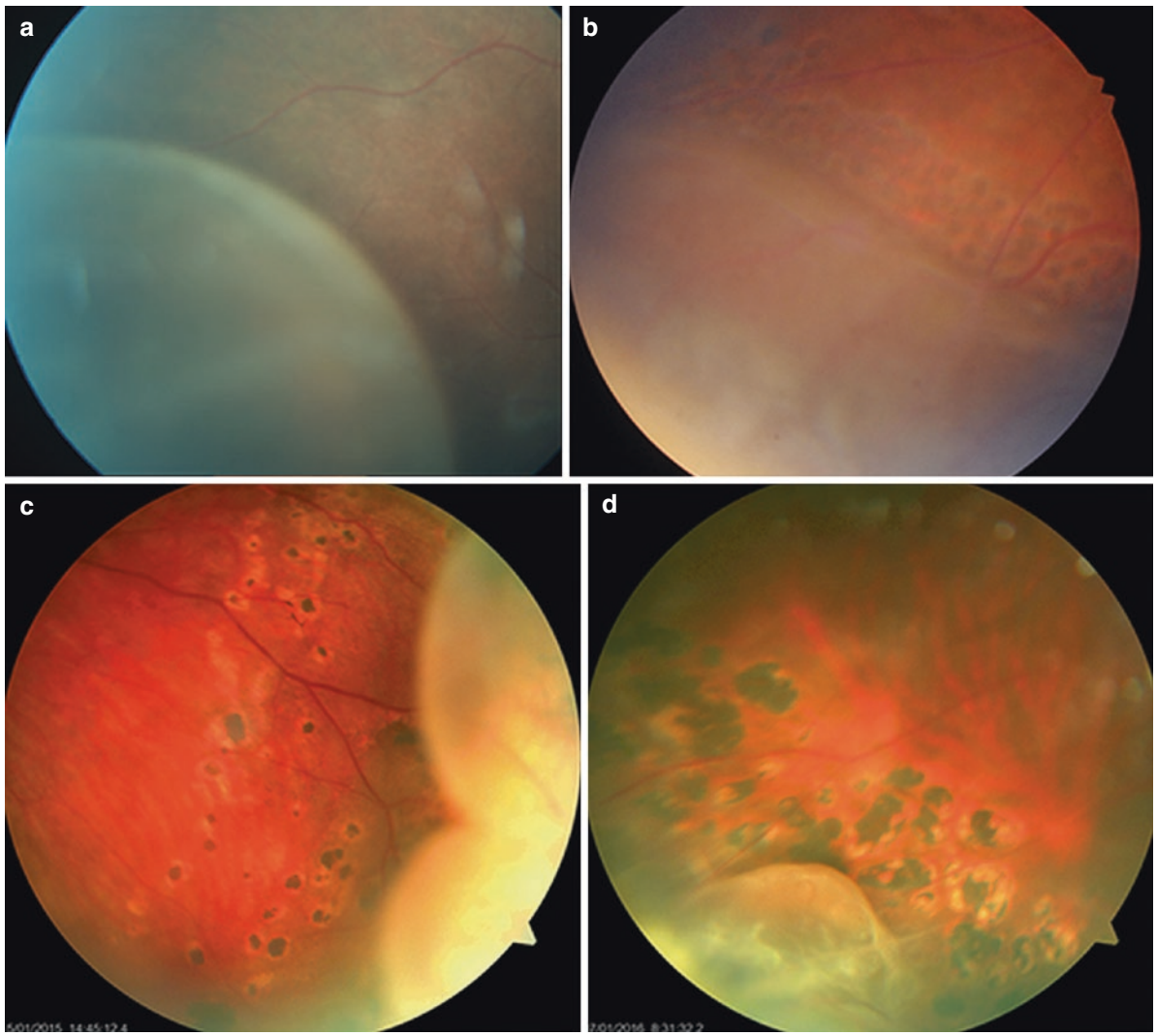

Fig. 10.19 (**a**–**d**) Fundus photographs show peripheral retinoschisis in different patients with pars planitis

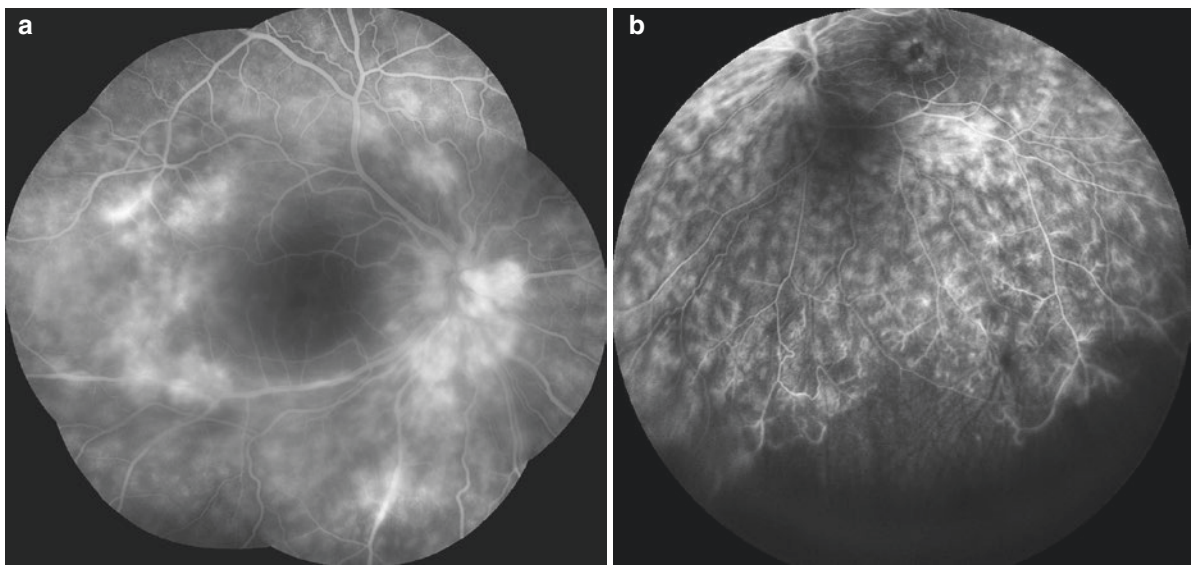

Fig. 10.20 Fluorescein angiography shows leakage from the veins, capillaries, and optic disc (**a**) and diffuse capillary and peripheral vascular leakage, macular edema, and inferior peripheral retinal ischemia (**b**) in pars planitis patients

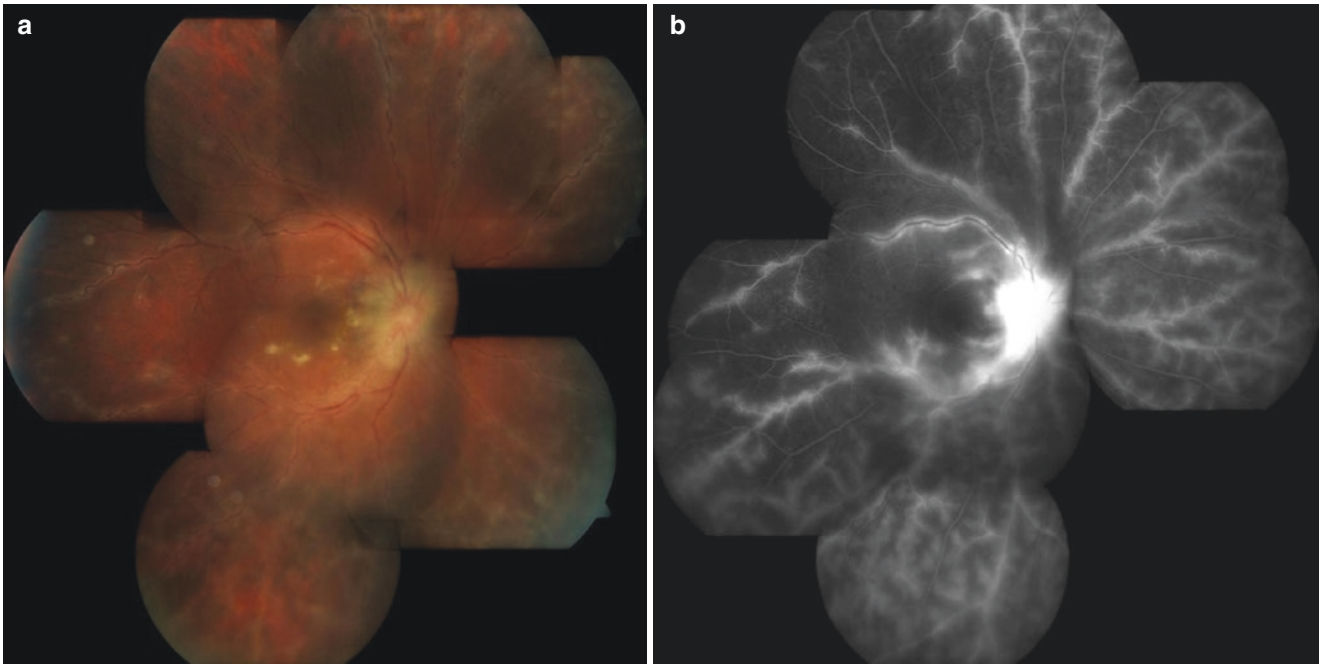

Fig. 10.21 Fundus photograph shows severe periphlebitis, snowballs, and optic disc edema (**a**) and diffuse vascular and optic disc leakage (**b**) in a patient with sarcoidosis

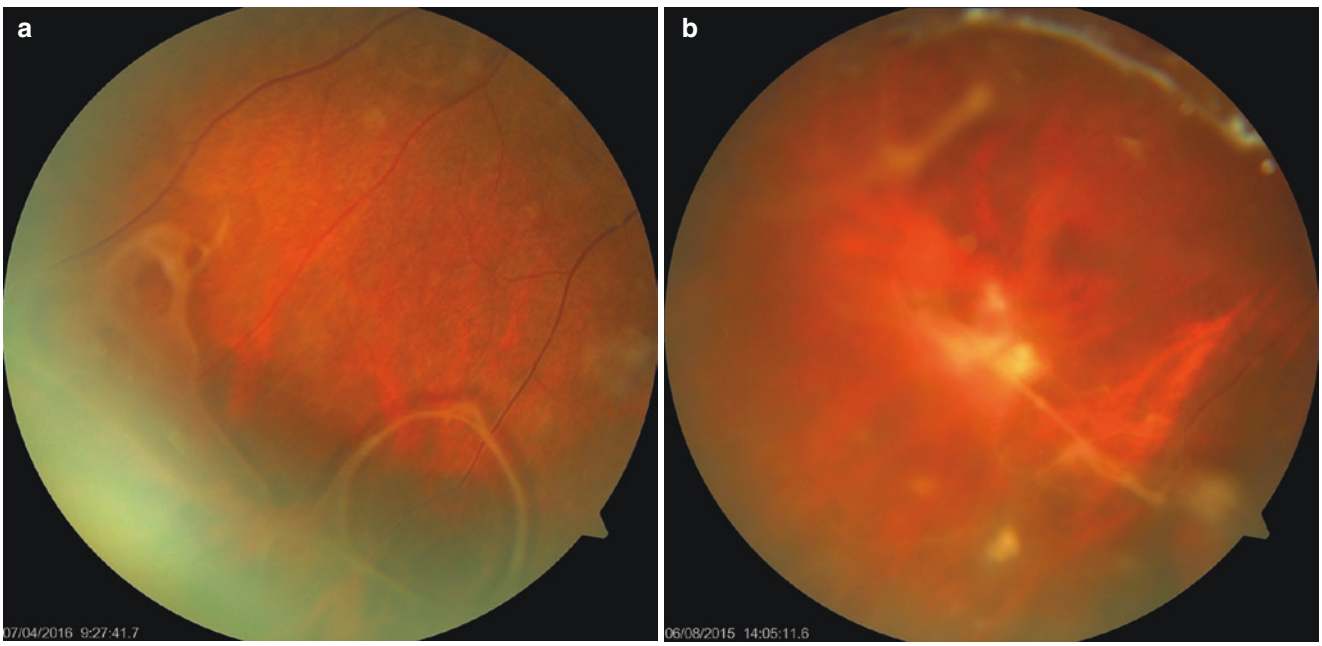

Fig. 10.22 Fundus photographs showing peripheral vitreous bands (**a**) and snowballs (**b**) in patients with multiple sclerosis-associated intermediate uveitis

synechiae, and cataract, these two entities should be differentiated. An attentive posterior segment evaluation is crucial in making the differentiation. Although rare, masquerades should also be considered in differential diagnosis of children presenting with pars planitis. Retinoblastoma may present as cellular reaction or white deposits in the anterior chamber and vitreous infiltrates. Diagnostic fine-needle aspiration biopsies are needed in such unusual cases (Ozdal et al. 2015).

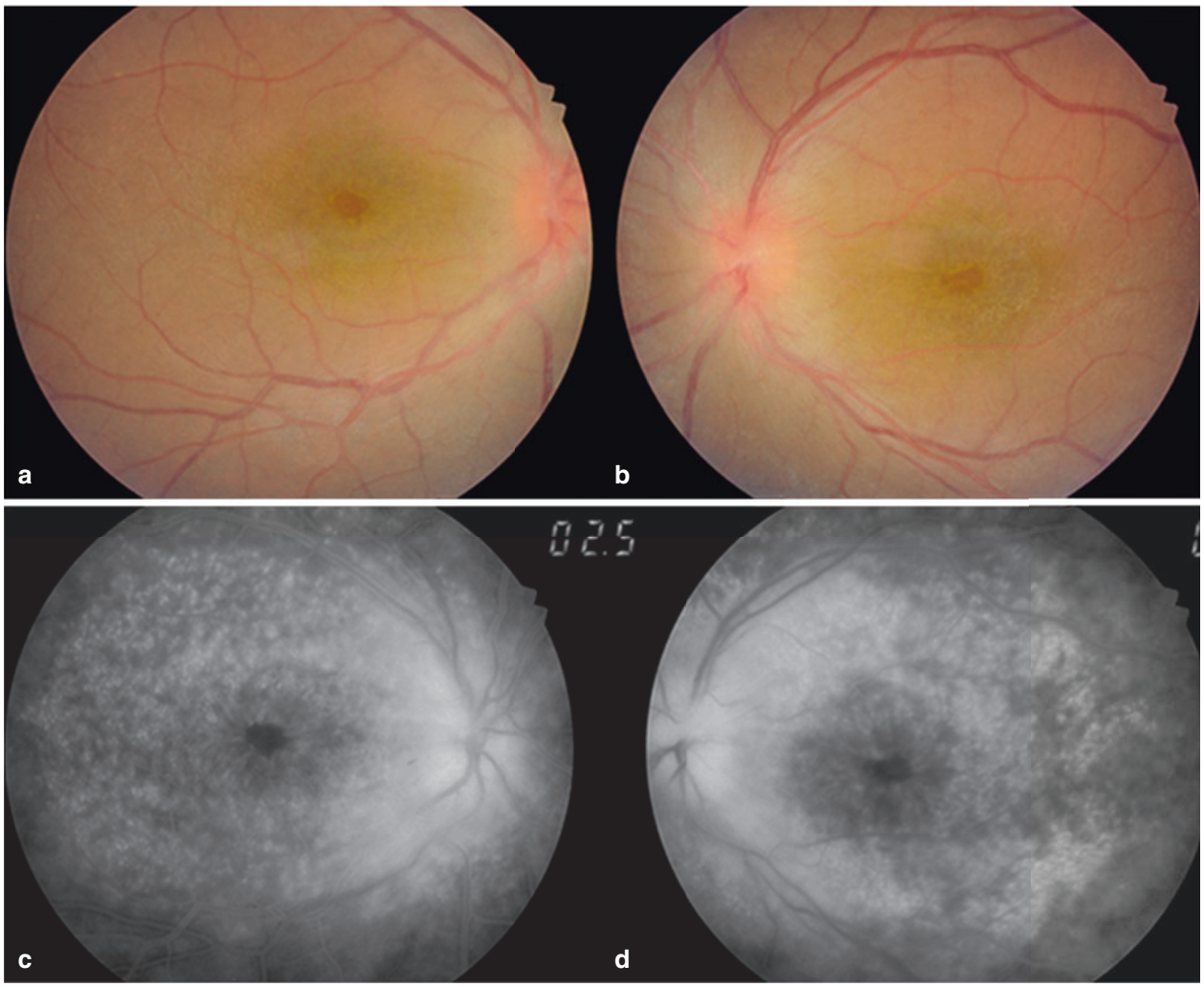

Fig. 10.23 Fundus photographs (**a**, **b**) show retinal vasculitis, cystoid macular edema, and optic disc edema, and fluorescein angiography (**c**, **d**) shows diffuse vascular leakage, optic disc, and macular edema in a patient with Lyme disease

In Adults

Inferior pearl-like precipitates occurring with the resolution of acute inflammatory attack in Behçet uveitis may lead to a misdiagnosis of pars planitis. Recurrent ocular inflammatory attacks, acute onset and spontaneous resolution of inflammation, appearance of inferior peripheral precipitates during resolution of vitreous haze, and absence of snowballs, snowbanks, or persistent vitreous condensates are typical characteristics of Behçet uveitis differentiating it from pars planitis. Pearl-like precipitates seen in Behçet uveitis are located on the surface of the retina and are small, uniform, and immobile (Fig. 10.24a, b), whereas snowball opacities are round, white collections located in the vitreous and are mobile (Tugal-Tutkun et al. 2013). Because of prominent vitreous infiltration and condensations, Fuchs' uveitis syndrome (FUS) should also be considered in the differential diagnosis of IU. Clinical findings of FUS including unilaterality, diffusely distributed small, round or stellate KPs, iris atrophy with or without heterochromia, and the absence of macular edema are helpful in making the differential diagnosis (Tugal-Tutkun et al. 2009) (Fig. 10.25a, b). In the elderly, primary intraocular lymphoma may present with diffuse vitreous infiltration, which may mimic intermediate uveitis. Not only severe vitreous inflammation but also poor or partial response to therapy is highly suggestive of primary intraocular lymphoma. As it is usually associated with primary central nervous system lymphoma, a brain MRI, cerebrospinal fluid analysis, and a careful neurologic history may provide useful information. However, cytological evaluation of vitreous samples, identification of cell surface markers by immunohistochemistry, cytokine analysis, retinal biopsy, and gene rearrangement are required for a definitive diagnosis of intraocular lymphoma. An elevated IL-10/IL-6 ratio in aqueous humor or vitreous is highly suggestive of intraocular lymphoma (Davis 2004).

Management

Exclusion of infectious and noninfectious associations which may present with intermediate uveitis is the most important step before starting a treatment. Infectious causes need a specific anti-infectious treatment. The treatment of pars planitis, how-

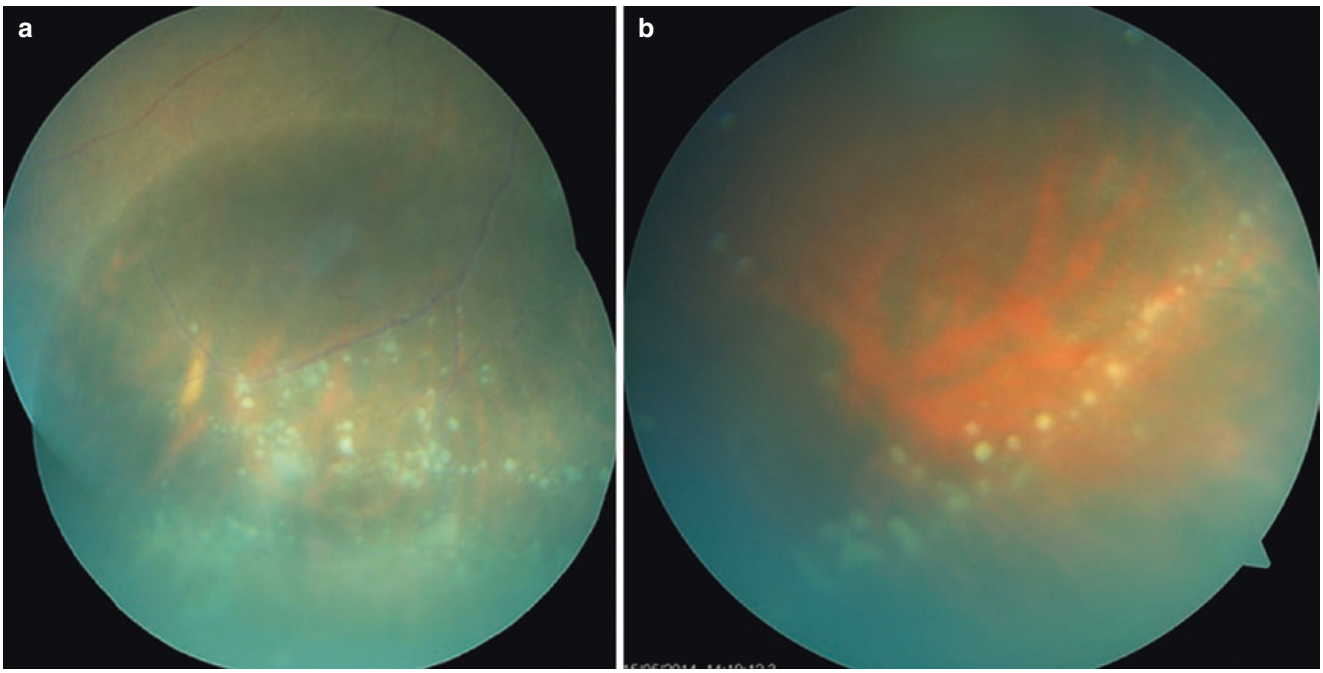

Fig. 10.24 (**a**, **b**) Fundus photographs show inferior pearl-like precipitates occurring with the resolution of acute inflammatory attack in Behçet uveitis in two different patients

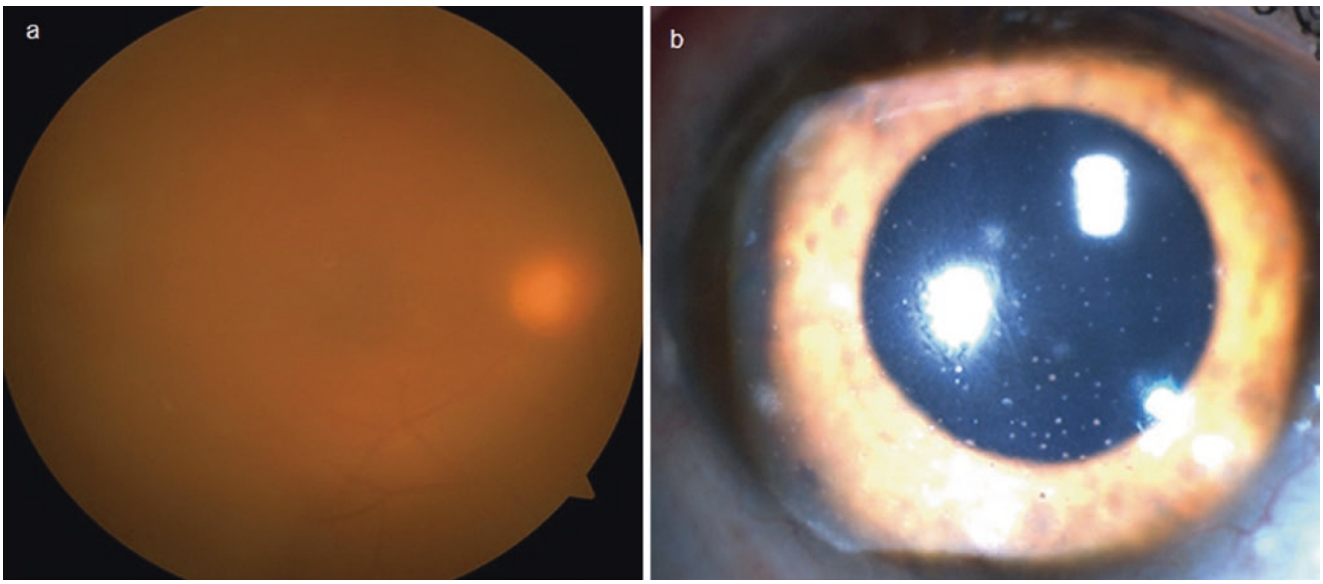

Fig. 10.25 (**a**, **b**) Fundus photograph shows severe vitreous haze in a patient with Fuchs uveitis, and the slit lamp photograph demonstrates diffusely distributed small, round keratic precipitates as a distinguishing feature

ever, is still a controversial issue. There is no consensus especially for cases with minimal inflammation and relatively good visual acuity. Pars planitis may present as a severe disease leading to several ocular complications and deserve an aggressive treatment. The presence of macular edema, vitreous haze leading to a decrease in visual acuity, complications such as band keratopathy, cataract or retinoschisis in at least one eye, vasculitis, and a severe infiltration of the pars plana are indications for treatment irrespective of the level of visual acuity. A stepladder approach is used while treating patients with pars planitis.

Medical Therapy

Corticosteroids: The first step of medical therapy includes corticosteroids (CS) which are still the mainstay of treatment. Topical CS are used only if there is anterior segment inflammation. Periocular CS injections are beneficial particularly in patients with unilateral or asymmetrical involvement and in the presence of macular edema. Posterior subtenon injection of 40 mg triamcinolone acetonide is the most frequently used method for employing periocular CS. Intravitreal CS injections

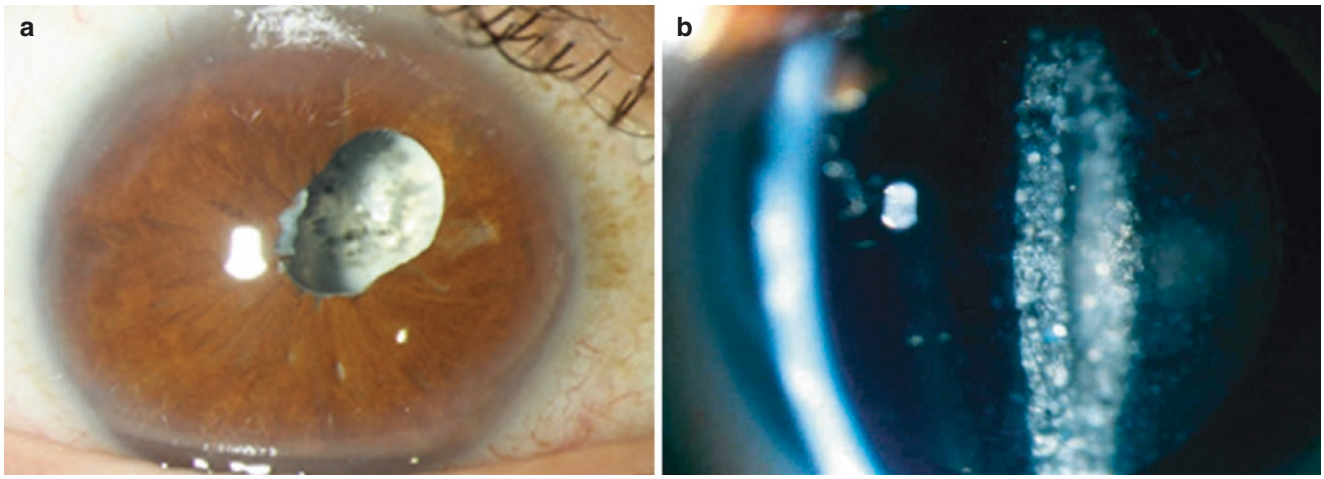

Fig. 10.26 Slit lamp photographs demonstrate severe posterior capsule opacification (**a**) and dense precipitates on the anterior and posterior surface of the intraocular lens forming a cocoon membrane (**b**) due to inadequate control of inflammation following cataract surgery

have also been found effective in treating intermediate uveitis and associated macular edema. The most common complications of periocular CS are increased intraocular pressure, cataract, and aponeurotic ptosis, and the most common complications of intravitreal CS injections are cataract, increased intraocular pressure, and glaucoma, while rare complications include vitreous hemorrhage, retinal detachment, and endophthalmitis. Because of these high complication rates, intravitreal CS injections should be used as an emergency procedure to save the macula immediately and allow time to organize the long-term management (Ozdal et al. 2015). Intravitreal dexamethasone implant has been shown to be effective and safe particularly in persistent chronic CME and vitritis due to noninfectious intermediate uveitis (Lightman et al. 2013; Palla et al. 2015). In patients with bilateral involvement, severe ocular inflammation or unilateral disease unresponsive to periocular, systemic CS treatment should be considered. A dose of 1–1.5 mg/kg/day of prednisone tapered according to clinical response is preferred by most uveitis specialists. Intravenous pulse methylprednisolone therapy (1 g/day for adults, 30 mg/kg/day for children) may be administered when more rapid and potent action is needed.

Immunosuppressive agents: Steroid-sparing immunosuppressive therapy should be considered as a second step in patients who require long-term treatment. Methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine may be used alone or in combination. Because of its long-term safety profile and well tolerance, methotrexate is the most widely used first-line immunosuppressive agent in children. It is of importance to remember that these agents need 4–8 weeks to become effective and CS should be given concomitantly until the immunosuppressive agent is expected to take action. In patients who present with serious ocular complications, immunosuppressive agents and CS combination may be started as the first step.

Biologic agents: In patients not responding to conventional immunosuppressive agents, anti-tumor necrosis factor-α (Anti-TNF-α) agents should be used as the third step of medical therapy. The use of these agents in refractory ocular inflammation including patients with intermediate uveitis suggests promising efficacy (Ozdal et al. 2015). As pars planitis is associated with an increased risk for MS development and anti-TNF-α agents may potentiate demyelinating disease, extreme caution is needed before starting such therapy in patients with pars planitis (Kump et al. 2013). Interferon-beta has also been shown to be effective in improving macular edema and vitreous haze due to intermediate uveitis (Mackensen et al. 2013).

Surgical Therapy

Pars plana vitrectomy comprises the fourth step of therapy. It should be considered particularly in patients developing complications such as vitreous condensation, vitreous hemorrhage, retinal detachment, and epiretinal membranes causing retinal traction. Surgical therapy has also been shown to be effective in patients with active inflammation and CME refractory to medical treatment (Stavrou et al. 2001). Pars plana vitrectomy provides the mechanical clearance of inflammatory mediators and debris, anatomical correction of retinal pathology such as vitreoretinal traction, opportunity to obtain vitreous samples and reduction of postoperative anti-inflammatory medication (Babu and Rathinam 2010; Stavrou et al. 2001). Cataract surgery may be safe when an adequate preoperative and postoperative inflammation control and a meticulous surgical technique are employed. If not, severe postoperative complications are inevitably encountered (Fig. 10.26a, b).

Adjunctive Therapies

Cryotherapy may aggravate blood–ocular barrier disruption and accelerate the rate of retinal detachment in predisposed eyes by inducing vitreous contraction (Kump et al. 2013). Compared to cryotherapy, laser photocoagulation is an easier and safer method with fewer ocular complications. However, it should not be considered as a treatment step alone but may be employed as an adjunctive treatment modality especially in cases associated with peripheral neovascularization, retinal traction, or retinoschisis.

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Sarcoidosis

11

Hiroshi Takase

Introduction

Sarcoidosis is a chronic inflammatory disease of unknown etiology characterized by the formation of noncaseating epithelioid granuloma in multiple systemic organs such as lung, lymph nodes, eyes, or skin. The other organs including heart, liver, bones, salivary glands, nervous, or muscles are also affected but the incidences are much less. Among all sarcoidosis patients, about 40–50% of the patients develop ocular complications including granulomatous uveitis (Obenauf et al. 1978; Jabs and Johns 1986; Ohara et al. 1992). The ocular symptoms such as photophobia, blurred vision, or floaters, often appear as the first symptoms of sarcoidosis. Although the etiology of sarcoidosis is not known yet, systemic cellular immune responses against certain microbes such as *Mycobacterium tuberculosis* (Fang et al. 2016), *Propionibacterium acnes* (Ishige et al. 2005; Negi et al. 2012), or *mumps virus* (Uzun et al. 2004) are hypothesized to be the causative antigen to form granulomas in sarcoidosis. Most frequently affected ages by sarcoidosis distribute between the third to fifth decade of life in both genders, and elderly women are also affected (Silver and Messner 1994). Sarcoidosis is currently the most frequent cause of uveitis in Japan (Ohguro et al. 2012), but it is not the case in other countries including neighboring Asian countries. In general, African American, Asian, and South Americans are often affected by sarcoidosis, while Caucasian people are less affected.

The gold standard to diagnose sarcoidosis is histopathological proof of noncaseating epithelioid granuloma, but biopsy is essentially not possible to perform using intraocular tissues, and biopsy in other organs could not easily be done because it is invasive procedure especially for the patients who do not have systemic symptoms other than the eye. Therefore, diagnosis of sarcoidosis is usually performed based on a combination of clinical intraocular signs and systemic investigational tests. In 2006, the first international workshop on ocular sarcoidosis (IWOS) was held, and the international diagnostic criteria for ocular sarcoidosis (IWOS criteria) were established (Herbort et al. 2009). These criteria were revised in 2017, but the intraocular clinical signs included in both criteria are identical as described in the next section.

Clinical Features

The intraocular clinical features suggestive of sarcoidosis described in IWOS criteria are: mutton fat keratic precipitates and/or iris nodules at the pupillary margin (Koeppe) or in the stroma (Busacca), trabecular meshwork nodules and/or tent-shaped peripheral anterior synechia, snowball/string of pearls vitreous opacities, multiple chorioretinal peripheral lesions (active and atrophic), nodular and/or segmental periphlebitis and/or macroaneurysm in an inflamed eye, optic disc nodule/granuloma and/or solitary choroidal nodule, and bilaterality assessed by clinical examination showing subclinical inflammation (Herbort et al. 2009) (Table 11.1). The granulomatous signs in the anterior segment can easily be diminished by local steroid therapy, so it is very important to actively look

Table 11.1 Clinical signs suggestive of ocular sarcoidosis by IWOS criteria (Herbort et al. 2009)

1.	Mutton-fat KPs (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Busacca)
2.	Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
3.	Snowballs/string of pearls vitreous opacities
4.	Multiple chorioretinal peripheral lesions (active and atrophic)
5.	Nodular and/or segmental periphlebitis (± candlewax drippings) and/or macroaneurysm in an inflamed eye
6.	Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
7.	Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)

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for the signs of granuloma in every tissue of the eye before initiating steroid treatment using slit lamp biomicroscopy, gonioscopy, indirect fundoscopy, and other imaging tools such as fluorescein or indocyanine green angiography (FA, ICGA) or optical coherence tomography (OCT).

Retinal and Choroidal Involvements

Multiple chorioretinal lesions are regarded to be the sign of retinal or choroidal granuloma which appears to be yellowish-white lesions in its active phase. The lesions in the shallow layer of the retina look similar to the scars of laser photo coagulation in its atrophic phase (Fig. 11.1). Only a few chorioretinal lesions sometimes appear (Fig. 11.2a), while a number of lesions are sometimes observed in a close formation (Fig. 11.2b).

Retinal lesions also appear as yellowish subretinal exudative lesions (Fig. 11.3), and FA shows mottled hyperfluorescence in the corresponding area (Fig. 11.4). Although the other area of the retina looks normal, FA sometimes shows extensive hyperfluorescence in the retina or the retinal veins.

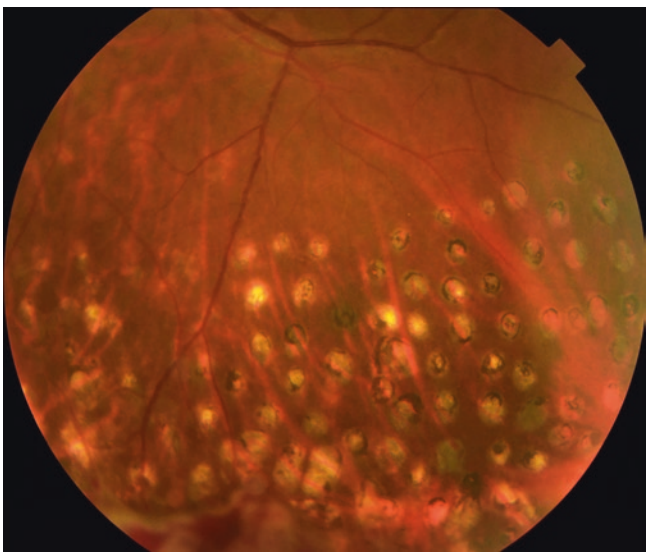

Fig. 11.1 Chorioretinal lesions composed of fresh yellowish-white lesions and atrophic laser-scar like lesions in the peripheral retina

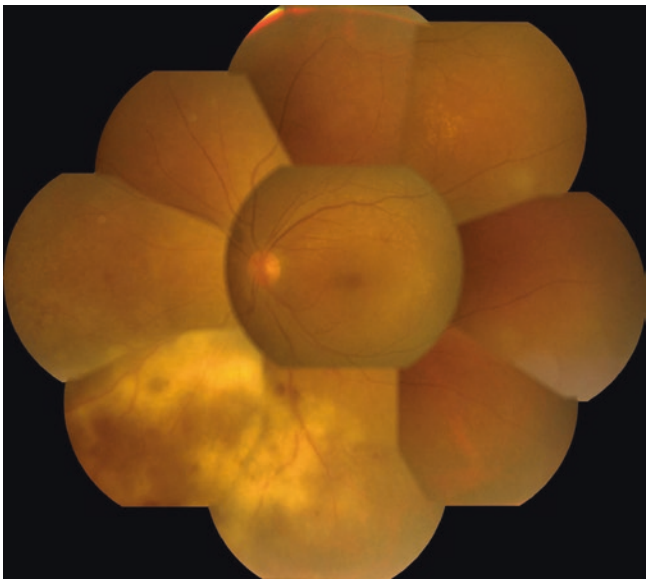

Fig. 11.3 Subretinal yellowish exudative lesions in the nasal-inferior part of the retina

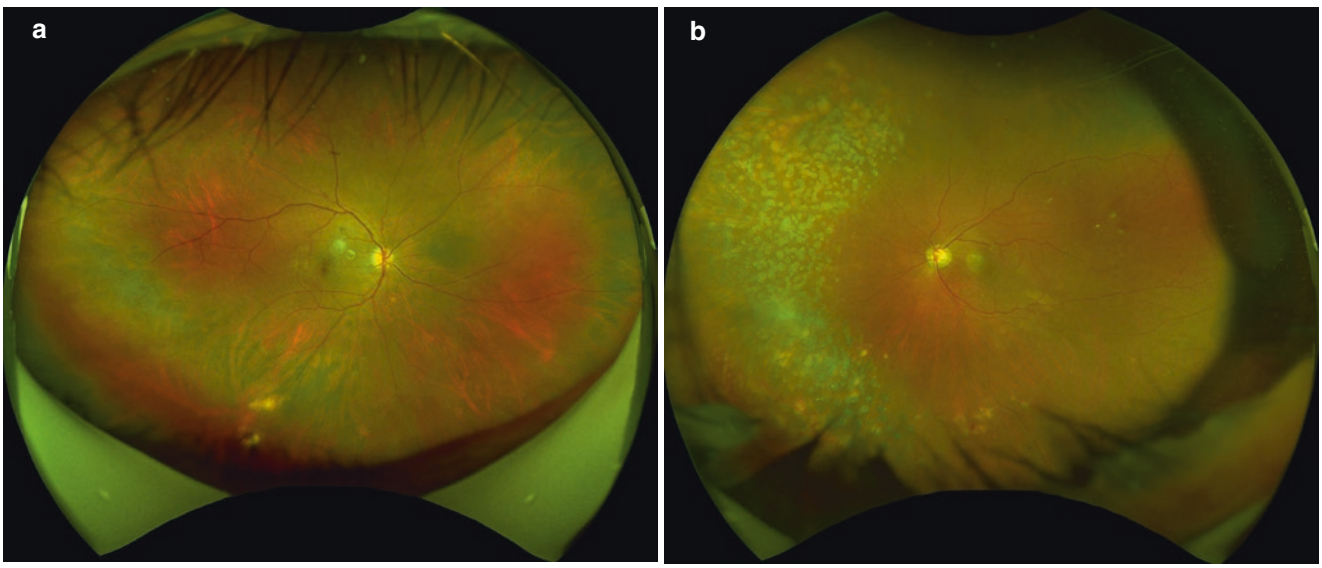

Fig. 11.2 (**a**) A few yellowish-white chorioretinal lesions are seen in the inferior part of the retina. (**b**) A number of chorioretinal lesions seen in close formation in the nasal part of the retina

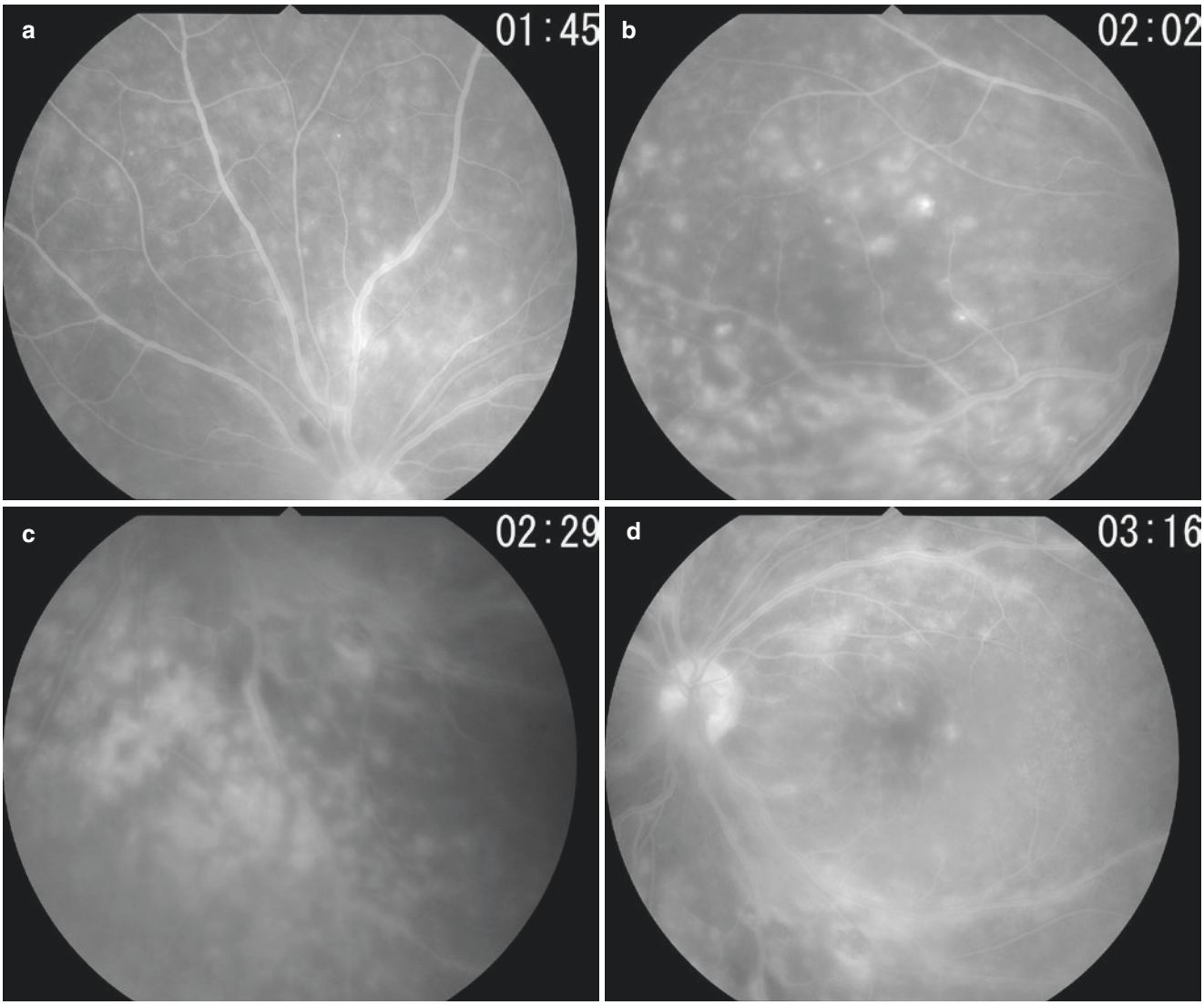

Fig. 11.4 Fluorescein angiography (FA) shows mottled hyperfluorescence corresponding to the subretinal exudative lesions (**a**–**d**). Although the other area of the retina looks basically normal in the color fundus photo (Fig. 11.3), FA shows small patchy hyperfluorescence in the whole fundus and segmental hyperfluorescence in the retinal vein

The chorioretinal lesions can present in the deeper layer of the retina or in the choroid (Fig. 11.5a). While FA does not detect such lesions, ICGA can show the presence of the chorioretinal lesions in the deeper layers as multiple hypofluorescence dots (Fig. 11.5b, c).

Choroidal granuloma is a rare form of intraocular sign of sarcoidosis. It is observed as subretinal yellowish lesion with dull margin (Fig. 11.6a). Ultrasound imaging shows the elevated lesion (Fig. 11.6b), and OCT shows the thickened choroid and elevated RPE (Fig. 11.6c). OCT also detects the subretinal infiltrates, and this may be shown as hyperfluorescein area by FA (Fig. 11.6d). ICGA shows broadly distributed dark spots, and choroidal folds surrounding the granuloma (Fig. 11.6e). Optic disc nodule also is a rare form of intraocular sign of sarcoidosis (Fig. 11.7). The specificity of choroidal granuloma and optic disc nodule is high in patients with sarcoidosis when compared to other types of uveitis (Takase et al. 2010; Acharya et al. 2018). Choroidal granuloma eventually causes chorioretinal atrophy and retinal pigment epithelium degeneration (Figs. 11.8 and 11.9).

Retinal Vascular Involvements

Sarcoidosis affects retinal veins as perivascular exudates, so-called candle-wax drippings, along with the retinal vein (Fig. 11.10a), or segmental nodular periphlebitis along with the retinal vein (Fig. 11.11a). FA shows diffuse hyperfluorescence in the perivascular exudates (Fig. 11.10b), while FA shows segmental hyperfluorescence in the nodular periphle-

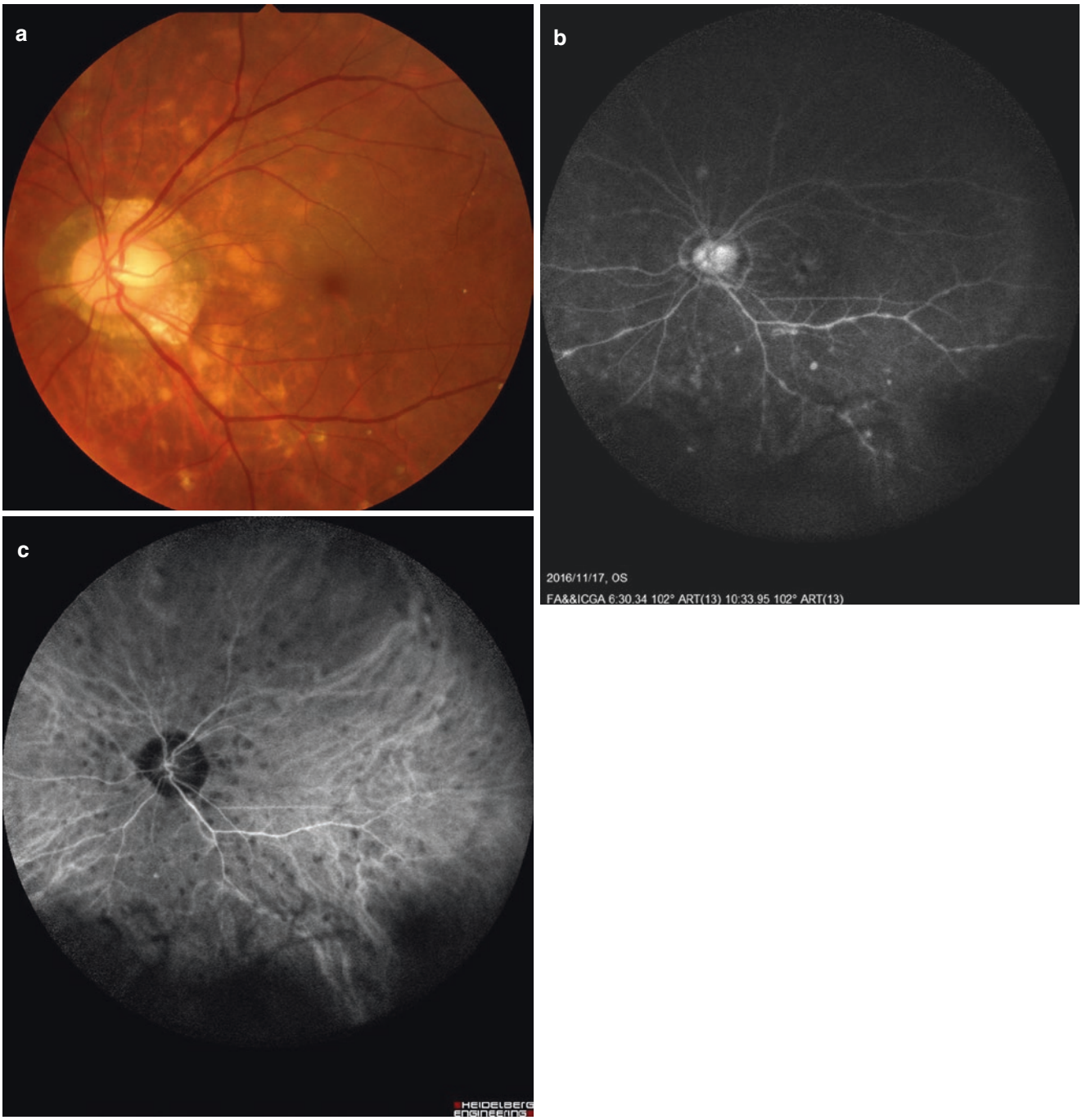

Fig. 11.5 (**a**) The chorioretinal lesions in the deeper layer of the retina or in the choroid are seen in the posterior pole. (**b**) Fluorescein angiography does not detect the chorioretinal lesions in the deep layer of the retina or in the choroid, but show some hyperfluorescein dots corresponding to the chorioretinal lesions in the shallow layer of the retina. Segmental hyperfluorescein are seen in the temporal-inferior retinal vein. (**c**) Indocyanine green angiography can show the presence of the chorioretinal lesions in the deeper layers as multiple hypofluorescence dots

bitis (Fig. 11.11b). Severe sheath formation of the retinal vein can also be seen although it is relatively rare (Fig. 11.12a). Fluorescein angiography shows diffuse hyperfluorescence in the corresponding retinal vein (Fig. 11.12b). Even when retinal periphlebitis is absent or just faint nodular periphlebitis is seen, FA sometimes shows nodular hyperfluorescence more than expected from the appearance of the fundus (Fig. 11.13). As for retinal artery involvement, macroaneurysm accompanied with intraocular inflammation is sometimes seen (Fig. 11.14).

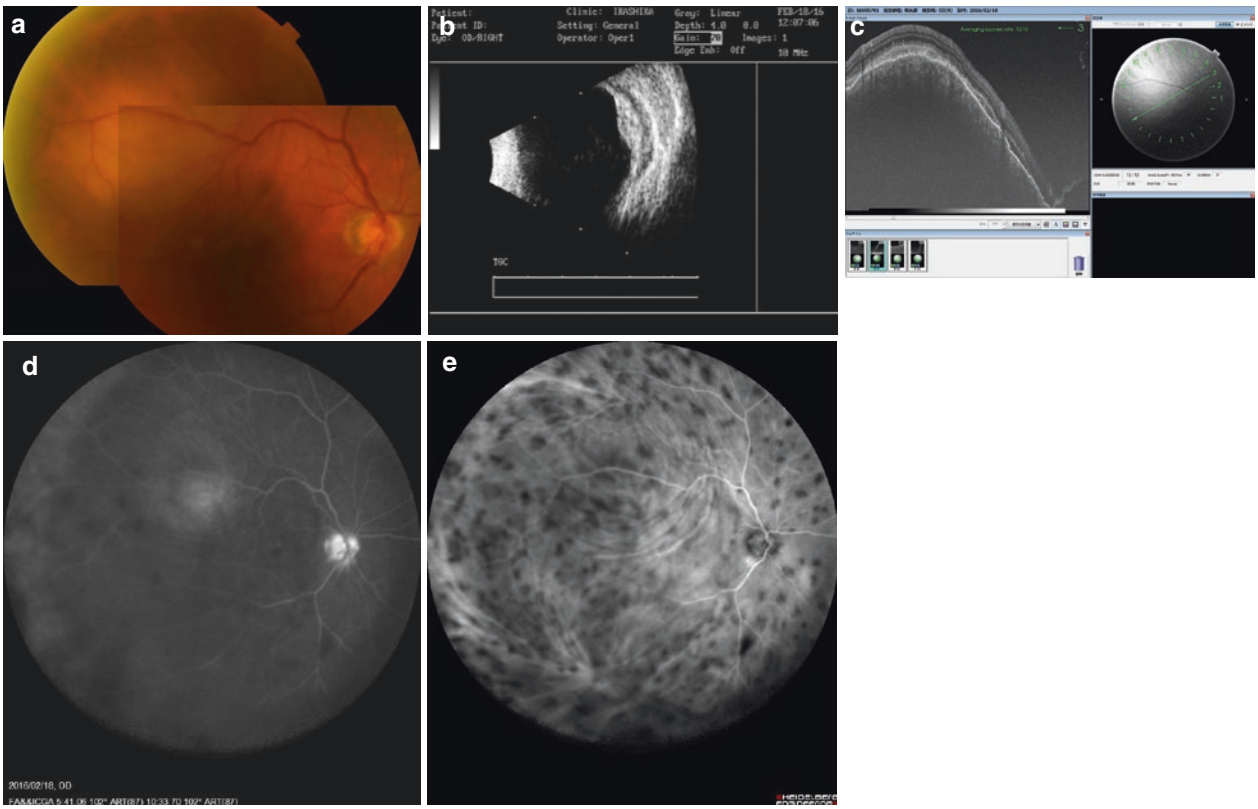

Fig. 11.6 (**a**) Choroidal granuloma is observed as subretinal yellowish lesion with dull margin. (**b**) Ultrasound imaging shows the elevated lesion corresponding to the choroidal granuloma. (**c**) Optical coherence tomography shows the thickened choroid, elevated RPE corresponding to the choroidal granuloma, and subretinal infiltrates. (**d**) The area of subretinal infiltrates corresponding to the choroidal granuloma is shown as hyperfluorescein area by fluorescein angiography. (**e**) Indocyanine green angiography shows broadly distributed dark spots, and choroidal folds surrounding the granuloma

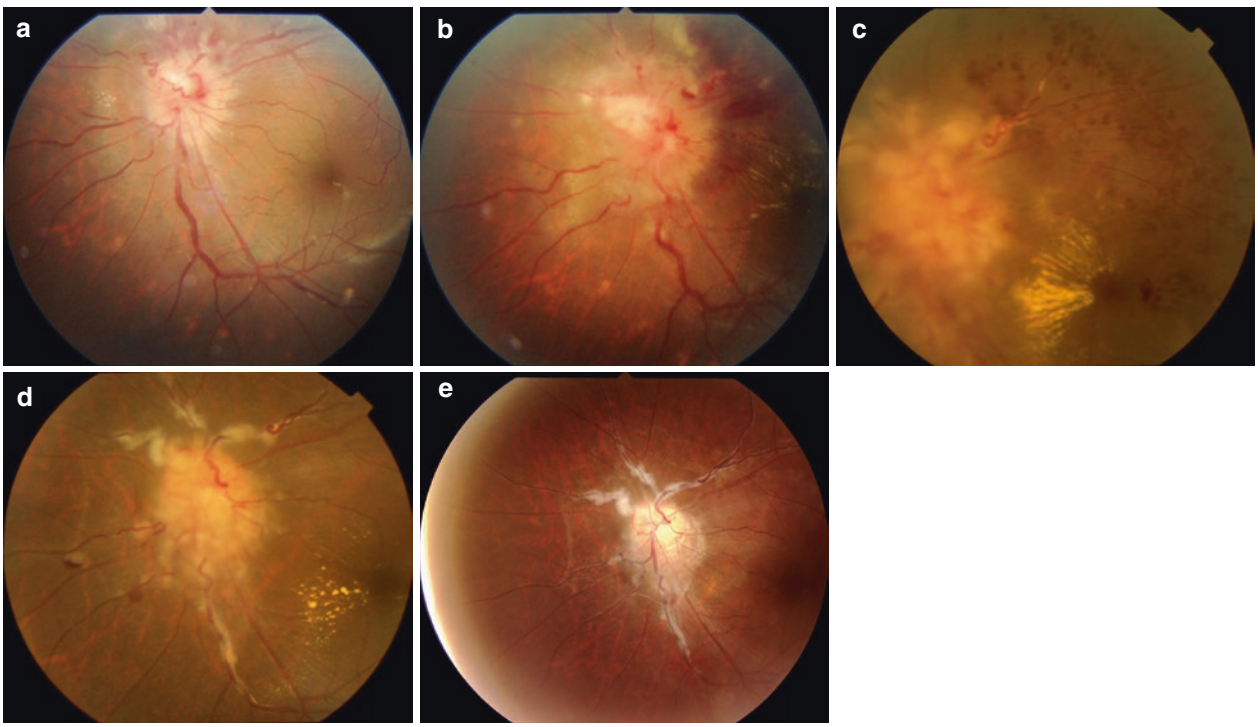

Fig. 11.7 Serial color photos of the optic papillitis from its occurrence (**a**) to remission (**e**). Following the inferior retinal vasculitis (**a**), optic disc edema (**b**) and multiple nodules occurred (**c**). After steroid pulse therapy and oral prednisolone, the optic edema improved (**d**), and the nodules disappeared (**e**)

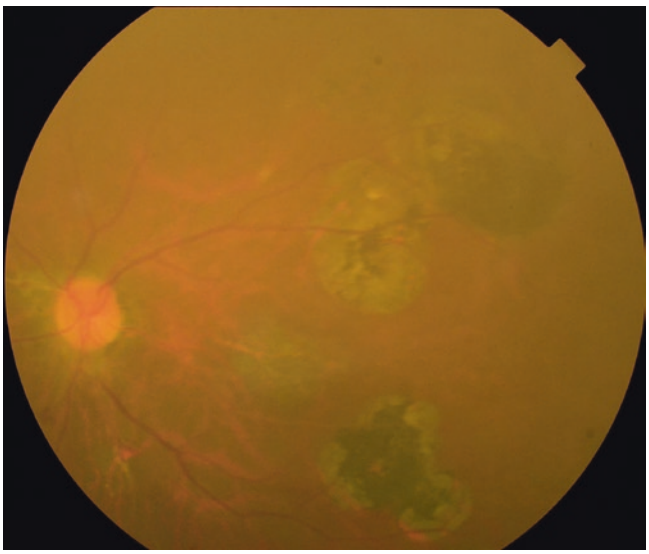

Fig. 11.8 Patchy subretinal atrophic lesions and retinal pigment epithelium degenerations are seen in the nasal part of the retina

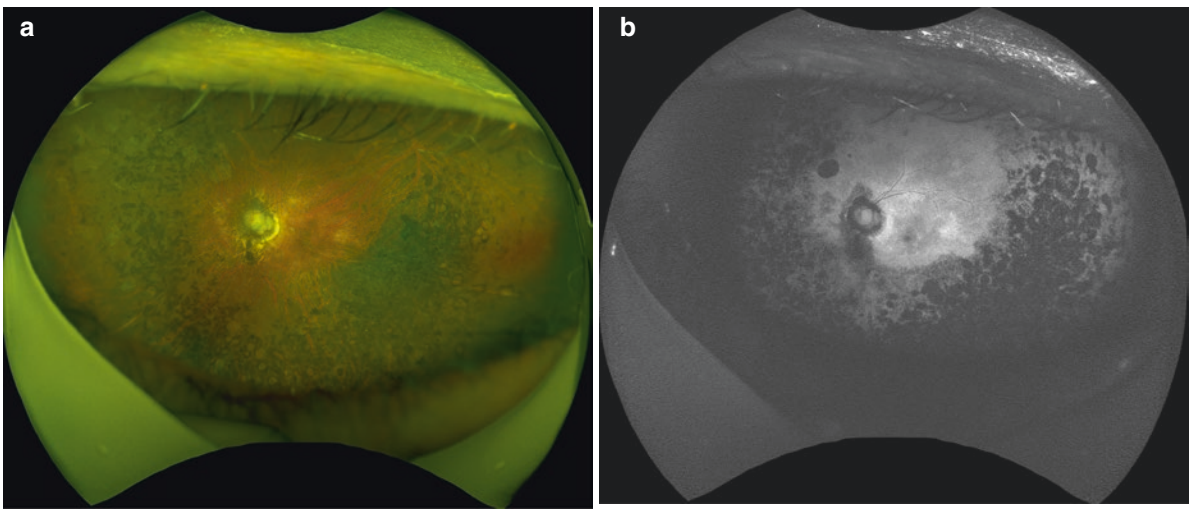

Fig. 11.9 (**a**) Broadly distributed chorioretinal degenerations as well as retinal pigment epithelium (RPE) degenerations are observed. (**b**) Fundus autofluorescence shows the degenerative RPE as mottled hypoautofluorescence area

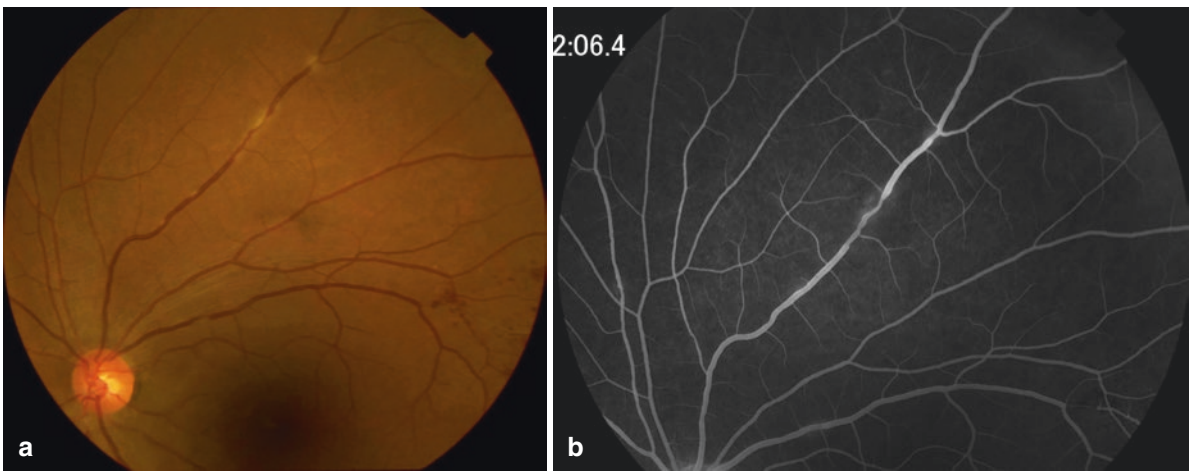

Fig. 11.10 (**a**) Perivascular exudates, so-called candle-wax drippings, are seen along with the retinal vein. (**b**) Fluorescein angiography shows diffuse hyperfluorescence in the corresponding area

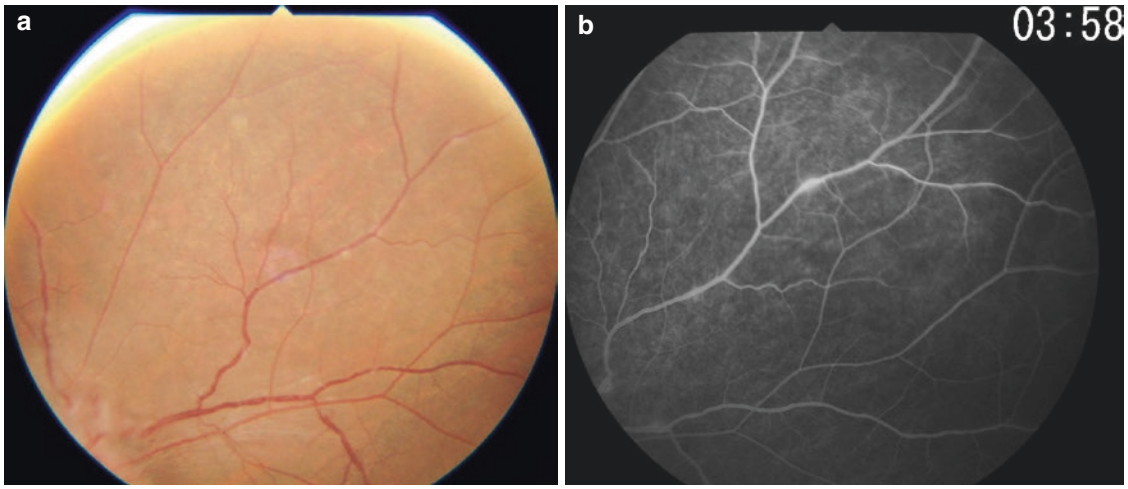

Fig. 11.11 (**a**) Nodular periphlebitis are seen along with the retinal vein. (**b**) Fluorescein angiography shows segmental hyperfluorescence in the corresponding area

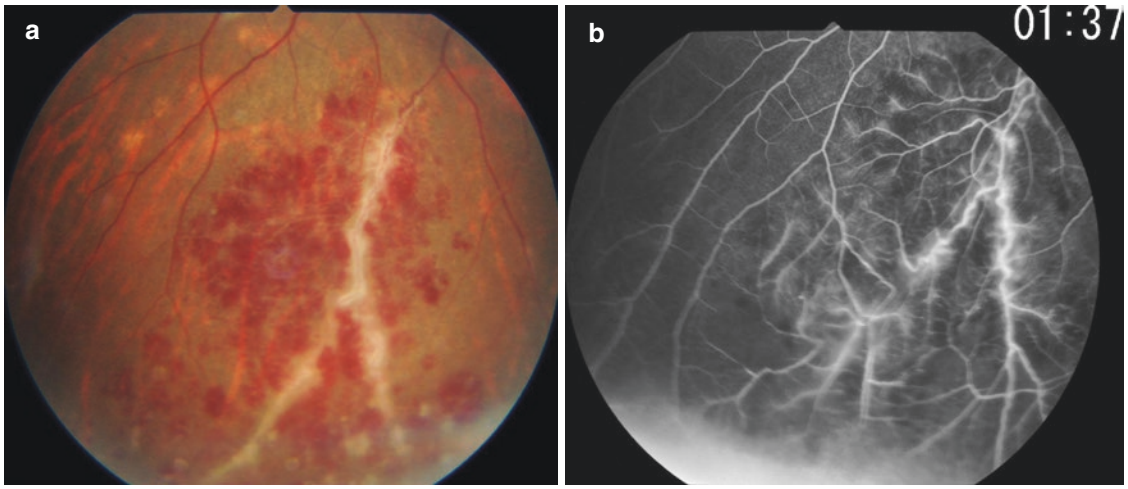

Fig. 11.12 (**a**) Severe sheath formation of the retinal vein surrounded by retinal hemorrhage. (**b**) Fluorescein angiography shows diffuse hyperfluorescence in the corresponding retinal vein

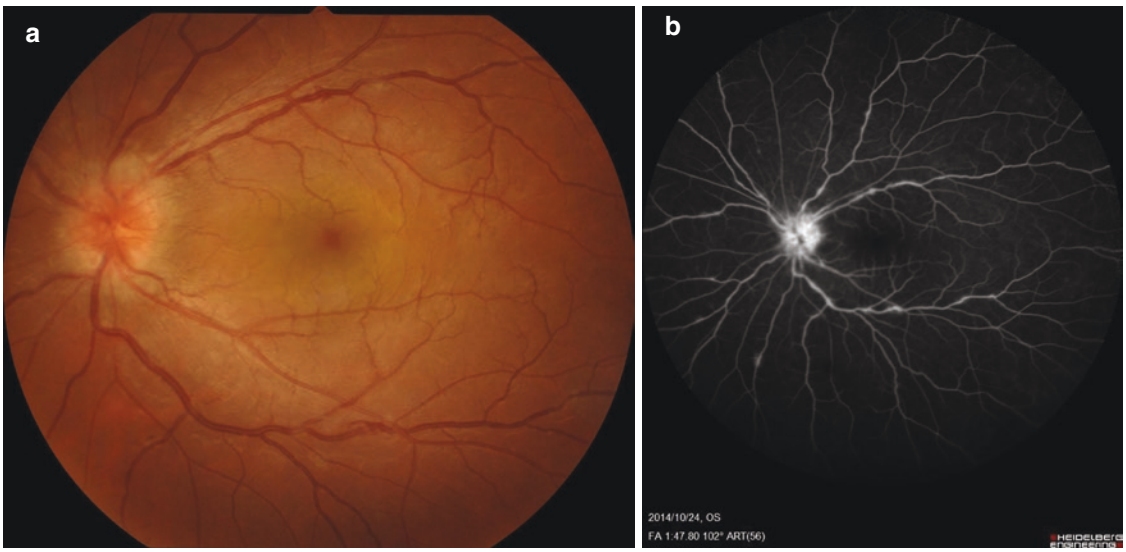

Fig. 11.13 (**a**) Optic disc swelling and only faint nodular periphlebitis are seen. (**b**) Fluorescein angiography shows nodular hyperfluorescence more than expected from the appearance of color fundus photo

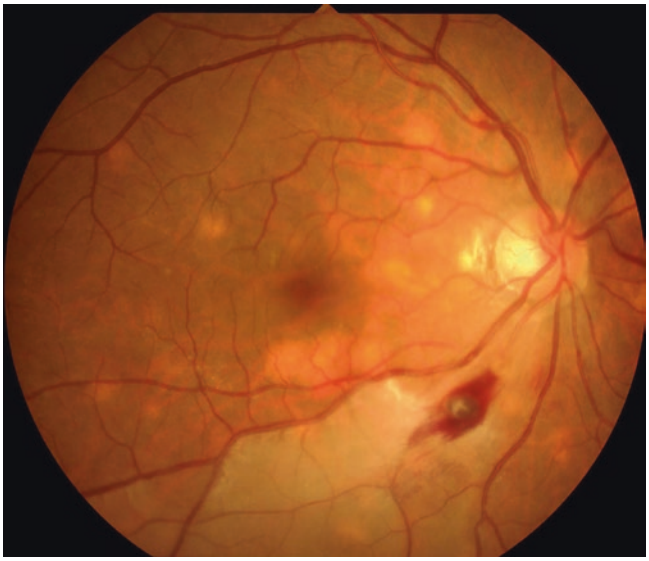

Fig. 11.14 A macroaneurysm is seen along with the temporal-inferior retinal artery. The peripheral retina is edematous suggesting the decreased retinal artery perfusion. Chorioretinal lesions in the deep layer of the retina are also present in the posterior pole

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Behçet Disease

12

Nobuyoshi Kitaichi, Kenichi Namba, and Shigeaki Ohno

Introduction

Behçet disease (BD) is a relapsing multisystemic disorder with obliterative vasculitis affecting both arteries and veins including vasculopathy of capillaries. In 1937, Hulusi Behçet described oral aphthous ulcers, genital ulcers, and hypopyon uveitis as a triad (Behçet 1937).

The definition has since been expanded and modified to include multisystemic clinical features, such as central nervous system (CNS) involvement. The Behçet's Disease Research Committee of Japan defined "major" and "minor" criteria for diagnosis, with "complete," "incomplete," and "suspect" types of the disease (1974). The International Study Group (ISG) criteria require the presence of two of the four features: genital ulceration, eye lesions, positive pathergy test, and either of the skin lesions (folliculitis, papulopustular lesions, acneiform nodules, and/or erythema nodosum) in addition to oral ulceration (1990). Moreover, the Dilsen Criteria include thrombophlebitis (Dilsen 2003). The Dilsen Criteria and the ISG Criteria fit better to the European BD patients. On the basis of ophthalmic manifestations, four subgroups have been described: ocular BD, internal BD, neurological BD, and combined BD.

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Diagnostic Criteria by Behçet Disease Research Committee of Japan

1. **Major symptoms**
   - A. Recurrent aphthous ulceration of the oral mucous membrane
   - B. Skin lesions
     - (a) Erythema nodosum-like lesions
     - (b) Thrombophlebitis
     - (c) Folliculitis or acne-like lesions
     - (d) Cutaneous hypersensitivity
   - C. Ocular symptoms
     - (a) Iridocyclitis
     - (b) Retinochoroiditis
     - (c) Sequelae of (a) and (b)
   - D. Genital ulcers
2. **Minor symptoms**
   - A. Arthritis
   - B. Intestinal lesions (intestinal Behçet's disease)
   - C. Epididymitis
   - D. Vascular lesions (angio-Behçet's disease)
   - E. Neuro-psychiatric lesions (neuro-Behçet's disease)
3. **Examination**
   - A. Skin prick test
4. **Diagnosis**
   - A. Complete type: patients with all four major symptoms
   - B. Incomplete type:
     - (a) patients with three major symptoms
     - (b) patients with two major symptoms and two minor symptoms
     - (c) patients with ocular symptom and one another major symptom
     - (d) patients with ocular symptom and two minor symptoms

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The International Study Group (ISG) Criteria

These criteria require recurrent oral ulceration (obligatory) plus the presence of two of the four features below:

1. Genital ulcers
2. Eye lesions
3. Pathergy test
4. Skin lesions (folliculitis, papulopustular lesions, acneiform nodules, and/or erythema nodosum)

The Dilsen Criteria

These criteria require the presence of three of the five features below:

1. Recurrent oral ulcerations
2. Recurrent genital ulcerations
3. Skin lesions
4. Eye lesions
5. Thrombophlebitis

+ Skin Pathergy test
Other causative factors should be excluded.

Etiopathogenesis

The exact etiology and pathogenesis of BD still remain unclear. A high prevalence of BD is found among the Asian and Eurasian populations along the historic Silk Road from the East Asia to the Mediterranean region. There is a strong association between HLA-B51 and BD patients in many different ethnic groups around the historical Silk Route: 50–80% of the patients possess HLA-B51 (Ohno et al. 1982). Association between HLA-B51 and ocular symptoms becomes stronger toward the east along the Silk Road (Horie et al. 2017). In spite of the genetic background, there are not so many family cases as found in other genetic diseases. It is interesting to note that there are no BD patients in the Japanese immigrant population in Hawaii (Masuda et al. 1975) and very few patients only in Brazil. These facts suggest that besides genetic factors, some environmental factors may also play an important role in the pathogenesis of BD. There are some reports on the association between BD and external factors, such as *Streptococcus sanguinis*, organophosphates, mycobacterial 65-kDa heat shock protein peptides, and some heavy metals (Ishikawa et al. 1979; Kaneko et al. 1997; Mizushima et al. 1988).

The most characteristic pathological feature is the occlusive necrotizing non-granulomatous vasculitis and perivasculitis. In these inflamed sites, neutrophil accumulation is found (Matsumura and Mizushima 1975). Neutrophils obtained from patients with BD have high ability of chemotaxis and hydroxyl radical production (Niwa et al. 1982; Takeno et al. 1995). It was recently reported that ocular BD patients were less complicated with allergic disorders in Japan (Horie et al. 2016). Etiology of BD probably depends on certain immunological abnormalities triggered by external environmental factors in individuals with particular genetic backgrounds.

Clinical Features

Systemic Manifestation

The common manifestations of BD are oral and genital ulcers (Table 12.1) (Deuter et al. 2008). They are long-lasting, tend to relapse, and are very painful. Typical oral aphthous ulcer is often seen on tongue and inner edge of the lip plurally (Fig. 12.1). The skin lesions occur in 41–94%. Papulopustules, acneiform pseudofolliculitis, and erythema nodosum are common, but pyodermia, ulcerations, necrotizing lesions, Sweet syndrome (febrile neutrophilic dermatosis), and superficial thrombophlebitis may also occur. The pathergy phenomenon is positive in 19–53%. Arthritis occurs in 47–69%

Table 12.1 General manifestations of Behçet disease

Manifestation	Incidence
Oral aphthous ulcerations	76.6–100%
Genital ulcerations	40–94%
Skin lesions	29–94%
Pathergy phenomenon	19–70%
Arthritis	8–69%
Gastrointestinal manifestations	3–26%
Neurological manifestations	2–44%
Vascular manifestations	6–37%
Cardiac manifestations	1–6%
Epididymitis	5–22%

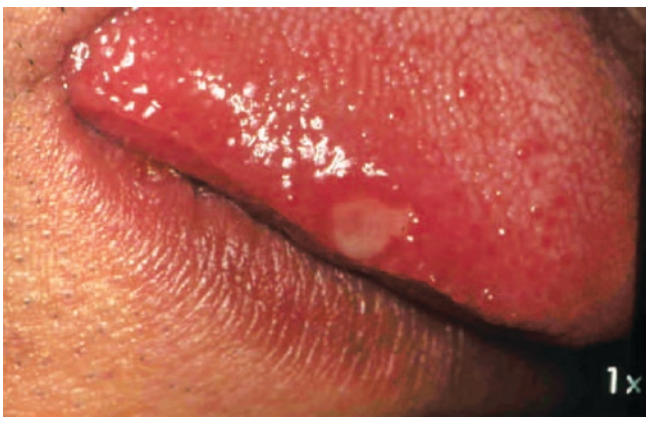

Fig. 12.1 Oral aphthous ulcer on tongue

of patients. Although a rare manifestation, myositis may be either localized or generalized and has also been described in juvenile BD. Gastrointestinal manifestations occur in 3–30% of patients, and main symptoms are abdominal pain due to diarrhea and gastrointestinal bleedings. Diffuse ulcerations are more common than localized aphthous ulcers. Neurological manifestations are present in 8–31% of BD patients. The site most commonly affected is the brainstem. Vascular manifestations such as thrombosis and arterial aneurysms occur in 28%. Most commonly, occlusions of superior or inferior vena cava, femoral veins, cerebral veins, veins of the upper extremities, and portal veins occur. Rare manifestations include cardiac manifestations (1–6%), epididymitis (4–31%), and renal manifestations (less than 1%).

Ocular Disease

Anterior Segment

The primary manifestation of ocular BD may start unilateral most often as an anterior uveitis, but later on, bilateral posterior uveitis occurs in 78% of the cases, and 60% of the patients develop panuveitis with a chronic relapsing course (Tugal-Tutkun et al. 2004). The disease is more severe in men than in women. Recurrences are common.

Hypopyon is smooth with niveau, different from the viscous hypopyon seen in HLA-B27 associated uveitis (Fig. 12.2). The cells easily move and curl up with patient's head tilt. In eyes with severe iridocyclitis, in which hypopyon is not seen by direct slit-lamp examination, a small layering of leucocytes can be observed in the inferior iridocorneal angle by gonioscopy, called "angle hypopyon" (Fig. 12.3). Nowadays, iridocyclitis with hypopyon occurs in only 12% of BD patients with ocular involvement, probably due to earlier and more aggressive treatment, which has resulted in dampening inflammatory responses.

The inflammatory response in the anterior chamber in BD is non-granulomatous in nature. Patients often complain of redness, periorbital pain, photophobia, and blurred vision.

Posterior Segment

In the posterior segment, retinal vasculitis (vein and artery) is present in both peripheral and central vessels with retinal hemorrhages and soft exudates. Sometimes only soft exudates appear in the widespread retina with any degree of diffuse vitreous opacity (Fig. 12.4). Optic disc is sometimes swollen and optic neuritis may be present. Macula is commonly affected (Fig. 12.5). Choroid is frequently involved with patches. The chorioretinal infiltrations resolve spontaneously in a few weeks, but a diffuse vitreous opacity may remain until a few months later. After posterior segment inflammation has disappeared, obliterated white retinal arteries and retinal and optic disc atrophy are seen.

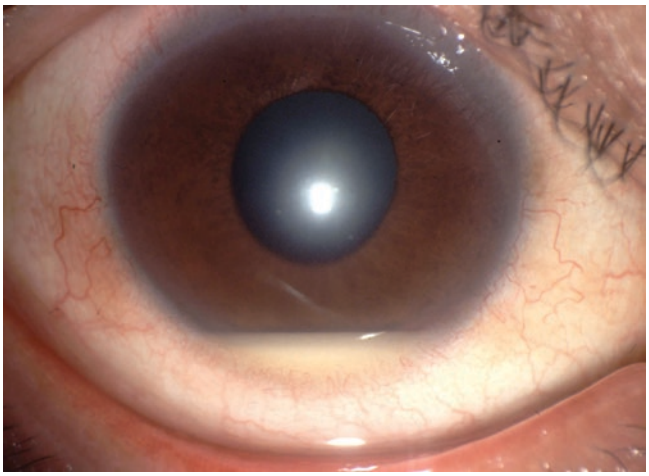

Fig. 12.2 Hypopyon iridocyclitis

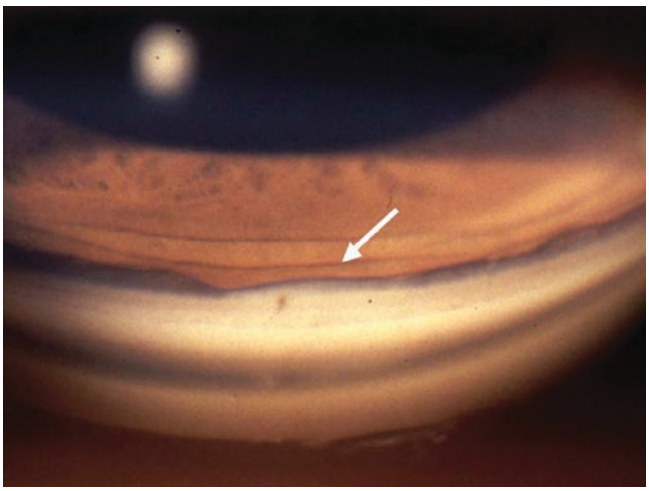

Fig. 12.3 Angle hypopyon

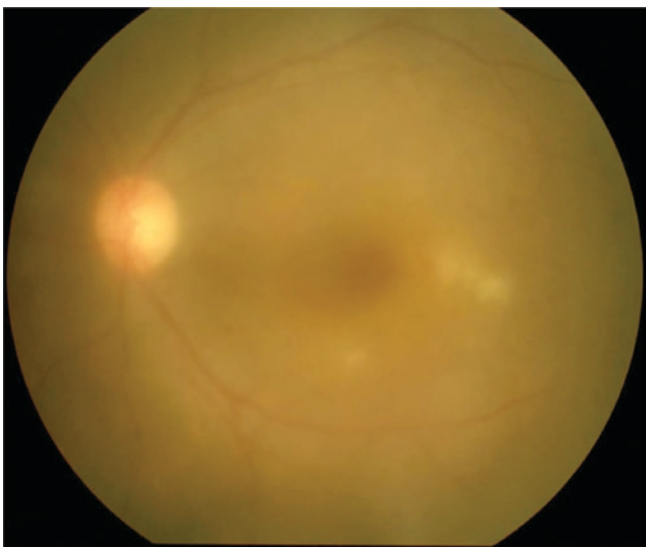

Fig. 12.4 Mild ocular inflammatory attack in posterior pole with soft exudates and mild vitreous opacity

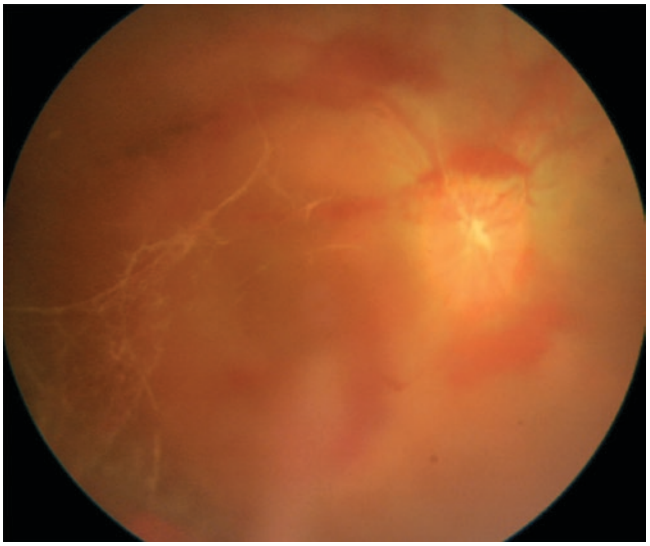

Fig. 12.5 Severe ocular attack in the posterior segment, leading to retinitis and retinal vasculitis with retinal and vitreous hemorrhages

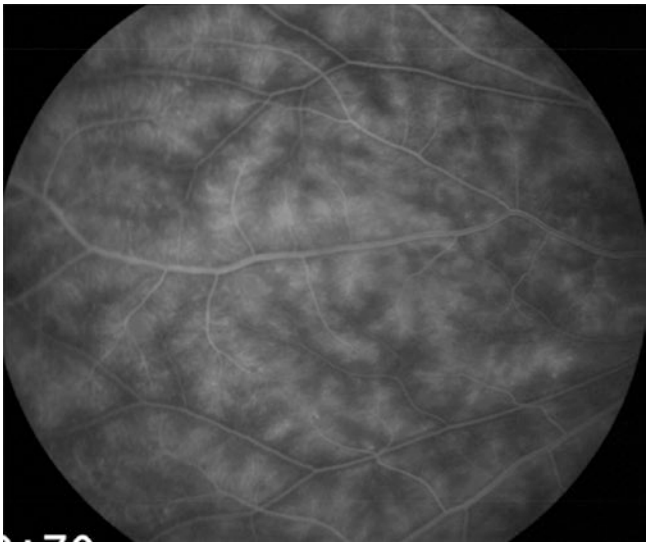

Fig. 12.7 Fern-like diffuse capillary fluorescein leakage from retinal vessels

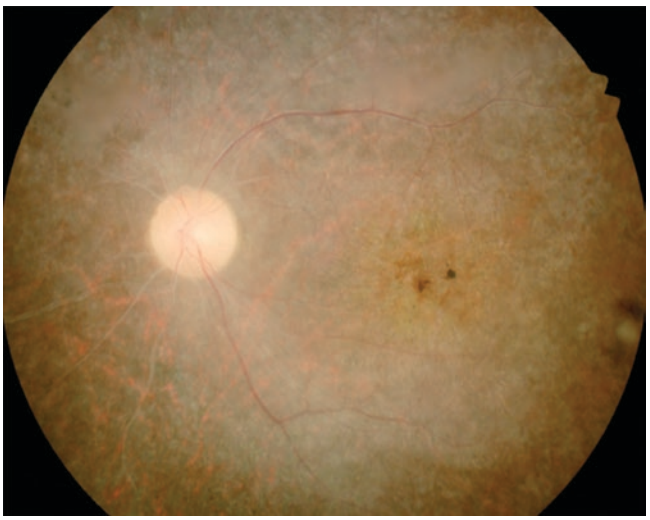

Fig. 12.6 Ocular fundus at the end stage with diffuse chorioretinal and optic nerve atrophy after recurrent ocular inflammation attacks

Due to necrotizing obliterative vasculitis, which may be found either in the anterior or posterior segment, or more commonly in both, neovascularization at the optic disc or at the periphery, can lead to retinal detachment with or without vitreous hemorrhage and neovascular glaucoma. This complication used to lead to enucleation.

Repeated intraocular inflammation causes complicated cataract and secondary glaucoma. Both open angle and angle closure glaucoma or even pupillary block (iris bombé) may result, but also, due to ciliary body involvement low intraocular pressure, which may lead to phthisis bulbi. This is the main cause of permanent visual loss in this disease (Fig. 12.6). Intraocular lens (IOL) implantation seems to be of no risk factor for induction of recurrences with adequate pre- and postoperative strategy.

Fluorescein Angiography

Fluorescein angiography (FA) can show better details of the retinal vessels in the acute stage than ophthalmoscopy. It can reveal non-perfusion area due to retinal artery occlusion, leakages from capillary vessels, vascular remodeling, and neovascularization. However, FA is quite useful for early diagnosis, and it may reveal "fern-leaf" shaped leakages from retinal capillary even in the convalescent stage (Fig. 12.7).

Management

There is no standard treatment regimen that is common in the world. Therefore, different protocols for the treatment are used in each region. In addition, the clinical effects of each treatment seem to differ from one patient to another. Broadly, the strategy of BD treatment is classified in two ways: (1) treatment of acute inflammatory attacks, and (2) suppression of future recurrent inflammatory attacks.

Treatment of Acute Ocular Inflammatory Attacks

Acute inflammatory attacks should be treated immediately to minimize the damage to ocular tissues especially at the posterior segment. For anterior uveitis, subconjunctival injection of soluble corticosteroids, e.g., 2 mg of dexamethasone, is effective in addition to frequent administration of

betamethasone or prednisolone acetate eye drops (e.g., every hour) besides mydriatic agents.

Regarding the local therapy, for posterior segment inflammation, posterior sub-Tenon's injection of soluble corticosteroids, e.g., 4 mg of dexamethasone, is effective. Repeated daily injection may be required for a week according to the severity of ocular attacks. Instead of posterior sub-Tenon's injection, intravitreal injection of corticosteroids may also be effective. Regarding the systemic therapy, there is general agreement that posterior segment inflammation needs systemic corticosteroid treatment, or in severe cases, additional immunosuppressive treatment.

Suppression of Future Recurrent Inflammatory Attacks

Colchicine

Colchicine has the effect to inhibit the migration of granulocytes into the inflamed tissue. The effects of colchicine to suppress the frequency of acute inflammatory attacks were reported in BD (Matsumura and Mizushima 1975). The adequate dose is 0.5–1.0 mg per day. Kotter et al. from Germany reported that colchicine was partially effective in 66% of their BD patients (Kotter et al. 1996). However, in a double blind study, Aktulga et al. could not show significant efficacy of colchicine in BD (Aktulga et al. 1980).

Cytotoxic Agents

Cytotoxic agents such as cyclophosphamide and chlorambucil are cheap. Therefore, today chlorambucil may be the choice of drug for mild BD, or in case of severe diseases, it is mostly ordered in developing countries. Azathioprine has been shown to maintain visual acuity and prevent the development of eye disease (Hamuryudan et al. 1997; Yazici et al. 1990); however, these drugs are not effective enough to completely suppress the recurrent inflammation in severe cases. Azathioprine is, besides cyclosporine, the only drug which has shown effective on BD by a RCT.

Cyclosporine

According to the results of a double-masked trial of cyclosporine versus colchicine, it was revealed that cyclosporine was more effective in reducing the frequency of ocular attacks than colchicine (Masuda et al. 1989). The initial dose of cyclosporine is usually 5 mg/kg/day and the dosage is adjusted according to the trough level or the area under the blood-concentration-time curve during the first 4 h after cyclosporine administration (AUC_{0-4}). Colchicine is usually stopped to avoid interacting side effects including myositis. However, in severe cases, both colchicine and cyclosporine may be administered together.

Cyclosporine has some important side effects. Due to its nephrotoxicity, some patients are required to reduce the dosage or stop the treatment. Central nerve system (CNS) symptoms are also considered as side effects of cyclosporine especially in BD patients. In Behçet patients on cyclosporine, 25.5% developed CNS symptoms, whereas only 6.6% of the patients did without cyclosporine in Japanese patients (Kotake et al. 1999).

Corticosteroids

Systemic corticosteroids are used in some regions. However, rapid tapering leads to severe recurrence of ocular attacks. In refractory cases, low-dose systemic corticosteroids may be given in addition to immunosuppressive drugs.

Systemic corticosteroids are used in acute attacks for the suppression of tissue damage, as well as in chronic cases with no or minimal recurrence under the therapy. However, in very acute cases, the use of any immunosuppressive agent would not lead to a fast control of the disease. If the attacks are very severe, high-dose oral corticosteroids are needed, but should not be given alone. In refractory cases, another agent or combination of corticosteroids and immunosuppressive agents, depending on the disease severity, should be started immediately. This will lead to faster control and reduce the risk of a flare-up during corticosteroid tapering.

TNF-α Blocking Agents

TNF-α is closely associated with the immunopathogenesis of BD. There are data available in ocular BD for the two agents, infliximab and adalimumab.

Infliximab

Infliximab is an anti-TNF-α chimeric monoclonal antibody composed of an antigen-binding variable region from mice with high affinity to human TNF-α and a constant region of human IgG1. Infliximab shows an excellent efficacy to suppress BD. In Japan, an open label trial was performed in Behçet patients who were refractory to cyclosporine therapy (Ohno et al. 2004). Administration of 5 mg/kg of infliximab was approved in Japan from January 2007 for BD complicated with refractory posterior uveitis, which does not respond to conventional therapy.

Some complications have been reported including infusion reaction and infections. Especially, screening tests for tuberculosis and hepatitis B virus have to be performed before starting infliximab. If there is some suspicion for inactive tuberculosis, the additional administration of anti-tubercular drugs is recommended to prevent reactivation of the disease.

Adalimumab

Adalimumab is also an anti-TNF-α antibody, but it is fully humanized, whereas Infliximab is human-murine chimeric.

In the first report of three cases who switched from infliximab to adalimumab, (Mushtaq et al. 2007), all three patients had sight-threatening bilateral panuveitis with BD that was poorly responsive to conventional immunosuppression. The introduction of infliximab therapy stabilized their ocular disease. Due to the difficulty in attending the hospital or coping with the intravenous infusion, they switched to adalimumab that could be self-administered as 40 mg subcutaneously. Switching to adalimumab has maintained their disease in remission and prevented relapse.

Interferon Alpha-2a (IFNα-2a)

At the induction of recombinant human interferon alfa-2a (rhIFNα-2a) treatment, three to six million international units (IU) of rhIFNα-2a are injected subcutaneously daily, which will be reduced according to the clinical effect, typically in between 3 weeks to 3 million IU every second day, and continued to taper until 6–12 months. Immunosuppressive drugs should be stopped and corticosteroids should be reduced one day prior to the initiation of IFN. The recurrence rate and the 5-year visual acuity rate for ocular BD after treatment with rhIFNα-2a were reported (Deuter et al. 2008). During a mean follow-up of 85 months (60–132 months) after initiation of rhIFNα-2a, 90.2% of 41 eyes improved or remained stable. There was no loss of originally better visual acuity. No patient had developed a pale optic nerve. The relapse-free period in the same group was at least 2 years in 60.9%, and at least 6 years in 26.1%, which shows that rhIFNα-2a can be stopped without resulting in recurrences.

Intravitreal Injection of Triamcinolone Acetonide (IVTA)

Repeated IVTA in BD refractory to conventional therapy has been shown to prevent the recurrence of posterior uveitis (Ohguro et al. 2006). However, recurrences developed once the TA particle disappeared from the vitreous cavity. The IVTA may need to be performed repeatedly before TA particle disappears. Despite preventing systemic complications, the high incidence of complications after intravitreal injection (progression of cataract and increased intraocular pressure) reduces its value, and today, this regimen may be only a second line treatment in care of active BD, which is vision threatening.

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Systemic Lupus Erythematosus

13

Joo Young Shin

Introduction

Systemic lupus erythematosus (SLE), a systemic, connective tissue disease that can affect multiple organ systems, affects women, especially Asian and African women more commonly (Silpa-archa et al. 2016). Up to one-third of SLE patients experience some kind of ocular manifestation (Palejwala et al. 2012), keratoconjunctivitis sicca being the most common form, and retinal and choroidal involvement being most associated with visual impairment (Sivaraj et al. 2007; Palejwala et al. 2012). Although, the prevalence of SLE as a cause of uveitis was estimated to be 0.47% in a recent review of the literature (Gallagher et al. 2015), ocular involvement in SLE is important as it may correlate with systemic disease activity and precede other systemic symptoms.

Pathogenesis

The pathogenesis of SLE is multifactorial. Inflammation is thought to be caused by the formation of autoantibodies and immune complexes, and following the activation of the complement system, causing multi-organ damage manifesting as nephritis, vasculitis, and arthritis.

Clinical Features

Anterior Segment Involvement

Anterior segment involvement reported in SLE include episcleritis, scleritis, and iridocyclitis. Heron et al. reported a 2% prevalence of SLE-associated scleritis (Heron et al. 2014). There are a few reports of iritis or iridocyclitis; hypopyon or fibrinous anterior uveitis has been reported (Stavrou et al. 2002; Zink et al. 2005), and one adult presenting with bilateral keratitis and iridocyclitis which responded well to chloroquine has also been reported (Halmay and Ludwig 1964).

Posterior Segment Involvement

Lupus Retinopathy

Posterior segment involvement includes lupus retinopathy (microangiopathy, vasculitis, vascular occlusion) and choroidopathy. The prevalence of retinopathy varies, considerably lower in patients with well-controlled disease (3–29%) (Davies and Rao 2008). Retinal or choroidal involvement is thought to correlate with systemic disease activity, especially cerebral disease (Jabs et al. 1986; Stafford-Brady et al. 1988). Microangiopathy is thought to be an immune complex-mediated vasculopathy (Levine and Ward 1970; Aronson et al. 1979) and includes cotton wool spots, microaneurysms, hard exudates, and dot hemorrhages, with usually a good visual prognosis (Fig. 13.1). Vasculitis, which is thought to be a result of immune complex deposition, complements activation with microvascular thrombosis and fibrinoid degeneration of the vascular wall, presents with vascular sheathing in arterioles and/or venules, and may result in vascular occlusion (Talat et al. 2014; Yen et al. 2013) (Fig. 13.2). In most cases, vasculitis is associated with antiphospholipid antibodies (Palejwala et al. 2012). Vascular occlusion is the more severe form, manifesting with widespread retinal capillary nonperfusion, multiple branch retinal artery occlusions, ocular neovascularization resulting in vitreous hemorrhage, tractional retinal detachment, neovascular glaucoma, and visual loss (Read et al. 2000; Au and O'Day 2004; Kim et al. 2013) (Fig. 13.3).

Lupus Choroidopathy

Lupus choroidopathy can occur either independently or with lupus retinopathy, including single or multiple areas of

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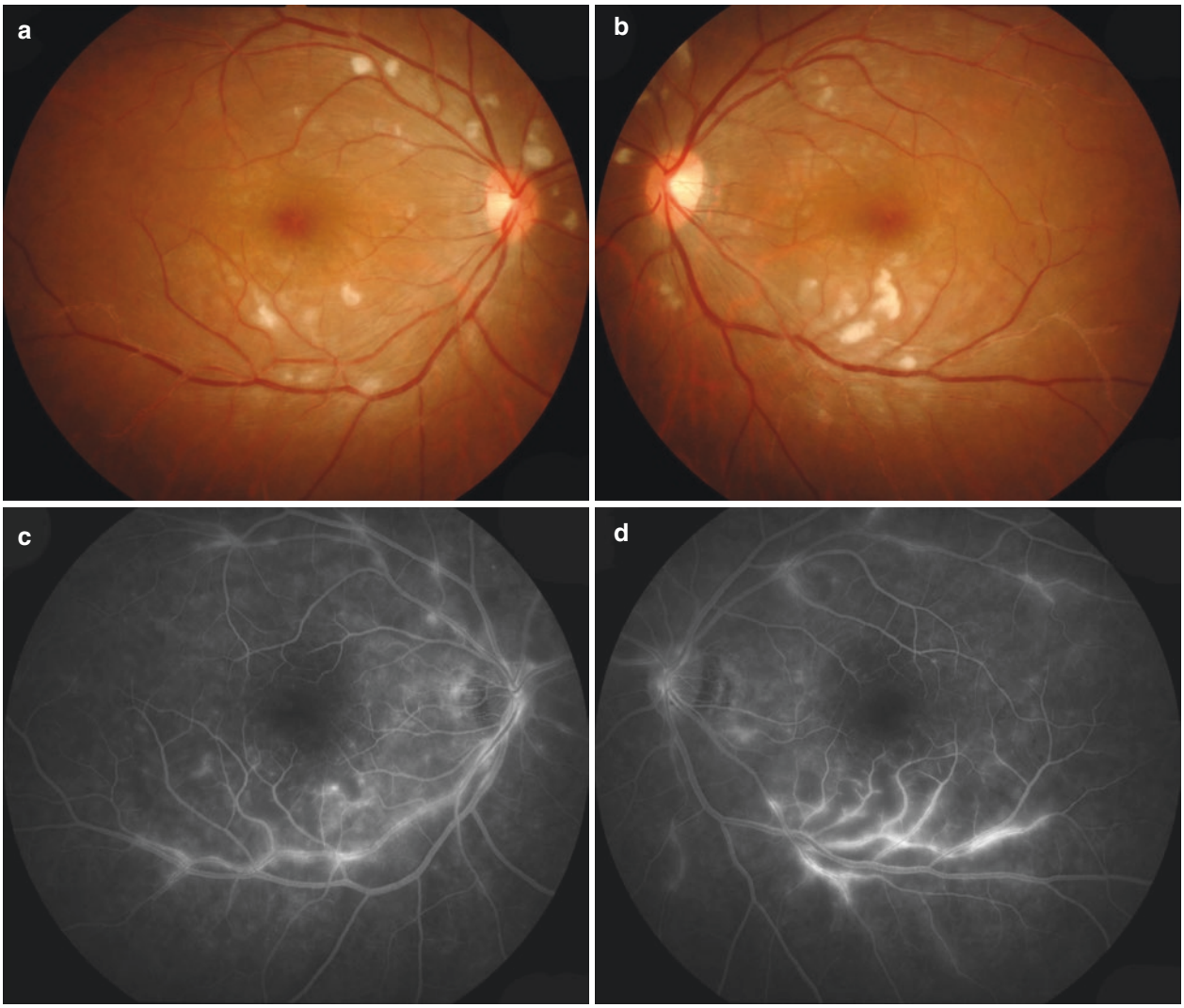

Fig. 13.1 32-year-old female with systemic lupus erythematosus. Bilateral multiple cotton wool spots and retinal hemorrhage with vascular sheathing is noted (**a**, **b**), with vessel wall staining on fluorescein angiography (**c**, **d**)

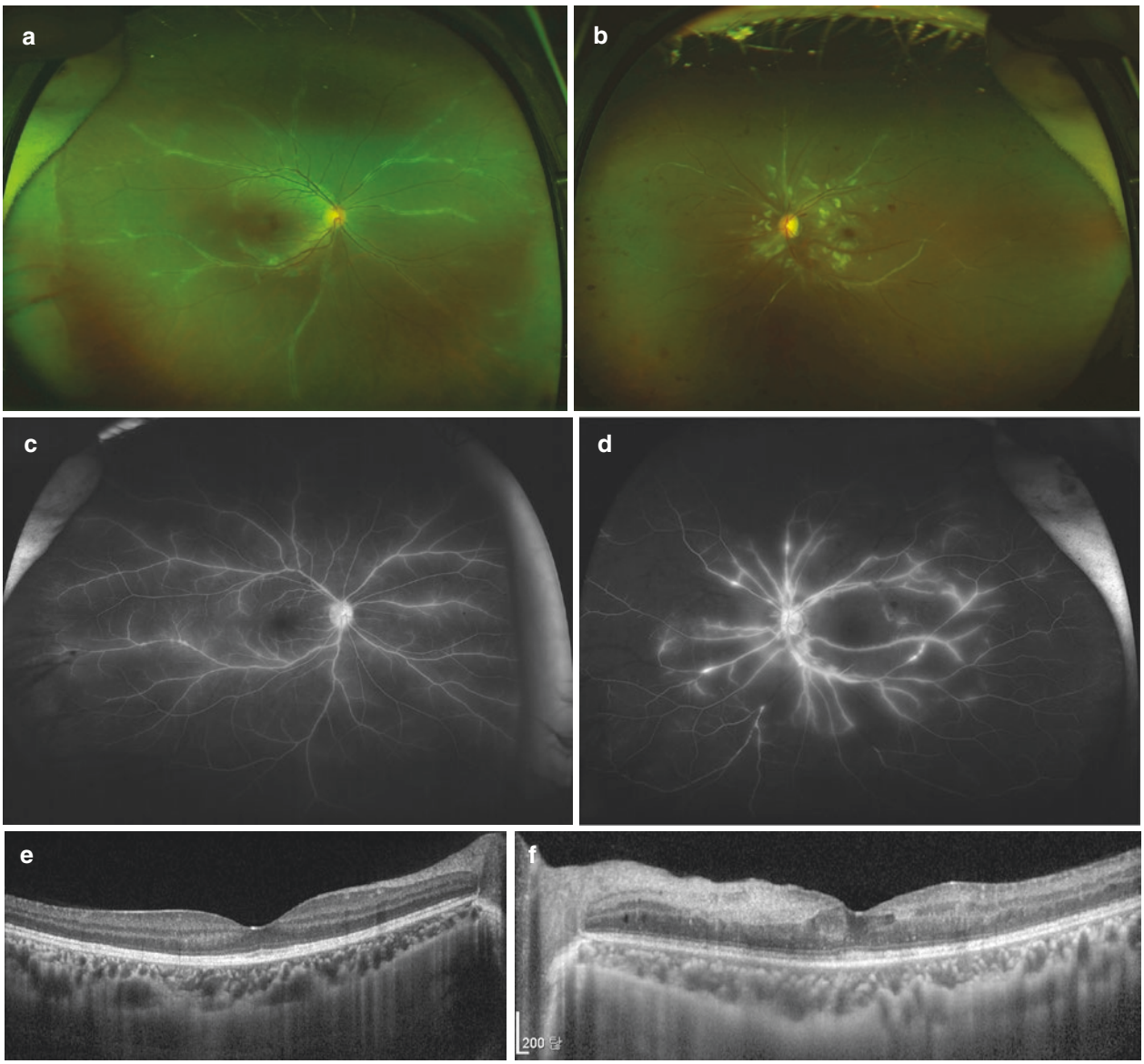

Fig. 13.2 19-year-old female with systemic lupus erythematosus with severe vasculitis and vaso-occlusive retinopathy. (**a**, **b**) Fundus findings revealed multiple cotton wool patches, retinal hemorrhage and diffuse retinal vascular sheathing. (**c**, **d**) Fluorescein angiography showed diffuse vessel wall staining in both eyes and severe capillary non perfusion in left eye. (**e**, **f**) Spectral-domain optical coherence tomographic findings showed severe inner retinal ischemic change in left eye

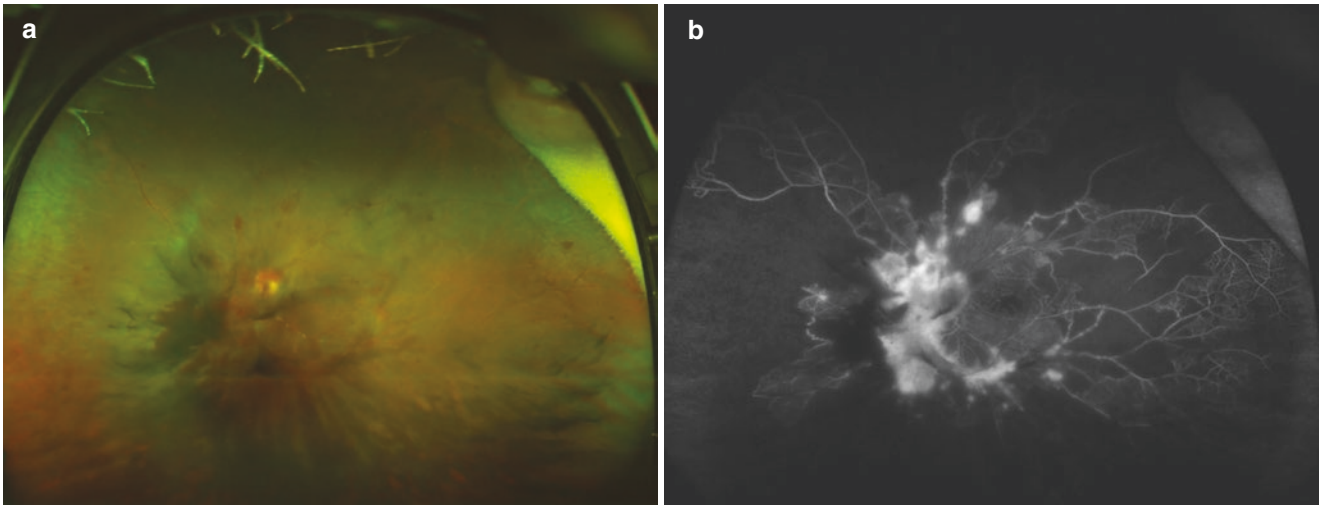

Fig. 13.3 The patient in Fig. 13.2 developed neovascularization (shown in fundus photograph (**a**), and fluorescein angiography (**b**)), causing vitreous hemorrhage in her left eye 6 months after presentation, requiring vitrectomy

serous or exudative retinal detachment, retinal pigment epithelium detachment or retinal pigment epitheliopathy (Nguyen et al. 2000). Subretinal hypopigmented patches on angiography which are areas of choroidal ischemia may also be present (Silpa-archa et al. 2016). Secondary angle closure glaucoma has also been reported from choroidal effusion leading to anterior shifting of the lens-iris diaphragm (Ahn and Choi 2016). Lupus choroidopathy resolves with appropriate immunosuppressive treatment and vision usually recovers (Nguyen et al. 2000).

Management

Systemic Management

Systemic treatment often requires a collaborative team approach. Nonsteroidal anti-inflammatory drugs, antimalarials (hydroxychloroquine), systemic corticosteroids, immunosuppressive therapy, and biologics may be effective. Systemic corticosteroids are used in the acute stage, and nonsteroidal anti-inflammatory drugs and hydroxychloroquine are used in mild patients. A variety of immunosuppressive agents have demonstrated efficacy in ocular SLE including methotrexate, mycophenolate mofetil, azathioprine, and cyclophosphamide (Palejwala et al. 2012; Silpa-archa et al. 2016). Biologics targeting cytokines, B and T lymphocytes, and B-cell-activating factors are also considered in patients refractory to other treatment. Belimumab is the first biologic agent approved by the Federal Drug Administration in 2011 for SLE, which inactivates B-cell-activating factor (Dooley et al. 2013; Navarra et al. 2011; Touma et al. 2013). Others include rituximab, epratuzumab, sifalimumab, and ocrelizumab.

Local Therapy

Local treatment according to the specific pathology along with systemic treatment may play a role in the treatment. For vascular occlusion and ischemia, laser photocoagulation can be used (Fig. 13.4). Vitrectomy may be performed for complicated neovascularization such as vitreous hemorrhage and tractional retinal detachment. Intravitreal anti-VEGF injection has also been reported as an effective therapy for vaso-occlusion and vasculitis in SLE (Kurup et al. 2009; Lee et al. 2013).

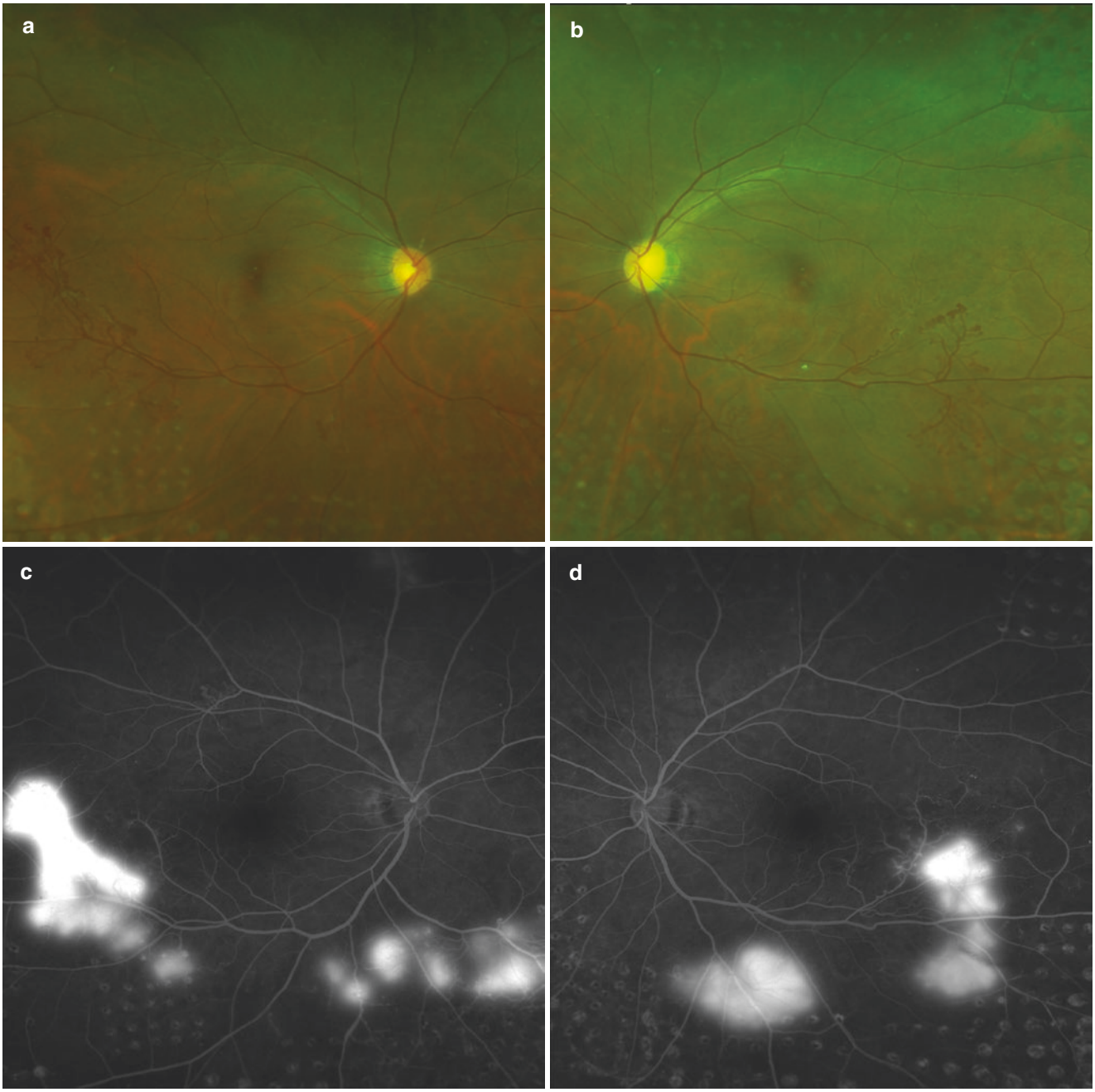

Fig. 13.4 The patient in Fig. 13.1 developed neovascularization in both eyes 4 years after presentation despite systemic therapy. She received laser photocoagulation in both eyes (shown in fundus photograph (**a**, **b**), and fluorescein angiography (**c**, **d**))

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Posterior Scleritis

14

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Introduction

Scleritis is a severe, potentially sight-threatening form of ocular inflammation characterized by oedema of episcleral and scleral tissues with involvement of the deep episcleral vascular plexus (Beardsley et al. 2013; Artifoni et al. 2014) (Fig. 14.1). Scleritis may be associated with infection, systemic vasculitis, autoimmune or be idiopathic in nature. A careful history, physical and ocular examination and targeted investigations are essential as scleritis may be the presenting feature of a potentially life-threatening systemic vasculitis or infectious disease (Albini et al. 2005a; Beardsley et al. 2013). Scleritis remains a therapeutic challenge, particularly in patients with severe ocular inflammation, a systemic vasculitis or associated autoimmune disorder.

The most widely used classification system for scleritis was published by Watson and Heyreh in 1976 and divides the disease into anterior and posterior subtypes, based on whether the inflammation affects the sclera anterior or posterior to the insertion of the rectus muscles (Watson and Hayreh 1976). Anterior scleritis is subdivided into diffuse nodular, necrotizing with inflammation and necrotizing without inflammation (scleromalacia perforans). Posterior scleritis can be subdivided into diffuse, nodular and necrotizing variants.

Posterior scleritis is defined by the involvement of the sclera posterior to the insertion of the rectus muscles (Accorinti et al. 2013). It is a severe form of scleritis and is frequently associated with complications such as uveitis, serous retinal detachment, optic disc oedema, peripheral choroiditis and multifocal subretinal exudates that can be a significant threat to vision (Albini et al. 2005a) (Fig. 14.2). Posterior scleritis has been reported in 2–11% of scleritis cases (Sainz de la Maza et al. 2012; Keino

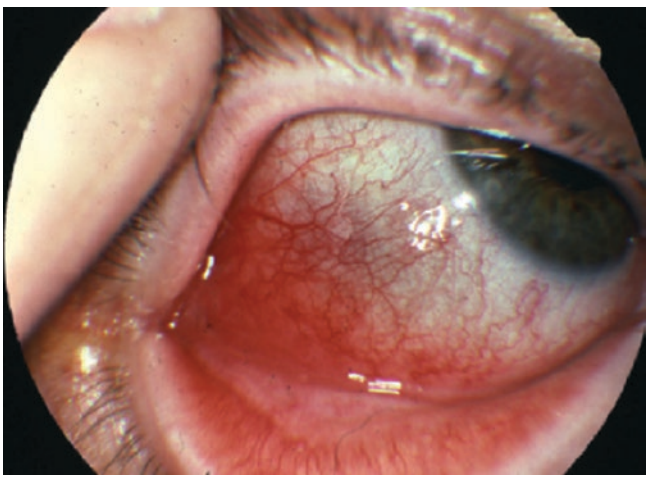

Fig. 14.1 Scleritis with characteristic blue hue

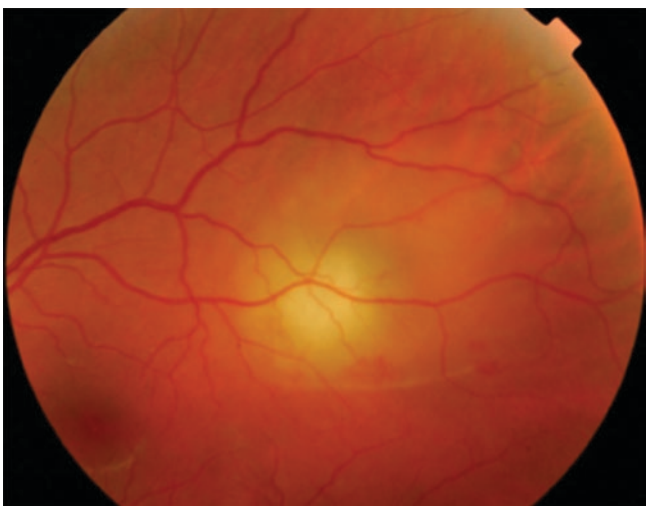

Fig. 14.2 Subretinal granuloma with posterior scleritis

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et al. 2010; Lavric et al. 2016). The diagnosis of posterior scleritis is often difficult. In an Indian study, 8.5% of the 94 cases of scleritis seen in a tertiary referral clinic were diagnosed as posterior scleritis; however, each of these cases were initially misdiagnosed by the referring ophthalmologist prior to evaluation in the tertiary clinic (Gonzalez-Gonzalez et al. 2014).

A scleritis severity grading scale for anterior scleritis was proposed and tested by McCluskey and Wakefield in 1991, using parameters of tenderness, area of inflammation, presence of nodules, necrosis, corneal involvement, vitreous cells and retinal detachment (McCluskey and Wakefield 1991). A score of 11 or higher carries a high chance of visual loss, associated disease, scleral necrosis, a diminished response to systemic steroids and a higher requirement for the use of immunomodulatory drugs. The scoring system uses some of the clinical signs seen in patients with posterior scleritis, but it is not specifically designed to assess posterior scleritis.

Clinical Features

The mean age of onset of scleritis is in the fifth decade, with females accounting for 56–71% of patients. Initially, scleritis is frequently unilateral, but bilateral disease develops in 35–51% of patients (McCluskey et al. 1999; Raiji et al. 2009; Jabs et al. 2000). In Watson's study, posterior scleritis was found to be predominantly unilateral (McCluskey et al. 1999; Watson and Hayreh 1976). A correlation between bilateral posterior scleritis and higher anti-nuclear antibodies (ANA) titres has been reported, although the ANA titre is usually not a good measure of disease severity in other autoimmune diseases, such as SLE (Gonzalez-Lopez et al. 2016).

The characteristic feature of scleritis is the subacute onset of deep, boring, periocular pain, which may radiate to the temple and jaw. The pain is typically worse at night, interfering with sleep and waking the patient early in the morning. It may be exacerbated by eye movement or accommodation and can be so severe as to interfere with normal activities—particularly in patients with necrotizing scleritis with inflammation. Pain is not always a prominent feature, particularly patients with posterior scleritis or those taking anti-inflammatory or immunosuppressive medications for an associated systemic disease, such as rheumatoid arthritis. Approximately, 30% of patients with posterior scleritis present with reduced vision (McCluskey et al. 1999).

The clinical signs of scleritis vary according to the location of the inflammation and its severity. Additionally, complications of scleritis, such as macula oedema, subretinal mass lesions, uveitis, raised intraocular pressure, cataract, uveal effusion, exudative retinal detachment and optic disc oedema, may be evident due to spillover of the scleral inflammation into adjacent structures and are often the clinical manifestations that lead to the patient seeking medical attention.

Table 14.1 Common symptoms and signs of posterior scleritis

Symptoms	Clinical signs
Periocular pain	Conjunctival chemosis
Blurred vision	Conjunctival hyperemia
Headache	Choroidal folds
Photophobia	Serous retinal detachment
Floaters	Anterior chamber reaction (cell or flare)
	Macula oedema
	Associated anterior scleritis
	Optic nerve swelling
	Vitreous cells
	Proptosis
	Ocular hypertension
	Vasculitis
	Peripheral keratitis

Posterior scleritis is commoner than previously recognized. It may occur in association with anterior scleritis, in which case the hallmark features of scleral oedema and congestion of the deep episcleral vascular plexus will be present. If it occurs in isolation, the eye may appear white although inflamed posterior sclera may sometimes be detected at the extremes of gaze (Okhravi et al. 2005). In a large series of patients with posterior scleritis (McCluskey et al. 1999), serous retinal detachment was the most common posterior segment finding (Table 14.1). In 17% of cases, there were no signs. B-scan ultrasonography is the key to diagnosis and demonstrates increased thickness of the ocular coats (greater than 2.0 mm is considered abnormal), fluid in Tenon's capsule (T-sign) (Fig. 14.3), optic disc swelling, retinal detachment and scleral nodules (McCluskey et al. 1999).

Aetiology

Posterior scleritis may be idiopathic in origin (Fig. 14.3), although it is critical to exclude local or systemic infection, systemic vasculitis or associated systemic autoimmune disorder. Other causes include surgically induced scleral infection following ocular surgery (Fig. 14.4), physical trauma, and drug induced, in particular due to bisphosphonate therapy. It can also be associated with intraocular and orbital neoplasms. In many cases, a presentation of scleritis can be the first clinical sign of a severe systemic disease. Between 36 and 57% (Berchicci et al. 2014; Akpek et al. 2004; Lavric

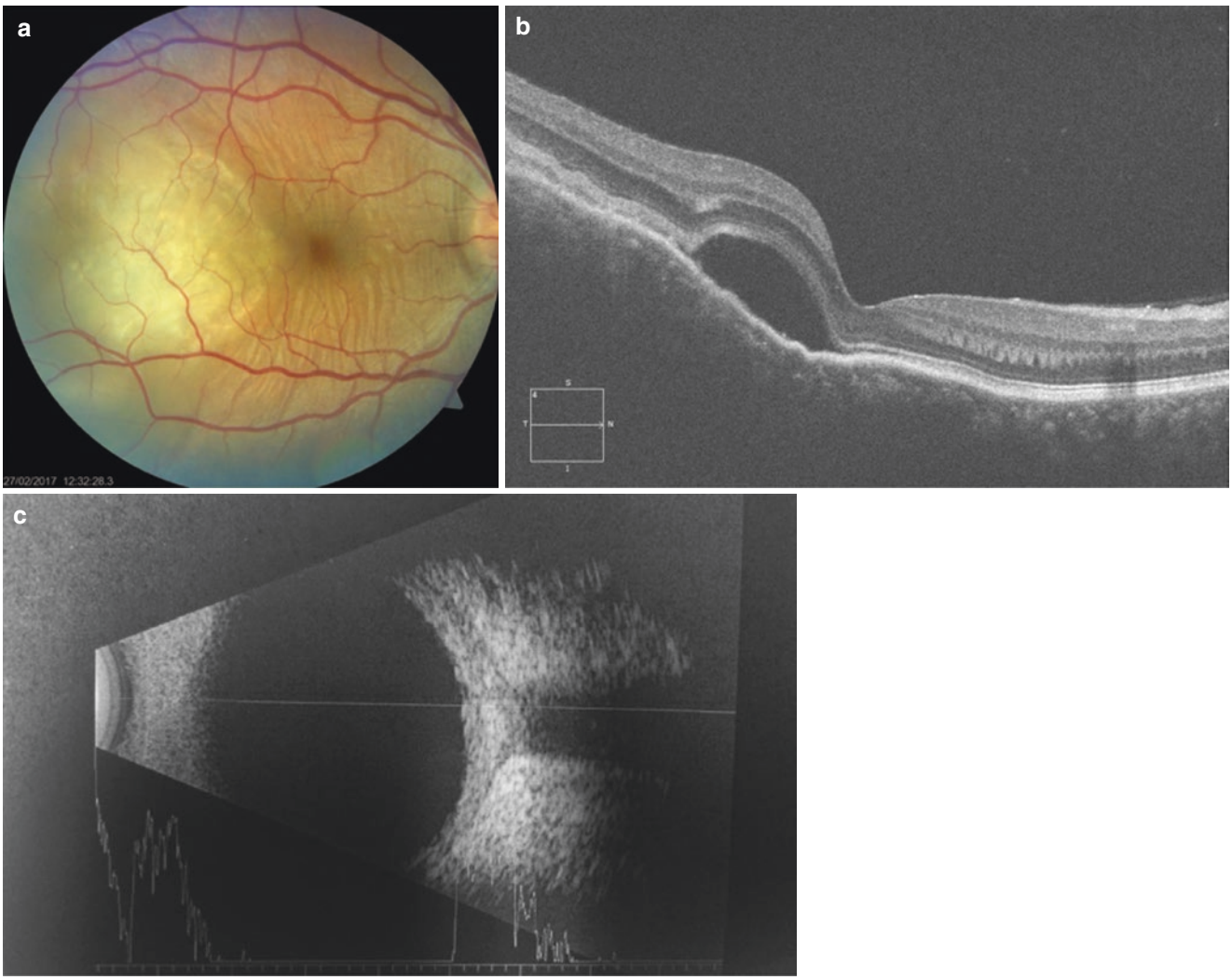

Fig. 14.3 33-year-old female with idiopathic posterior scleritis. She had a history of intermittently red (temporal), painful eye for 2–3 weeks. Visual acuities were 6/18 in right eye 6/6 in left eye, and IOP was normal. (**a**) Colour fundus image showing choroidal folds and temporal detachment with fluid tracking through macula. (**b**) OCT images of patient showing serous detachment and choroidal folds. (**c**) B scan of the right eye showing increased thickness of sclera and T sign

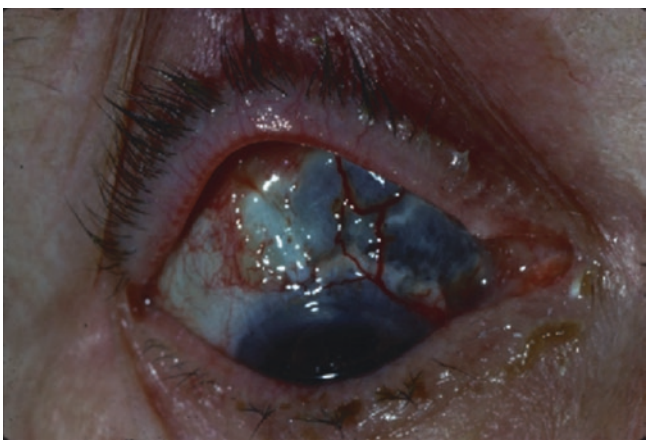

Fig. 14.4 Surgically induced necrotizing scleritis (SINS)

et al. 2016) cases of posterior scleritis are associated with systemic disease. In contrast, 5–15% of cases are due to infection (Accorinti et al. 2013; Albini et al. 2005a).

Associated systemic disease in patients with posterior scleritis are either inflammatory disorders, such as rheumatoid arthritis, psoriatic arthritis and reactive arthritis, systemic autoimmune disease, such as systemic lupus erythematosus, and Sjogren's syndrome or systemic vasculitis, such as the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Artifoni et al. 2014) (Fig. 14.5). One review (Hakin and Watson 1991) reported that over 50% of patients had an associated systemic disease, whereas others have found a range of between 29 and 37.7% (Lavric et al. 2016; McCluskey et al. 1999).

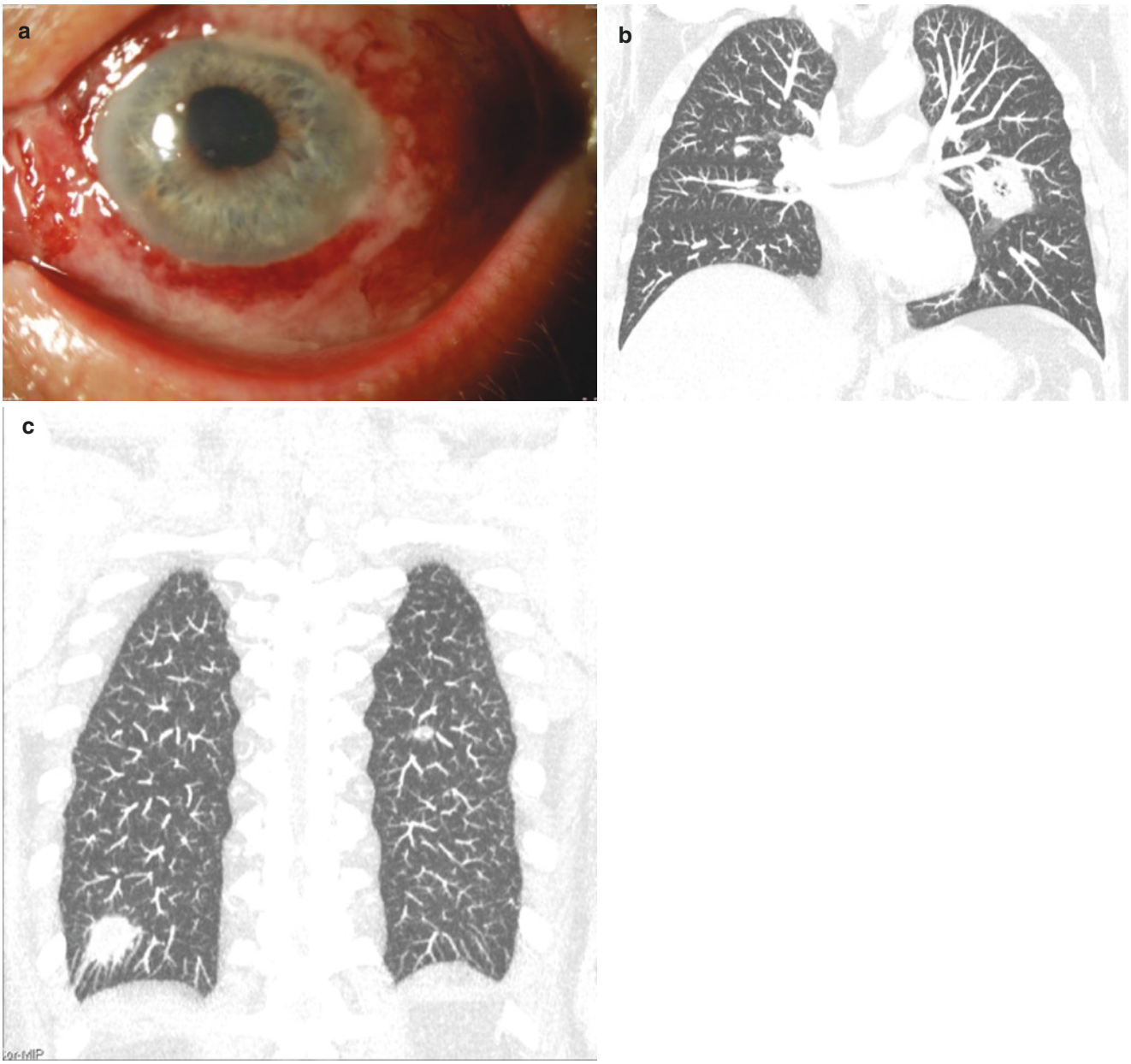

Fig. 14.5 (**a**) Bilateral cANCA necrotizing scleritis with associated anterior uveitis in a 68-year-old man. (**b**, **c**) CT scan of chest in the same patient shows multiple cavitating lesions throughout the lung

Systemic Autoimmune Disease Associations

In a large series of patients with both anterior and posterior scleritis and an associated systemic disease, 78% had a pre-existing diagnosis, 14% were diagnosed as a result of the initial evaluation and 8.4% developed a systemic disease during follow-up. Systemic vasculitis was less likely to have been previously diagnosed than other rheumatic diseases (59% vs. 84%) and more likely to be diagnosed as a result of the initial evaluation (27% vs. 9%) (Akpek et al. 2004). Subsequent studies have reported similar results and have recommended a workup to exclude primary vasculitic disease even in patients with scleritis and a known non-vasculitic systemic disease (Raiji et al. 2009).

A UK tertiary referral centre series of patients with posterior scleritis reported that 29% of patients had an associated systemic disease. Patients older than age 50 years and those who developed an associated anterior scleritis had a significantly increased risk of associated systemic autoimmune disease (McCluskey et al. 1999). In a study by Lavric et al., rheumatoid polyarthritis (12.28%), systemic lupus erythematous (4.38%) and pANCA(+) systemic vasculitis (5.26%) were the most frequent systemic associations of posterior scleritis (Lavric et al. 2016). Uncommon and rare associations

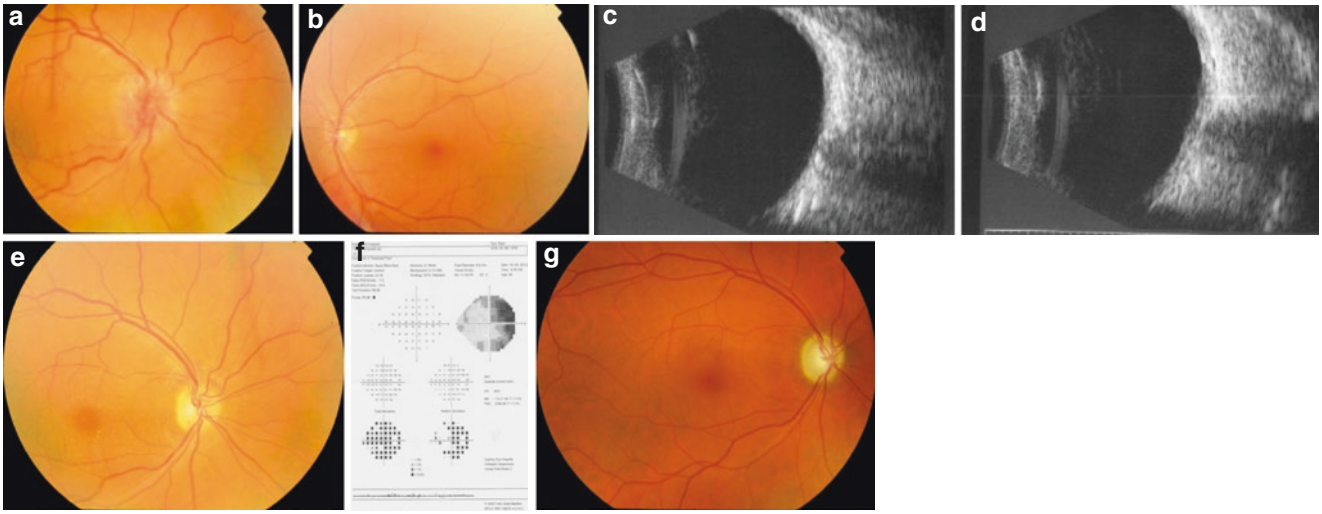

Fig. 14.6 36-year-old male with herpes zoster ophthalmicus. He had no visual symptoms or pain, and visual acuities were 6/6 in both eyes. (**a**, **b**) Note right optic disc swelling in funds photo. B scan of ultrasonography of the right eye (**c**) with posterior scleritis compared to left eye (**d**). (**e**) Colour fundus photo of the right eye showing partially resolved optic disc swelling with some exudation around the macula. (**f**) HVFs showing right optic nerve damage secondary to posterior scleritis. (**g**) Right optic neuropathy after resolution of the posterior scleritis

include: relapsing polychondritis, polyarteritis nodosa, Takayasu disease, giant cell arteritis, juvenile idiopathic arthritis, Vogt-Koyanagi-Harada disease, sarcoidosis, lymphoma, carcinoma of the lung, Cogan syndrome, congenital erythropoietic porphyria and graft-versus-host disease following allogenic bone marrow transplantation (Okhravi et al. 2005).

Scleritis occurs in 0.15–6.3% of patients with RA; conversely up to 30% of patients presenting with scleritis will have RA (Hakin and Watson 1991). The most common phenotype is diffuse anterior scleritis; however, there are no clinical features to distinguish the scleritis seen in patients with RA from that in other conditions, except that scleromalacia perforans only occurs in patients with advanced vasculitic RA. Patients with RA-related scleritis tend to be older and are more likely to develop necrotizing scleritis, decreased vision and peripheral ulcerative keratitis, compared with patients with idiopathic scleritis (Sainz de la Maza et al. 1994). The advent of effective biological therapy of RA has resulted in a dramatic decrease in the incidence of RA-related posterior scleritis (Artifoni et al. 2014).

Scleritis (both anterior and posterior) occurs in approximately 10% of patients with granulomatous polyangiitis (GPA) (Hoffman et al. 1992). The clinical features of scleritis can be helpful in pointing to a diagnosis of GPA; there may be a raised granulomatous mass and the inflammatory changes involve conjunctiva, episclera and sclera. Patients with GPA-related scleritis are more likely to develop necrotizing scleritis, decreased vision and peripheral ulcerative keratitis compared with patients with scleritis associated with any other systemic vasculitic disease (Sainz de la Maza et al. 1995).

Scleritis occurs in approximately 40% of patients with relapsing polychondritis (Hoang-Xaun et al. 1990). The most common phenotype is diffuse anterior scleritis but it can be of any type. Along with RA-related scleritis, it is considered a disease of intermediate severity (Sainz de la Maza et al. 1995). Although the inflammation rarely causes destruction of the globe or decreased vision, the pain may be very severe and resistant to treatment (Hakin and Watson 1991). Scleritis occurs uncommonly in patients with systemic lupus erythematosus. It is usually diffuse or nodular and considered relatively mild. Scleritis associated with the spondyloarthropathies is similar. It can be quite resistant to treatment until the systemic disease is brought under control (Hakin and Watson 1991).

Infectious Scleritis

It is critical not to miss a diagnosis of infectious posterior scleritis. Infectious scleritis should be suspected in patients with a history of ocular trauma or ocular surgery such as scleral buckling procedures, recurrent attacks of herpes zoster or simplex and systemic review consistent with infection or progression of disease whilst on immunomodulatory therapy (Bhat et al. 2009) (Fig. 14.6). Unifocal or multifocal scleral abscesses and contiguous corneal infiltration may be present (Jain et al. 2009). Viruses, bacteria, fungi and parasites can all cause infectious scleritis, either by direct invasion of organisms or via an immune response induced by the organism (Okhravi et al. 2005). The most common causative pathogens include: varicella zoster virus (VZV), herpes

simplex virus (HSV), *Treponema pallidum*, Mycobacterium spp., *Pseudomonas aeruginosa*, Acanthamoeba and Aspergillus spp. (Okhravi et al. 2005).

Posterior scleritis occurs in around 0.87% of cases and up to 8% of all scleritis in patients with a history of herpes zoster ophthalmicus. It often manifests months after an episode (Liesegang 1991; Lavric et al. 2016) (Fig. 14.7). Active herpetic scleral disease is typically diffuse or nodular in subtype; whereas immune-mediated is usually of the necrotizing subtype (Liesegang 1991). There is a high risk of scleral thinning, staphyloma formation and globe perforation (Bhat et al. 2009). HSV-related scleritis is an under recognized clinical entity. It presents as a chronic or recurrent scleritis refractory to conventional therapy.

Pseudomonas aeruginosa is the most common pathogen associated with postsurgical scleritis, particularly pterygium surgery with or without adjunctive beta irradiation or Mitomycin C (Lin et al. 1997) (Fig. 14.8). Syphilis has been

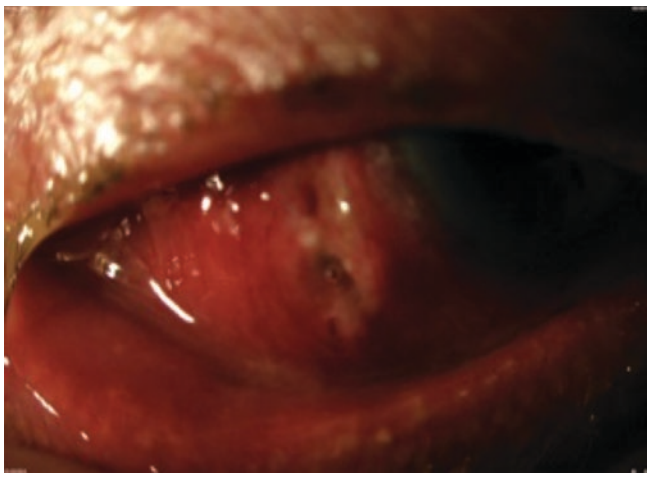

Fig. 14.7 Necrotizing scleritis with inflammation secondary to herpes zoster ophthalmicus

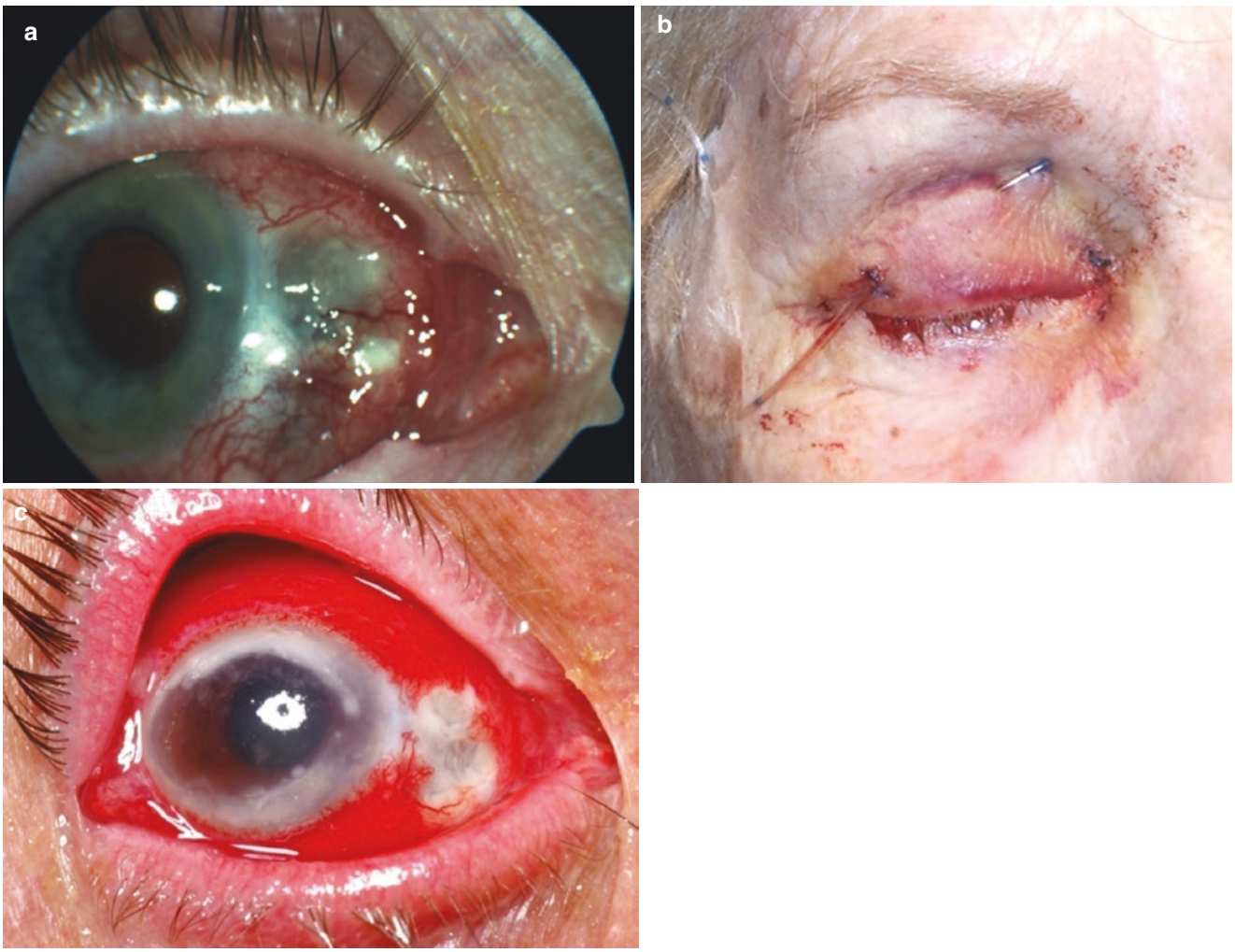

Fig. 14.8 (**a**) Surgically induced necrotizing scleritis (SINS) with pseudomonas infection secondary to pterygium removal and beta irradiation. (**b**) Irrigating antibiotics for pseudomonas-infected SINS. (**c**) Infective scleritis with Aspergilla after pterygium surgery and MMC

reported to be a common bacterial pathogen associated with scleritis (Okhravi et al. 2005), as well as tuberculosis (TB) in a study from Japan, where 6 of 83 (7.2%) cases of scleritis were secondary to TB (Keino et al. 2010). Tuberculosis-associated scleritis is mostly seen in endemic regions, where it is typically nodular and multibacillary such that TB organisms can be cultured from the nodules. It comprises up to 40% of cases of all scleritis in Thailand (Reinprayoon et al. 2015). Fungal scleritis is a rare entity; however, it is more common in hot and humid climates, such as in India (Jain et al. 2009). A series of cases of infectious scleritis from India found fungi to be the most common pathogen, occurring in 8 of 21 (38%) eyes, with *Aspergillus flavus* being the most common fungus isolated in these cases (Jain et al. 2009).

Pathogenesis of Posterior Scleritis

There is a dearth of knowledge of the pathology and pathogenesis of noninfectious scleritis, particularly posterior scleritis. This is due to the lack of availability of ocular tissue and the absence of an animal model of the disease. Studies of ocular specimens from patients with severe scleritis are derived from subjects with chronic, severe end stage disease, likely modified by therapy and often burnt out or quiescent disease. Posterior scleritis is a clinical diagnosis, and scleral biopsy is not usually performed to confirm the diagnosis unless a diagnosis of infection (e.g. suspected fungal scleritis) or malignancy (masquerade syndrome) is suspected.

Most studies of the histopathology of scleritis are derived from specimens of anterior scleritis. Riono et al. described the histological findings in ocular tissue specimens from patients with severe end stage noninfectious scleritis (Riono et al. 1999). Two major histological types of scleritis were described. Biopsy specimens from patients with rheumatoid arthritis (RA)-associated scleritis had necrosis associated with granulomatous inflammation. In contrast, scleral tissue from patients with noninfectious scleritis had a chronic inflammatory infiltrate, without necrosis. Recent studies indicate that the majority of inflammatory cells in RA-associated scleritis were B cells (CD20) (43%) and CD68 positive macrophages (35%). In patients with idiopathic scleritis, histological studies indicate that most cells were macrophages (CD68+ (43%)) and T cells (CD3+ (23%)), with 17% B cells (CD20) and 7% CD8+ T cells. Thus, CD20+ B cells and macrophages are the predominant cell types in ocular tissue derived from patients with severe chronic scleral inflammation.

Based on clinical observations, angiographic studies and the association of posterior scleritis with systemic vasculitic syndromes, such as GPA, it has been proposed that scleritis is a localised form of vasculitis. Watson first studied anterior segment angiography and histology in a patient with severe anterior scleritis, which revealed evidence of vascular occlusion and ischemia. In one study of biopsied anterior scleritis vasculitis with fibrinoid necrosis of scleral vessels and neutrophil invasion of the blood vessel wall was observed in three quarters of the scleral biopsies and over 50% of the conjunctival biopsy specimens.

Recent research into the pathogenesis of systemic autoimmune diseases and vasculitis has important implications for understanding the immunopathogenesis of posterior scleritis. Systemic vasculitis is one of the most common clinical associations of posterior scleritis. ANCA-associated vasculitis (AAV) diseases comprise three distinct clinical syndromes: granulomatosis with polyangiitis (GPA) previously known as Wegener's granulomatosis, microscopic polyangiitis (MPA) previously known as polyarteritis nodosa, and Churg–Strauss syndrome (CSS). These syndromes feature necrotizing vasculitis of small vessels, which commonly involves the eye as well as kidneys, lungs, joints and skin. A unifying clinical feature of these diseases is the presence of serum ANCA antibodies. The two major antigenic specificity of ANCA are proteinase 3 (PR3) and myeloperoxidase (MPO). PR3 and MPO are enzymes present in the cytoplasmic granules of neutrophils and monocytes. PR3 and MPO are found intracellularly, except when cells are activated by cytokines or microbes, which result in cell surface expression of these enzymes (Harper et al. 2001). As neutrophil and macrophage infiltrates are commonly present in the early lesions of scleritis and vasculitis (Brouwer et al. 1994), the release of oxygen radicals and proteases from the infiltrating cells augments inflammation and injury in the involved tissue.

The role of ANCA in the pathogenesis of vasculitis and scleritis is evidenced by the placental passage of ANCA antibodies to new born children that are able to induce disease in the neonate. In addition, clinical trials have demonstrated the efficacy of B cell depletion therapy and plasma exchange in the treatment of patients with ANCA associated vasculitis and scleritis.

The aetiology and/or initiating factors associated with posterior scleritis and systemic vasculitis remain unclear. Microbial infections with Hepatitis B and C are known to cause microscopic polyangiitis and cryoglobulinemic vasculitis, and colonisation with *Staphylococcus aureus* (*S. aureus*) has been implicated in the pathogenesis of AAV. Nasal carriage of *S. aureus* is a risk factor for disease relapse in AAV and antibiotic therapy reduced the rate of disease relapse. AAV may be triggered by a microbial infection of the respiratory tract and such infection may result in super-antigens, membrane proteins and/or peptidoglycans that stimulate antigen-presenting cells (APCs) to secrete a variety of inflammatory mediators such as IL-17 and IL-23 that promote a chronic inflammatory response.

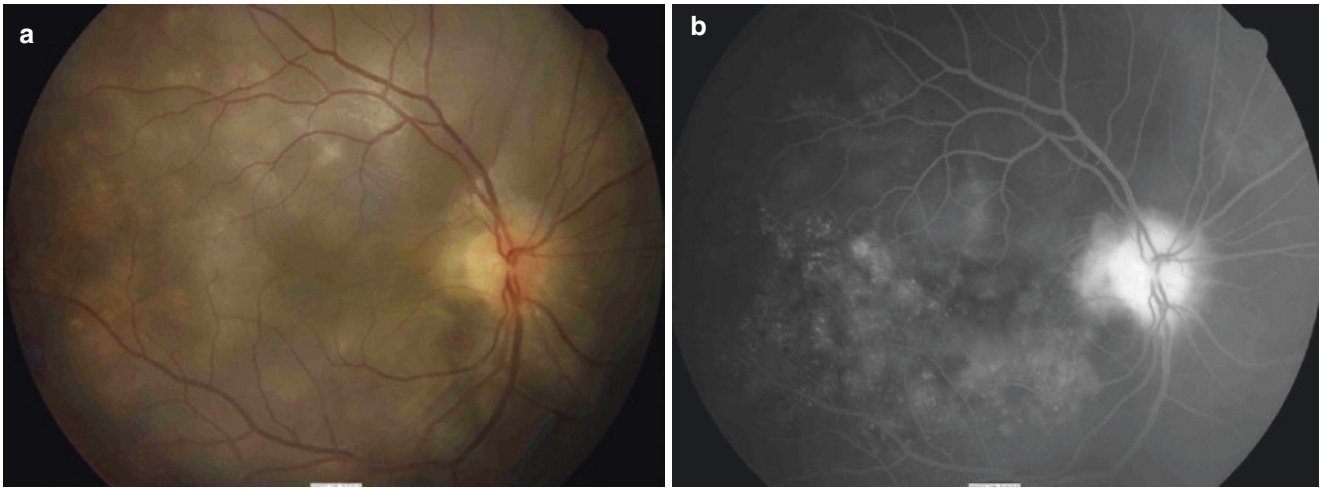

Fig. 14.9 Fundus photo (**a**) and fluorescein angiogram (**b**) of a posterior scleritis patient with multifocal serous detachments and retinal pigment epithelium changes

A characteristic feature of posterior scleritis is the destruction of the sclera and adjacent tissue. The tissue destruction is mainly due to the activity of matrix metalloproteinases (MMP). These proteolytic enzymes play a key role in tissue remodelling. Studies indicate that scleral fibroblasts, as well as inflammatory cells, such as macrophages and T lymphocytes, express MMP-3, MMP-9 and TIMP-1 in tissue from patients with necrotizing scleritis (Di Girolamo et al. 2013). In addition, the cytokine tumour necrosis factor-alpha (TNF-α), a well-recognised inducer of MMPs, was detected in infiltrating inflammatory cells, particularly plasma cells. Furthermore, cultured human scleral fibroblasts stimulated with interleukin-1 alpha (IL-1α) and TNF-alpha increased TIMP-1 and MMP-3 by sevenfold. It is likely that increased knowledge of the molecular mechanisms involved in the pathogenesis of posterior scleritis will result in more selective therapy for this disease.

Ocular Complications

Ocular complications are frequent in patients with scleritis, with complication rates typically reported in 49–60% of cases (Berchicci et al. 2014; Jabs et al. 2000). However, this was much higher in a Japanese study at 78% (Keino et al. 2010) and higher again in a study from the Netherlands with a rate of 84.6% (Wieringa et al. 2013). Complications are found far more frequently in those with necrotizing anterior and posterior scleritis than the other forms of the disease (Sainz de la Maza et al. 2012; Gonzalez-Lopez et al. 2016).

Reduction of visual acuity with posterior scleritis at presentation is a common feature, with 38.6% of patients having a visual acuity worse than 6/12 (logMAR 0.3) at presentation (Lavric et al. 2016). Similar figures were found in a study by McCluskey, with 31% of 99 patients having a reduction in visual acuity (McCluskey et al. 1999). Reduction of visual acuity in posterior scleritis can result from changes to the curvature of the posterior pole resulting in refractive shift secondary to subtle posterior staphyloma formation or from forward movement of lens-iris diaphragm due to ciliary body rotation, serous retinal detachment, macular change including macular oedema, optic nerve atrophy, vitritis, pars planitis and optic nerve head oedema (Anshu and Chee 2007; Beardsley et al. 2013) (Fig. 14.9).

In the study of Watson and Hayreh, every case of posterior scleritis was complicated by posterior uveitis (Watson and Hayreh 1976) (Fig. 14.10). In his study, uveitis did not correlate with any specific associated disease. Other common complications include—cataract (up to 7.6%) and ocular hypertension/glaucoma (ranging between 0.9 and 22%). The rise in ocular pressure is mostly able to be controlled on glaucoma drops (Jabs et al. 2000; Lavric et al. 2016).

Investigations

In every patient with posterior scleritis, it is essential to exclude infection and an associated systemic disease, particularly AAV such as GPA or PAN, as these disorders commonly present as scleritis and are potentially fatal (Raiji et al. 2009; Akpek et al. 2004).

Initial evaluation of patients with posterior scleritis involves a comprehensive history with a detailed systemic review, thorough examination, OCT, (Figs. 14.11 and 14.12), FFA and B-scan ultrasonography (Fig. 14.13) with CT scan and MRI as indicated (Fig. 14.14). Blood pressure measurement and urine analysis should be performed on the day of presentation.

All patients should undergo a chest X-ray and ANCA testing. Other relevant blood tests include liver and renal function, urinalysis, rheumatoid factor, anti-CCP antibodies and ANA. A positive ANCA titre requires specific anti-myeloperoxidase and anti-proteinase 3 ANCA titres to determine the specificity of ANCA antibodies. Additional investigations, such as acute phase response reactant levels, HLA-B27 determination, serum angiotensin converting enzyme, sinus imaging and biopsies of other involved organs, are determined by clinical assessment, consultation with other medical specialists and abnormalities detected on investigations.

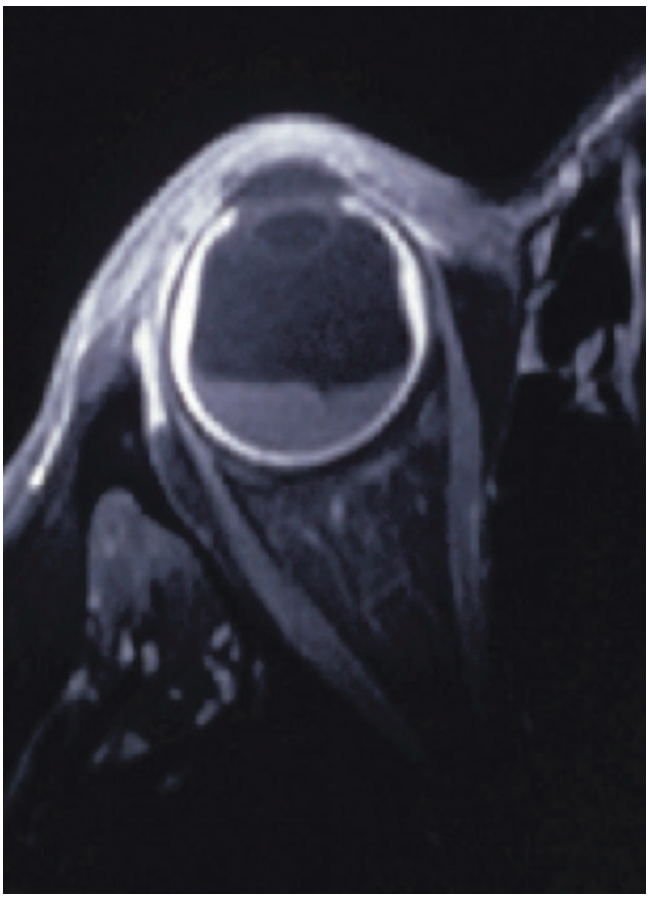

Fig. 14.10 MRI showing serous retinal detachment with contrast enhancement of choroid in posterior scleritis

Diagnosis of infectious scleritis is of critical importance as the management is completely different, as systemic immunosuppressive therapy will worsen the condition. All patients should have syphilis, HBV, HCV and Lyme serology and exclusion of TB. If bacterial, fungal or acanthamoeba infection is suspected, scleral scraping or biopsy should be performed. If an ulcerative lesion is present, scleral scrapings are taken from the base of the active lesion. If a biopsy is planned, it is often best undertaken in the operating theatre, where adequate anaesthesia enables a sterile, pain free procedure. If there is a non-ulcerative lesion, episcleral and scleral specimens are collected following careful dissection of the overlying conjunctiva. Specimens should be collected for microscopy and culture on blood and chocolate agar, brain-heart infusion broth, thioglycollate broth, non-nutrient agar with an overlay of *Escherichia coli* and Sabouraud's dextrose agar (Jain et al. 2009). If a herpes infection is suspected, conjunctival or sclero-conjunctival biopsy is required for PCR testing and immunofluorescence studies (Bhat et al. 2009). Specimens should also be collected for histopathology and immunopathology.

Pretreatment Evaluation

We have recently published recommendations for the pretreatment assessment of patients with severe inflammatory eye disease prior to commencing glucocorticoids, steroid sparing drugs and biologicals (Wakefield et al. 2017). This approach is also applicable to patients with posterior scleritis who often require high dose steroids and similar second line drugs as used in the management of severe uveitis. This approach is mainly aimed at predicting and preventing the potential side effects of long-term immunosuppressive therapy.

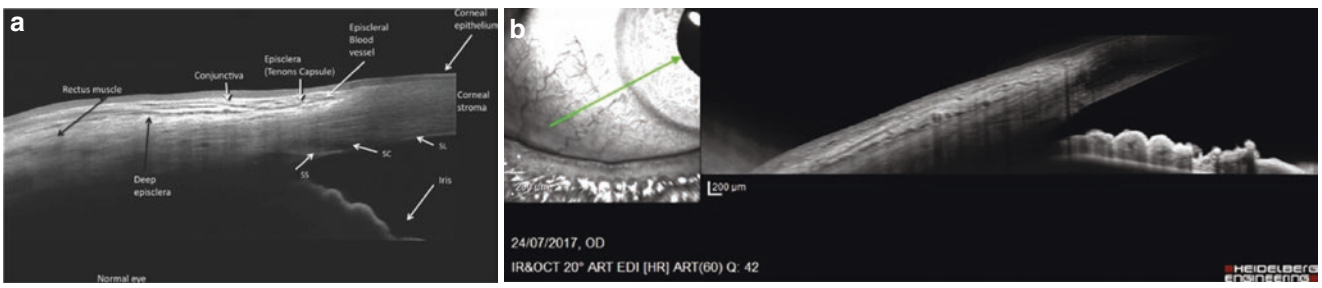

Fig. 14.11 (**a**) Normal anterior sclera and chamber angle with anterior segment OCT. (Watson and Romano 2014 with permission) (**b**) Anterior OCT of patient with scleritis showing marked oedema of the sclera with separation of the collagen fibres and infiltration with inflammatory cells in the deeper layers of the sclera

Management

Management of scleritis is based on clinical assessment of the type of and severity of disease, presence of systemic disease or infection and presence of ocular complications. A careful history, detailed ocular and physical examination and targeted investigations are critically important to determine if there is an underlying systemic autoimmune disease or a local or systemic infectious cause. Treatment of posterior scleritis requires systemic therapy and usually involves a stepped approach.

Treatment of posterior scleritis involves a stepped approach. While the majority of patients will respond to oral prednisolone, a significant percentage require steroid sparing and second-line immunosuppressive agents. Biologic agents are increasingly used in refractory cases, especially when associated with a systemic vasculitis.

To date, there have been no randomized control trials to guide scleritis therapy. In a large retrospective series (Jabs et al. 2000) data on treatment and response to treatment was

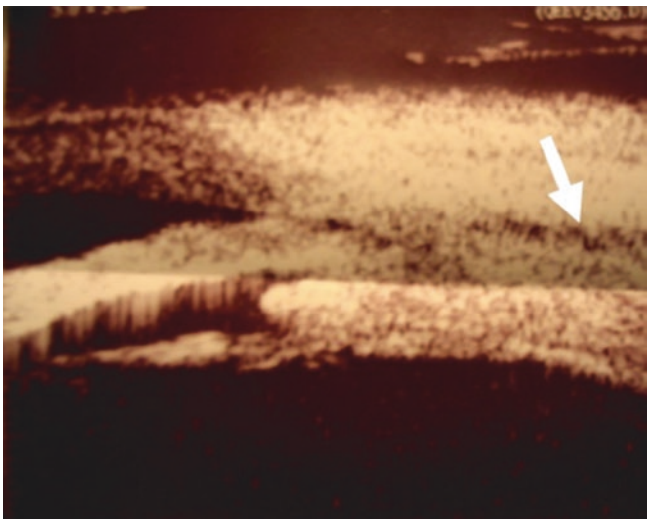

Fig. 14.12 Anterior segment UBM showing supraciliary body fluid, anterior rotation of ciliary processes and secondary angle closure

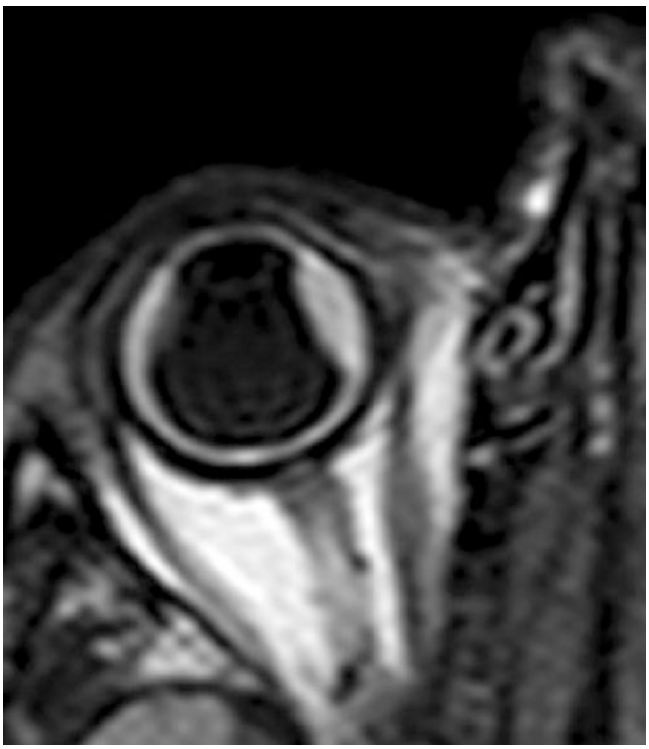

Fig. 14.14 High resolution MRI showing sclera thickening (black), contrast enhancement of choroid (white), suprachoroidal effusion and serous retinal detachment

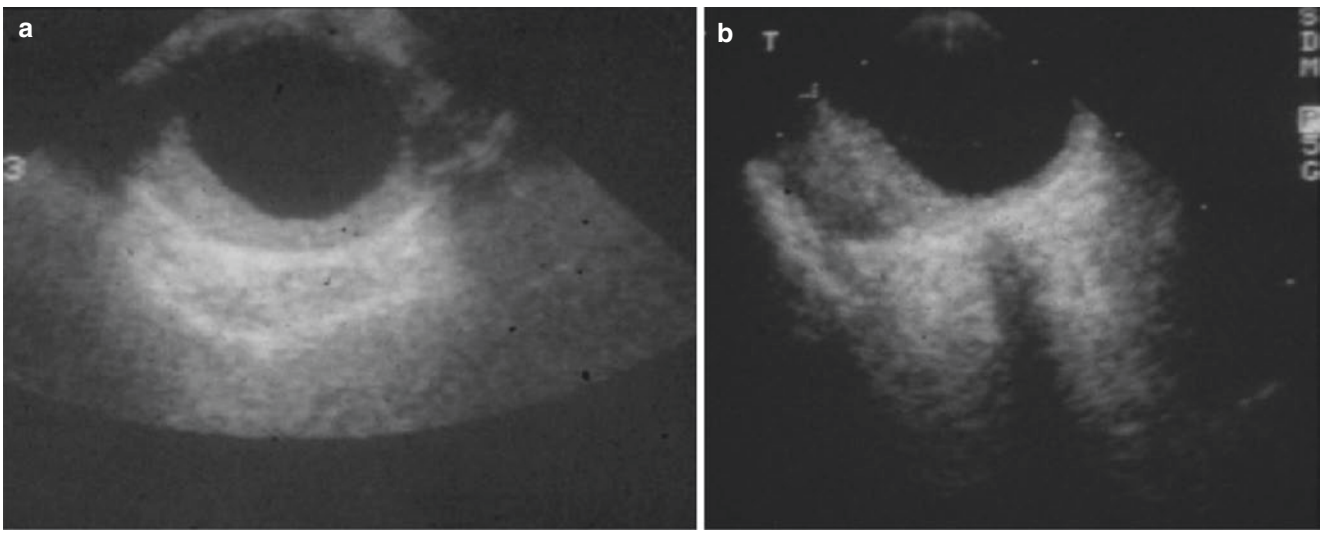

Fig. 14.13 (**a**) Diffuse verse (**b**) Nodular scleritis on B scan

available for 69 patients with scleritis. Overall, approximately 30% of patients were treated with NSAIDs, 32% required oral prednisolone and 26% needed additional immunosuppressive drugs. This series, in addition to an earlier analysis of therapeutic failure for initial regimens in 132 patients with noninfectious anterior scleritis (Sainz de la Maza et al. 1993), has provided useful treatment guidelines for the various subtypes of scleritis. Noninfectious scleritis is generally treated with systemic NSAIDs, systemic steroids, immunomodulatory agents or a combination of these (Albini et al. 2005b). The use of NSAIDs varies from 30 to 49%, systemic steroids in 12–31.9% and immunomodulatory agents in 26.1–34% (Jabs et al. 2000; Berchicci et al. 2014).

Posterior scleritis is treated with oral corticosteroids (83%), and less frequently immunosuppressive agents (17%) (Jabs et al. 2000). An associated systemic autoimmune disorder increases the need for more aggressive systemic immunosuppressive therapy (McCluskey et al. 1999). In a 2016 retrospective study looking at the use of flurbiprofen in noninfectious non-necrotizing scleritis, treatment failure was 10-fold higher in those with an associated systemic autoimmune disease (Cunningham et al. 2016). Patients with systemic vasculitis have a greater requirement for systemic immunosuppression (Akpek et al. 2004). A Swiss study found that at 5 years, 52% of patients with autoimmune-mediated scleritis had ongoing symptoms, and the presence of circulating autoantibodies tended to favour prolonged inflammatory episodes (Bernauer et al. 2014). Even in patients with no detectable clinical evidence of systemic vasculitis, the presence of an elevated c-ANCA has been associated with more refractory scleritis requiring systemic immunomodulator therapy (Hakin and Watson 1991). In general, those with bilateral disease, necrotizing scleritis, or systemic associations tend to have a poorer prognosis, more frequent complications and a greater chance of requiring systemic immunological therapy (Wieringa et al. 2013).

Corticosteroids are highly potent anti-inflammatory drugs, with the potential for severe side effects from long term use, such as cushingoid changes, iatrogenic diabetes mellitus, hypercholesterolaemia, osteoporosis and increased risk of infection (Charkoudian et al. 2012). Some have advocated the use of pulsed intravenous high-dose corticosteroids and triamcinolone injections as a means of reducing the side effect profile while maintaining rapid anti-inflammatory activity (Charkoudian et al. 2012).

Immunomodulatory agents commonly used in the treatment of posterior scleritis include methotrexate, azathioprine, cyclosporine, cyclophosphamide, mycophenolate and chlorambucil (Lavric et al. 2016). Recent studies indicate that monoclonal antibodies (infliximab and adalimumab) are superior to the soluble TNF receptor fusion protein etanercept for the treatment of scleritis in patients that do not respond to corticosteroids and/or to immunosuppressive treatment. Rituximab has been reported to be effective in patients with scleritis associated with systemic vasculitis (De Fidelix et al. 2015). As a general observation, aggressive systemic treatment of an associated systemic autoimmune disease or vasculitis will also be effective in managing the posterior scleritis.

Infections such as Tuberculosis, Varicella Zoster, *Pseudomonas aeruginosa* and *Staphylococcus aureus* can each cause necrotizing scleritis that are clinically similar to noninfectious scleritis (Biswas et al. 2012). Missed or delayed diagnosis can have disastrous consequences, potentially leading to vision loss, evisceration, or reactivation/worsening of systemic infection (Cunningham et al. 2016). Clinicians must ensure they have carefully considered an infectious cause for posterior scleritis prior to initiating systemic immunosuppression.

Management of infectious scleritis remains a challenge, and poor penetration of antibiotics into the avascular sclera makes systemic therapy difficult (Sainz de la Maza et al. 2012). Up to 60% of cases of infectious scleritis lead to complete loss of vision or evisceration according to one review article (Accorinti et al. 2013), and is as high as 75% in cases of pseudomonas infection (Helm and Holland 1993). Treatment often requires use of immunomodulatory agents in addition to antibiotic therapy.

Posterior scleritis is an uncommon disease causing pain and visual loss. It can be associated with other systemic diseases, in around 40% of cases, mainly rheumatoid arthritis and systemic lupus erythematous. Response to systemic corticosteroid therapy is usually good, although around 1 in 3 patients will require systemic immunosuppression, with good visual outcome, even in those presenting with reduced vision (Lavric et al. 2016).

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Autoimmune Retinopathy

15

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Introduction

Autoimmune retinopathy (AIR) is a group of presumed immune-mediated disorders characterized by antiretinal antibodies, retinal neuronal dysfunction, and visual impairment. It is thought that AIR is caused by cross-reactivity of serum autoantibodies directed against retinal and retinal-like antigens, leading to retinal degeneration (Comlekoglu et al. 2013; Grange et al. 2014; Forooghian et al. 2015; Grewal et al. 2014).

AIR can be divided into paraneoplastic AIR and nonparaneoplastic AIR. Paraneoplastic AIR includes cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). The CAR was first described by Sawyer et al. in 1976, and MAR was first described by Berson et al. in 1988 (Sawyer et al. 1976; Berson and Lessell 1988). The MAR, a paraneoplastic syndrome associated with cutaneous malignant melanoma, is associated with characteristic clinical and laboratory features, which distinguish MAR from CAR. Laboratory investigations revealed autoantibodies against recoverin in the serum of patients with CAR, representing the underlying etiology of CAR (Thirkill et al. 1992). In 1997, nonparaneoplastic AIR was first described in two patients with similar clinical features to CAR but without malignancy (Mizener et al. 1997).

Pathogenesis

All types of AIRs including CAR, MAR, and nonparaneoplastic AIR may share a common mechanism of retinal damage secondary to circulating anti-retinal antibodies. Several retinal proteins have been suggested as auto-antigens, including recoverin, alpha-enolase, transient receptor potential melastatin 1 (TRPM1), carbonic anhydrase, arrestin, transducin, TULP1, heat shock protein-70, etc. (Comlekoglu et al. 2013; Grange et al. 2014; Forooghian et al. 2015; Grewal et al. 2014).

Studies have suggested that paraneoplastic AIR is caused by molecular mimicry between tumor antigens and retinal proteins. For example, TRPM1, which is required for depolarizing light response of retinal ON-bipolar cells, is expressed in the tumor cells of melanoma patients with MAR. Sera from some of the MAR patients contain autoantibodies that label retinal bipolar cells (Keltner et al. 2001). These autoantibodies are not present in healthy individuals but may be present in patients with melanoma without reported visual problems (Ladewig et al. 2005). A recent study found that TRPM1 autoantibodies in MAR patients recognize a short, intracellular segment of TRPM1, encoded by exon 9 and 10 (Duvoisin et al. 2017). This TRPM1 region is highly conserved with TRPM3, with which MAR sera were found to cross-react (Duvoisin et al. 2017). This cross-reactivity with TRPM3 may account for other ocular changes associated with retinal pigment epithelium, where TRPM3 is expressed (Duvoisin et al. 2017).

Clinical Features

Patients with AIR have diverse symptoms such as vision loss, visual field defect, photopsia, dychromatopsia, nyctalopia, and photoaversion (Comlekoglu et al. 2013; Grange et al. 2014; Forooghian et al. 2015; Grewal et al. 2014). The AIR is usually bilateral, but can be asymmetric. The fundus examination may show cystoid macular edema, retinal vascular attenuation, atrophy of retina, RPE changes such as bony spicules-like lesions, and pale disc (Comlekoglu et al. 2013; Grange et al. 2014; Forooghian et al. 2015; Grewal et al. 2014). However, in many cases, the fundus appears normal or unremarkable initially. Although AIR is an immune-mediated disease, anterior chamber or vitreous inflammatory reaction is minimal or absent. The mean age of

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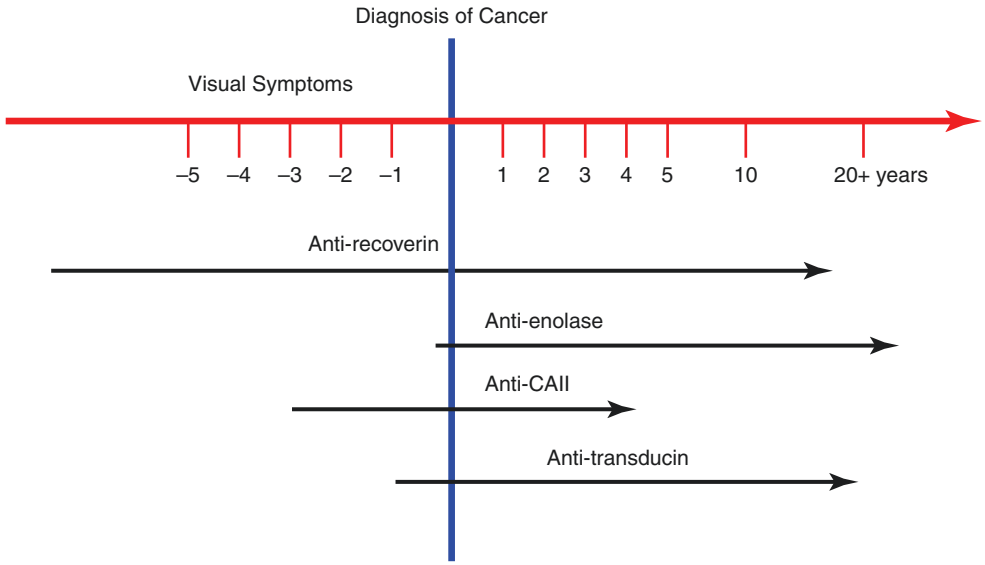

Fig. 15.1 A diagram showing a relationship between the detection of specific autoantibodies and the time of cancer diagnosis in patients with visual symptoms (Adamus 2009 with permission)

onset is about 50–65 years, but AIR can also be found in young patients (Grange et al. 2014; Forooghian et al. 2015; Adamus 2009).

The CAR is characterized by acute, progressive loss of vision associated with photopsia, attenuated retinal vessels, visual field defects, and abnormal electroretinogram (ERG) (Comlekoglu et al. 2013; Grange et al. 2014; Forooghian et al. 2015; Grewal et al. 2014). The MAR is characterized by night-blindness, visual field defects, and markedly reduced dark adapted b-wave, indicating compromised bipolar cell function. The CAR usually manifests at the onset of a malignancy with variable duration between cancer detection and development of AIR, while MAR commonly presents after the melanoma has been diagnosed. The MAR often occurs at the time of metastases. Figure 15.1 shows a relationship between the detection of specific anti-retinal antibodies and the time of cancer diagnosis in patients with visual symptoms (Adamus 2009). Autoantibodies specific against recoverin, transducin-α, α-enolase, and carbonic anhydrase II can be found months to years before cancer is clinically detected (Adamus 2009).

Visual-field tests show constriction or various types of scotomas. Full-field ERG may show severely decreased amplitude in dark-adapted or light-adapted responses, bipolar cell responses or a combination of these responses (Grange et al. 2014). Spectral domain OCT (SD-OCT) can show disruption of the photoreceptor layer or cystoid macular edema (Grange et al. 2014). Fundus autofluorescence (FAF) showed abnormal autofluorescence patterns, mainly in the form of an hyperautofluorescent ring in the parafoveal region that corresponds to loss of outer-retinal structures on SD-OCT (Grange et al. 2014). Grange et al. mentioned that in their experience with 24 patients with nonparaneoplastic AIR, about half of the patients showed loss of the inner/outer segment on SD-OCT and parafoveal hyperautofluorescent ring or at least mild speckling on FAF (Grange et al. 2014). An example of fundus photographs and SD-OCT in a patient with nonparaneoplastic AIR is shown in Fig. 15.2 (Eo et al. 2015).

Diagnostic Approaches

The diagnosis of nonparaneoplastic AIR is usually made based on the presence of antiretinal antibodies and a combination of certain clinical features, in the absence of another specific cause. Recently, criteria and tests for the diagnosis of nonparaneoplastic autoimmune retinopathy including clinical criteria and a standardized assay system for antiretinal antibody detection were suggested by expert panel consensus (Table 15.1) (Fox et al. 2016). The diagnostic criteria include five essential and three supportive criteria. This consensus report mentioned that experts agreed that in order to make the diagnosis of AIR, all essential diagnostic criteria needed to be present. However, the significance of supportive criteria in making the diagnosis was not explored. In this report, consensus was also reached on the six core diagnostic tests to be performed at the initial diagnostic examination (Table 15.1). The core diagnostic tests do not include visual field test or color vision test. Table 15.2 shows basic laboratory survey summary on the detection of antiretinal antibodies for diagnosis of AIR from the expert panel consensus (Fox et al. 2016). Experts agreed that a diagnostic assay system should have a 2-tier design to maximize sensitivity and specificity (i.e. Western blot or immunohistochemistry can be performed initially and subsequently followed by a different diagnostic method among the three methods listed in Table 15.2) (Fox et al. 2016). An example of

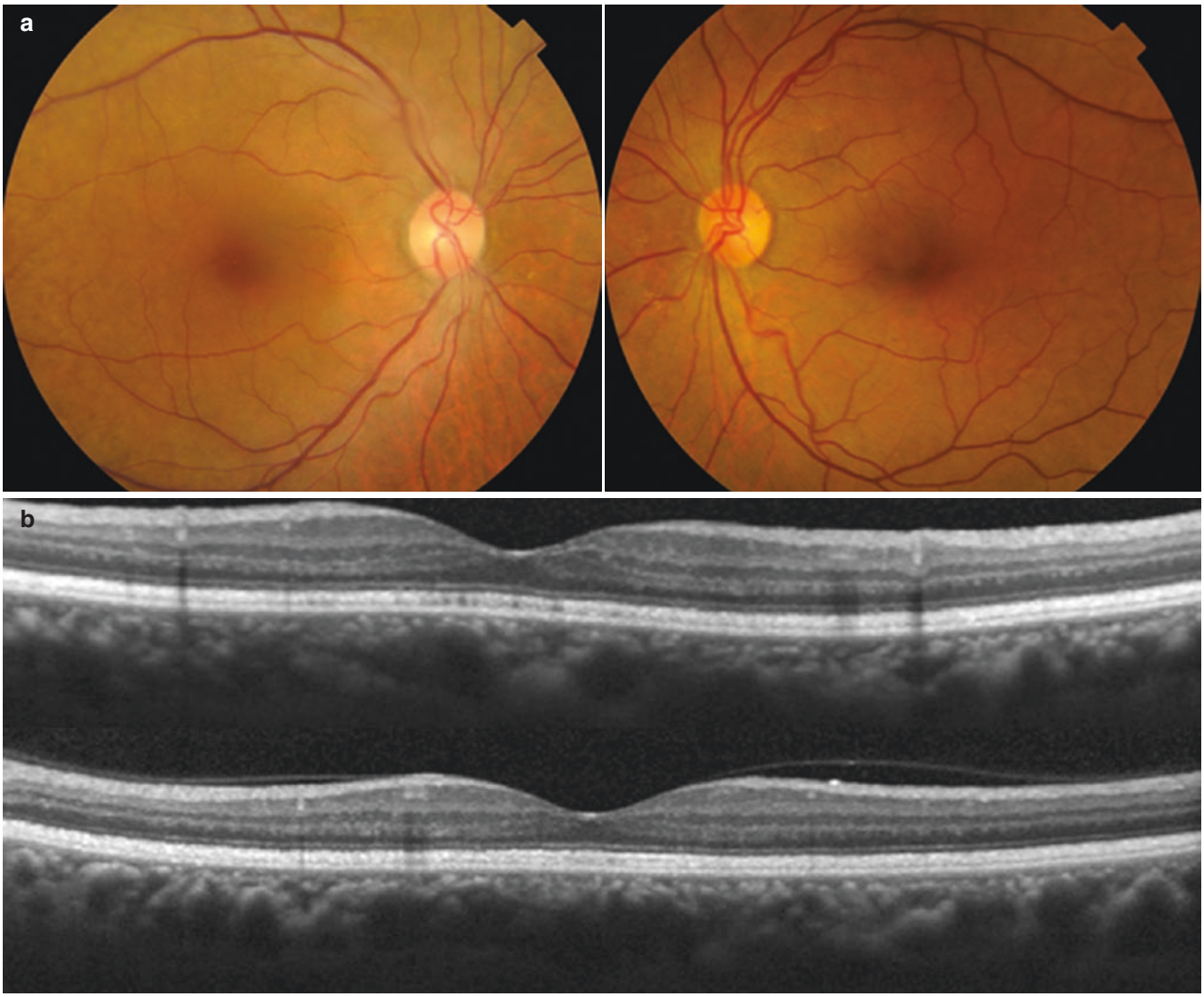

Fig. 15.2 Fundus photographs (**a**) and Spectral-domain coherence tomography (SD-OCT) images (**b**) from a patient with nonparaneoplastic autoimmune retinopathy. Fundus photographs shows no remarkable findings. SD-OCT shows subtle obscuration and interruption of the inner segment/outer segment junction of the photoreceptors in both eyes (Eo et al. 2015 with permission)

Western blot in a patient with nonparaneoplastic AIR is shown in Fig. 15.3 (Eo et al. 2015). However, consensus was not reached on the ideal tissue type to use for fixation and detection of serum antiretinal antibodies: three experts selected human tissue and three selected monkey tissue as the ideal tissue type (Fox et al. 2016). This report also mentioned that a simple majority consensus agreed that the number of positive antiretinal antibody subtypes should have more weight toward the diagnosis of AIR (Table 15.2); however, multiple experts stated that more evidence and studies are needed before developing a more complex, weighted assay system (Fox et al. 2016). The MAR and CAR can be diagnosed with similar approaches but with the presence of skin melanoma or other types of cancer, respectively.

Management

There is no established treatment guideline or protocol for AIR due to lack of prospective clinical trials in AIR. However, various immunomodulatory therapies have been tried because AIR is presumably caused by cross-reactivity of serum autoantibodies against retinal and retinal-like antigens. In paraneoplastic AIR, treating underlying malignancy may be helpful. Most previous clinical studies are retrospective case series studies.

In 2009, Ferreyra et al. reported the results of immunosuppression therapy including cyclosporine, infliximab, azathioprine, and mycophenolate in six patients with CAR and 24

Table 15.1 Criteria and tests for the diagnosis of nonparaneoplastic autoimmune retinopathy (Fox et al. 2016 with permission)

Criteria and tests for the diagnosis of autoimmune retinopathy	
Diagnostic criteria for AIR[a]	
Essential diagnostic criteria	Supportive diagnostic criteria
No apparent cause responsible for visual function abnormality[b] ERG abnormality (with or without visual field abnormality) Presence of serum antiretinal antibodies Absence of fundus lesions and retinal degeneration or dystrophy that may explain visual function loss[c] Absence of overt intraocular inflammation[d]	Symptoms: Photopsias or scotomas or dychromatopsia or nyctalopia or photoaversion Systemic autoimmune disease: personal or family History Rapidity of onset of vision change[e]
Core diagnostic test[f]	
Malignancy workup by appropriate physician Electroretinogram Serum antiretinal antibody testing	Fundus Autofluorescence Optical Coherence Tomography Fluorescein Angiogram

AIR = autoimmune retinopathy
[a]All Essential Diagnostic Criteria must be present and Supportive Diagnostic Criteria are not necessary to make the diagnosis of AIR
[b]Including no evidence of malignancy
[c]Absence of chorioretinal lesions (other than incidental/small peripheral benign degenerations such as pavingstone, lattice, etc, or old toxoplasmosis scar) or absence of retinal dystrophy, retinitis pigmentosa, or other hereditary retina vitreal disorders
[d]Less than 1+ intraocular cells or haze present
[e]Acute (0–3 months) or subacute (3–6 months)
[f]Essential to the diagnosis of AIR and should be performed at the initial or first diagnostic evaluation when AIR is suspected

Table 15.2 Basic laboratory survey summary: detection of antiretinal antibodies for diagnosis of autoimmune retinopathy (Fox et al. 2016 with permission)

Basic laboratory survey consensus items[a]
Standardization of a diagnostic assay system is essential to understanding the role of antiretinal antibodies in the pathogenesis of AIR
A 2-tier diagnostic assay system should be used to detect antiretinal antibodies
Methods to identify antiretinal antibodies should include: Western blot, immunohistochemistry, or enzyme-linked immunosorbent assay[b]
Number of positive antiretinal antibody subtypes identified should have more weight toward the diagnosis of AIR[b]
There is not enough evidence for or against determining whether antiretinal antibody subtypes should have differential weight toward the diagnosis of AIR[b]

AIR = autoimmune retinopathy
[a]Includes items meeting simple or supermajority consensus
[b]Items meeting simple majority consensus

patients with nonparaneoplastic AIR (Ferreyra et al. 2009). In this study, all six CAR patients, 7 of 13 (54%) with nonparaneoplastic AIR, and 8 of 11 (73%) with nonparaneoplastic AIR and cystoid macular edema showed improvement. About 5 of 21 patients (24%) had improvement in visual acuity, and 15 of 21 (71%) had expansion of visual field area.

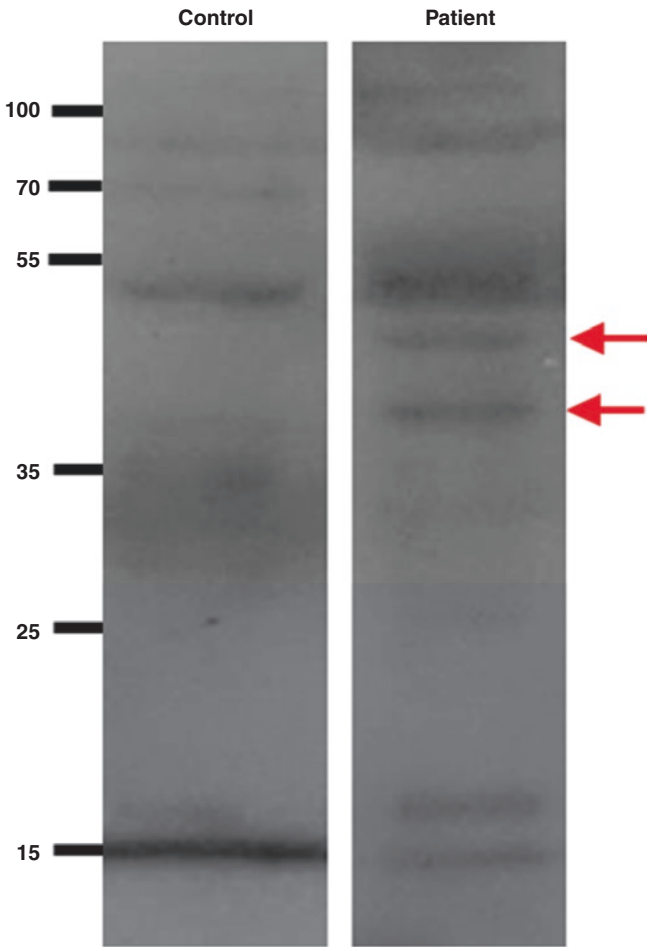

Fig. 15.3 Western blot to detect anti-retinal autoantibody using human retinal tissue and serum from a patient with nonparaneoplastic autoimmune retinopathy. Arrows indicate proteins that react with serum from patient, not with serum from control. Band A near 46 kDa and band B near 39 kDa (Eo et al. 2015 with permission)

In 2017, Davoudi et al. reported the outcomes of rituximab in patients with AIR. Rituximab is a monoclonal antibody against CD20+ B cells and approved for several rheumatologic and hematologic diseases (Davoudi et al. 2017). This retrospective interventional case series included 30 eyes of 16 consecutive AIR patients (6 CAR, 1 MAR, and 9 nonparaneoplastic AIR) treated with rituximab. Fifteen patients had been treated with immunosuppressive therapy prior to rituximab initiation. One patient was treatment-naïve. In total, 23 of 30 eyes (77%) had stable or improved visual acuity 6 months after rituximab initiation, and the rate of visual decline was less after rituximab initiation compared with the rate prior to rituximab initiation. In this study, two patients showing significant visual improvement were treated early on in their disease course, and the majority of patients whose vision worsened despite rituximab treatment were initiated at an advanced stage, suggesting earlier treatment with rituximab may be more effective.

Table 15.3 Treatments and follow-up tests to consider in autoimmune retinopathy (Fox et al. 2016)

Treatment and management of air	Follow-up tests
Steroids (systemic or local)[a]	Electroretinography
Conventional immunosuppressives[a] (such as antimetabolites and T cell inhibitors)	Humphrey visual fields, Goldmann visual fields
Biologics (such as monoclonal antibodies)	Visual acuity
Intravenous immunoglobulin	Optical coherence tomography
	Color vision testing

AIR = autoimmune retinopathy

[a]All experts agreed that steroids and conventional immunosuppressives should be considered as first- or second-line treatment in the management of AIR patients

The expert panel consensus published in 2016 suggested that that steroids (local or systemic) and conventional immunosuppressives (antimetabolites or T cell inhibitors) should be used as first- or second-line treatments for AIR (Table 15.3) (Fox et al. 2016). Consensus was achieved for the following treatment types to be considered appropriate regardless of the stage of disease: steroids (local or systemic), conventional immunosuppressives (such as antimetabolites or T cell inhibitors), biologics (such as monoclonal antibodies), and intravenous immunoglobulin. Expert panel consensus on the treatments and follow-up tests in AIR are shown in Table 15.3 (Fox et al. 2016).

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Intraocular Tuberculosis

16

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Introduction

Tuberculosis (TB) is an endemic disease in many countries of the developing world and is associated with severe morbidity and mortality. Intraocular tuberculosis (IOTB) is a rare condition that may present with severe visual debilitating symptoms and often presents as a diagnostic challenge due to its protean manifestations (Gupta et al. 2007, 2015b). IOTB often presents as posterior uveitis (Gupta et al. 2015b). Thus, early recognition of IOTB and its prompt management with specific therapy are an important aspect of uveitis practice especially in developing countries.

IOTB can affect various ocular structures resulting in a wide spectrum of clinical manifestations. Due to its widespread involvement of the ocular tissue, there can be various reasons for visual loss and the patient may present with a wide range of ocular symptoms and signs. Involvement of the anterior chamber can result in inflammation involving the iris and ciliary body. The choroid is the most common site of IOTB due to its high vascularity. *Mycobacterium tuberculosis* may reside inside retinal pigment epithelial (RPE) cells resulting in various posterior segment manifestations. TB-related posterior uveitis can present as choroidal tubercles, choroidal granulomas/subretinal abscesses, serpiginous-like choroiditis (also known as multifocal serpiginoid choroiditis), retinal vasculitis, neuroretinitis, endophthalmitis, and panophthalmitis (Bansal et al. 2012; Gupta et al. 2003, 2015a, b; Ni et al. 1982).

The index chapter focuses on the clinical and imaging features of patients with IOTB including anterior as well as posterior segment disease. In addition, the treatment of TB and its challenges such as drug-resistant TB have been highlighted.

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Intraocular Tuberculosis

IOTB is often a bilateral disease resulting in severe visual symptoms (Bansal et al. 2012). In case the disease is unilateral, it can recur in the opposite eye if not treated with appropriate anti-tubercular therapy (ATT). Patients with IOTB are diagnosed on the basis of positive laboratory evidence of active or latent TB, in contrast to patients with autoimmune serpiginous choroiditis. In addition, there may be evidence of radiological features of past (or present) active TB in the form of lung parenchymal involvement or presence of lymphadenopathy.

Prevalence of IOTB is reported differently in worldwide literature. In developed countries, the incidence rate of IOTB is much lower than the developing countries such as India. In India, IOTB may represent one of the most common causes of posterior uveitis based on studies from North and South India. IOTB has no age or sex predilection. *Mycobacterium tuberculosis* can affect any part of the eye.

IOTB is a predominately a paucibacillary disease that is believed to represent an immune-mediated hypersensitivity reaction to the acid-fast bacilli sequestrated in the ocular tissues, notably the RPE. The exact role of various cytokines and interleukins involved in the pathogenesis of IOTB is yet to be elucidated in the literature.

Manifestations of Ocular Tuberculosis

Anterior Uveitis

IOTB presenting as anterior uveitis is classically a chronic granulomatous disease, although a non-granulomatous uveitis may also occur. Anterior uveitis is characterized by mutton-fat keratic precipitates which may be few or diffuse, broad-based posterior synechiae and iris nodules (Fig. 16.1). Uncommonly, it may be associated with granulomas in the angle of the anterior chamber. Chronic, recurrent course of inflammation in the anterior chamber

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produces posterior synechiae, which are typically broad-based and have been identified as having high specificity for TB etiology as compared to other causes of uveitis. However, IOTB may also present as non-granulomatous inflammation including hypopyon uveitis that can mimic noninfectious variety of uveitis related to spondyloarthropathies (Helm and Holland 1993; Karaconji et al. 2013; Velu et al. 2013).

Chronic recurrent anterior uveitis may be complicated with the development of posterior subcapsular cataract. In addition, the posterior synechiae may lead to pupillary block and secondary glaucoma. Band keratopathy and iris neovascularization are other associations in anterior segment disease.

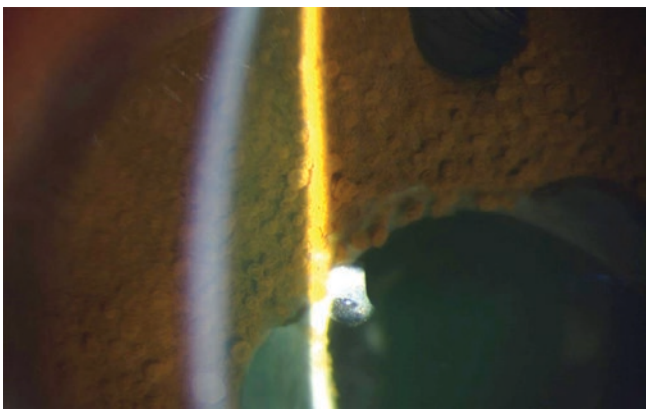

Fig. 16.1 A 4-year-old female presented with vision decrease for the past 6 months. Examination of the anterior segment revealed cells 1+ and flare 2+. The iris was studded with diffuse nodules suggestive of granulomatous inflammation. Her tests for tuberculosis were positive. She was initiated on oral steroids and anti-tubercular therapy

Intermediate Uveitis

IOTB may also present as intermediate uveitis that has nonspecific presentation, but vitritis with snowballs and peripheral retinal phlebitis is common (Parchand et al. 2011). This phenotype is most commonly likely to be mistaken for pars planitis, a disease that has typical phenotype but is believed to be idiopathic.

Intermediate uveitis typically presents with a wax-and-wane course. There may be pars plana exudates, snow balls, and moderate-to-severe vitritis. Usually, there is a presence of cystoid macular edema and peripheral vascular sheathing (Fig. 16.2). Ciliary body tuberculomas may be detected on ultrasound biomicroscopy.

Posterior and Panuveitis

Posterior uveitis is the most common form of uveitis in TB (Gupta and Gupta 2005). Posterior segment manifestations of ocular TB include *serpiginous-like choroiditis* (or *multifocal serpiginoid choroiditis)*, tubercular granulomas or tubercles, subretinal abscesses, neuroretinitis, retinal vasculitis, and rarely endophthalmitis or panophthalmitis (Gupta et al. 2007, 2010; Gupta and Gupta 2005). The following sections describe clinical and imaging characteristics of tubercular lesions that primarily involve retina or choroid.

1. *Choroidal Tubercles/Tuberculoma:*
   Choroidal tubercles were the earliest sign described in IOTB, mostly in association with disseminated TB. They appear as round, small, multiple, well-defined lesions. Choroidal granulomas or tuberculomas or subretinal granulomas are larger in size, solitary, unilateral, and usually in the posterior pole with surrounding exudative retinal detachment (Gupta et al. 2015b; Singh et al. 2012).

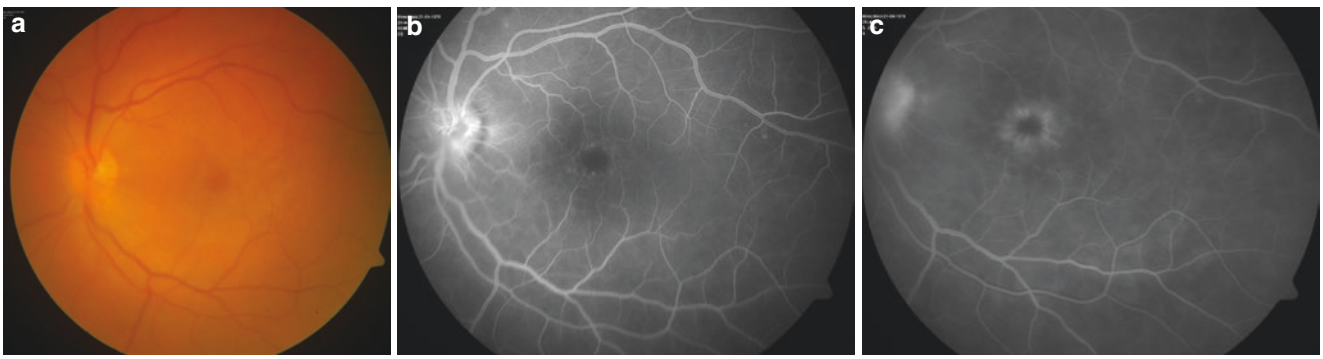

Fig. 16.2 A 30-year-old female presented with decreased vision in both eyes for the past 1 month (only left eye shown). Ocular examination revealed 1+ cellular reaction in the anterior chamber. (**a**) There was significant vitritis in both eyes. (**b**, **c**) Fluorescein angiography revealed early disc hyperfluorescence with late leakage and petalloid pattern of dye accumulation in the macula suggestive of cystoid macular edema. She was diagnosed as probable tubercular intermediate uveitis since her immunological and radiological investigations were positive. She received intravitreal dexamethasone depot injection in both eyes and anti-tubercular therapy

2. *Serpiginous-like choroiditis (multifocal serpiginoid choroiditis):*
   Serpiginous-like choroiditis (SLC) typically affects young to middle-aged adults from TB-endemic areas such as India and immigrants in other countries such as UK (Bansal et al. 2012; Gupta et al. 2003). Unlike autoimmune serpiginous choroiditis, tubercular serpiginous-like choroiditis occurs at a younger age, associated with mild vitritis and is bilateral in majority of the cases (Nazari Khanamiri and Rao 2013). This entity may have different morphological patterns (Fig. 16.3) (Bansal et al. 2012).
   (a) **Placoid chorioretinitis**: In this phenotype of IOTB, a diffuse plaque-like lesion is observed, which has a characteristic amoeboid pattern and active edge. The borders of the lesions are yellowish-white and elevated, whereas the center of the lesion is less elevated with pigmentary changes suggestive of a healing process in the center of the lesion.
   (b) **Multifocal choroiditis**: This phenotype of IOTB presents with discrete lesions, yellowish-white in color with well-defined margins and slightly raised edges. The edges of these lesions are non-contiguous initially and show a wave-like progression over a period of 1–4 weeks and gradually become confluent.

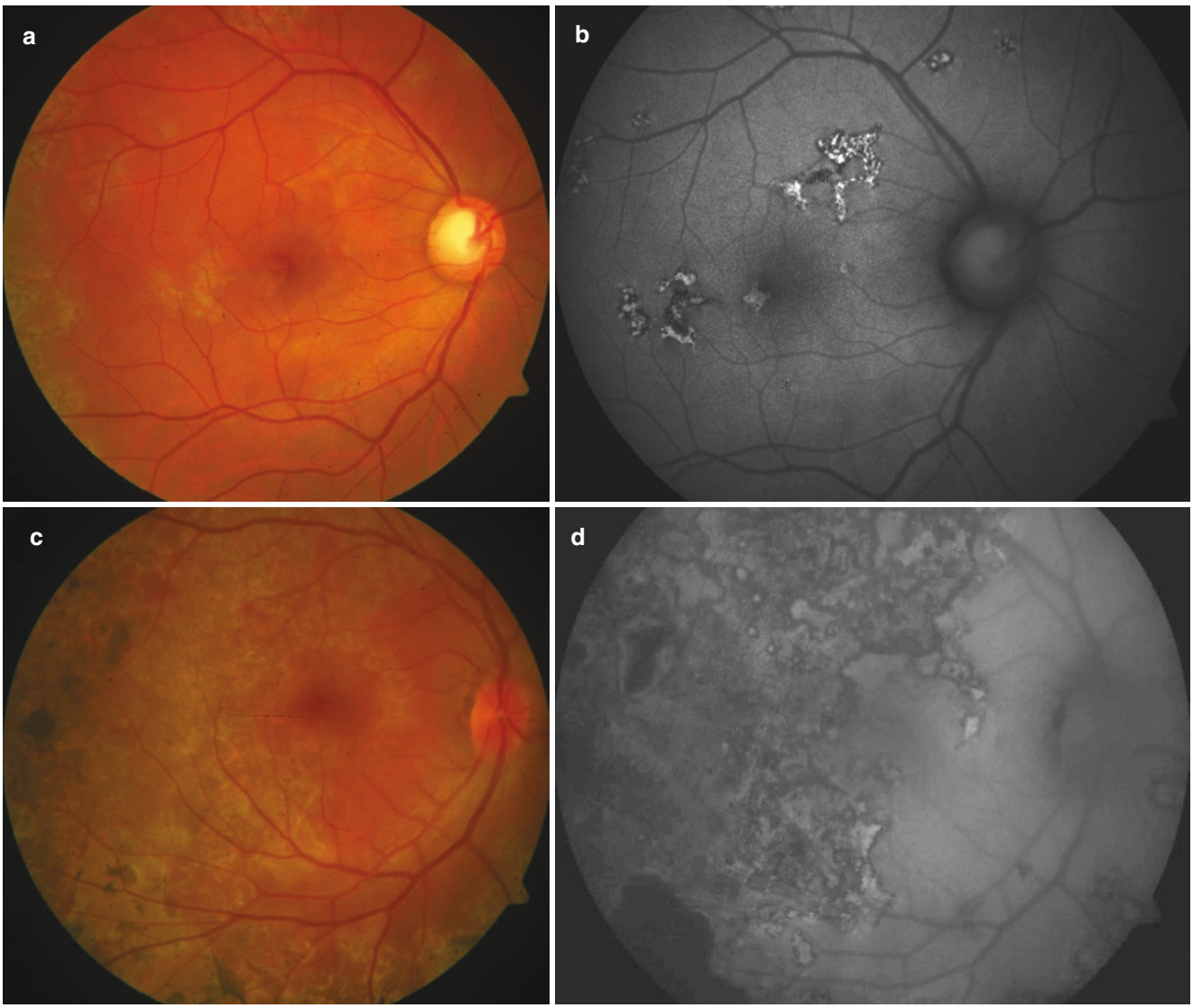

Fig. 16.3 Fundus photography and autofluorescence (FAF) imaging of two patients with tubercular serpiginous-like choroiditis. Patient #1 (**a**, **b**) shows presence of yellowish-white choroiditis lesions in the posterior pole that appear hyper-autofluorescent with hypo-autofluorescent halos on FAF imaging. Similarly, patient #2 (**c**, **d**) shows diffuse involvement of the posterior pole and mid-periphery by choroiditis lesions that appear active on FAF. The lesions show predominant hyper-autofluorescence suggestive of the need for continued anti-tubercular therapy and systemic immunosuppression

(c) **Mixed/Undetermined pattern**: These lesions of IOTB present with overlapping features of both multifocal and placoid chorioretinitis. There have been descriptions of TB choroiditis lesions that may appear as other white dot syndromes such as ampiginous choroiditis.

3. *Tubercular Subretinal Abscesses:*
TB-related subretinal abscess appears distinct and more yellowish in color compared to a small choroidal granuloma. They usually have overlying retinal hemorrhages, and have a tendency to develop retinal angiomatous proliferation over a period of time.

Imaging Features of Posterior/Panuveitis

1. *Color Photography and Ultra-wide Field Imaging*
In order to accurately study the morphology of the IOTB lesions, it is important to obtain color fundus photography at regular intervals. This greatly aids in the analysis of the fundus lesions and provides an objective assessment of change in the lesions over an extended period. Serial fundus photography (from acute stage to the stage of healing) is very useful in assessment of morphological evolution of the lesions (Bansal et al. 2012). Ultra-wide field (UWF) fundus imaging is a recent addition in the imaging modalities used for the assessment of various chorioretinal pathologies. Compared to conventional imaging (fundus photography and fluorescein angiography), UWF imaging systems aid in detection of additional features such as perivascular choroiditis, retinal vasculitis, and retinal neovascularization (Aggarwal et al. 2016). In addition, UWF imaging may be superior to conventional imaging in identifying *peripheral paradoxical worsening*, which may be otherwise missed on conventional imaging (Aggarwal et al. 2016).
2. *Fundus Autofluorescence*
Studies have shown that fundus autofluorescence (FAF) is a very useful noninvasive imaging modality in the management of IOTB, specifically TB serpiginous-like choroiditis. Staged of lesions using FAF (Gupta et al. 2012) is as follows: active lesions demonstrate ill-defined hyper-autofluorescence throughout the lesions. Thus, the lesions have a diffuse, amorphous appearance (Stage 1). In the stage of early healing (Stage 2), a thin rim of hypo-autofluorescence is seen surrounding the lesion, which remains predominantly hyper-autofluorescent with a stippled pattern. With further healing, the lesion becomes predominantly hypo-autofluorescent (Stage 3) on FAF imaging. On complete healing, the lesions become uniformly hypo-autofluorescent without hyper-autofluorescent areas (Stage 4) (Gupta et al. 2012).
3. *Fluorescein Angiography*
Fluorescein angiography (FA) is a very useful modality in the diagnosis and follow-up of patients with IOTB. TB choroiditis lesions appear hypofluorescent in the early phase and show hyperfluorescence in the late phase. Due to RPE damage and choriocapillaris atrophy, the areas of healing may demonstrate window defects (Bansal et al. 2012). Thus, FA is very helpful in demonstrating the activity of the lesions. In addition, complications of the disease such as inflammatory choroidal neovascularization may be detected using FA, though it may be very challenging in the absence of high index of suspicion (Bansal et al. 2016).
4. *Indocyanine Green Angiography*
On Indocyanine green angiography (ICGA), active lesions of TB SLC remain hypofluorescence from early to late phase on ICGA. ICGA is very useful in detecting choriocapillaritis and presence of choriocapillaris hypoperfusion among patients with IOTB. Other changes of tubercular uveitis include presence of numerous hyperfluorescent spots, fuzzy appearance of choroidal vessels in the intermediate phase, and late choroidal hyperfluorescence due to dye leakage, which tends to regress after the completion of treatment with ATT and corticosteroids.
5. *Optical Coherence Tomography*
Spectral-domain OCT, especially enhanced-depth imaging (EDI) OCT, has provided numerous insights into the pathogenesis of IOTB. OCT permits identification of peripapillary retinal atrophy, disruption of the photoreceptor and other outer retinal layers, thinning of the RPE, mild cystic changes as well as subretinal fibrosis in area of old choroidal neovascularization and marked attenuation of the interdigitation zone in the outer retina (Punjabi et al. 2008; Rifkin et al. 2015). TB choroiditis may also result in alteration of the ellipsoid and the myoid zones in the outer retina along with choriocapillaris thinning. Active edges of the lesions show localized, fuzzy area of hyper-reflectivity in the outer retinal layers involving the RPE, photoreceptor outer segment tips, external limiting membrane, and the outer nuclear layer without increased backscattering from the inner choroid. As the lesions begin to heal from the center, the hyper-reflective fuzzy areas begin to disappear and are replaced by irregular, hyper-reflective knobbly elevations of the outer retinal layers. Eventually, there is loss of RPE and outer retinal layers, and persistent increased reflectance from the choroid on OCT (Bansal et al. 2011).

With the introduction of advanced technologies such as EDI and swept-source (SS)-OCT, there has been tremendous advancement in the diagnostic capabilities in the field of IOTB. Recent introduction of OCT angiography, a dye-less noninvasive technique to obtain photographs of retinochoroidal endoluminal networks, has furthered our capabilities to understand the pathological involvement in IOTB.

Tubercular Endophthalmitis

IOTB may rarely present as severe vitritis with hypopyon and no view of the retina, with echoes in the vitreous cavity on ocular ultrasonography mimicking infectious endophthalmitis. In such cases, the diagnosis may be established by a high index of suspicion and evaluation of ocular fluids for mycobacteria. Therapeutic response to ATT and corticosteroids is observed in these patients.

Other Manifestations

Mycobacteria may rarely affect the scleral tissue leading to either diffuse or nodular tubercular scleritis (Fig. 16.4). There are few case reports where authors have demonstrated acid fast bacilli (AFB) either by microscopy or by culture from enucleated eyes and scleral biopsy. In a series of 42 enucleated eyes, 1–2 bacilli were found close to areas of necrosis (Wroblewski et al. 2011). These cases may be challenging to diagnose and differentiate from autoimmune scleritis.

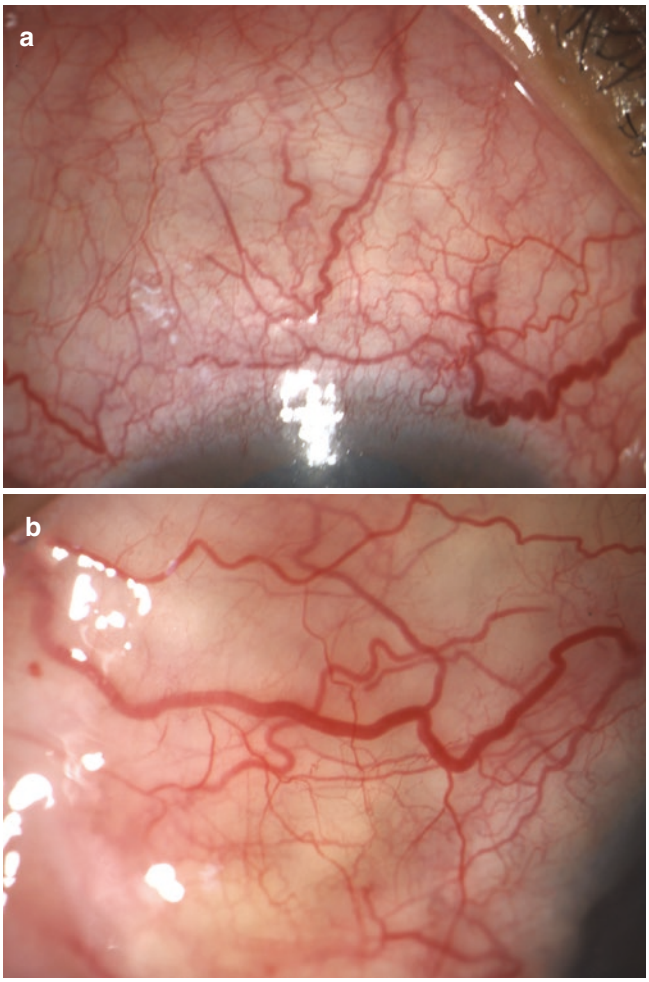

Fig. 16.4 A 35-year-old female presented with bilateral diffuse scleritis and panuveitis with a history of decreased vision and pain for the past 4 weeks in both eyes (**a**, **b**). Her Mantoux text was highly positive and QuantiFERON TB Gold® was positive. Chest computerized tomography (contrast-enhanced) revealed mediastinal lymphadenopathy. She was diagnosed with probable tubercular scleritis and started on oral corticosteroids and anti-tubercular therapy

Retinal vasculitis has long been recognized feature of IOTB in young healthy males, previously known as Eales disease (Gupta and Gupta 2005). However, recent studies have indicated that so-called Eales disease indeed is a phenotype of tubercular uveitis. Typically, the veins are more commonly affected than arteries and is accompanied by vitritis, perivascular cuffing by the exudates, choroiditis lesions (active or healed), cystoid macular edema, occlusive features in the form of capillary non-perfusion, vitreous hemorrhage, or neovascularization of the optic disc/retina. Though the presence of occlusive vasculitis with/without perivascular choroiditis scars is likely to be tubercular in origin, many other diseases such as sarcoidosis and collagen vascular diseases can have similar phenotype (Singh et al. 2012).

Tuberculous optic neuropathy is also uncommon, and may manifest as papillitis, neuroretinitis, and optic nerve tubercle (Gupta et al. 2007). These cases may be challenging to diagnose and treat, and high index of suspicion must be maintained.

Treatment of Intraocular Tuberculosis

Systemic tuberculosis treatment consists of multidrug regimen including first-line agents such as isoniazid, rifampin, ethambutol, and pyrazinamide, and second-line agents such as levofloxacin, streptomycin, amikacin/kanamycin. Second-line agents are used in the presence of mycobacterial resistance. The duration and dosing regimen depend on the organ system involved, severity of disease, and the history of prior anti-TB therapy.

IOTB treatment comprises of four-drug regimen of isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), ethambutol (15 mg/kg/day), and pyrazinamide (20–25 mg/kg/day) along with pyridoxine divided into 2-month induction course of isoniazid, rifampicin, and pyrazinamide administered daily, followed by a continuation phase of 4–7 months of isoniazid and rifampicin. ATT is given in combination with systemic steroids (oral prednisolone 1 mg/kg/day), which is tapered off over the next 6–12 weeks depending upon the level of inflammation seen. Topical steroids may be employed in cases with anterior segment inflammation. Addition of systemic immunosuppressive agents such as azathioprine, cyclosporine, or mycophenolate mofetil may be considered when needed (Gupta et al. 2007).

Paradoxical Worsening of IOTB

A subset of patients treated with ATT may develop paradoxical worsening of ocular disease (Gupta et al. 2011). Paradoxical worsening of the disease is also known as ocular Jarisch-Herxheimer reaction that occurs due to release of tubercular antigens from the dying bacilli. These patients require increase in systemic steroids/immunosuppressive therapy to prevent damage to ocular tissues due to excessive release of inflammatory mediators. Paradoxical worsening of the disease must be differentiated from worsening of primary disease.

MDR IOTB

Recently, rifampin resistance has been demonstrated in ocular TB (Sharma et al. 2014). Drug-resistant tuberculosis with increasing cases of multidrug-resistant TB (MDR TB) as well as extensively drug-resistant TB (XDR TB) is a major challenge. Thus, it is important to obtain the sensitivity profile of the mycobacteria since resistance of this organism is increasing. Failure of response to therapy due to resistance may result in diagnostic and therapeutic challenges.

Complications of IOTB such as inflammatory choroidal neovascularization or macular edema may be treated with the use of intravitreal anti-vascular endothelial growth factor injections.

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Evaluation of Ocular Tuberculosis

17

S. R. Rathinam and P. Lalitha

Introduction

Mycobacterium tuberculosis is a slow-growing acid-fast bacteria. It causes an airborne communicable disease. Inhalation of a droplet containing bacilli reaches alveoli and causes primary tuberculosis (TB) or gets cleared by the immune system. Alternatively, a patient may develop asymptomatic, latent TB. If the infection is not cleared by the immune system, the bacilli spread from regional lymph nodes to the lungs and give rise to pulmonary TB. Subsequent lymphatic and hematogenous dissemination result in extrapulmonary disease.

Ocular tuberculosis is a form of extrapulmonary disease which can affect all ocular layers. It can occur in isolation or with a pulmonary or with another extrapulmonary focus. It presents with a variety of clinical manifestations and may mimic several other uveitis. Confirming the etiology remains a challenge because of varying clinical picture and paucibacillary nature of ocular tuberculosis. Early diagnosis and an appropriate treatment are most essential for prompt regression of inflammation (Cunningham et al. 2015).

Epidemiology

Tuberculosis is the ninth leading cause of death worldwide. Poverty, human immunodeficiency virus (HIV), and drug resistance are major drivers of the global tuberculosis epidemic. The highest rates (higher than 100 per 100,000) occur in sub-Saharan Africa, India, and Southeast Asia. Intermediate rates of TB (26–100 cases per 100,000) are seen in China, Central and South America, Eastern Europe, and northern Africa. Low rates (less than 25 cases per 100,000 inhabitants) are seen in the United States, Western Europe, Canada, Japan, and Australia. In 2016, there were 600,000 new cases with resistance to rifampicin (RRTB), the first-line drug, of which 490,000 had multidrug-resistant TB (MDR-TB). Almost half (47%) of these cases were in India, China, and Russia. However, globally, the TB mortality rate is falling at about 3% per year. TB incidence is falling at about 2% per year with a declining trend in TB prevalence and mortality over the last decade (WHO 2017a, b).

Systemic Tuberculosis

Patients may present with pulmonary or extrapulmonary TB (EPTB) (Gonzalez et al. 2003) or a combination of both. Depending upon the organ involved, the patients present with specific symptoms and signs. Respiratory symptoms, fever, appetite loss, weight loss, and easy fatigability are common in pulmonary tuberculosis. Organs affected in EPTB include lymph nodes, central nervous system, eyes, musculoskeletal system, genitourinary tract, and gastrointestinal tract. Patients may have palpable lymph nodes, abdominal pain, diarrhea, monoarticular arthralgia, nerve palsies, seizures, meningism, or infertility. Extrapulmonary tuberculosis patients may have neither respiratory symptoms nor an abnormal chest X-ray. Ophthalmologists have to include appropriate questions in the history and relevant systemic examination. Based on the clinical examination, tailored laboratory workup is performed to rule out both pulmonary TB and EPTB.

Ocular Tuberculosis

Tuberculosis is one of the common causes that affect episclera, sclera, cornea, and all intraocular structures, and ocular TB is now recognized more often than before (Rathinam and Namperumalsamy 2007). Ocular TB manifests as either unilateral or asymmetrically bilateral disease. Course may be

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recurrent, chronic, and insidious. Anatomically, it may present as anterior, intermediate, posterior, or panuveitis, more often a granulomatous than non-granulomatous uveitis (Gupta et al. 2010; Krassas et al. 2018).

Ocular TB can cause recurrent nodular episcleritis, scleritis, sclerokeratitis, and sclerokeratouveitis. When cornea is involved, the deeper layers of the cornea get inflamed with a clear superficial layer. The course is usually chronic, recurrent, and insidious. Anterior segment may show granulomatous mutton-fat keratic precipitates (Fig. 17.1), iris granulomas, Bussaca nodules, broad posterior synechiae, and complicated cataract with scanty flare and cells in the anterior chamber. Tubercular granulomas and hypopyon can be seen in tubercular inflammation. In developing countries, tubercular uveitis can cause anterior uveitis and band keratopathy in children. It is very important to differentiate it from juvenile idiopathic uveitis.

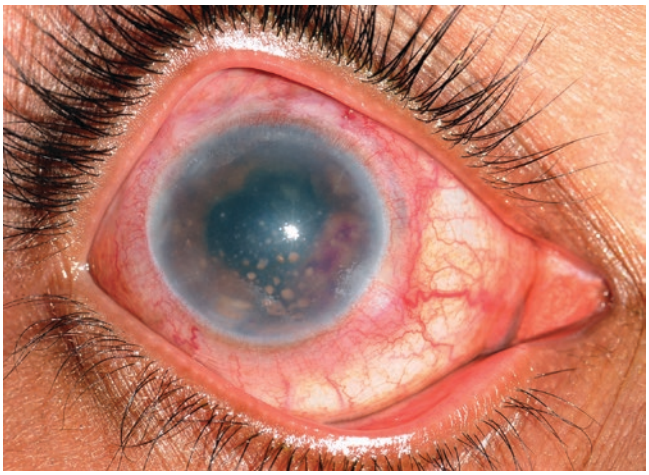

Fig. 17.1 Anterior chamber color photograph showing circumcorneal congestion with chronic pigmented granulomatous keratic precipitates and iris granuloma

Intermediate uveitis of TB and sarcoidosis mimic each other as both are granulomatous and recurrent. Ciliary body tuberculoma can be demonstrated with ultrasonic biomicroscopy. Other findings include vitritis, pars plana snowballs, snow banking, peripheral granulomas, pigmented pars plana scars, and cystoid macular edema.

Posterior segment findings include focal or multifocal yellow choroidal granulomas (Fig. 17.2) or multifocal chorioretinal pigmented scars specifically along retinal vessels (Fig. 17.3) (Gupta et al. 2010). The retinitis may be seen with an associated choroiditis, although a direct retinal involvement is rare. Other signs include subretinal granuloma or abscesses, retinal vasculitis, optic neuritis, retrobulbar neuritis, neuroretinitis, optic disc granuloma, and disc edema. TB can cause serpiginous-like choroiditis (SLC) which sometimes mimic a classic serpiginous choroidopathy (SC). Tubercular SLC show multifocal, scattered, highly pigmented lesions with significant vitreous cells. Unlike classic SC, SLC do not respond to corticosteroid therapy, and inflammatory control is achieved only after anti-TB treatment (Vasconcelos-Santos et al. 2010).

Rarely, an acute and robust inflammatory response may result in hypopyon in tubercular panuveitis. Yellowish subretinal abscess can rupture into the vitreous and result in endophthalmitis or panophthalmitis.

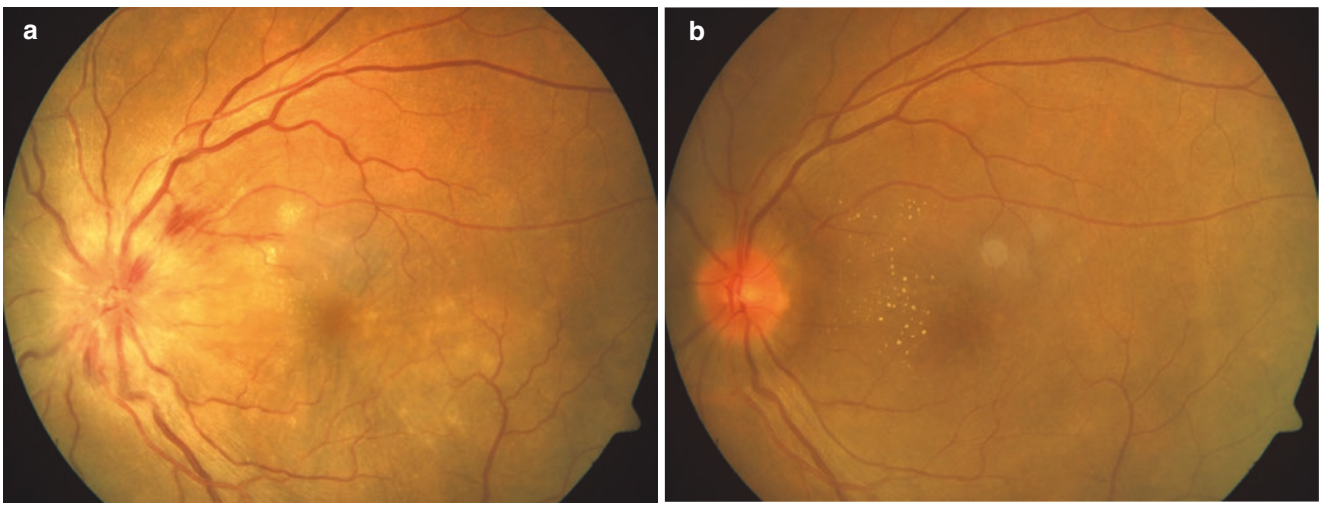

Fig. 17.2 (**a**) A 45-year-old woman presented with optic nerve granuloma, superficial hemorrhage, and multifocal choroidal granulomas. Her Mantoux test was necrotic positive. (**b**) Resolution of fundus findings and choroidal granulomas were observed after 3 months of antituberculous treatment. Edema is resolved leaving white proteinaceous material

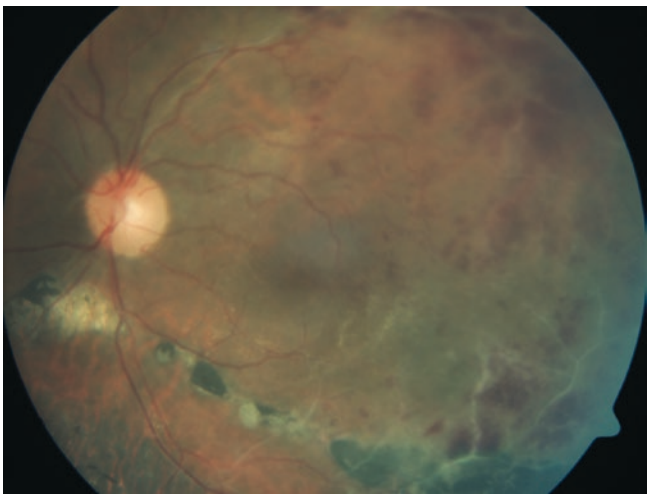

Fig. 17.3 Fundus photography of left eye showing healed multifocal choroiditis with highly pigmented scars along the blood vessels. Superior quadrant shows multiple hemorrhagic spots because of branch retinal vein occlusion

Latent TB

The term latent TB infection (LTBI) is used when an asymptomatic person presents with a positive tuberculin skin test (TST) with no clinical or radiographic signs of active TB. Usual interpretation is that they are infected but not diseased. Among these, 5–15% may progress to active disease in future when the environmental conditions are favorable. However, they cannot spread the disease to other people. Decision for prophylactic treatment for this population varies among countries.

Differential Diagnosis

Differential diagnosis includes other granulomatous uveitis such as sarcoidosis, Vogt–Koyanagi–Harada disease, sympathetic ophthalmia, herpetic infection, phaco-antigenic uveitis, syphilis, and leprosy. Other causes of choroidal granulomas include sarcoidosis, syphilis, and fungal lesions (Babu 2013; Vasconcelos-Santos et al. 2010).

Diagnostic Criteria and Laboratory Tests

Definitive diagnosis of ocular TB is possible only when the bacilli are isolated from the ocular tissues. As definitive evidence of *Mycobacterium tuberculosis* is rarely found in intraocular specimens, its diagnosis is usually clinical, supported by laboratory tests and favorable response to antitubercular therapy. The diagnosis is considered presumed ocular TB when the clinical picture is consistent with known clinical signs (broad-based posterior synechiae, retinal vasculitis with choroiditis, choroidal granuloma, or pigmented SLC) and supported by a positive tuberculin skin test or QuantiFERON TB Gold test or any other relevant anxillary tests, such as chest radiography and computed tomography. Inflammatory control after anti-tubercular treatment and absence of recurrence further supports the diagnosis of presumed ocular TB (Gupta et al. 2010).

The confirmation of etiological diagnosis of ocular tuberculosis remains a clinical challenge because of difficulty in getting a specimen from inflamed eye and paucibacillary tuberculosis. Ocular TB is diagnosed on the basis of a combination of clinical signs such as chronic granulomatous uveitis, choroidal granulomas, and multifocal pigmented chorioretinitis. Microbiological, histopathologic, or molecular evidences assist the confirmation of the diagnosis. Sometimes supportive evidences such as radiographic features (infiltrates, fibrosis, and cavitation in chest x-ray/computerized tomography (CT) chest) aid the diagnosis (Fig. 17.4).

Detection of acid-fast bacilli (AFB) from anterior chamber granuloma or from vitreous is possible with Ziehl–Neelsen staining. Alternatively, histopathological examination can demonstrate caseous necrosis and Langerhans giant cells. The conventional diagnostic method like isolation of the pathogen may not be possible in all patients, as ocular TB is paucibacillary (Vasconcelos-Santos et al. 2009).

In patients with co-existence of pulmonary or extrapulmonary TB, detection of acid-fast bacilli (AFB) in the sputum samples or in the lymph nodes is performed with Ziehl–Neelsen and auramine–rhodamine fluorescent dye. Culturing

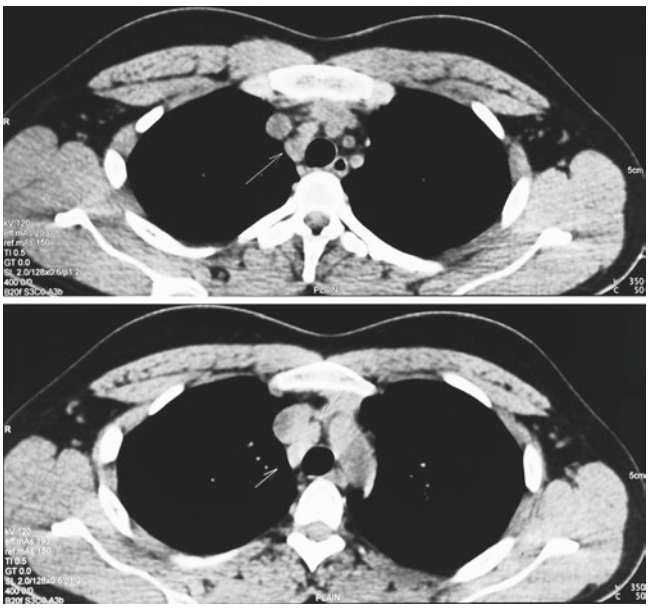

Fig. 17.4 Chest computed tomography revealed enlarged mediastinal lymph nodes (arrow) with necrosis with the largest lymph node measuring 1.89 × 1.35 cm

in liquid media using semi-automated and automated systems are popular for quicker process of less than 2 weeks. Isolation of the organism allows testing for antibiotic resistance as well.

Positive Mantoux or TST (tuberculin skin test) following intradermal injection of tuberculin purified protein derivative (PPD) indicates a successful cellular immune response after exposure to TB bacilli. However, it has limited specificity as the antigen can cross-react with other species of Mycobacterium. The American Thoracic Society and Center for Disease Control (CDC) considers reactions of 5 mm or more to be positive in very high-risk patients (e.g., chest x-ray sign and HIV patients), 10 mm or more in high-risk patients (e.g., patients from endemic areas), and 15 mm or more in patients with no identified risk factors. However, negative test does not rule out TB. In a study on patients with histopathologically proven ocular tuberculosis, 40% had negative TST results.

Molecular studies and sequencing of the *M. tuberculosis* genome have identified specific and highly immunogenic antigens, ESAT-6 and CFP-10 proteins. Using these antigens, novel in vitro tests have been developed, namely QuantiFERON (QFT) and TSPOT.TB. They are named as Interferon Gamma Release Assays (IGRA). They can be used to study the immune response of the patients. QuantiFERON (QFT) and TSPOT.TB are now commercially available. The CDC guidelines state that IGRAs can replace the TST. Canada and the United Kingdom national guidelines suggest using IGRAs only to confirm a positive TST (Schluger and Burzynski 2010). These tests were initially designed to screen latent tuberculosis; however, they were found to be useful in both active systemic and ocular tuberculosis cohorts.

A positive skin test or an IGRA indicates exposure to TB, but it does not necessarily indicate active infection. The lack of a gold standard for the diagnosis of TB infection challenges interpretable comparison of the IGRAs and the TST in ocular tuberculosis. In addition, predictive values of IGRA depend on prevalence of TB in the study population. In low endemic countries, the results of IGRA have to be interpreted with caution as false-positive tests may be seen in patients with sarcoidosis (Albini et al. 2008).

Imaging studies include both ocular imaging and systemic imaging. Computed tomography (CT) is the method of choice in detecting early bronchogenic spread, hilar and abdominal lymphadenopathy, and also in characterization of the infection as active or not (Fig. 17.4) (Bansal et al. 2018). Chest CT is more sensitive than plain chest radiographs. Magnetic resonance imaging (MRI) is considered superior to CT for the detection of tuberculosis of bone and joints and central nervous system TB.

Intraocular TB can involve various tissues in the eye and can be demonstrated by several ocular imaging techniques such as fluorescein angiography, ultrasonography (Fig. 17.5), and optical coherence tomography (Fig. 17.6). These imaging tests are used individually or in combination with follow-up response to treatment and find out any sequelae of intraocular TB.

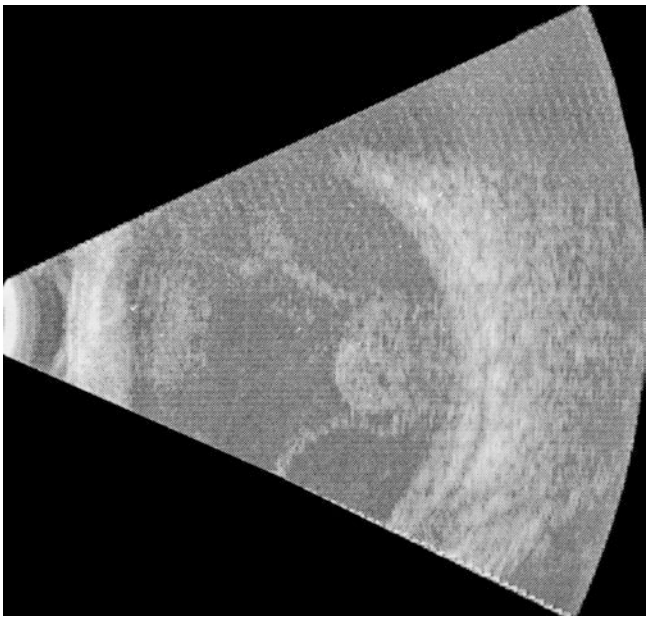

Fig. 17.5 Ocular ultrasonography of a patient with a massive choroidal tubercular granuloma with choroidal detachment

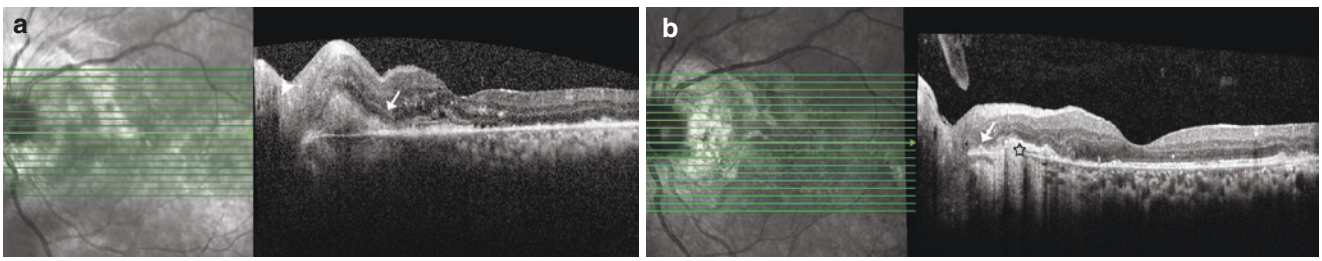

Fig. 17.6 A 23-year-old female with decreased vision in her left eye. (**a**) Spectral-domain optical coherence tomography showed subretinal hyperreflective choroidal tubercular granuloma (arrowhead) temporal to the disc with minimal subretinal fluid and exudates at macula (arrow). (**b**) After intravitreal bevacizumab injection, the hyperreflective lesion regressed (arrow) with resolution of subretinal fluid and disruption of IS-OS junction (asterisk)

Molecular diagnostic tests such as PCR (or RT-PCR) are rapid tests, and detection of rifampicin and isoniazid resistance can also be achieved. Several new primers have been published (Kharel Sitaula et al. 2018).

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Cat-Scratch Disease

18

Cindy Ung and Lucy H. Young

Introduction

Cat-scratch disease (CSD) was first recognized by Parinaud in 1889 in three patients with granulomatous conjunctivitis, preauricular lymphadenopathy, chronic fever, and contact with animals. This constellation of symptoms initially became known as Parinaud oculoglandular syndrome, and subsequent reports noted a history of cat exposure in some patients with this syndrome (Cassady and Culbertson 1953; Henry 1952). Sweeney and Drance (1970) first suggested an association between CSD and neuroretinitis in 1970, a finding later confirmed by Gass (Dreyer et al. 1984; Gass 1977). In 1994, Golnik and associates provided the first serologic evidence of systemic *Bartonella* infection in patients with neuroretinitis (Golnik et al. 1994). Cat-scratch disease is the most common cause of neuroretinitis with approximately two thirds of patients demonstrating seropositivity for gram-negative bacillus, *Bartonella henselae*.

The incidence of cat-scratch disease in the United States is estimated at 9.3 per 100,000 population (Jackson et al. 1993). Cat-scratch disease is almost always benign and self-limited, with the majority of cases reported in persons under 20 years of age (Carithers 1985). More than 90% of all cases of CSD are associated with a history of some type of contact with cats (Carithers 1985; Warwick 1967), and 57–83% have a history of a scratch from a cat (Margileth 1993; Spaulding and Hennessy 1960). It is the leading cause of regional lymphadenopathy in children and young adults.

Clinical Features

Cat-scratch disease is a systemic infectious disease and is often a self-limited condition. The transmission of *B. henselae* is usually from a cat scratch or bite, although it may occur from contact between cat saliva and an open wound. A small localized papule is usually first seen at the site of inoculation 3–10 days after inoculation. Mild local infection is followed by tender regional lymphadenopathy and then low-grade fever, malaise, headache, and myalgias several weeks after exposure (Dreyer et al. 1984). Ocular involvement has been estimated to occur in 5–10% of patients (Carithers 1985).

Posterior segment manifestations of CSD include neuroretinitis, intermediate uveitis, focal or multifocal chorioretinitis, peripapillary retinal edema, and vascular occlusions. Neuroretinitis appears to be the most common and is found in 1–2% of patients infected with *B. henselae* (Ormerod and Dailey 1999; Carithers 1985). It is characterized by optic disc edema and the presence of stellate macular exudates (Figs. 18.1a and 18.2a). The optic disc is the principal target in neuroretinitis with fluorescein leakage confined to the disc (Figs. 18.1b and 18.2b). Even in the presence of a full macular star, there is no fluorescein leakage in the macula on fluorescein angiography. The optic disc edema is often accompanied by peripapillary subretinal fluid (Fig. 18.3). Neuroretinitis is usually unilateral but can be asymmetrically bilateral as shown in Fig. 18.4 (Schlossberg et al. 1989). Disc edema usually occurs prior to the formation of a macular star by 1–4 weeks (Wade et al. 2000) (Figs. 18.3b and 18.5a). The macular star may be partial and is usually present in the nasal macula. The disc edema and macular star can take up to 6–12 months to resolve leaving the eye with mild disc pallor (Fig. 18.5). A relative afferent pupillary defect is seen in 90% of patients (Chi et al. 2012). Multifocal areas of retinitis or chorioretinitis can also occur in the absence of optic disc edema and macular exudates (Fig. 18.6). Other findings include a neurosensory detachment of the macula or peripapillary region as well as anterior and posterior chamber inflammation.

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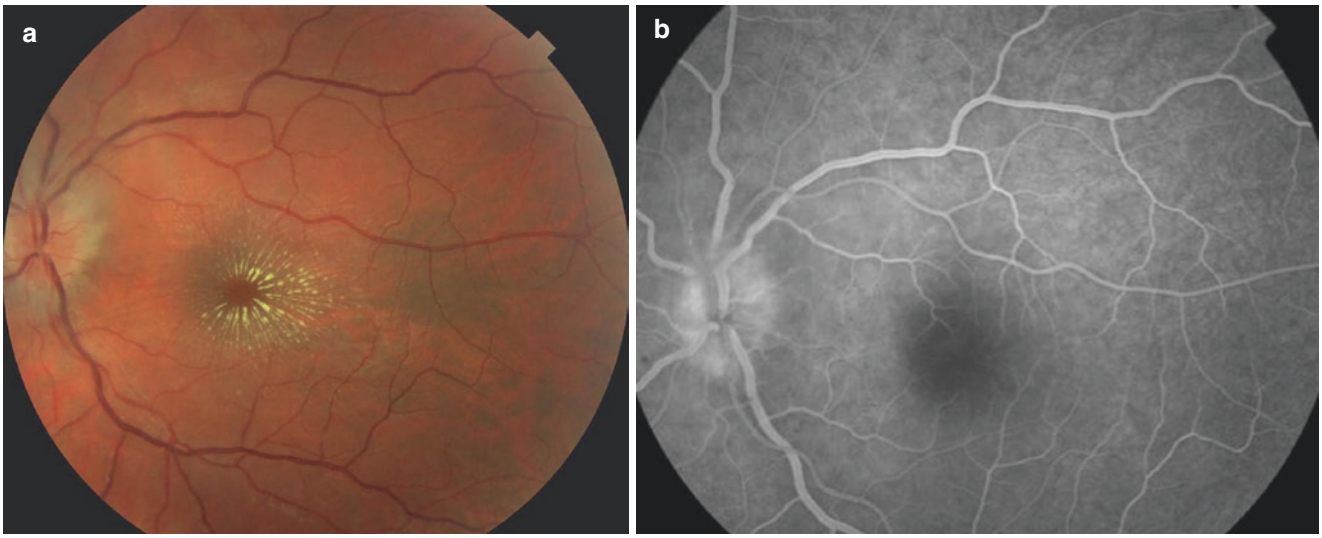

Fig. 18.1 (**a**) Fundus photograph shows disc edema and macular scar in the left eye of a 22-year-old healthy man with 1 week history of blurry vision OS (20/200). (**b**) Fluorescein angiography shows leakage confined to the optic nerve

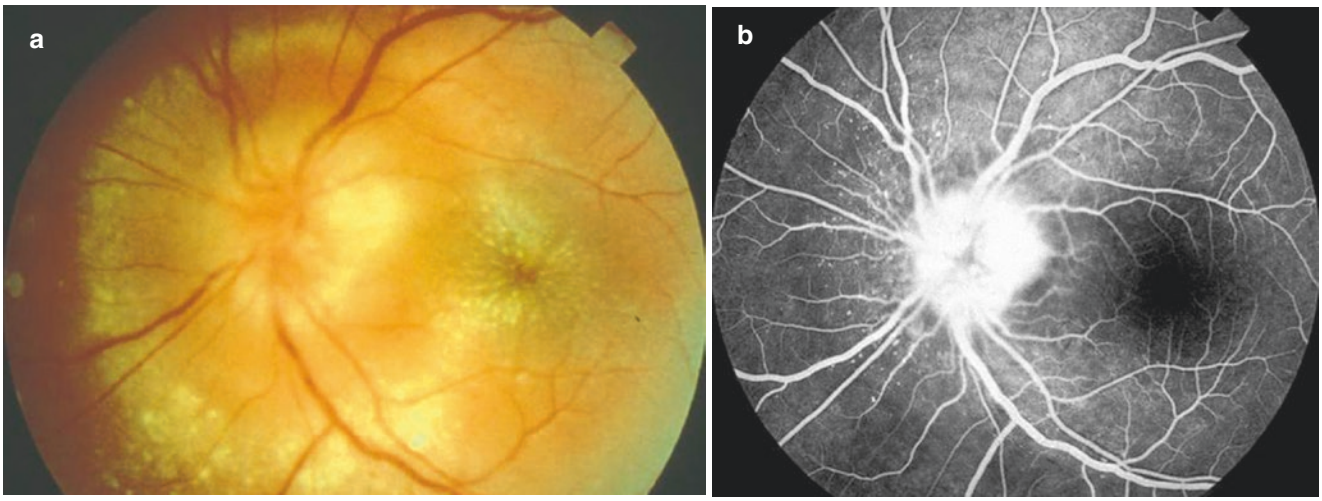

Fig. 18.2 (**a**) Fundus photograph shows unilateral disc edema. (**b**) Fluorescein angiography shows disc leakage without macular leakage

The more common ocular complication caused by *Bartonella* infection is Parinaud's oculoglandular syndrome, which affects approximately 2–5% of symptomatic patients (Carithers 1985). Parinaud's oculoglandular syndrome is a rare condition consisting of chronic low-grade fever, granulomatous follicular conjunctivitis, and ipsilateral regional lymphadenopathy involving either the preauricular or the submandibular of cervical lymph nodes. Transmission is generally from hand–eye contact from infected cat feces. Most patients experience localized disease that resolve within several months.

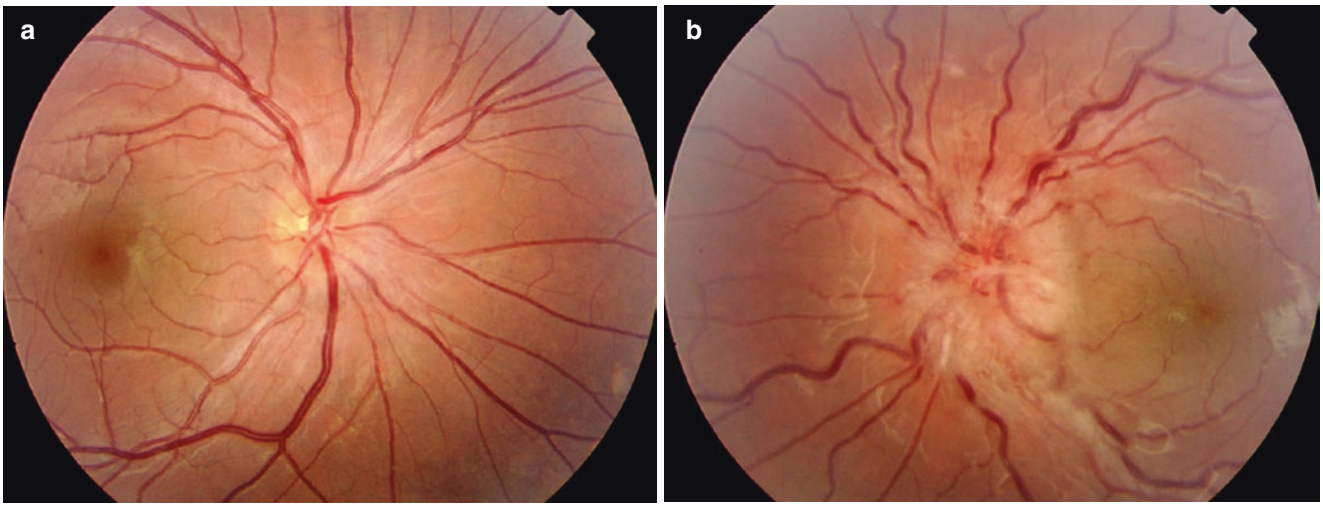

Fig. 18.3 Twelve-year-old healthy girl referred for a neuro-ophthalmologic consultation of disc edema OS > OD of unclear etiology. Sinus X-rays, head CT scan, MRI with contrast and lumbar puncture with opening pressure were ordered by the outside ophthalmologist, and these were all normal. Visual acuities were 16/13 OD and 16/200 OS (down from 20/60 2 weeks earlier). A positive left afferent pupillary defect was present. (**a**) Trace disc hyperemia with mild blurring of the inferonasal margin was noted in the right eye. (**b**) In the left eye, moderate disc edema with peripapillary subretinal fluid extending into the fovea was noted

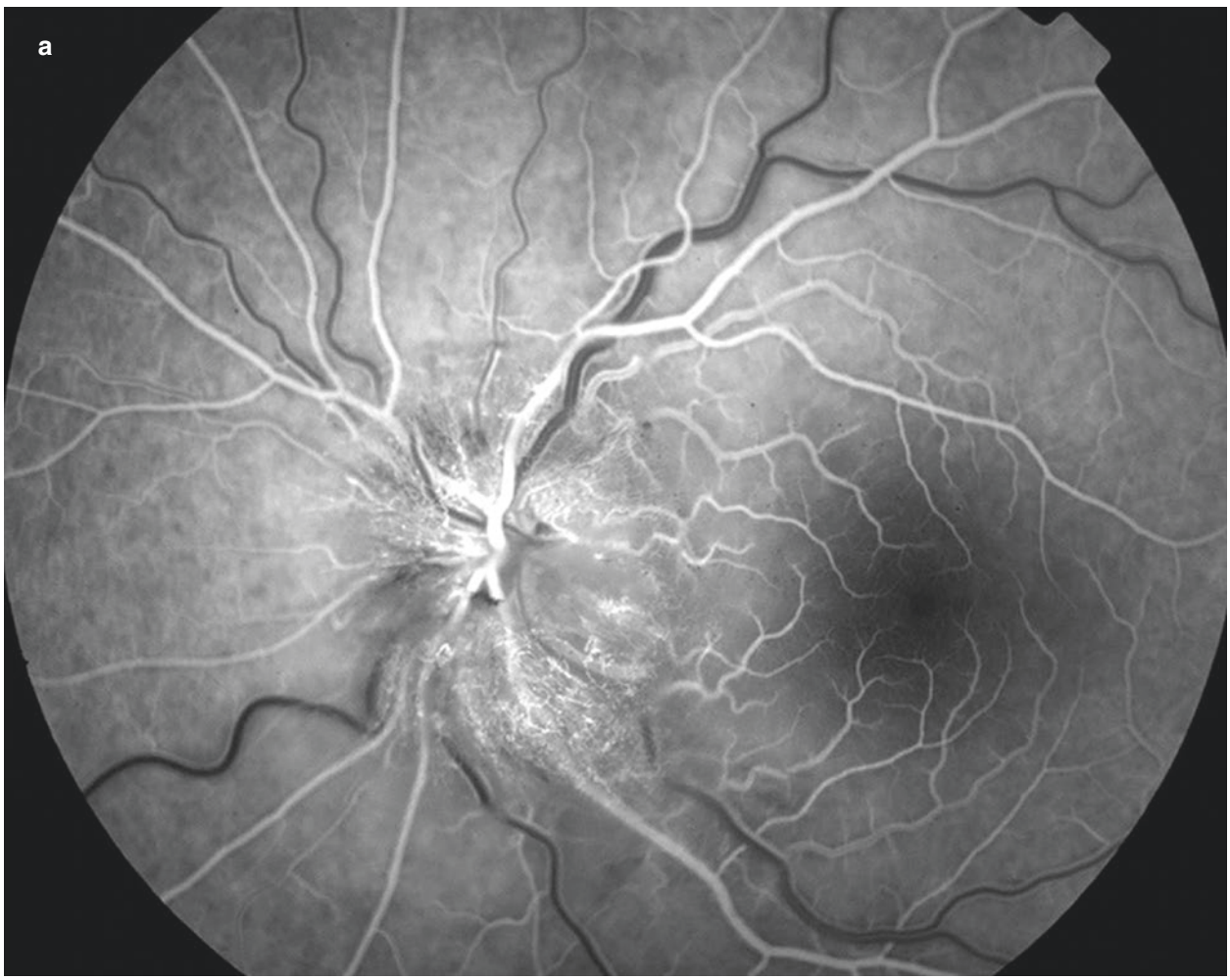

Fig. 18.4 Fluorescein angiography shows dilated disc capillary OS in the early phase (**a**) followed by increasing disc leakage with time (**b**). Late images show mild disc leakage and no macular leakage OD (**c**)

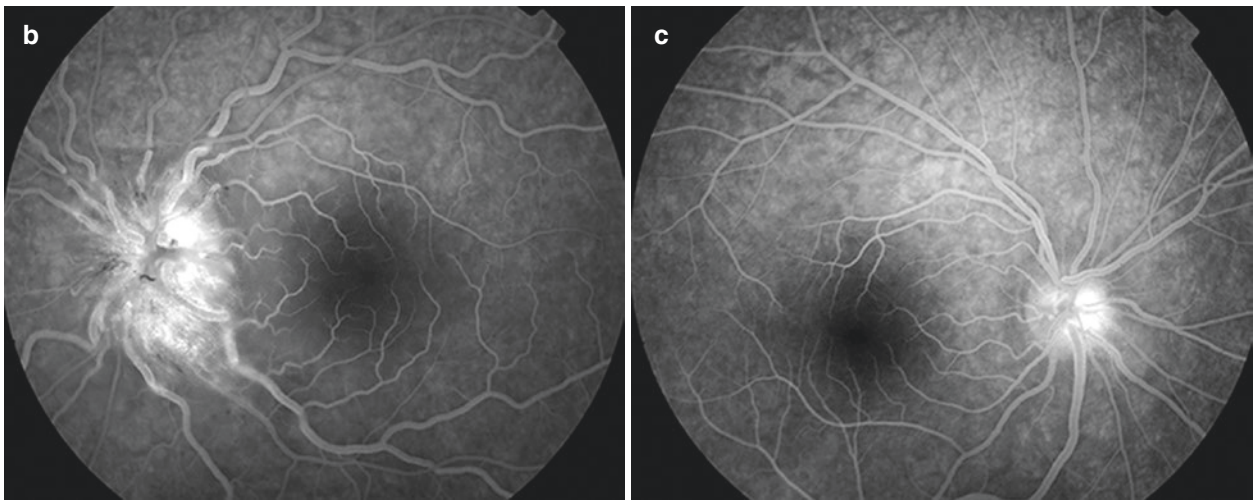

Fig. 18.4 (continued)

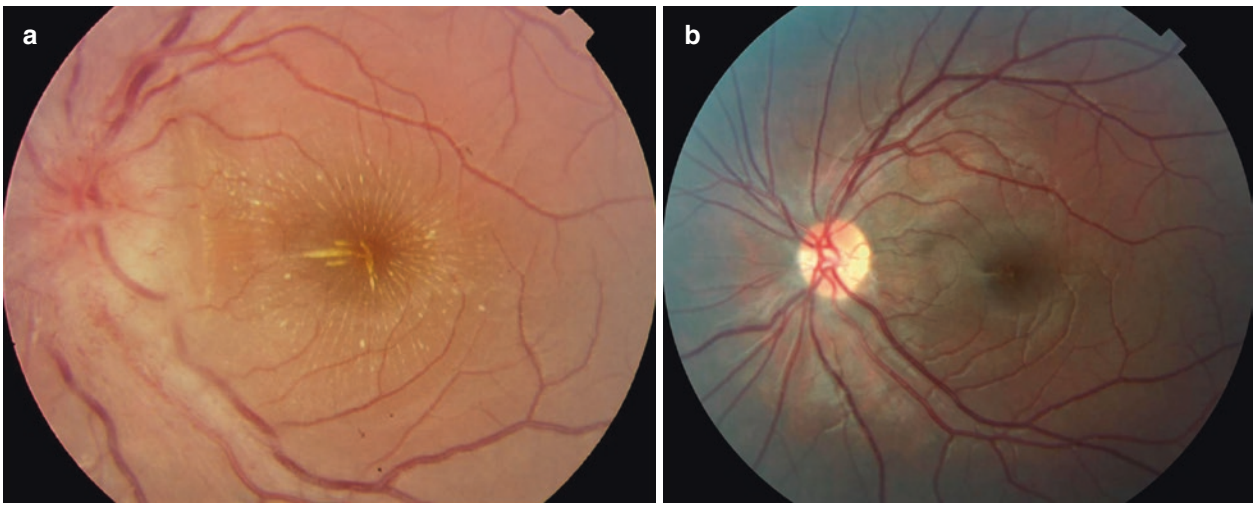

Fig. 18.5 In the same patient, fundus photography of the left eye at 8 days after initial consultation shows marked disc edema and a newly formed macular star (**a**). Fundus photography at 11 months later shows normal appearing macula and mild disc pallor (**b**). Visual acuity improved from 16/200 to 16/30 OS. (Courtesy of Joseph F. Rizzo, MD)

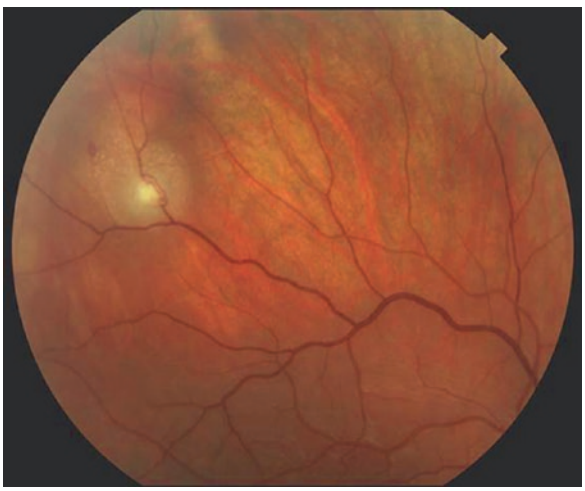

Fig. 18.6 A small chorioretinitis lesion in the contralateral eye of a patient with classic neuroretinitis

Differential Diagnosis

The differential diagnosis for neuroretinitis includes malignant hypertension, central retinal vein occlusion, diabetes mellitus, pseudotumor cerebri, sarcoidosis, syphilis, tuberculosis, toxoplasmosis, toxocariasis, Lyme disease, mumps, varicella, herpes simplex, and leptospirosis (Dreyer et al. 1984). It is important to remember that unilateral disc edema precedes the formation of a macular star by 1–4 weeks. As in the case in Fig. 18.2, this 12-year-old patient presented with asymmetrically bilateral disc edema and underwent extensive workup including a lumbar puncture prior to the development of a macular star and subsequent diagnosis of Bartonella. Invasive diagnostic procedures can be avoided by obtaining a thorough history and considering Bartonella in the differential for disc

edema even in the absence of a macular star. Causes of a macular star include hypertensive retinopathy, papilledema, anterior ischemic optic neuropathy, diabetic papillopathy, posterior vitreous traction, disc, and juxtapapillary tumors. Either by inflammatory or ischemic mechanisms, these entities can compromise the microvasculature of the optic disc and result in leakage of serum and lipids with macular star formation.

Bartonella henselae has been isolated as the etiologic agent, and serologic testing for *B. henselae* is available. There are two different serologic tests for the diagnosis of cat scratch. The first is an indirect fluorescent antibody test (IFA) for the detection of serum anti-*B. henselae* antibodies. This test was found to be 88% sensitive and 94% specific in the immunocompetent host and may fall to 70% or below in HIV-infected individuals (Dalton et al. 1995). The second is an enzyme immunoassay (EIA) with a sensitivity of 86–95% and specificity of 96% compared with IFA (Litwin et al. 1997; Barka et al. 1993). All tests have the potential for cross-reactivity with *B. quintana* as well as other species.

Management

There are no treatment guidelines for CSD as it is known to have a self-limited course in immunocompetent patients. The visual prognosis is good with or without treatment. Antibiotics are generally reserved for those with the most severe infections. Immunocompromised patients affected with CSD tend to require antibiotics such as erythromycin or doxycycline to control their infection (Schlossberg et al. 1989).

Given its superior intraocular penetration, doxycycline is preferred to erythromycin in patients older than 9 years of age. Doxycycline is contraindicated in younger children given its propensity for teeth discoloration. Both doxycycline and erythromycin can be given intravenously or combined with rifampin in more severe infections. Other antibiotics that can be used include azithromycin, ciprofloxacin, gentamycin, and trimethoprim-sulfamethoxazole (Relman et al. 1990). After resolution of the disease, final outcome can include residual visual field defect, decreased visual acuity, and contrast sensitivity and disc pallor on examination.

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Syphilis

19

Sulaiman Alhumaid and Janet L. Davis

Introduction

Syphilis is an infectious disease caused by the spirochete *Treponema pallidum*, a non-cultivable helical bacterium self-propelled with flagella. It causes disease only in humans. Early origins are unknown, but it was present in Europe around the sixteenth century (Fornaciari et al. 1989). Some historians refer to syphilis as the "Great Pox" as opposed to small pox caused by variola virus and believe that Columbus and his sailors introduced this disease to Europe from the New World (Rothschild et al. 2000). Sir William Osler described syphilis as "the great imitator" because of the varied and complex clinical stages of the disease (Singh and Romanowski 1999; Tramont 1995).

Syphilis can be transmitted by sexual contact, through blood by sharing needles or blood product transfusion, vertically from mother to fetus through the placenta or by direct contact with a cutaneous lesion (Chambers et al. 1969; Rolfs et al. 1990). There was a declining incidence of new infections in the United States until 2000 when there was a reversal of that trend, prompting the Centers for Disease Control and Prevention (CDC) for health care providers to recognize syphilis as an ongoing public health problem.

Epidemiology

Incidence of Syphilis

The World Health Organization estimates that 12 million new cases of syphilis occur each year (Gerbase et al. 1998). The CDC reported an incidence rate of 8.7 cases of primary or secondary syphilis per 100,000 people in 2015–2016, versus 2.1 cases per 100,000 in 2000. In the United States, syphilis is primarily diagnosed in men who have sex with men, but cases in women have increased more rapidly than in men (Centers for Disease Control 2016). The overall rise in incidence was associated with clustering of ocular syphilis cases in Seattle and San Francisco (Matthias et al. 2016) that led the CDC to issue a clinical advisory in 2015 to remind clinicians to screen for visual complaints in patients at risk for syphilis and to report cases to local health authorities within 24 h (Advisory 2016). Congenital syphilis rose each year from 2012 to 2016 with 15.7 cases per 100,000 live births in 2016, reaching the highest rate since 2001 (Bowen et al. 2015).

Incidence of Ocular Syphilis

The CDC investigated the incidence of ocular syphilis in 2014–2015 in eight jurisdictions: California (excluding Los Angeles and San Francisco), Florida, Indiana, Maryland, New York City, North Carolina, Texas, and Washington (Oliver et al. 2016).

Three hundred eighty eight cases were identified as suspected ocular syphilis, accounting for 0.6% of the total reported syphilis cases. Ninety-three percent of cases were in men, of which 68% were men having sex with men and 51% were HIV infected. Of the HIV patients, one third were first diagnosed with HIV at their presentation with ocular syphilis. In addition to shared risk factors, infection with syphilis is felt to facilitate the acquisition of HIV by mucosal injury. Ocular manifestations of syphilis were reported in both eyes in about 53%. The most common reported ocular diagnoses were syphilitic uveitis (45.6%), followed by retinitis (12.7%) and optic neuritis (11.4%). At the same time, an increase in ocular syphilis cases was reported at an Ophthalmologic Reference Center in France (Pratas et al. 2015); Nantes, France (Lefebvre et al. 2013); Manchester, UK (Jones 2015); and Barcelona, Spain (Fonollosa et al. 2009). The CDC subsequently requested pre-antibiotic samples of ocular fluid for molecular typing (Advisory 2016).

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Unlike the United States, United Kingdom has a prospective national registry of ocular syphilis (The British Ocular Surveillance Unit). The British annual incidence of ocular syphilis is 0.3 per 1 million persons, which represent 41 new cases. Of those reported cases, 90% were male patients, 31% were HIV positive, and 56% of the cases had bilateral involvement (Mathew et al. 2014).

Classification of Syphilis

Congenital Syphilis

Syphilis is broadly classified into congenital and acquired types. Congenital syphilis is the oldest recognized congenital infection, first described in the fifteenth century (Shafti et al. 2008). Congenital syphilis is transmitted vertically through the placenta. Syphilis can cause spontaneous abortion, stillbirth, or neonatal death. Among survivors, early congenital syphilis in the first 2 years of life can demonstrate mucocutaneous lesions, periostitis, osteochondritis, and hepatosplenomegaly. Uveitis is the most common ocular complication of early congenital syphilis with associated chorioretinitis and retinal vasculitis producing a salt-and-pepper pattern of retinal pigmentary mottling (Fig. 19.1). Late congenital syphilis presents with bone and dental abnormalities including Hutchinson teeth, mulberry molars, abnormal faces and saber shins, as well as cranial nerve eight deafness, and perforation of the hard palate. The most common ocular manifestation of late congenital syphilis is interstitial keratitis, anterior uveitis, and glaucoma. Interstitial keratitis, neurosensory deafness, and Hutchinson teeth are collectively known as the Hutchinson triad.

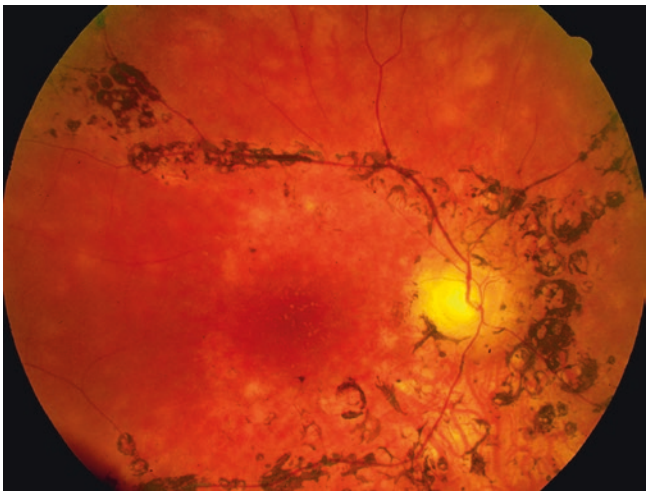

Fig. 19.1 This 59-year-old woman, born in 1923, had lifelong poor vision with chorioretinal scarring and optic atrophy. Serological testing with a treponemal-specific test was positive, and she was felt to have had congenital syphilis infection

Acquired Syphilis

Acquired syphilis is usually transmitted sexually. It is subclassified by its stage in the disease to primary, secondary, latent, and tertiary types. The primary infection appears as a chancre, which may be undetected, with associated painless lymphadenopathy. A delayed hypersensitivity reaction resolves the lesions, but some organisms survive and may cause a persistent infection. Secondary syphilis manifests as a cutaneous eruption with lymphadenopathy, along with fever, malaise, sore throat, and joint pain (Wilhelmus and Lukehart 1996). This stage remits even if not treated, but relapses can occur in up to 25% of people, usually during the first year of infection but up to decades later during the phase of latent syphilis.

Seventy-two percent of patients with latent syphilis will develop no further complications or relapses, but 28% will progress to tertiary syphilis (Kolker et al. 1997). This is an advanced disease state with cardiovascular and neurological conditions involving the meninges, brain vessels, brain parenchyma, optic nerve, and posterior column in the spinal cord. The most common ocular manifestation of secondary and tertiary syphilis is uveitis (Wilhelmus and Lukehart 1996). Ocular syphilis can occur in any stage of disease (Fig. 19.2).

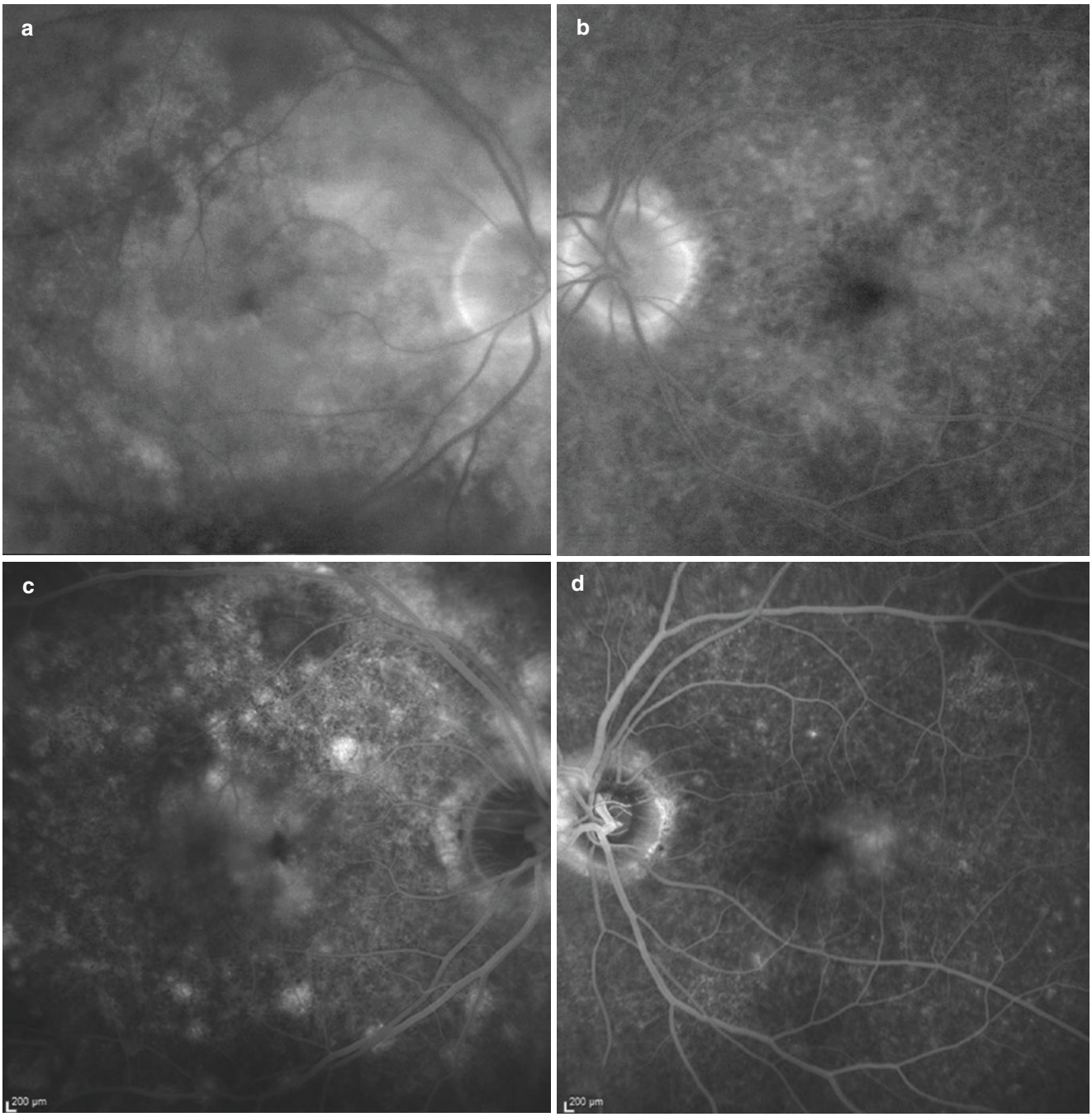

Fig. 19.2 This 56-year-old non-HIV-positive man had been treated for 3 years for a smoldering intermediate uveitis with mild vision loss in the right eye. There was a history of bicillin penicillin treatment for syphilis within the last 5 years. Lumbar puncture revealed a positive VDRL. (**a**) Late stage fluorescein angiogram of the right eye at the time of presentation showing diffuse retinal leakage, optic nerve leakage, and pigmentary changes. The vessels are emptied of dye. Vision was 20/30. (**b**) Late stage fluorescein angiogram of the left eye at presentation showing similar retinal and optic nerve leakage and pigmentary changes. Retinal perfusion was somewhat better in this eye, which was 20/20. (**c**) Late stage fluorescein angiogram of the right eye 2 years after two courses of intravenous penicillin. Optic nerve leakage has resolved, the retina is better perfused. There is persistent leakage in the center of the macula and extensive pigmentary change. (**d**) Late stage fluorescein angiogram of the left eye 2 years after treatment. Retinal perfusion is improved, with resolved optic nerve leakage and residual central leakage. Pigmentary changes are noted

Clinical Presentations

Anterior Segment Findings in Ocular Syphilis

Compared to other infectious and inflammatory etiologies affecting the eye, syphilis is highly variable in presentation with the ability to involve all structures of the eye (Davis 2014) (Table 19.1). Although there are some characteristic features, syphilis can also present as a nonspecific anterior, intermediate, posterior, or panuveitis (Cunningham et al. 2014). Interstitial keratitis typically occurs in children and adolescents with congenital syphilis and is often associated with conjunctival hyperemia and iritis (Aldave et al. 2001; Margo and Hamed 1992). Dilated iris vessels known as roseola are rare but specific (Margo and Hamed 1992). Large granulomatous keratic precipitates, hypopyon, posterior synechiae, and elevated intraocular pressure can accompany iridocyclitis (Reddy et al. 2007). Episcleritis/scleritis has been reported (Fenolland et al. 2016).

Posterior Segment Findings in Ocular Syphilis

Posterior segment findings of acquired syphilis are varied. Rather than necrosis, the infection produces retinal edema, often with subretinal fluid. The inflamed retina usually has an opacified appearance that differs from the classical whitening of herpetic necrotizing retinitis or toxoplasma chorioretinitis. The edema can be focal (Fig. 19.3) or diffuse (Fig. 19.4). If there is substantial subretinal fluid, there can

Table 19.1 Ocular features of syphilis by site and stage of disease

Site/ stage	Congenital	Secondary	Tertiary
Uveal tract	Acute iritis Secondary cataract or glaucoma	Iridocyclitis Iris nodules Isolated vitritis	Iridocyclitis Single or multiple gummas
Retina	Retinal pigmentary mottling in "salt-and-pepper" pattern Retinal vasculitis	Focal or multifocal chorioretinitis Multifocal choroidal infiltrates Necrotizing retinitis Neuroretinitis Retinochoroiditis Retinal vasculitis Serous retinal detachment Cystoid macular edema	Focal or multifocal chorioretinitis Necrotizing retinitis Neuroretinitis Retinochoroiditis Retinal vasculitis Serous retinal detachment Cystoid macular edema
Optic nerve	Optic atrophy	Inflammatory disc edema Papilledema	Inflammatory disc edema Papilledema Optic atrophy Gumma of optic disc

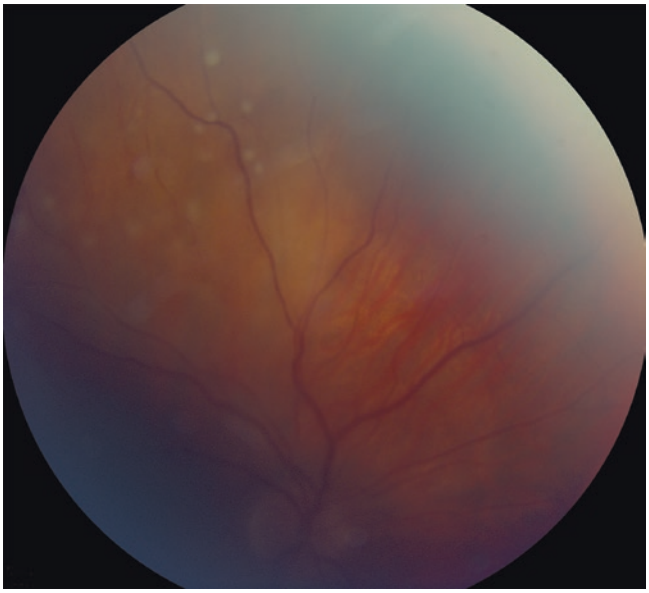

Fig. 19.3 This 43-year-old HIV-positive man complained of cloudy vision in the right eye for a few months. Fundus examination showed a region of retinal swelling above the superotemporal arcade with vitreous inflammation. The photograph depicts white, focal preretinal opacities. There is some irregularity of the vascular caliber in the region of greatest retinal whitening. He was serologically positive by both treponemal and non-treponemal tests, confirming the diagnosis of syphilitic uveitis

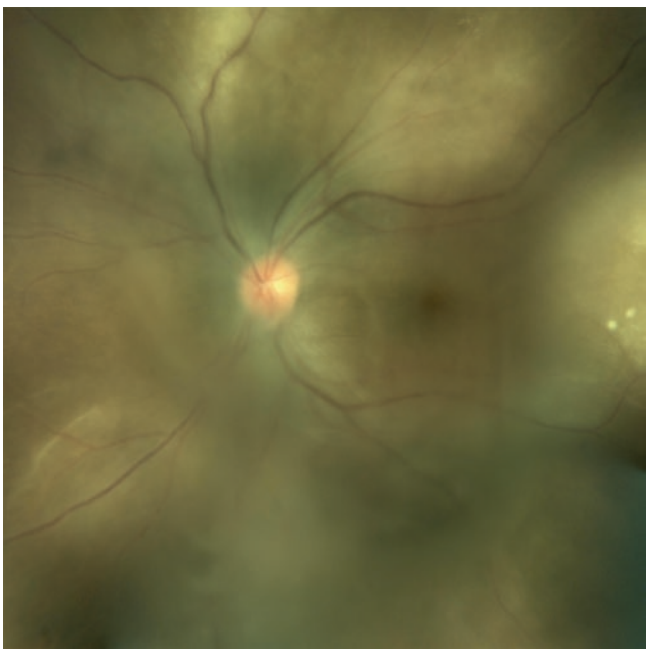

Fig. 19.4 Left fundus photograph of a 36-year-old HIV-positive man who presented with subacute vision loss in both eyes in the setting of secondary syphilis. Diffuse retinal edema with possible shallow subretinal fluid was present in both eyes. Focal preretinal vitreous opacities are visible at the edge of the frame. Sheathing of vessels is seen inferonasally

be actual serous detachment, although this is usually shallow (Fig. 19.5). Fluorescein angiography is important in detecting retinal vasculitis, which is often nonspecific and confused with a noninfectious uveitis (Fig. 19.6). Cystoid macular edema is common in eyes with retinal vascular leakage (Fig. 19.7). Necrotizing retinitis and branch vein occlusion have been described (Jumper et al. 2000; Villanueva et al. 2000; Venkatesh et al. 2002; Yokoi and Kase 2004). Optic nerve manifestations include inflammatory disc edema (Fig. 19.8), neuroretinitis, pallor, and optic nerve gumma, a solid inflammatory lesion (Margo and Hamed 1992).

Some distinctive posterior segment features may help support the diagnosis of syphilis. Superficial retinal precipitates may occur in syphilitic panuveitis, often associated with other inflammatory signs (Fu et al. 2010; Wickremasinghe et al. 2009) (Fig. 19.9). These small,

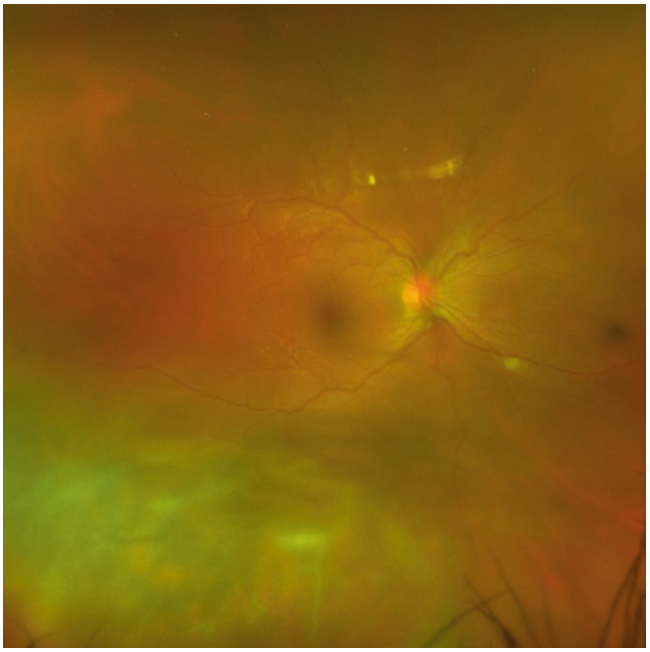

Fig. 19.5 Color photograph of the right fundus of a man presenting with syphilitic uveitis. The inferotemporal quadrant shows retinal whitening and vascular sheathing. There is substantial subretinal fluid and retinal edema around the nerve

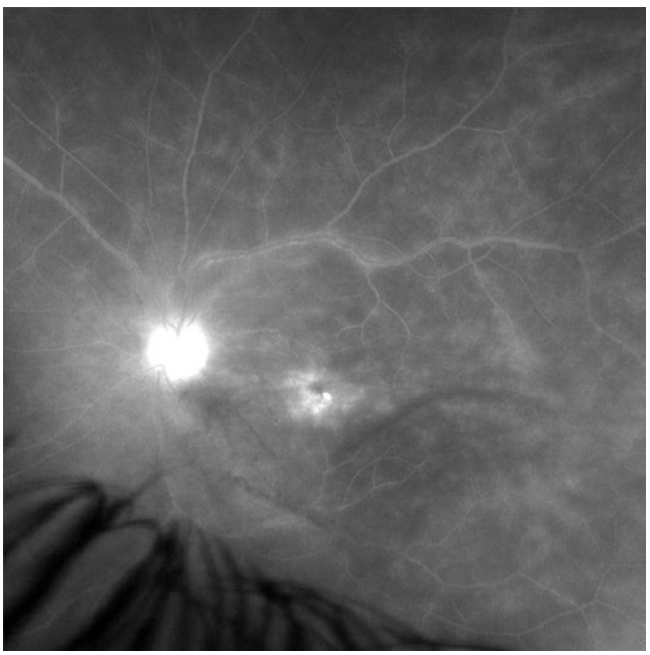

Fig. 19.6 A nonspecific diffuse small and large retinal vasculitis with optic nerve hyperfluorescence and cystoid macular edema is depicted in this late stage fluorescein angiogram of a left eye in a patient with ocular syphilis

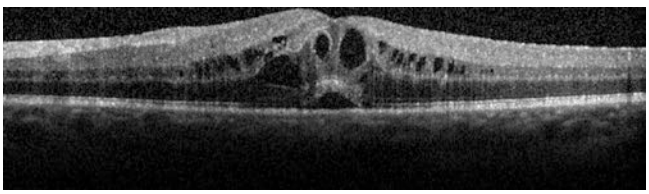

Fig. 19.7 The OCT scan of the macula of the eye depicted in Fig. 19.6. There is typical cystoid macular edema with subfoveal fluid. Although the outer retina can be disrupted in syphilitic uveitis, it appears mostly intact in this patient

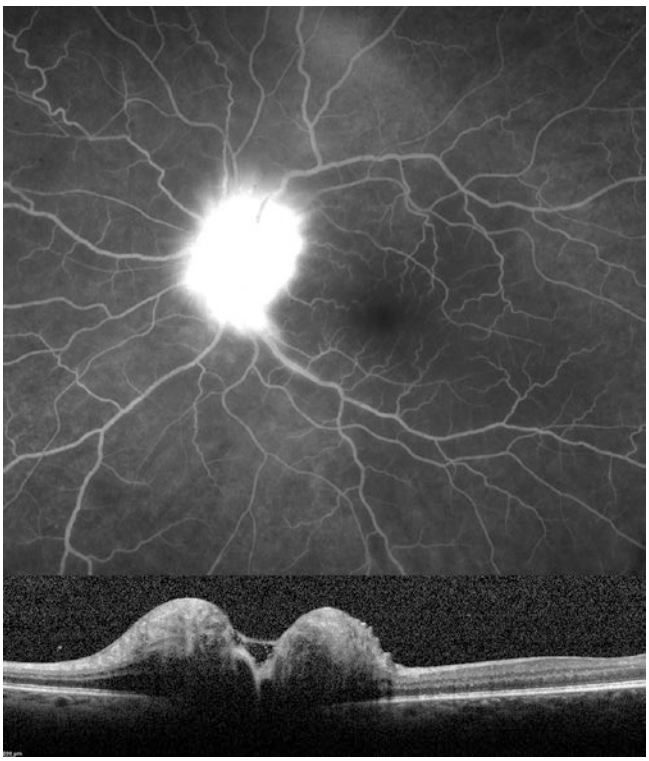

Fig. 19.8 Relatively isolated syphilitic optic nerve edema is depicted in this fluorescein angiogram of a left eye. The OCT scan through the nerve shows diffuse thickening of the perineural tissue. The macular contour is normal. The amount of retinal leakage is small although there is some vascular tortuosity

creamy white focal opacities appear to migrate over the surface of inflamed retina during the course of disease and treatment, but do not float. Other focal opacities line up along the retinal arteries in some cases, similar to the so-called Kyrieleis plaques described in toxoplasma chorioretinitis (Krishnamurthy and Cunningham 2008). The involved retina in cases of syphilitic retinitis usually heals with milder alteration of the retinal pigment epithelium and less retinal scarring than in herpetic retinitis, but chronic cases can experience substantial scarring (Baglivo et al. 2003) (Figs. 19.10 and 19.11).

Another distinctive finding is acute syphilitic posterior placoid chorioretinitis (Gorovoy and Desai 2013; Gass et al. 1990). This finding is attributed to a uniform inflammatory process involving the outer retina and inner choroid in a circular fashion on the posterior pole (Eandi et al. 2012) (Fig. 19.12). On spectral domain optical coherence tomography (OCT), there may be subretinal fluid and disruption of the ellipsoid zones (Pichi et al. 2014) (Fig. 19.13). With treatment, the subretinal fluid resolves with longer persistence of the disruption of the outer retina. Deposits may develop at the level of the RPE, which may resolve in time. Angiography may also help in distinguishing placoid syphilis from other etiologies, such as viral retinitis, lymphoma, and sarcoidosis. On indocyanine green (ICG) angiography, placoid lesions typically show diffuse early and late hypofluorescence, and fluorescein angiography shows a progressive diffuse leakage (Eandi et al. 2012) (Fig. 19.14). This pattern is specific to syphilitic uveitis compared to other types of infectious retinitis. The placoid lesion is hyperautofluorescent, probably due to the loss of the masking effect of the outer retina (Jumper and Randhawa 2012; Knecht et al. 2013).

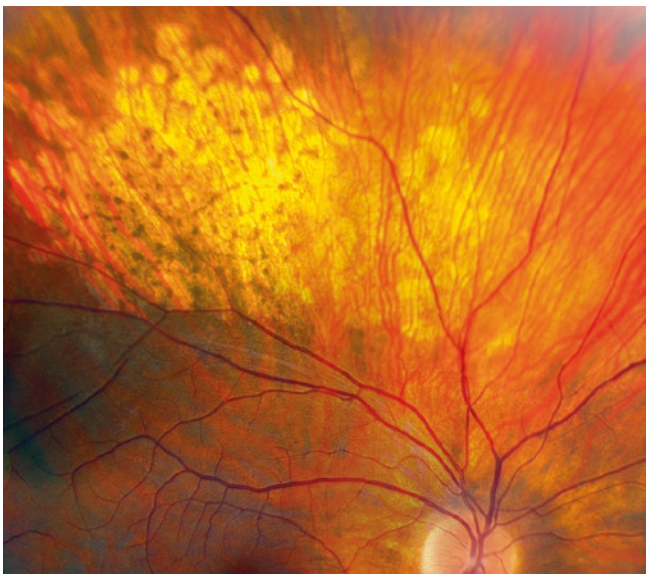

Fig. 19.10 Follow-up photograph of the patient in Fig. 19.3 after treatment of syphilitic uveitis with intravenous penicillin. There is extensive destruction of the retinal pigment epithelium, retinal thinning, and a permanent scotoma

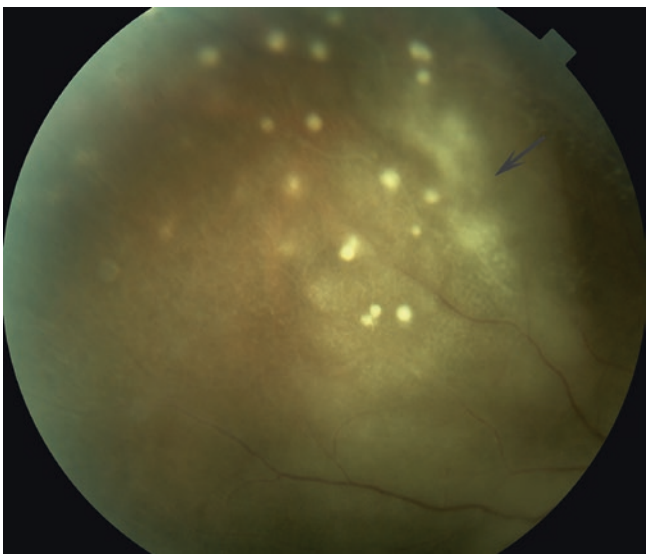

Fig. 19.9 White focal preretinal opacities overlying inflamed retina are virtually pathognomonic for syphilitic uveitis. They are migratory and transient, occurring only in the acute stages of the disease. In this photograph of the superonasal region of a right eye, there are also many sheathed and occluded retinal vessels. In some areas, there appear to be retinal infiltrates (arrowhead)

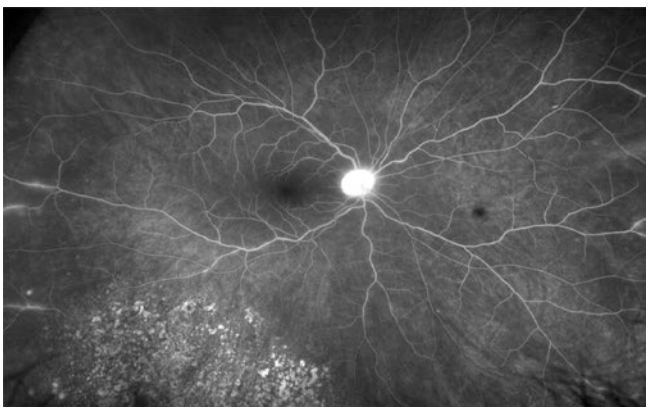

Fig. 19.11 Follow-up photograph of the patient in Fig. 19.5 after treatment of syphilitic uveitis with intravenous penicillin. There is a leopard spot pattern of RPE destruction in the region of subretinal fluid. Retinal vascular closures are present in the areas of pigmentary change. There is residual staining of large retinal veins in the peripheral and hyperfluorescence of the optic nerve

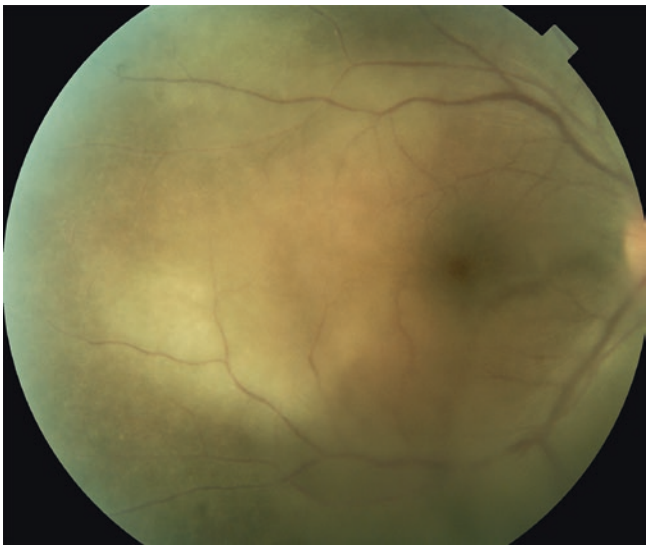

Fig. 19.12 Dense retinal swelling and pigment change affecting the temporal macula. This may be a preferential site of involvement in syphilitic uveitis

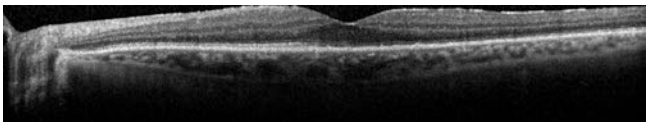

Fig. 19.13 Outer retinal disruption in a man complaining of recent vision loss in the left eye. The outer retina is diffusely abnormal without cystoid macular edema or, in this case, subretinal fluid. Other clinical findings of this case are depicted in Fig. 19.14

Diagnosis

Direct Detection of *Treponema pallidum*

Direct tests for Treponema such as dark field, polymerase chain reaction (PCR), and direct fluorescence test for *T. pallidum* are not commonly done because these methods are not widely available, and their sensitivity is less than optimal for detecting primary syphilis, missing a portion of the cases (Cornut et al. 2011). Multiplex PCR has the capability to test for multiple infectious organisms in a specimen. This technology has an application in ocular specimens where it tests for several causative agents including *Treponema pallidum* (Nakano et al. 2017).

Serologic Testing for Syphilis

Serological testing is the common practice to screen, confirm, and follow up. The CDC recommends a reverse sequence algorithm to test patients for syphilis. This approach has the benefit of detecting early primary as well as treated cases that would have been missed if other testing approaches were applied. The reverse sequence algorithm starts with a treponemal-specific test (fluorescent treponemal antibody, FTA), by either enzyme immunoassay (EIA) or chemiluminescent immunoassay (CIA), since these tests have the highest sensitivity. A negative result has a high negative predicative value. If the treponemal test is positive, a quanti-

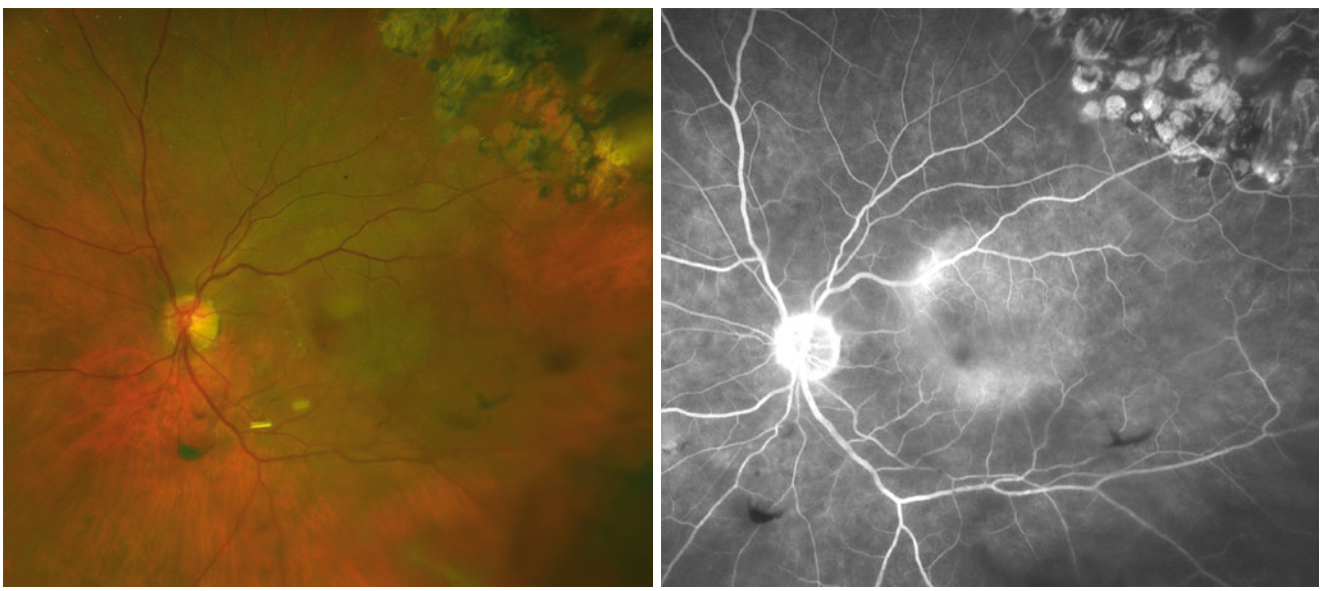

Fig. 19.14 This elderly non-HIV-positive man complained of vision loss. Left: color fundus photograph. The macula appeared to have lost translucency, but there was no thickening on OCT (Fig. 19.13). There was a past history of retinal detachment repair with extensive scarring superotemporally. Right: fluorescein angiography. There was late diffuse leakage in the macula typical for syphilitic posterior placoid retinitis. He was serologically positive for syphilis and responded to treatment with penicillin

tative rapid plasma regain (RPR) test is reflexively performed. If both treponemal and non-treponemal tests are positive, syphilis infection is diagnosed, which is usually considered confirmatory of ocular syphilis. If results are discordant, a treponemal pallidum particle agglutination (TP-PA) is performed, and if negative, it is considered that syphilis is unlikely (CDC 2008, 2011).

Reinfection can occur. If the treponemal test is positive in a previously treated but subsequently re-exposed patient, repeating the non-treponemal test in 2–4 weeks will help confirm a recent infection.

Testing for HIV and CNS Infection

Diagnosing syphilis in a patient with ocular inflammation is a trigger to test the patient for HIV because of the strong association of syphilis with high-risk sexual practices in men (Restivo et al. 2013; Butler and Thorne 2012; Chiquet et al. 2014; Abdul Wahab et al. 2013; Amaratunge et al. 2010). Since ocular syphilis is by definition a neurosyphilis, any patient who presents with ocular symptoms and has a positive serology test for syphilis should undergo a lumbar puncture with the analysis of cerebrospinal fluid. This is important to determine whether a follow-up tap will be needed in 6 months to monitor the effectiveness of treatment. Signs of inflammation such as elevated protein or inflammatory cells may be taken as presumptive evidence of central nervous system infection even in the absence of a positive non-treponemal test.

Treatment

Treatment According to Neurosyphilis Guidelines

Treatment of ocular syphilis should follow the CDC guidelines for neurosyphilis (Centers for Disease Control and Prevention 2010) or those of the local health authority (Nurfahzura et al. 2013). Parenteral penicillin is the drug of choice for ocular syphilis. The recommended adult regimen is aqueous crystalline penicillin G 18–24 million units per day administered as 3–4 million units intravenously every 4 h or by continuous infusion, for 10–14 days. The alternative adult regimen if access to therapy can be insured is procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day, also for 10–14 days. An extended course of benzathine penicillin 2.4 million units intramuscularly once per week for 3 weeks provides a longer duration of therapy commensurate with that recommended for latent syphilis. In case of penicillin allergy, penicillin is still the drug of choice to treat neurosyphilis, ocular syphilis, HIV patients, and pregnant women. These patients require prior desensitization before starting treatment. Intravitreal administration of ceftazidime to provide rapid control of ocular syphilis during the desensitization process has been described (Sood et al. 2019).

Monitoring Response to Treatment

Aside from diagnosis, non-treponemal tests such as RPR and Venereal Disease Research Laboratory (VDRL) are used to monitor response to treatment. The results are not interchangeable, and only one of the tests should be used for monitoring. A change in titer needs to be at least fourfold to be considered meaningful. Reduction in the RPR titer to 1:1–1:2 and resolution of the cerebrospinal fluid abnormalities is generally accepted as success. Follow-up is necessary as resolution of the indirect measures of infection may be slow. Anatomic recovery on OCT may occur by 1 month, with visual recovery lagging for 6–9 months, and multifocal electroretinogram abnormalities persisting for more than 1 year (Alexander et al. 2012).

Managing Inflammation During Treatment

The Jarisch–Herxheimer reaction is a systemic reaction with fever resembling sepsis due to spirochete death caused by penicillin. It is more common in early syphilis than latent syphilis when the bacterial burden is higher. Neurosyphilis occurring in earlier stages of syphilis, including ocular syphilis by extension, may warrant concomitant treatment with corticosteroid in some cases to limit inflammation (Danesh-Meyer et al. 1999). It has been reported in a case of ocular syphilis (Marty et al. 2015) but not specifically involving the eye. In practical terms, a large increase in ocular inflammation after starting penicillin is uncommon; however, the resolution of inflammatory signs is typically slow. The role of corticosteroid in managing inflammation in cases of ocular syphilis is not clearly established. Topical corticosteroid is almost always used, and intravitreal injections of triamcinolone appear to be harmful (Eandi et al. 2012). Oral corticosteroids increased acute posterior placoid signs in one case (Zamani and Garfinkel 2003). Oral corticosteroid and periocular steroid injections may be useful after antibiotic treatment is completed for non-resolving vitreous opacities or secondary inflammatory complications such as macular edema.

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Leptospirosis

20

Sivakumar Rathinam, Rajesh Vedhanayaki, and Somanath Anjana

Introduction

Leptospirosis is a zoonotic disease caused by a spirochete Leptospira. It occurs secondary to exposure to urine of infected animals or contaminated environment. Leptospirosis can cause a wide range of symptoms. Unless thought of, symptoms may be mistaken for other diseases such as dengue or influenza. The systemic presentation may be as mild as fever, joint pain and myalgia to life-threatening hepatorenal failure. Ocular manifestations are more common in the second or immune phase of the illness after a latent period. This latent period between initial systemic disease and ocular manifestation makes it difficult for the ophthalmologist to make a diagnosis.

Epidemiology

Leptospirosis occurs worldwide, but is more prevalent in the tropical and subtropical countries (Maze et al. 2018; Hartskeerl et al. 2011). According to the report from WHO, the incidence rate in tropical countries is 10–100/1,000,000, and during an epidemic, it may increase to over 100/1,000,000. Under-reporting is very common in leptospirosis due to lack of awareness and non-availability of diagnostic investigations (World Health Organization 2013). The disease can occur in different epidemiological settings from villages, urban slums and in travellers (de Vries et al. 2018). The risk factors and the chance of exposure vary accordingly (Vimal Raj et al. 2018).

Rodents and domestic mammals such as cattle, pigs and dogs serve as major reservoir host. Leptospira get excreted in animal urine to the external environment. Direct transmission from animal to human being is common among farmers, slaughter house and sewage workers. Inhabitants of flooded areas are at a high risk of developing leptospirosis because of excessive contamination of stagnant water (Rathinam et al. 2018; Holla et al. 2018; Maze et al. 2018). Men are more affected due to increased exposure to leptospires in their occupation. Travellers who participate in water sports are also at risk when they visit endemic countries, if the water is contaminated.

Microbiology

There are totally six genera in spirochetal family, of which three are pathogenic to human beings which include Treponema, Borrelia and Leptospira. Leptospires belong to the order Spirochaetales and genus Leptospira. Till now more than 250 pathogenic serovars of Leptospira have been recognised (Cerqueira and Picardeau 2009). The size of the leptospires range from 6 to 20 μm in length and about 0.1 μm in thickness, and they are seen only under high-power magnification (1000×) (Adler 2015). They cannot be stained with grams stain; they are seen well with silver staining. They need special culture media, such as Ellinghausen-McCullough-Johnson-Harris (EMJH) medium, Korthof's medium, Fletcher's medium and Stuart's medium.

Leptospires enter the body through abraded skin and intact mucous membranes. They are present in the blood up to 4–7 days, and specific IgM antibodies appear after 7 days to clear the bacteria from the blood. These IgM antibodies can persist for many months after initial presentation.

Systemic Manifestations

The incubation period of leptospirosis is 5–10 days. Leptospirosis can occur as two clinical forms: 90% of them present with mild to moderate febrile illness and 10% present with severe icteric Weil's disease. Poor clinical prognosis

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Table 20.1 Systemic and ocular manifestations of leptospirosis

Phase	Systemic manifestations	Ocular manifestations
Acute septicemic phase	Fever Hepatic/renal failure Multi-organ haemorrhages Systemic hypotension Psychosis	Chemosis/congestion without discharge Sub-conjunctival haemorrhage
Immune phase	Chronic headache Recurrent arthralgia Recurrent abortion Infertility	Non-granulomatous uveitis[a] Hypopyon[a] Cataract[a] Vitreous membrane[a] Papillitis[a] Retinal vasculitis[a]

[a]Important diagnostic predictors for clinical diagnosis

and high mortality rate are reported when hepatic dysfunction, acute kidney damage, and/or pulmonary haemorrhage occur in icteric Weil's disease (De Brito et al. 2018).

The systemic leptospirosis has two phases: the acute septicemic phase and the delayed immune phase. The two phases are distinct in the milder form while indistinguishable in the icteric leptospirosis. The acute phase which is seen in the first week is characterised by conjunctival congestion, fever, myalgia, headache, abdominal pain, muscle tenderness and severe fatigue. The symptoms of immunological phase result in late complications; it can be delayed by months in some patients. Late complications include chronic headache, uveitis, arthralgia, recurrent abortion and infertility (Table 20.1).

Ocular Manifestations

Ocular manifestations in the initial bacteraemia phase are conjunctival congestion without discharge, chemosis, subconjunctival haemorrhage and yellow sclera. The severity of systemic presentation has no influence over the ocular severity. Uveitis is an important ocular manifestation of immunological stage. In this phase, patient presents with non-granulomatous anterior uveitis. Slit lamp examination shows keratic precipitates on endothelium with moderate to severe anterior chamber inflammation. Hypopyon is seen when the inflammation is severe (Fig. 20.1). Unlike other complicated cataracts, these patients may occasionally develop white pearly cataract early in the course of the disease (Fig. 20.2). This cataract may rarely get spontaneously absorbed (Rathinam et al. 2000). Vitritis, papillitis and periphlebitis are important posterior segment findings (Fig. 20.3). Veil-like vitreous membranes may be present in the posterior

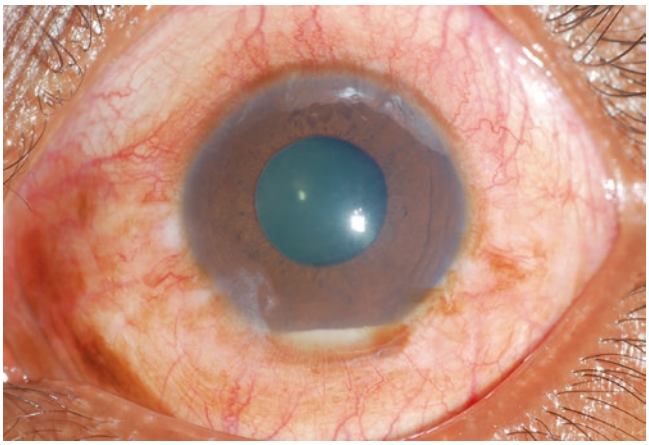

Fig. 20.1 A 40-year-old male presented with hypopyon in the absence of posterior synechiae. He was started on oral doxycycline and topical steroids and responded well

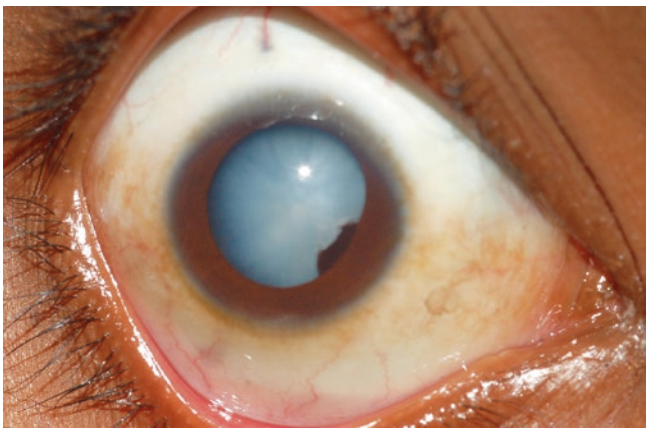

Fig. 20.2 A 35-year-old male, who was farmer, was diagnosed to have lepto cataract (clouding and separation of cortical matter) in a white eye

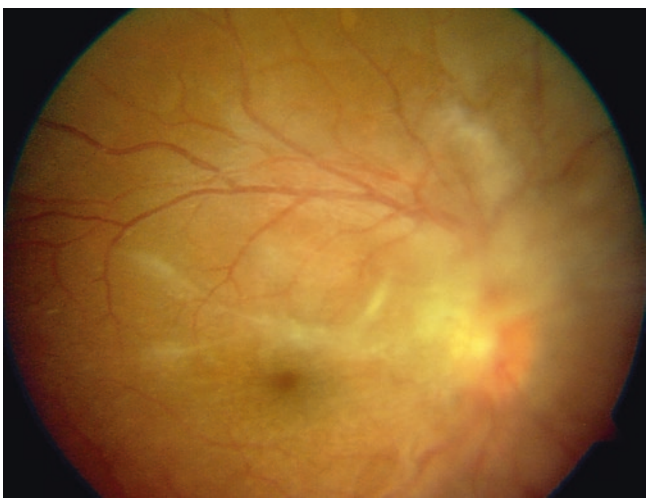

Fig. 20.3 Fundus photograph of retinal vasculitis in leptospiral uveitis

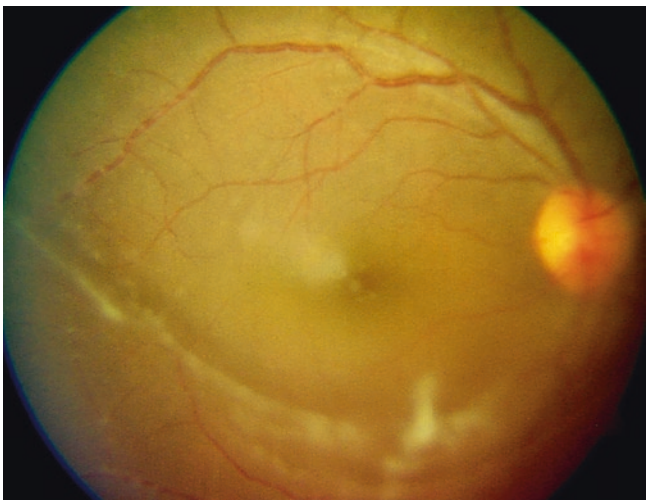

Fig. 20.4 Fundus photograph of veil-like vitreous membrane

segment, and persistence of this membrane is noted even after the inflammatory control (Fig. 20.4). Absence of retinitis and choroiditis in the above setting usually clinches the diagnosis.

In summary, the pathognomonic ocular findings are non-granulomatous uveitis with or without hypopyon, cortical cataract, veil-like vitreous membranes, papillitis, and vasculitis in the absence of retinal and choroidal involvement (Rathinam et al. 2018).

Differential diagnoses of non-granulomatous hypopyon uveitis include Behcet's disease and HLA-B27-associated uveitis. Intense vitreous reaction of leptospiral uveitis closely mimics the vitreous reaction of endogenous endophthalmitis, toxoplasmosis and acute retinal necrosis.

Investigations

In case of systemic leptospirosis, the diagnosis can be made from blood, CSF and urine samples by direct methods such as microscopy, culture or molecular methods. Indirect serological methods include detection of IgM antibodies by Micro Agglutination Test (MAT) or Enzyme-Linked Immuno Sorbent Assay (ELISA). Micro Agglutination Test (MAT) is the gold standard test. Although it is less sensitive, this test is highly specific and detects serovar-specific antibodies. MAT can be performed only in laboratories where maintenance of strains is possible, and it is labour intensive. ELISA kit for leptospirosis is available commercially. The methods available are detailed in Table 20.2 (Budihal and Perwez 2014).

Additional laboratory findings are moderately elevated white blood cell count, elevated erythrocyte sedimentation rate. Impaired liver/renal function tests depending on the systemic presentation.

Table 20.2 Laboratory investigations for leptospirosis

Diagnostic test	Window of positivity	Result availability	Remarks
Direct isolation			
1. Dark field microscopy	From first week	Within 1 h	Neither specific nor sensitive
2. Histochemical stains (Warthin–Starry stain) 3. Immunostaining	From first week	Within 1 h	Relatively more specific and sensitive
Culture EMJH medium	From first week	30 days	Expensive and cumbersome
PCR	From day 5–10	In 1 day	Expensive, DNA is needed in large quantity
Indirect serological methods			
IgM ELISA	From day 6–8	In 1 day	Cannot be detected in acute phase Persistence of antibodies
Microagglutination test (MAT)	From day 10–12	1 week	Gold standard, but not sensitive in early phase Labour intensive and complicated as maintenance of alive Leptospira is needed

Treatment

Systemic Disease

Patients with mild disease can be treated with either oral doxycycline 100 mg twice a day or oral azithromycin 500 mg once a day for 2 weeks. Severe systemic disease needs treatment with intravenous penicillin or third-generation cephalosporin. Monitoring and supportive care like dialysis and mechanical ventilation may be needed in cases of organ failure. Jarisch–Herxheimer reaction may be seen in few patients after starting anti-microbial therapy (Haake and Levett 2015) which needs intensive care.

Ocular Disease

Depending on the primary site of inflammation, uveitis is treated with topical, oral or periocular steroids along with oral doxycycline 100 mg twice daily for 2 weeks.

Prevention

National eradication is not possible because of large number of serovars and of infection sources and the wide difference in transmission conditions. Direct contact of leptospirosis

can be avoided by use of protective wear by farmers, livestock workers, butchers and sewage workers.

Chemoprophylaxis

Post exposure prophylaxis can be used after exposure to flood or heavy rain or after high-risk activities. Oral doxycycline (200 mg/week) is the most commonly used prophylactic antibiotic against leptospirosis (Schneider et al. 2017).

Prognosis

Ocular manifestation responds well to the treatment. Patients usually regain good visual acuity once inflammation is under control, except for the persistence of vitreous membrane. Cataract in leptospiral uveitis has good visual prognosis, when operated after control of inflammation.

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Fungal Infection

21

Un Chul Park

Introduction

Fungi are eukaryotic organisms which have different ribosome, nuclear structure, and cellular wall composition from bacteria. They are usually divided into yeasts and molds. Yeasts are typically round or oval and reproduce by budding. They include *Candida*, *Cryptococcus*, *Blastomyces*, and *Coccidioides* species. Molds are composed of tubular structures called hyphae and grow by branching in a longitudinal extension. They include *Aspergillus* and the agents of *mucormycosis*. There are also dimorphic fungi, which grow in the host as yeasts but in vitro as molds, and they include *Histoplasma* and *Blastomyces*. Fungi are ubiquitous in nature, but only a limited number of fungal species causes human infection, especially in eye in the form of fungal retinitis and endophthalmitis. The most common organisms that cause fungal infection are the *Candida* species, followed by *Aspergillus* species.

Fungal infection of the eye has increased in the past few decades. Ocular fungal infection is relatively rare, but can be severely devastating for visual function in the affected eye. Recent studies have reported that fungi accounts for 8–13% of culture-positive cases of infectious endophthalmitis (Moloney and Park 2014). Fungal infection of the eye may be endogenous or exogenous in its nature. In the endogenous fungal infection, fungi reach the eye through bloodstream (hematogenous spread from a systemic infection) and anchor at the choroid or retina, resulting in choroiditis, retinitis, or chorioretinitis (Parke et al. 1982). Ocular involvement is reported to occur in 10–29% of fungemia cases. Risk factors include systemic antibiotics or corticosteroid treatment, bacterial sepsis, alcoholism, hemodialysis, intravenous drug abuse, immunosuppression, and diabetes (Narndran et al. 2008). Endogenous fungal infection ranges from isolated chorioretinitis to endophthalmitis, which develops when initial focus of chorioretinal lesion by fungal infection spreads into the vitreous involving the entire inner structure of the eye. Exogenous fungal infections are usually complications of penetrating ocular trauma or intraocular surgery.

The diagnosis and management of ocular fungal infection is challenging even to the experienced retina specialists, and suspicion based on the systemic condition and clinical history of a patient is important. Untreated fungal endophthalmitis can result in blindness, and delayed initiation of antifungal treatment even after correct diagnosis may not successfully restore vision. Postoperative fungal endophthalmitis may mimic a chronic idiopathic uveitis and become symptomatic even several months after intraocular surgery.

Candida

Pathogenesis

Candida species are one of normal flora of the gastrointestinal, respiratory, and genital tract. Although they usually have low virulence as a commensal yeast, they may become pathogenic and can cause fatal disease in patients in immunocompromised status. The most common form of candidiasis in immunocompetent patients is superficial involvement, such as skin/nail infection and vulvovaginitis. The incidence of nosocomial candidemia has dramatically increased over the recent 20 years (Brooks 1989), but incidence of ocular candidiasis has decreased. Due to early identification and treatment of candidemia, recent incidence of ocular candidiasis is reported to be 2.8–14% among patients with candidemia (Donahue et al. 1994; Rex et al. 1994; Sallam et al. 2006; Shah et al. 2008). In acute form of systemic candidiasis, central nerve system, eyes, joints, kidney, and lungs are frequently affected. Systemic spread (dissemination) of candida usually occurs hematogenously, and the most common

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source of candidemia is gastrointestinal tract. Patients with immunosuppression or AIDS, those who have undergone parenteral hyperalimentation, gastrointestinal surgery, organ transplantation, and intravenous drug abusers are at increased risk of developing candidemia and disseminated candidiasis including candida chorioretinitis and endophthalmitis (Pappas et al. 2009; Tanaka et al. 2001).

Clinical Features

Candida albicans is the most commonly isolated fungus in patients with ocular infection, followed by *C. parapsilosis*, *C. tropicalis*, or *C. glabrata* (Edwards et al. 1974). Intraocular candidiasis usually presents as chorioretinitis or endophthalmitis. Chorioretinitis usually manifests as a single or multifocal deep, white-yellowish infiltrative lesion at the posterior pole (Figs. 21.1 and 21.2). Lesions may progress in number and size, and extensive tissue necrosis can develop at later stages (Fig. 21.3). But more commonly, with the progression of disease, inflammation finally spreads into the vitreous forming fluffy opacities which appear as cotton ball or to be connected by strands ("string of pearls") (Fig. 21.4). Abscesses can be formed in the retina, choroid, and vitreous (Fig. 21.5). At this stage of endopthalmitis, variable anterior chamber reaction or hypopyon may be observed. In cases with severe vitritis, fundus is severely obscured making clinical diagnosis difficult.

Initial symptoms are usually scarce or very mild and include blurred vision with mild ocular discomfort, floater, photophobia, and injection (Donahue et al. 1994). As intraocular candidiasis may show indolent course, fundus examination is recommended in all patients with candidemia, especially in those with higher risk of ocular involvement.

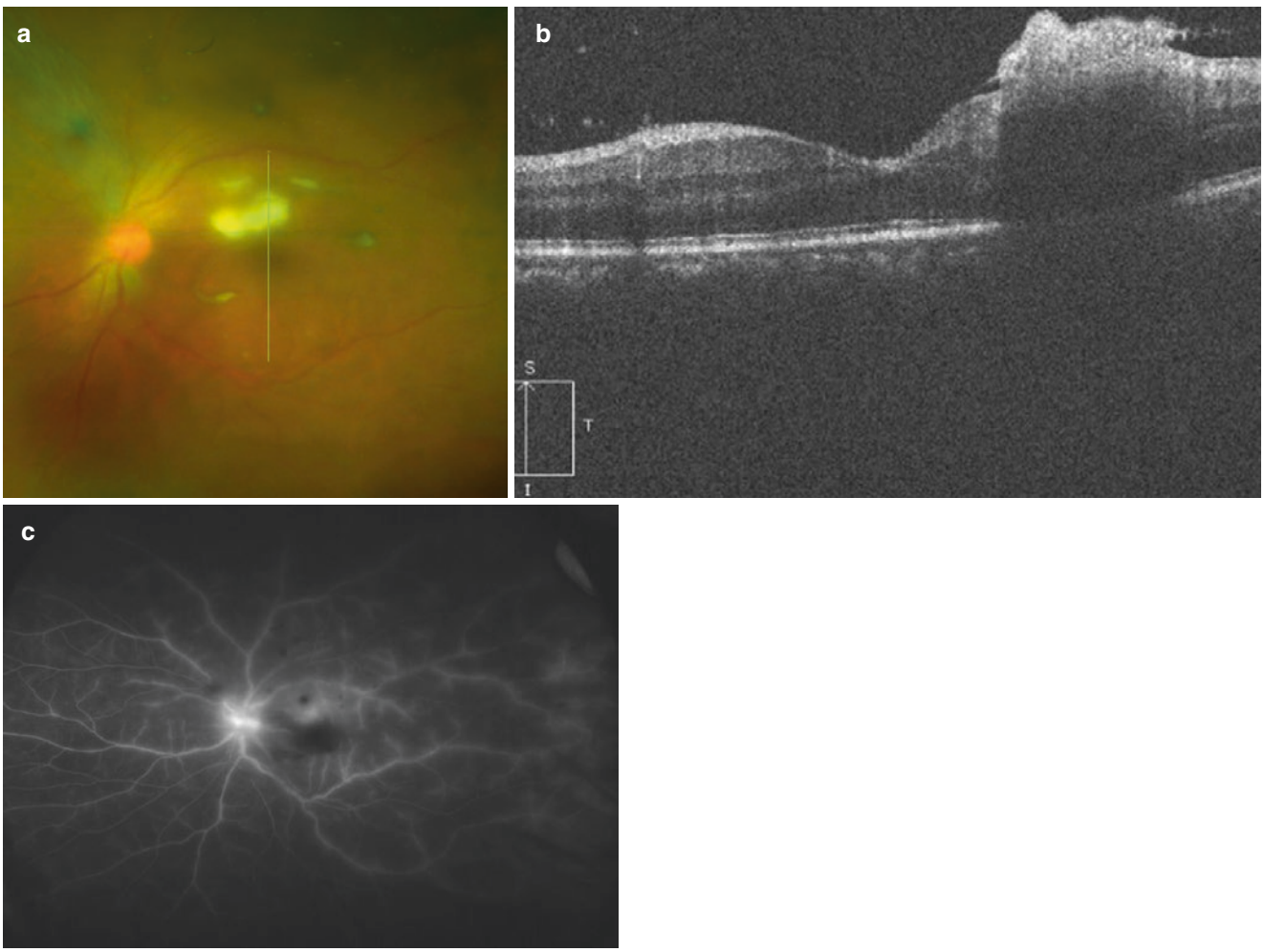

Fig. 21.1 (**a**) Fundus photo of a patient with *Candida albicans* infection shows chorioretinal infiltration with mild vitritis. (**b**) OCT image scanned along the green line in (**a**) shows hyperreflective lesion over retina. (**c**) In fluorescein angiogram, hyperfluorescence at chorioretinal lesion and diffuse leakage from disc and retinal vessels are seen

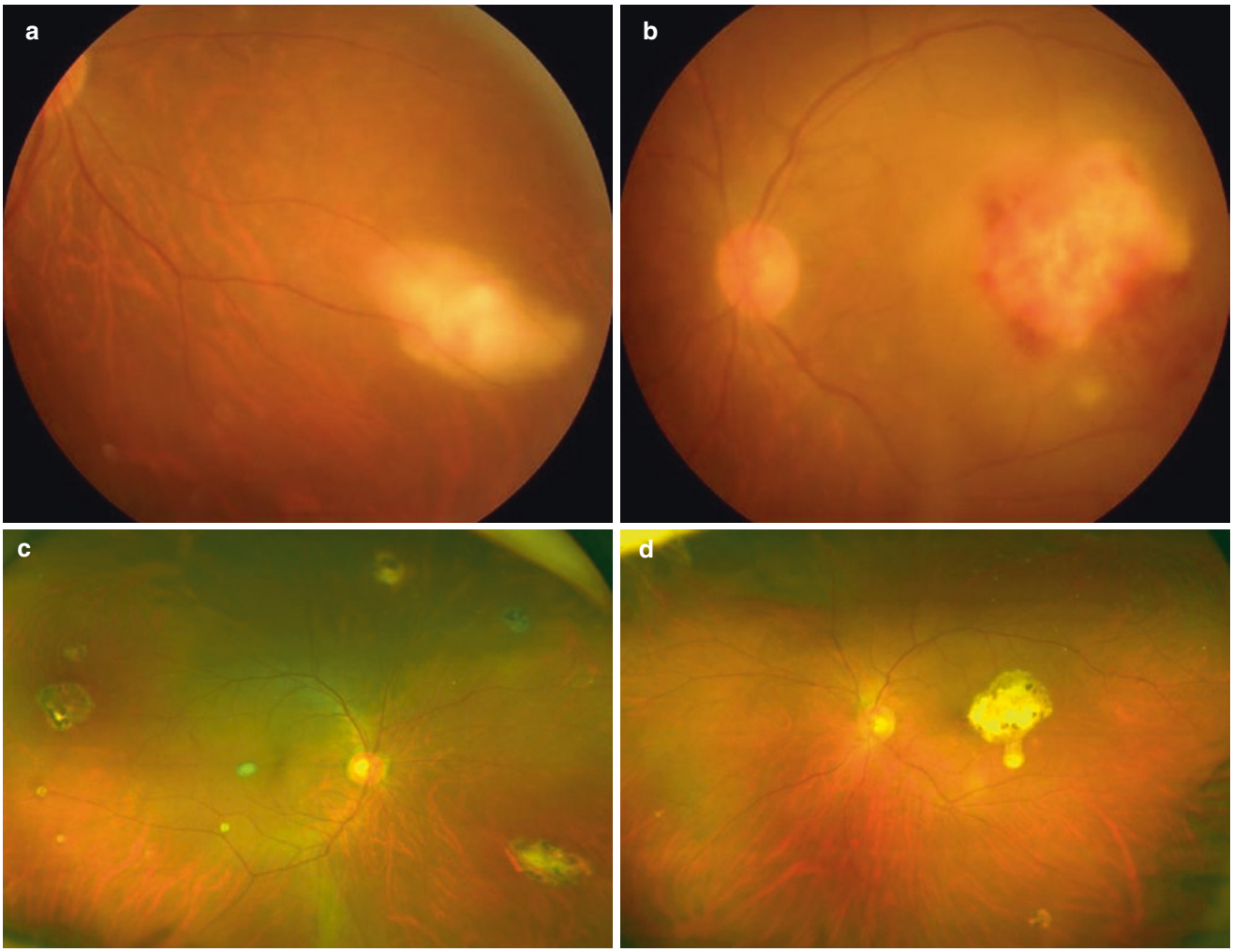

Fig. 21.2 Fundus photographs showing choroioretinal infiltrates at inferonasal periphery (**a**) or at macula with hemorrhage (**b**) in a patient with *Candida tropicalis* fungemia. (**c**, **d**) Ultrawide field retinal images taken 3 years later show multiple chorioretinal atrophic lesions

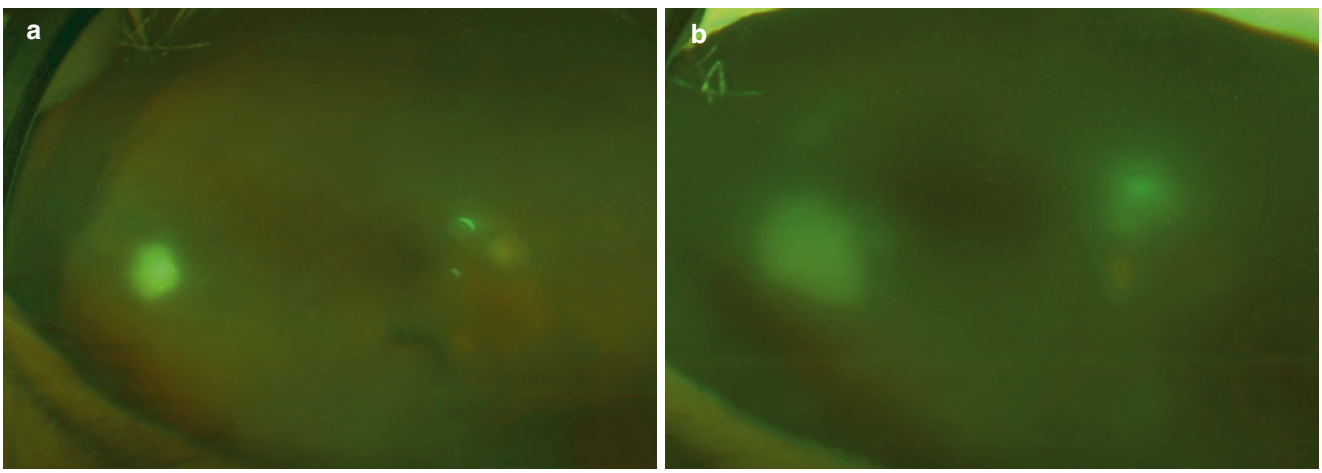

Fig. 21.3 (**a**) Ultrawide field retinal image shows yellow-whitish chorioretinal lesion at temporal periphery with vitreous involvement. (**b**) A week later, the chorioretinal lesion at temporal periphery became a large fluff ball, and new chorioretinal lesion is seen superior to disc. Fundus is more obscured by severe vitritis. The patient was later diagnosed as *Candida albicans* infection based on the vitreous culture

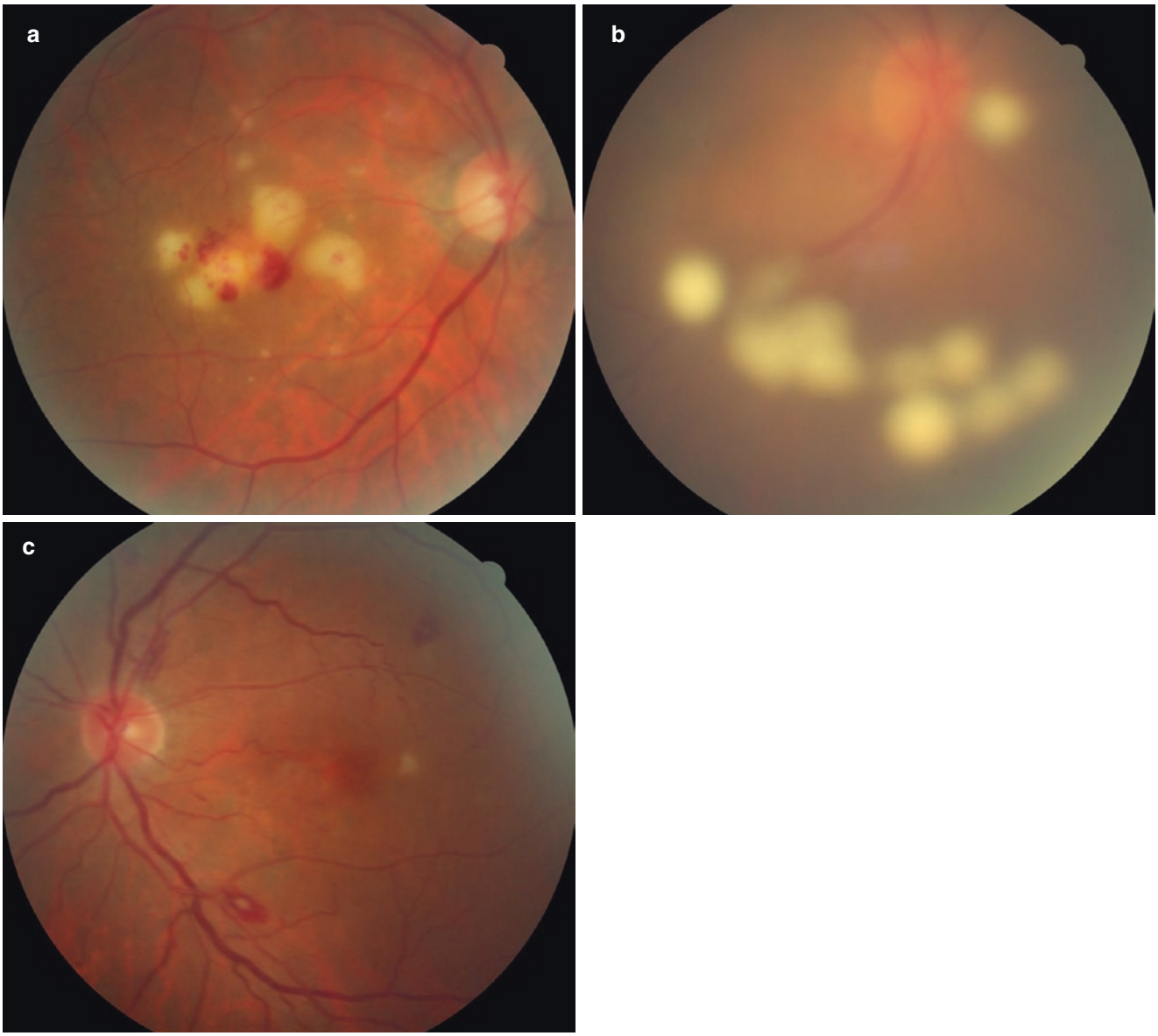

Fig. 21.4 Candida endophthalmitis. (**a**) Confluent multiple chorioretinitis lesions and retinal hemorrhage at macula. (**b**) Fluff ball appearance of vitreous exudate. (**c**) Flame-shaped retinal hemorrhage and Roth spots. (Courtesy of Prof. Joo Yong Lee)

Other signs of intraocular candidiasis include lens abscess, vitreous abscess, intraretinal hemorrhage, and Roth spots (Fig. 21.4). In addition, Candida is also the most common etiology of fungal keratitis, taking up nearly half of all culture-proven fungal keratitis (Galarreta et al. 2007). Prior history of ocular trauma with vegetable material, ocular surface disease, and penetrating keratoplasty are known risk factors.

Diagnosis

Diagnosis of systemic candidiasis may be assisted by the identification of fungus on direct microscopic examination or its growth in biological samples. Yeast growth in respiratory sample or urine should be interpreted with caution considering the normal colonization, but growth of candida in blood sample strongly supports systemic infection by candida.

In the diagnosis of intraocular candidiasis, recognition of characteristic fundus findings and thorough review of clinical history and medical status of a patient are fundamentally important, and laboratory test supports the diagnosis. Some fungal antigens or metabolites have been investigated for their efficacy in the diagnosis of systemic candidiasis, but they are not commonly employed in real-world clinical practice.

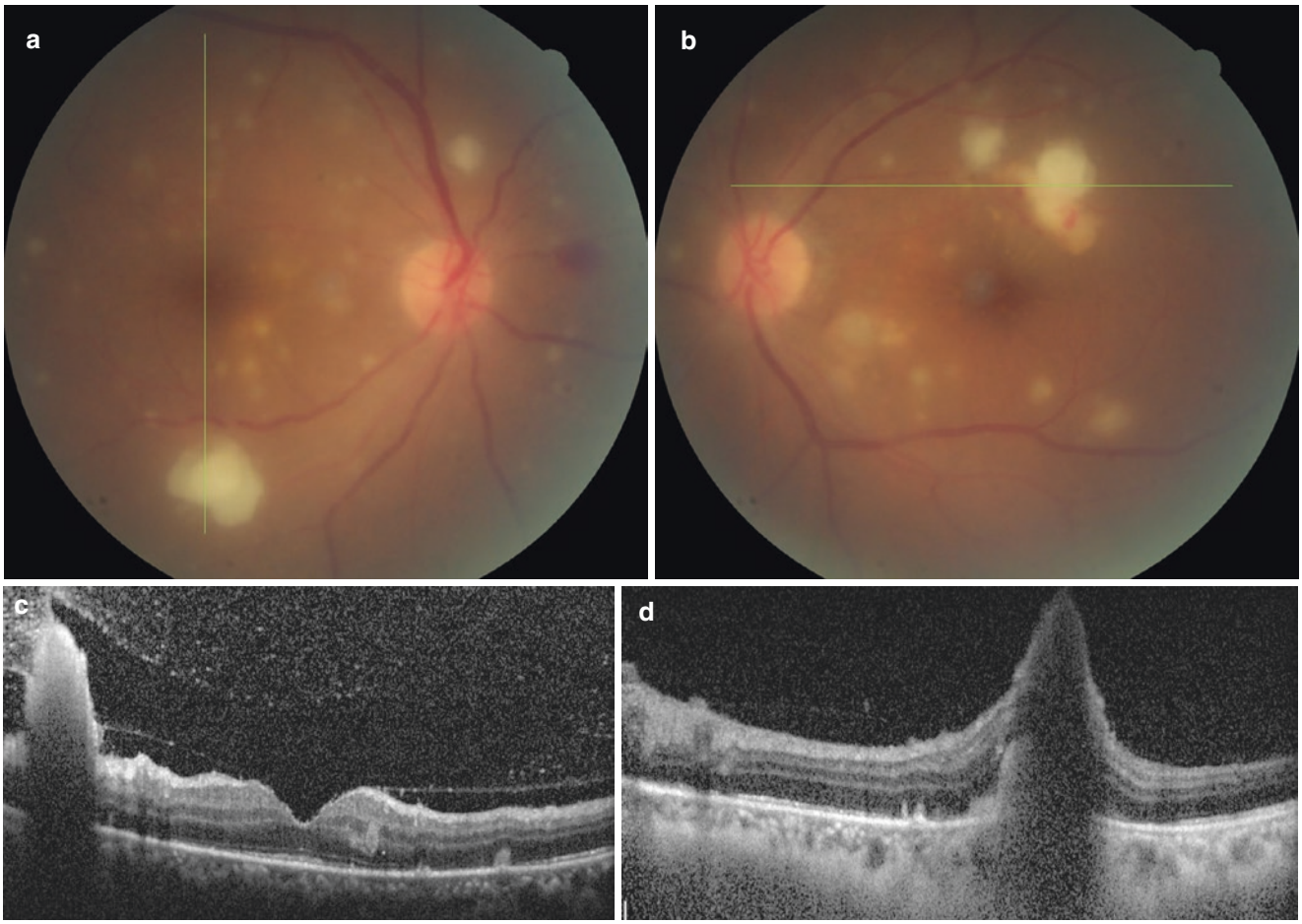

Fig. 21.5 Fundus photographs and spectral-domain optical coherence tomography (OCT) images in a patient with *Candida albicans* infection. (**a**, **b**) Fundus photographs show a creamy lesion extending to the vitreous as well as multiple yellow-whitish chorioretinal infiltrates. (**c**, **d**) OCT images scanned along the green lines show a well-circumscribed, dome-shaped hyperreflective lesion overlying the retina. In addition, (**d**) shows a subretinal lesion corresponding to yellow-whitish infiltration with hemorrhage in fundus photograph. (Courtesy of Prof. Joo Yong Lee)

In case with significant vitreous involvement, vitreous fluid collection by pars plana vitrectomy for both diagnostic and therapeutic purposes allows possible isolation of the fungus. Sensitivity of vitreous culture in the suspected cases of endogenous fungal endophthalmitis is about 50% (Martinez-Vazquez et al. 1998). Polymerase chain reaction (PCR) can be applied to vitreous sample for fungal infection, and recent studies suggested promising role of PCR in the diagnosis of candida endopthalmitis (Anand et al. 2001; Okhravi et al. 1998) because PCR is more sensitive and rapid compared to conventional methods. Recently, broad-range PCR techniques, which uses primers and probes for the conserved regions in the ribosomal DNA of fungi of many species (18S or 28S rDNA) can be performed with ocular fluids to diagnose intraocular fungal or bacterial infection (Sugita et al. 2013). They can provide evidence of the presence of fungal infection in the eye but are not able to identify the species or strains of fungi.

Aspergillus

Pathogenesis

Aspergillus is a filamentous fungus with saprophytic feature. It is usually found in soil, air, plant, and decaying organic material. Most of human infections are caused by *Aspergillus fumigatus* followed by *A. niger*, *A. flavus*, or *A. clavatus*, although more than 200 species have been identified. The most common route of transmission to the human host is via inhalation into the pulmonary alveoli and paranasal sinus (Bakri et al. 2010). *Aspergillus* is normally isolated from the skin and mucous membranes including the conjunctiva.

There are three main forms of Aspergillus infection: allergic bronchopulmonary aspergillosis, aspergilloma, and invasive aspergillosis. The first two forms are confined to bronchopulmonary or sinus lesions. However, mainly in immunocompromised individuals, invasive aspergillosis

occurs showing further dissemination into various organs such as skin, brain, kidney, gastrointestinal tract, myocardium, liver, spleen, and eyes.

Clinical Features

Although eyes are rarely involved organ in invasive aspergillosis, Aspergillus is the second most common etiology of intraocular fungal infection next to *Candida*. Similar to ocular candidiasis, Aspergillus infection of the eyes also presents as yellow-white chorioretinal infiltration and vitritis with fluff balls. Chorioretinitis, which is characterized by yellowish confluent deep lesions with ill-defined margins, is usually the initial finding in ocular aspergillosis (Fig. 21.6). Chorioretinitis lesions are usually located in the macula and are sometimes associated with retinal necrosis, exudates, and hemorrhages.

There are some features of chorioretinitis in ocular aspergillosis compared with candidiasis. There are usually only one or two lesions in Aspergillus infection, whereas chorioretinitis by *Candida* species often presents with multiple lesions. Rao and Hidayat described histopathologic features of enucleated eyes with intraocular candida and Aspergillus infection (Rao and Hidayat 2001). Extensive outer retinal necrosis and choroiditis with subretinal/sub-RPE involvement was usually noted in aspergillosis cases, whereas vitreous was the main focus of inflammation in Candida. In addition, fungal invasion along the retinal vessel or choriocapillaris, which causes retinal or choroidal infarction, was usually noted in aspergillosis cases but not in candidiasis (Jampol et al. 1988). Patients' history may also be helpful in differentiating etiological fungal agent. Intraocular fungal infections in patients with a history of gastrointestinal surgery, hyperalimentation, or diabetes are more likely to be caused by *Candida* species, while those with the history of organ transplantation or cardiac surgery are prone to *Aspergillus* (Rao and Hidayat 2001).

Diagnosis

As in candidiasis, clinical diagnosis of (disseminated) aspergillosis based only on clinical features or history is difficult, and high clinical index of suspicion is important. Direct examination and culture testing in biological material such as blood or bronchoalveolar lavage are helpful in reaching a correct diagnosis. Pulmonary computer tomography scan or detection of galactomannan antigen, which is a component of the Aspergillus cell wall, by ELISA can also be helpful.

Gold standard for the ocular aspergillosis diagnosis is the identification of fungus in ocular fluids through isolation and culture, but because of more frequent location of Aspergillus in outer retina or subretinal space, the result is often negative. As described earlier, PCR enabled increased sensitivity compared to conventional culture methods as well as shorter time for diagnosis of fungal endophthalmitis (Anand et al. 2001).

Cryptococcus

Ocular cryptococcal infection is usually caused by *Cryptococcus neoformans*. Most common source of infection is dropping from birds, especially pigeons, and the fun-

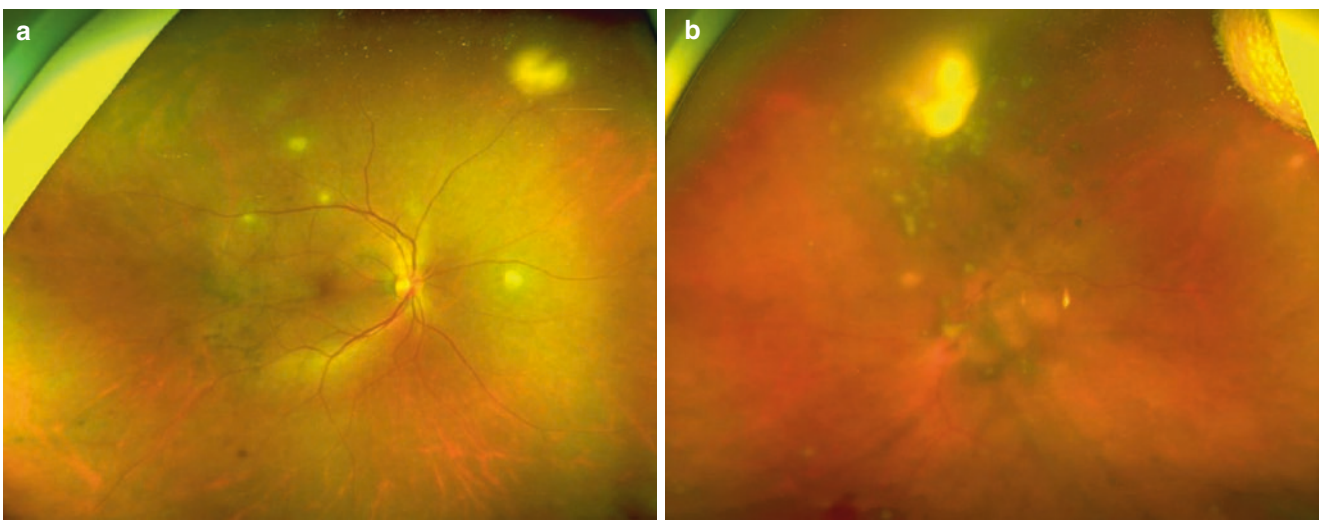

Fig. 21.6 Ultrawide field retinal image of a patient with disseminated aspergillosis. (**a**) Right eye shows multiple yellow-whitish chorioretinal lesions with mild vitritis. (**b**) Left eye shows superior large fluff ball with satellite vitreous opacities and more severe vitritis

gus is also isolated from soil, fruit, and plant. Inhalation of airborne spores of *C. neoformans* is the main route of infection in the human body, and they disseminate hematogenously most commonly to the brain, meninges, and spinal cord. Intraocular cryptococcosis usually occurs through direct extension from optic nerve sheath or hematogenously from the primary focus, but direct ocular involvement of cryptococcus is rare (Henderly et al. 1987). Normal host immune response is capable of managing *C. neoformans* infection, but immunosuppression, malignancy, AIDS, and systemic lupus erythromatosus are reported to be risk factors for systemic cryptococcocal infection.

In the eyes, the main site of *C. neoformans* involvement is the choroid, and retina or vitreous is involved secondarily (Henderly et al. 1987). Chorioretinitis is characterized by discrete, multiple, yellow-whitish lesions with slight elevation and is sometimes accompanied by retinal hemorrhage (Shulman et al. 2009). Exudative retinal detachment, retinal vessel sheathing, optic disc edema, and optic atrophy can also occur (Fig. 21.7).

The diagnosis of ocular cryptococcal infection is suspected when a patient has a disseminated form of cryptococcal infection, which most commonly involves the central nervous system. When causative organism is unknown, early diagnostic vitrectomy or vitreous tap may be performed to obtain vitreous fluid for culture or PCR. Identification of encapsulated organism in cerebrospinal fluid stained with India ink is sufficient for the diagnosis of cryptococcal involvement. Among the serological tests for *Cryptococcus*, the latex agglutination test to detect cryptococcal polysaccharide capsule antigen is most commonly used.

Histoplasma

Histoplasma capsulatum is a dimorphic unencapsulated fungus endemic to the central area of the United States, Central America, and Asia, but presumed ocular histoplasmosis syndrome is rather a distinct disease entity found almost in the United States but rare even in other endemic areas. The fungus enters body via respiratory tract through inhalation of spores. Infection in normal host is usually asymptomatic (Cohen et al. 1991), but in immunocompromised patients, a progressive disseminated form of histoplasmosis can occur via hematogenous spread to the organs including the eyes.

There are three major clinical manifestations of the ocular histoplasmosis: disseminated granulomatous chorioretinitis healing as atrophic "histo spots," maculopathy which can result in exudative episode and choroidal neovascularization, and peripapillary atrophy with pigmentary changes. Contrary to other ocular fungal infection, vitreous is not involved and remain clear. Chorioretinitis in histoplasmosis shows multifocal granulomatous creamy white intraretinal and subretinal infiltrates with retinal hemorrhages. As the lesion resolves, typical punched-out atrophic scars develop. Maculopathy in histoplasmosis is sight-threatening. At the initial stage, macular elevation with ground-glass appearance is seen, and macular lesion is hemorrhagic in more than half of cases (Walma and Schlaegel 1964). After multiple recurrence of macular attacks, disciform scar develops. Peripapillary pigmentary changes are also presumably resulted from choroiditis.

Diagnosis of ocular histoplasmosis is based on the isolation of the organism via staining, culture, or immunofluorescent techniques, though this fungus is rarely isolated or

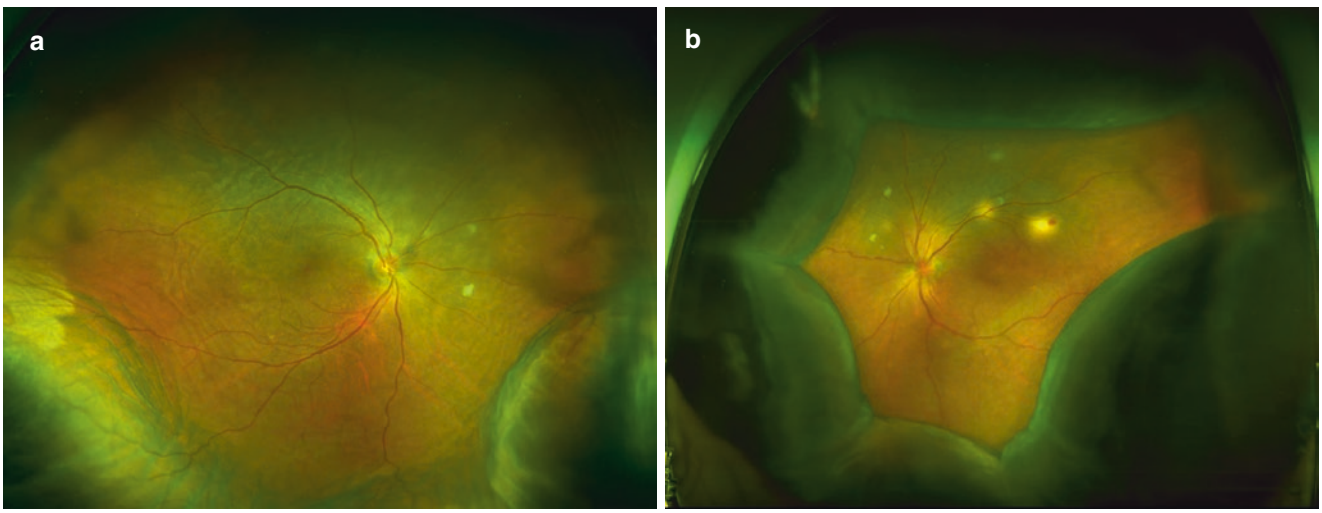

Fig. 21.7 (**a**, **b**) Ultrawide field retinal images show multifocal chorioretinitis, optic neuritis, and choroidal effusion in a patient who developed *Cryptococcus neoformans* infection during the treatment for IgA nephropathy. (Courtesy of Prof. Seung Jun Lee)

cultured from ocular fluid. In case of choroidal neovascularization, fluorescein angiography shows leakage from neovascularization in the late phase, and optical coherence tomography is helpful to identify the presence of subretinal fluid and pigment epithelial detachment.

Management of Ocular Fungal Infection

Treatment of ocular fungal infection is challenging, and untreated fungal endophthalmitis results in blindness in most cases. A high index of suspicion is important for the proper diagnosis and early treatment of fungal infection, which can improve anatomic and visual results. Even after proper diagnosis of fungal endophthalmitis, delayed treatment may not be effective for vision restoration. Treatment strategies for fungal chorioretinitis or endophthalmitis include systemic or intravitreal administration of antifungal agents and pars plana vitrectomy in severe vitreous inflammation (Chakrabarti et al. 2008).

Systemic fungemia is treated with intravenous antifungal drugs. Amphotericin B is a polyene class medication which works in part by interfering with the cell membrane of the fungus. Due to prominent antifungal activity, intravenous administration of amphotericin B has long been used as the standard treatment of intraocular fungal infection. Although amphotericin B is currently the most effective antifungal agent available, its use has decreased after the advent of new-generation antifungal drugs because of its limited intraocular penetration and multiple systemic toxicities including renal failure, hypotension, anemia, thrombocytopenia, and cardiac arrhythmia (Thompson et al. 2009). Flucytosine, another traditional antifungal drug, can be combined with amphotericin B in severe cases with macular involvement, extensive inflammation, and rapid progression (Schmid et al. 1991). It is converted to 5-fluorouridine triphosphate or 5-fluorodeoxyuridine monophosphate within fungal cells which inhibit protein and DNA synthesis, respectively. It has excellent gastrointestinal absorption and good intraocular penetration after oral administration.

Azoles are an alternative antifungal class, and new drugs such as fluconazole or voriconazole have good bioavailability, excellent intraocular penetration, and broad range of antifungal activity. Fluconazole has excellent oral bioavailability, and the once-a-day administration is enough due to long half-life. It is less toxic and penetrates better into the eye than amphotericin B, but *Aspergillus* tends to be resistant to fluconazole. Voriconazole is a second-generation triazole derived from fluconazole with broader spectrum of antifungal activity and can be given intravenously or orally. Systemic voriconazole can induce rapid clinical response compared to other antifungal drugs (Riddel et al. 2011). It is highly effective against *Candida* species, but its usage is limited by relatively high cost. In resistant species to amphotericin B, especially *Aspergillus* or *Cryptococcus*, voriconazole can be a promising regimen with better activity (Maschmeyer et al. 2007). In case of severe intraocular fungal infection, adjunctive intravitreal injection of dexamethasone can be used to control the marked vitreous inflammation and promote faster vitreous clearance, although it remains controversial. Systemic corticosteroid should be avoided in fungal endophthalmitis.

Recently, candidiasis management guideline by the Infectious Diseases Society of America (IDSA) recommended intravenous amphotericine B, fluconazole, or voriconazole in case of chorioretinitis without vitritis (Pappas et al. 2016). Duration of antifungal treatment should be longer than 4–6 weeks, depending on the resolution of the chorioretinal lesions. When macula is involved, intravitreal injection of amphotericin B (5–10 μg/0.1 mL) or voriconazole (100 μg/0.1 mL) is recommended in addition to systemic treatment to establish high antifungal activity within vitreous cavity. Amphotericin B was widely used as intravitreal injection, but voriconazole has been successfully employed more recently (Riddel et al. 2011). Also in case of chorioretinitis with vitritis, intravitreal amphotericin B or voriconazole is recommended. Because of retinal toxicity, amphotericin B should be injected slowly into the vitreous cavity with caution.

Pars plana vitrectomy should be considered in case of abscesses that are inaccessible to systemic antifungal drugs, significant vitreous involvement, or lack of improvement after intravitreal treatment of antifungal agents. It can also improve the possibility of establishing a definite diagnosis in a case with high clinical suspicion but without culture-proven results from anterior chamber or vitreous tapping samples (Chee and Eliott 2017). Sampling of vitreous for culture or PCR and injection of antifungal agents should be performed during the vitrectomy. Intravitreal burden of organisms can be decreased after vitrectomy, but half-live of intravitreal antifungal agent is reduced when given in a vitrectomized eye.

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Toxoplasmosis

22

Eun Kyoung Lee

Introduction

Ocular toxoplasmosis is one of the most common causes of posterior uveitis caused by an intracellular parasite *Toxoplasma gondii* (Holland 2003). Since the 1950s, ocular toxoplasmosis has been recognized as a form of inflammatory eye disease that follows the infection with the parasite, *T. gondii* (Wilder 1952). *T. gondii* is an ubiquitous obligate intracellular parasite, which infects both humans and warm-blooded animals as a zoonotic pathogen widespread in nature (Holland 2003). It is estimated that approximately one third of the world's population is chronically infected with *T. gondii* (Subauste et al. 2011). Ocular toxoplasmosis represents 50–85% of the posterior uveitis case in Brazil and about 25% of cases in the United States (Jones et al. 2001).

Toxoplasmosis may manifest as systemic disease or may be localized to the eye. Systemic manifestations of toxoplasmosis in newborns and immunocompromised patients can have life-threatening consequences. Ocular toxoplasmosis may occur either in a congenital or a postnatal acquired form. During the congenital infection, the fetus is infected via placental bloodstream, and fetal toxoplasmosis tends to occur only when the woman acquires the infection during or before gestation. During the acquired infection, parasite transfer is mediated typically through the gastrointestinal tract. Postnatal acquired form is now thought to be a more common cause of ocular toxoplasmosis (Subauste et al. 2011; Glasner et al. 1992; Gilbert and Stanford 2000).

Pathogenesis

T. gondii exists in three infectious forms including sporozoites, which are contained within oocysts, tachyzoites, and bradyzoites, which reside in tissue cysts. In humans, only tachyzoites and tissue cysts are present, and oocysts are produced only in cat intestines. Once the cyst is ingested by the intermediate host, it causes disease with the production of tachyzoites. Tachyzoite is the fastest replicating form and responsible for systemic dissemination and active tissue infection in intermediate hosts. Lysis of the host cell results in release and spread of tachyzoite. As a result of this cycle, necrotizing retinitis may occur. Under the pressure of the immune response, bradyzoites are formed. They can remain dormant in the host for years without tissue damage, and they are isolated in tissue cysts. When the cyst ruptures for unknown causes, retinitis may be reactivated (Silveira et al. 2011).

Most of the ocular toxoplasmosis is acquired by ingestion of food or water that is contaminated with oocysts shed by cats or by eating undercooked or raw meat containing tissue cysts (Montoya and Liesenfeld 2004). Lamb, pork, and chicken are more likely the sources of *T. gondii* infection than beef (Kijlstra and Jongert 2008). Less commonly, the tachyzoites passes vertically from mother to fetus as seen in congenital form. Transmission can also occur via organ transplantation and blood transfusion (Montoya and Liesenfeld 2004). Water reservoirs that become contaminated may deliver *T. gondii* oocysts to a large population in a short time interval (Jones and Dubey 2010).

Ocular toxoplasmosis most often presents as a focal necrotizing retinitis. The histology of the lesion in immunocompetent patients was characterized by foci of granulomatous chorioretinal inflammation and coagulative necrosis of the retina with sharply demarcated borders. Immunocompromised patients with ocular toxoplasmosis have both tachyzoites and tissue cysts in areas of retinal necrosis and within retinal pigment epithelial cells (Holland 2004).

Diagnosis

The diagnosis of ocular toxoplasmosis is made on distinctive clinical findings, that is, an area of active necrotizing retinochoroiditis satellite lesion adjacent to old hyperpigmented

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scars accompanied by vitreous inflammation and anterior uveitis. The seropositivity for *T. gondii* infection indicates previous systemic exposure to the parasite, though this finding is not sufficient to confirm the diagnosis of ocular toxoplasmosis. Therefore, the best clue to diagnosis is recognition of the clinical presentation (Dodds 2006). Toxoplasmic retinochoroiditis lesions have the similar fundus characteristics, whether they result from congenital or acquired infections (Fig. 22.1).

Clinical Features

Active and new lesions are usually focal and intensely white with overlying vitreous inflammatory haze. When active lesions are obscured by severe vitritis, it produces the classic "headlight in the fog" appearance (Fig. 22.2) (Park and Nam 2013). Eyes with active lesions will occasionally develop retinal vasculitis with vascular sheathing and hemorrhages (Smith and Cunningham 2002).

In the acute phase, active toxoplasmic retinochoroiditis lesions demonstrate disruption, thickening, and hyperreflectivity of the neurosensory retinal layers with interruption of the photoreceptor layer as well as retinal pigment epithelial (RPE) elevation in spectral-domain optical coherence tomography (SD-OCT) images (Goldenberg et al. 2013). Active lesions also reveal significant choroidal thickening beneath the active lesion with hypo-reflectivity of the choroid (Fig. 22.3). The changes in submacular choroidal thickness turned out to occur even when the active retinochoroidal toxoplasmic lesion lies outside the macula (Freitas-Neto et al. 2016).

With the improvement of disease, the borders of active lesions become more defined and may become hyperpigmented after several months (Figs. 22.4 and 22.5). The old

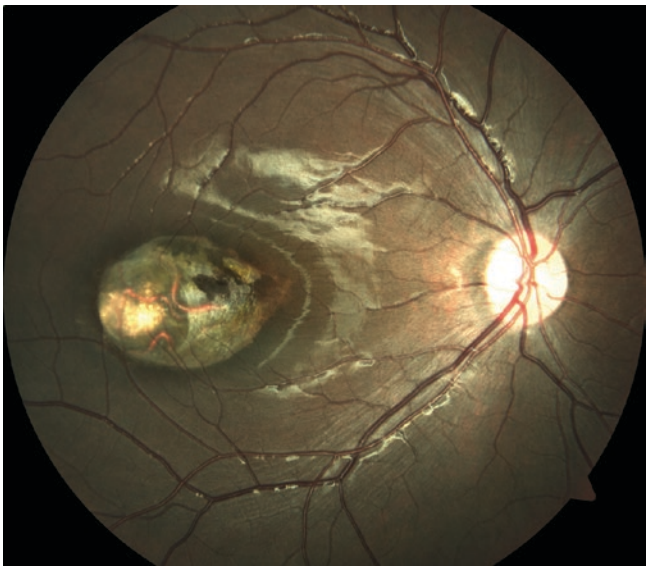

Fig. 22.1 Color fundus photograph shows toxoplasmic scar in a patient with congenital toxoplasmosis

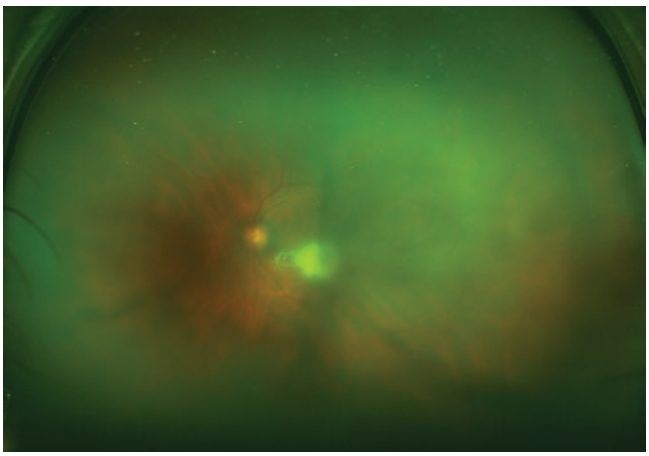

Fig. 22.2 Wide field fundus photograph shows yellow-white retinal focus with severe vitritis (headlight in the fog)

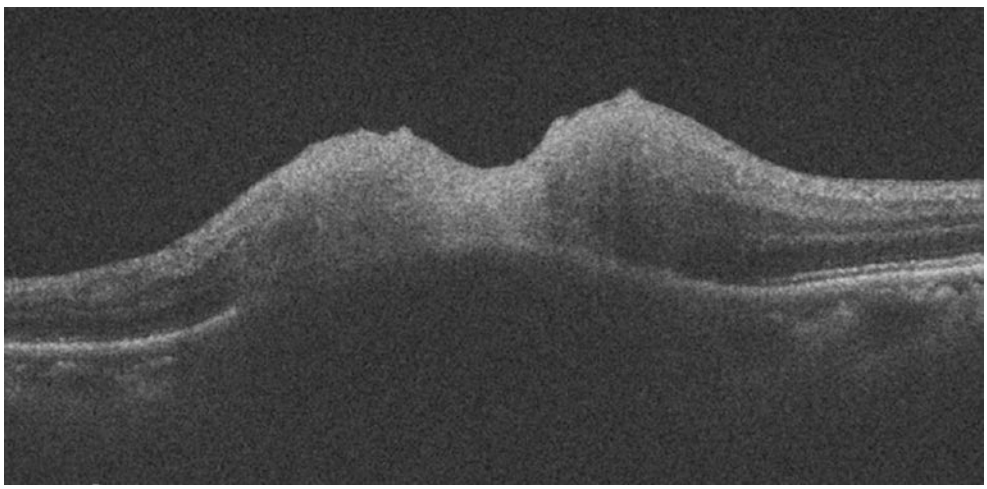

Fig. 22.3 SD-OCT image demonstrates disorganized neurosensory retinal layers and choroidal thickening beneath the active lesion

and inactive lesions demonstrated sharply demarcated borders and thinning in fundus examination, and disorganization of the neurosensory retina, disappearance of photoreceptor layer, and RPE atrophy in SD-OCT images (Goldenberg et al. 2013). In scars of inactive lesions, the choroid structure was ruined and impossible to identify the normal architecture (Goldenberg et al. 2013).

Recurrence of ocular toxoplasmosis has been reported to occur in 79% of patients followed up for over 5 years (Bosch-Driessen et al. 2002a). Infection appears to recur at the border of healed scar as a satellite lesion (Fig. 22.6) (Hovakimyan and Cunningham 2002). Cataract surgery and pregnancy have both been associated with an increased risk of reactivation (Holland 2004; Bosch-Driessen et al. 2002b).

Ocular toxoplasmosis can result in permanent visual loss because of retinal necrosis, uveitis, and its complications. The complications of ocular toxoplasmosis include chronic iridocyclitis, cataract formation, secondary glaucoma, band keratopathy, cystoid macular edema, retinal neovascularization, epiretinal membrane, retinal detachment, and optic atrophy secondary to optic nerve involvement (London et al. 2011).

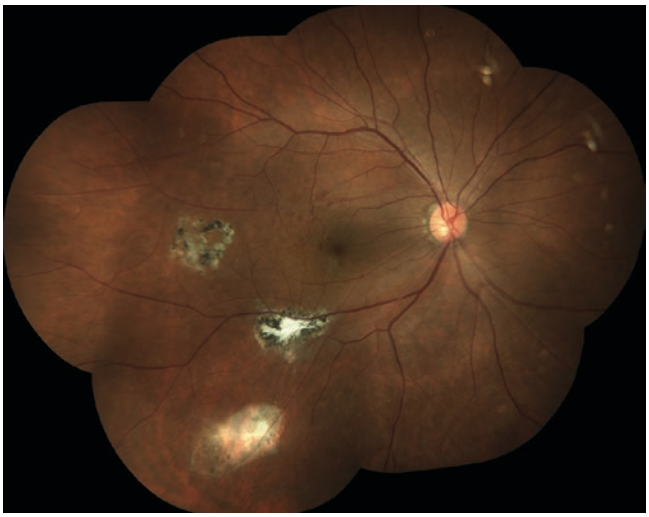

Fig. 22.4 Color fundus photograph shows multiple toxoplasmic retinochoroidal scars

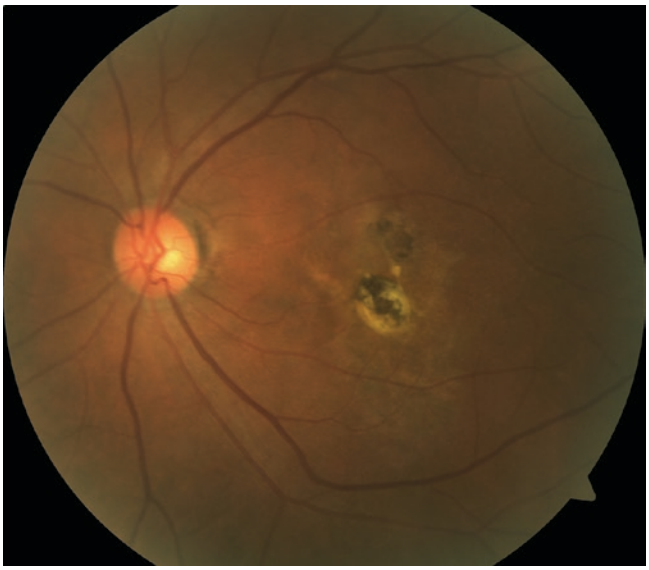

Fig. 22.5 Color fundus photograph shows macular toxoplasmic retinochoroidal scar

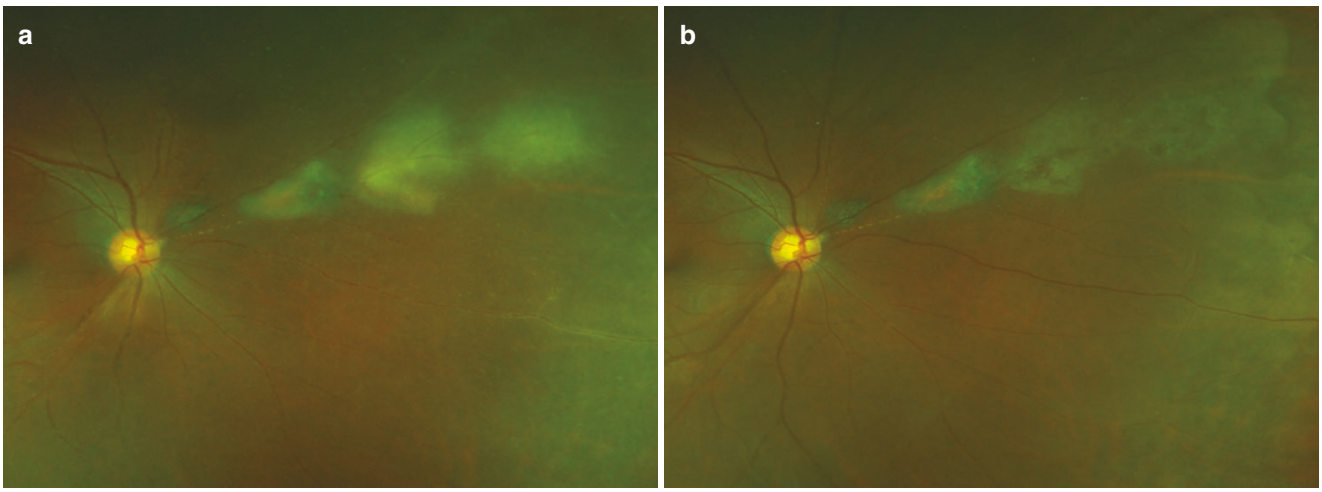

Fig. 22.6 Color fundus photographs show recurrent toxoplasmosis lesions. (**a**) Active lesions adjacent to the old lesion. (**b**) After 3 months of treatment, the borders of active lesions become more defined. (**c**) Two month later, the lesion recurred at the border of healed scar. (**d**) The lesion healed after 2 months of treatment

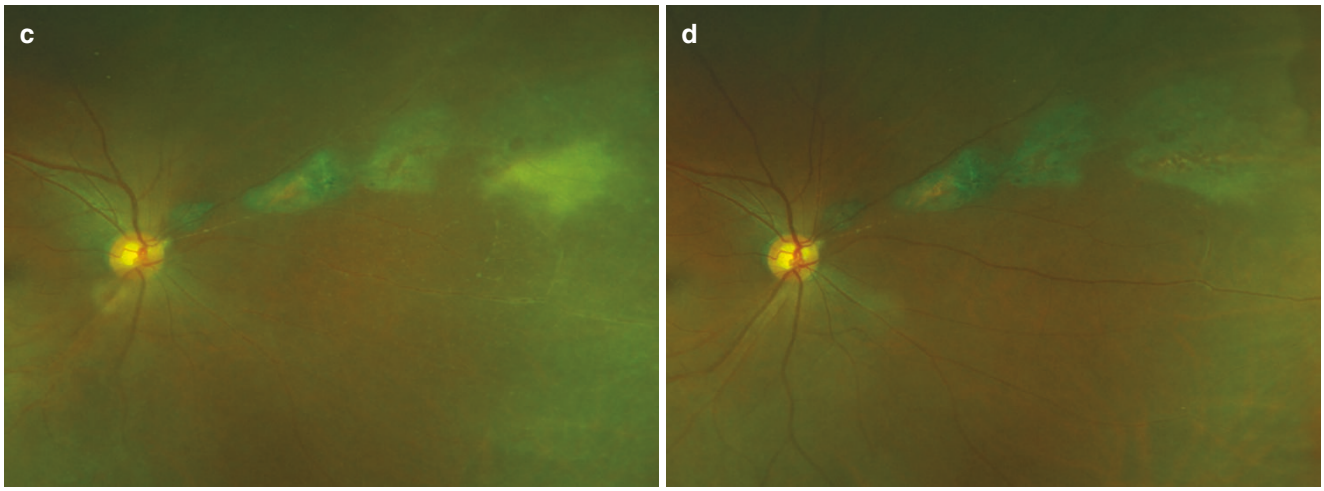

Fig. 22.6 (continued)

Laboratory Techniques

Although the diagnosis of ocular toxoplasmosis is usually based on typical clinical presentation, laboratory tests can be helpful when the clinical diagnosis cannot be made definitely by a funduscopic examination. Serologic tests are used to confirm past exposure to *T. gondii*. The IgM and IgG antibodies to *T. gondii* appear in the serum within 1–2 weeks after infection (Marcolino et al. 2000). IgM levels increase within the first week and become undetectable after 6–9 months. IgG levels can often persist for years after the acute infection, and there is a high prevalence of such antibodies in the general population giving false-positive results (Ongkosuwito et al. 1999). Therefore, elevated levels of antibodies alone should not be considered as an evidence of recent infection, nor should low serum IgG levels be considered as inactive disease.

The advance in molecular biology techniques has enabled the identification of *T. gondii* DNA in the aqueous humor and the vitreous by polymerase chain reaction (PCR) (Fekkar et al. 2008). It has even allowed the identification of *T. gondii* DNA in ocular tissue sections of patients with presumed ocular toxoplasmosis when organisms could not be identified on histopathologic examination. However, the sensitivity of PCR in patients meeting clinical diagnostic criteria for ocular toxoplasmosis is variable, and the sensitivity of PCR also depends on the immune status of the patient (Garweg et al. 2011).

Management

In immunocompetent patients, toxoplasmic retinochoroiditis is usually a self-limited infection and generally resolves spontaneously over a period of 1–2 months (Butler et al. 2013). Considering this benign natural history and the potential toxicity of anti-parasitic medication, the risk of treatment may be greater than any benefit provided. However, treatment is recommended for immunocompetent patients with active inflammation who have reduced visual acuity, lesion located within the vascular arcades or adjacent to the optic disc, lesion larger than two optic disc diameters to reduce the chance of vision loss, and/or vitreous haze above grade 1+ (Holland and Lewis 2002). There is no cure for toxoplasmosis infection since the tissue cysts are resistant to the available drugs and remain viable for many years (Stanford et al. 2003). Therefore, the aim of the treatment of ocular toxoplasmosis is to arrest parasite multiplication during the active stage and to minimize damage to the retina and optic disc (Holland and Lewis 2002; de-la-Torre et al. 2011). Atypical presentations and disease in immunocompromised patients require immediate treatment (Smith and Cunningham 2002).

Medical Therapy

The combination of pyrimethamine (25–50 mg daily orally in one to two doses) (Holland and Lewis 2002) and sulfadiazine (1 g four times daily orally) (Holland and Lewis 2002), which have a synergistic effect on different steps of the nucleic acid synthesis in *T. gondii*, and corticosteroids (often in the form of prednisone) have remained as the "classic therapy" or "triple-drug therapy" (Eyles and Coleman 1953). Patients treated with classic therapy showed a greater reduction in the size of the retinal lesion than patients receiving other treatments or no treatment (Rothova et al. 1993). However, this classical treatment may have some risks that depend on patient susceptibility to drug toxicity or allergic reactions.

An alternative to classic treatment, trimethoprim-sulfamethoxazole (160–800 mg twice daily orally) (Holland and Lewis 2002) is an attractive option for reasons that include low cost, less adverse effects, and good compliance due to the reduced number of daily pills. This drug combination of trimethoprim-sulfamethoxazole plus corticosteroids was shown to have similar efficacy to classic treatment in a randomized clinical trial (Holland 2005; Soheilian et al. 2005). However, sulfonamide-related reactions may still occur (Soheilian et al. 2005).

Other drugs, such as clindamycin (300 mg four times daily orally) (Holland and Lewis 2002), have also been used. It is often added to triple therapy, which is then referred to as "quadruple therapy." In other situation, clindamycin has been substituted for pyrimethamine.

The duration of treatment depends on the individual and patients' clinical situations. It is recommended that corticosteroids should not be used without anti-toxoplasmic drugs in order to avoid the worsening of the infection (Stanford and Gilbert 2009).

Intravitreal Injection

Intravitreal injection of clindamycin and dexamethasone as local treatment for ocular toxoplasmosis is a promising approach (Lasave et al. 2010; Soheilian et al. 2011). Because intravitreal drug administration bypasses ocular barriers, high concentration of drug can be delivered directly to the intraocular tissues, thus reducing systemic side effects. Intravitreal clindamycin (1 mg) and dexamethasone (400 μg) were shown to have similar efficacy in terms of reduction in lesion size, increase in visual acuity, and decrease in vitreous inflammation to triple therapy in a randomized clinical trial (Soheilian et al. 2011).

Local treatment appears particularly useful for patients with recurrent infection and for those systemic side effects of the drug are a concern, such as pregnant women. On the other hand, the local treatment would not be recommended in immunocompromised patients (Butler et al. 2013).

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Toxocariasis

23

Tae Wan Kim

Introduction

Toxocariasis is a zoonosis caused by *Toxocara canis* (dog ascarid) or *Toxocara cati* (cat ascarid) larvae. Humans become infected by ingesting eggs or larvae from contaminated sources (soil, water, and raw food) or via fecal–oral transmission. Ocular toxocariasis, manifesting as ocular granuloma, was first described by Wilder (1950) in patients with endophthalmitis, Coats disease, or pseudoglioma. Six years later, Nichols found second-stage larvae of *T. canis* in histological sections from 24 of 46 enucleated eyes with suspected retinoblastoma (Nichols 1956). Human toxocariasis comprises two clinical entities: systemic toxocariasis (also termed visceral larva migrans) and ocular toxocariasis (also termed ocular larva migrans).

Toxocariasis is a worldwide condition, and ocular toxocariasis is an important cause of visual loss during childhood (Stewart et al. 2005). However, few reports have explored the prevalence of the condition. Human seropositivity rate ranges from 2.4% to 76.6% (Stensvold et al. 2009; Fan et al. 2004). Ocular toxocariasis develops in 1/1000 to 11/1000 subjects; the wide range may be explained by variations in the clinical presentation. In Japan, ocular toxocariasis accounts for about 1.1% of all cases of uveitis (Goto et al. 2007). In Ireland, the prevalence of ocular toxocariasis is 9.7 per 100,000 subjects aged 4–19 years (Good et al. 2004).

Ocular toxocariasis commonly affects both healthy children and young adults. The male:female ratio is usually greater than 1 (Biglan et al. 1979; Good et al. 2004; Mirdha and Khokar 2002; Park et al. 2000; Yokoi et al. 2003). The age at symptom onset ranges from 2 to 27 years (Good et al. 2004). The disease is more common in tropical and rural populations.

Pathogenesis

Although dogs and cats are important sources of childhood infections, the etiology of adult disease is more variable; ingestion of contaminated water and soil is most commonly in play. Other sources of infection include touching of the eyes by contaminated hands and ingestion of raw vegetables or meat (Ahn et al. 2014a; Yokoi et al. 2003). The definitive hosts are domestic dogs and cats, wherein larvae mature into adult forms, liberating eggs into the feces. Humans are accidental hosts; larvae resident in human tissues never develop in adults capable of reproduction.

After human ingestion, infective larvae are released in the small intestine and subsequently penetrate the intestinal wall, enter the circulation, and migrate to various organs (e.g., liver, heart, lungs, brain, muscle, and eyes) wherein they trigger inflammatory reactions and induce various symptoms. Systemic toxocariasis is characterized by fever, cough, malaise, rash, leukocytosis, hepatosplenomegaly, and occasional seizures (Smith et al. 2009). Ocular toxocariasis appears to reflect hypersensitivity triggered by the death of juvenile larvae. Only 2% of all such cases present with a history of systemic toxocariasis; this remains subclinical or self-limiting in most patients (Shields 1984).

Diagnosis

A diagnosis of ocular toxocariasis is usually based on careful history-taking and clinical observation, or sometimes the histological identification of *Toxocara* larvae. However, histopathological diagnoses of biopsy specimens are uncommon; it is difficult to obtain ocular specimens because of potential vision-threatening complications, including vitreous hemorrhage and retinal detachment. Therefore, a diagnosis is usually made by identifying clinical signs consistent with the disease upon ophthalmological examination, supported by serum *T. canis* antibody positivity.

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Clinical Features

The most common clinical findings of ocular toxocariasis are conjunctival injection, leukocoria, vitritis, and strabismus (Chieffi et al. 2009; Stewart et al. 2005). The signs and symptoms are unilateral in 90% of cases (Chieffi et al. 2009; Stewart et al. 2005; Rubinsky-Elefant et al. 2010; Cortez et al. 2010). Clinical suspicion should be raised when at least one of the following manifestations is evident (Table 23.1): a focal posterior granuloma, a whitish subretinal or intraretinal elevated nodule (pigmented or not), and vitreous haze in the posterior pole (Fig. 23.1). The condition may present as choroidal neovascularization (Fig. 23.2), a macular hole (Fig. 23.3), or epiretinal membrane, a peripheral granuloma (a focal, elevated white mass in the retinal periphery) with or without intraocular inflammation, accompanied by different extents of adjacent retinal folding and a peripheral or epiretinal membrane (Fig. 23.4), tractional retinal detachment (Fig. 23.5), a pigmentary change, chronic endophthalmitis (panuveitis accompanied by a conjunctival infection, pain, and/or diffuse intraocular inflammation; Fig. 23.6). The condition may be associated with the formation of tractional membranes in the retina and vitreous, triggering severe visual morbidity (Ahn et al. 2013; de Visser et al. 2008; Woodhall et al. 2012).

Ocular toxocariasis also exhibits various manifestations, including iridocyclitis, focal iris nodules, cataracts (Fig. 23.7), the presence of motile subretinal larvae, optic disc swelling, neuroretinitis (Fig. 23.8), and diffuse chorioretinitis. A recent report described small, round, white motile granuloma-like opacities in the subcapsular levels of the lenses of eyes with ocular toxocariasis (Ahn et al. 2013). Intraocular migration of granulomas is a unique feature of the condition (Sivaratnam et al. 2008; Suzuki et al. 2005). Continuous migration (development of new lesions adjacent

Table 23.1 Clinical features of ocular toxocariasis

Presentation	Features
Posterior pole granuloma	A focal, white subretinal or intraretinal nodule (with or without pigmentation) evident in the posterior pole, with or without inflammation and vitreous haze
Peripheral granuloma	A focal, elevated, white mass in the retinal periphery (with or without intraocular inflammation) accompanied by variable folding of the surrounding peripheral membranes, tractional retinal detachment, and/or pigmentary changes
Chronic endophthalmitis	Panuveitis presenting with conjunctival injection, pain, and diffuse intraocular inflammation
Atypical presentation	Iridocyclitis, focal iris nodules, cataracts, optic disc swelling, motile subretinal larvae, and diffuse chorioretinitis

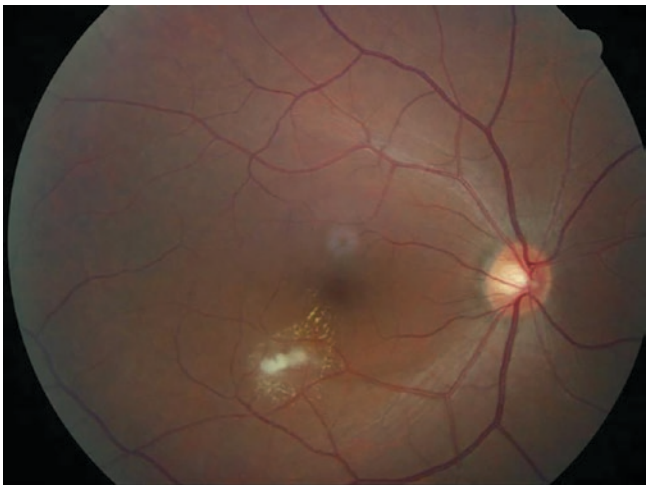

Fig. 23.1 Color fundus photograph shows posterior pole granuloma along with retinal exudates (courtesy of Se Joon Woo, MD)

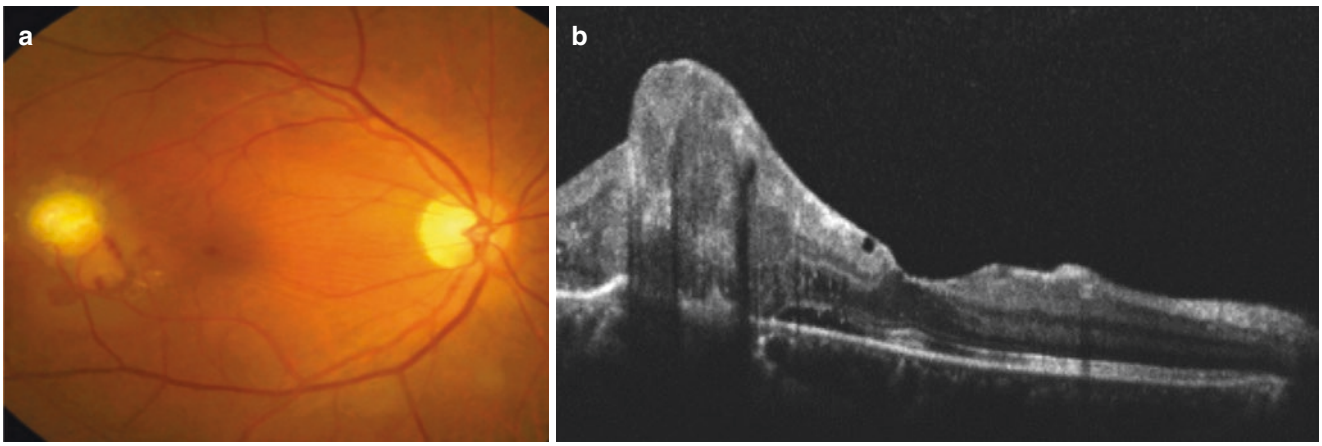

Fig. 23.2 Color fundus photograph (**a**) and optical coherence tomography (**b**) show choroidal neovascularization secondary to ocular toxocariasis (courtesy of Se Joon Woo, MD)

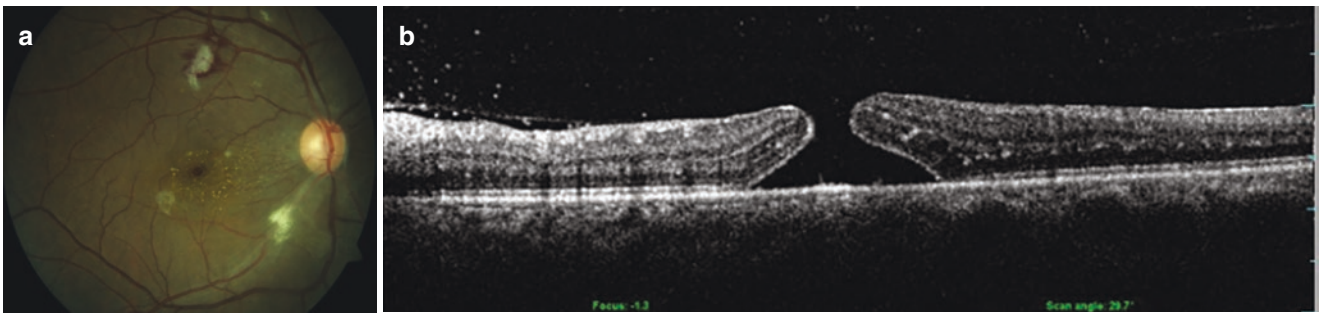

Fig. 23.3 Color fundus photograph (**a**) and optical coherence tomography (**b**) show the formation of macular hole secondary to ocular toxocariasis

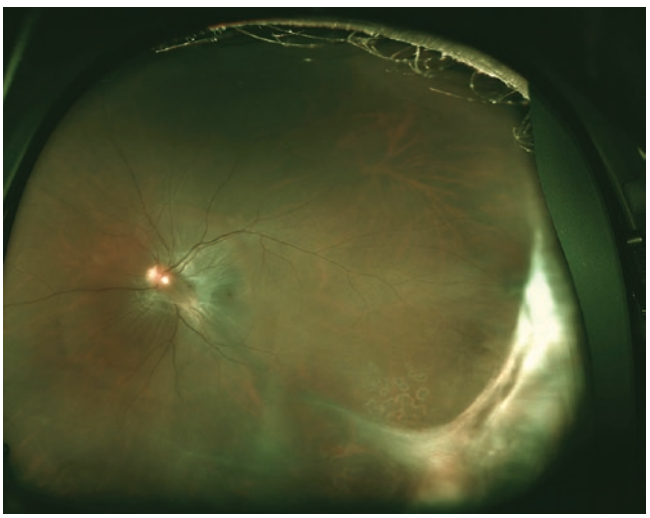

Fig. 23.4 Color fundus photograph shows epiretinal membrane with peripheral granuloma secondary to ocular toxocariasis (courtesy of Se Joon Woo, MD)

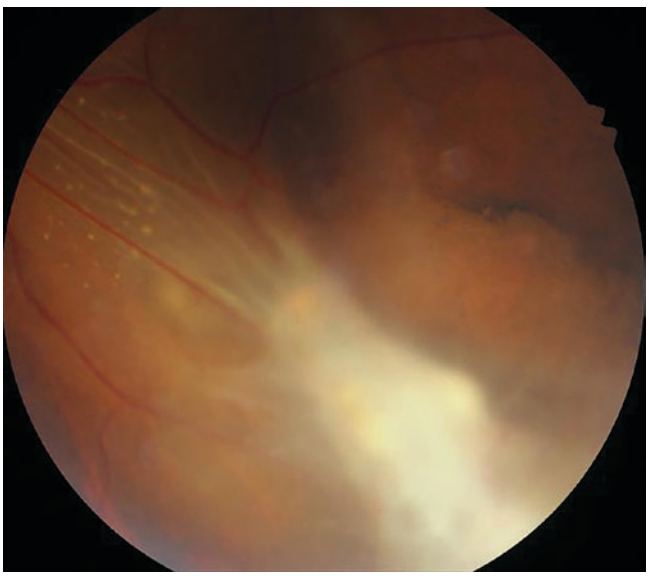

Fig. 23.5 Color fundus photograph shows peripheral granuloma with vitreous traction and tractional retinal detachment (courtesy of Se Joon Woo, MD)

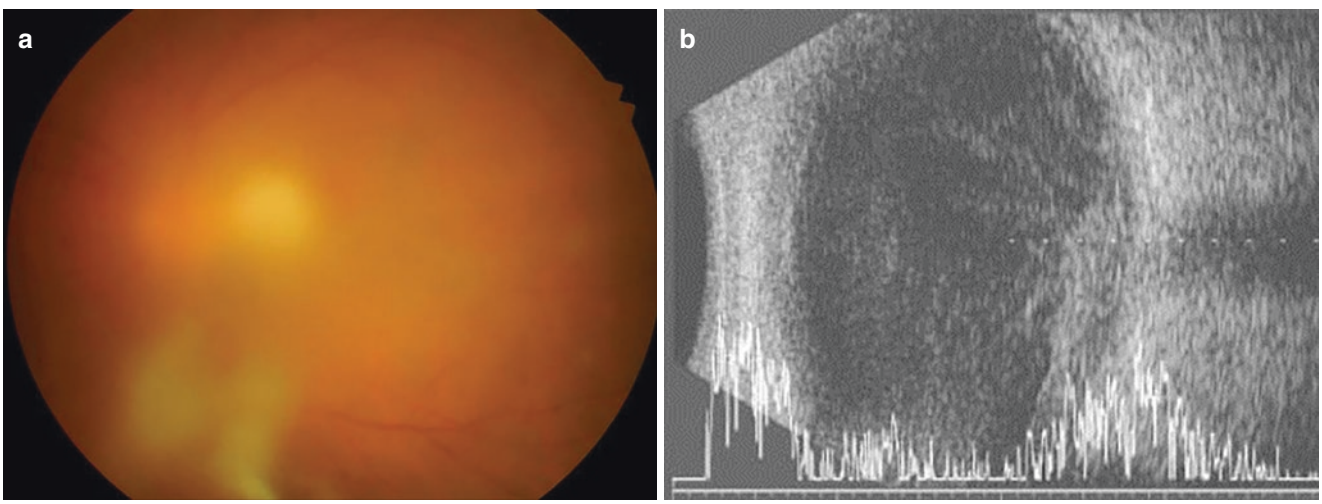

Fig. 23.6 Color fundus photograph (**a**) shows vitreous haze obscuring the disc and retinal vessels. Ultrasonography (**b**) shows severe vitreous opacity (courtesy of Se Joon Woo, MD)

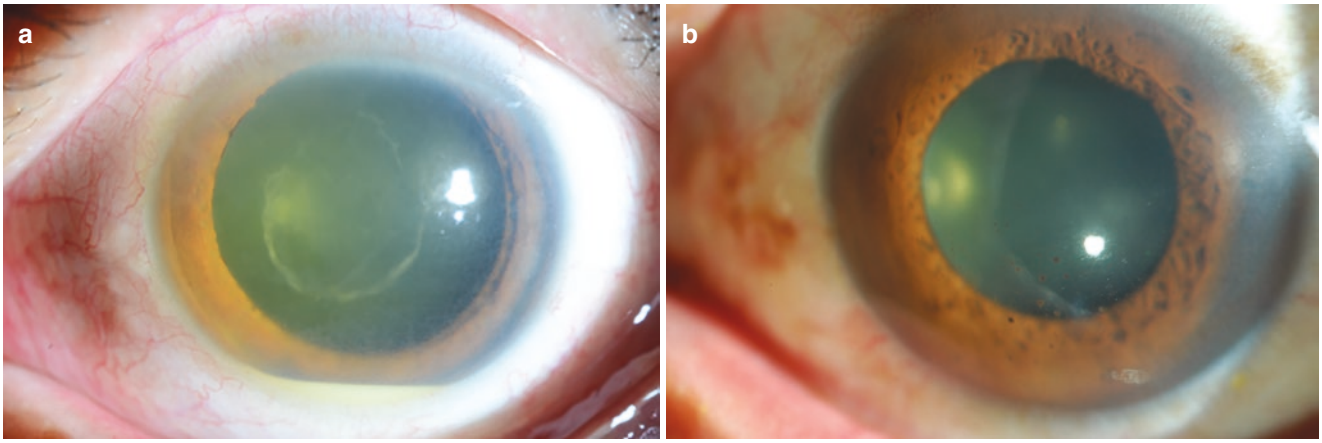

Fig. 23.7 Anterior segment photographs show cataract formation (**a**, **b**) in patients with ocular toxocariasis (courtesy of Se Joon Woo, MD)

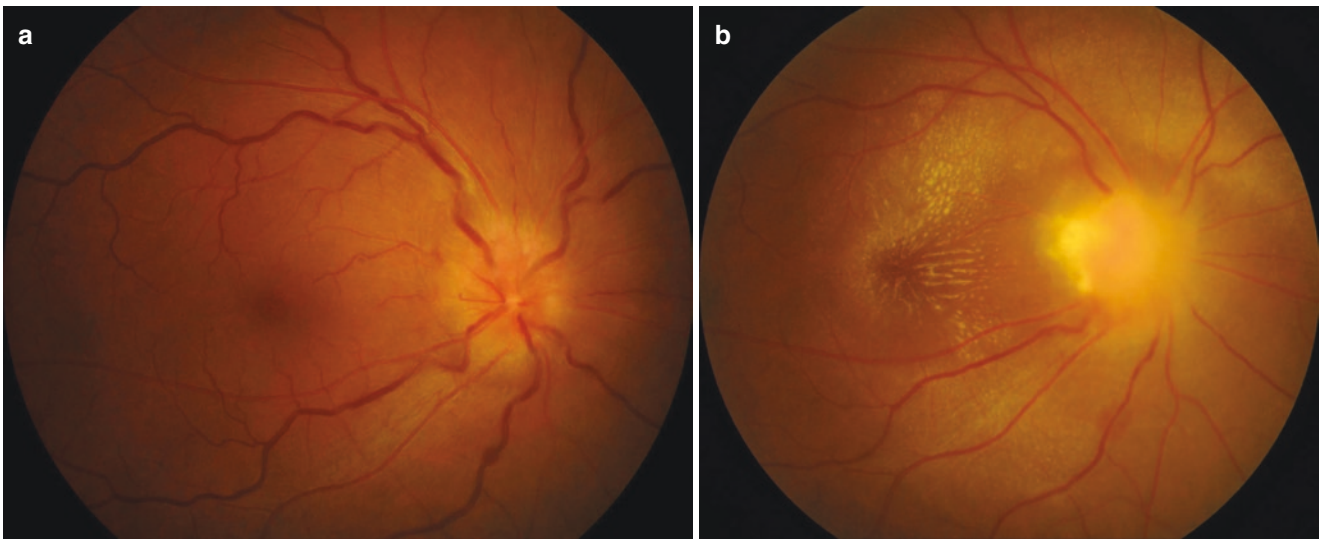

Fig. 23.8 Fundus photographs show optic disc edema without granuloma at initial presentation (**a**). At 2 months later, vitritis and macular exudates appear with newly developed granuloma (**b**)

to the original granulomas) and discontinuous migration (new lesions developing in positions remote from the original granulomas) developed in 12.9% and 4.3%, respectively, of patients with ocular toxocariasis (Fig. 23.9) (Ahn et al. 2014b). This is of major clinical importance; intraocular migration is unique to this condition, allowing ocular toxocariasis to be distinguished from similar conditions.

Vitritis is the most common cause of vision loss in patients with ocular toxocariasis, followed by cystoid macular edema, tractional retinal detachment, and epiretinal membrane formation (Stewart et al. 2005). In addition, granuloma development may damage the retina and photoreceptors, triggering significant vision loss (Ahn et al. 2014b). Thus, the causes of vision loss in eyes with ocular toxocariasis can be grouped into three categories: intraocular inflammation; retinal comorbidities, including epiretinal membrane formation, vitreous opacity, tractional/rhegmatogenous retinal detachment, macular edema, cataracts, and macular holes; and retinal damage caused by granulomas per se.

Serology

Serological data supposedly supporting a diagnosis of ocular toxocariasis can be misleading and are inherently limited by the fact that no reliable in vivo gold standard for the confirmation of the presence of *T. canis* larvae is yet available (Chieffi et al. 2009). In contrast to systemic toxocariasis, in which

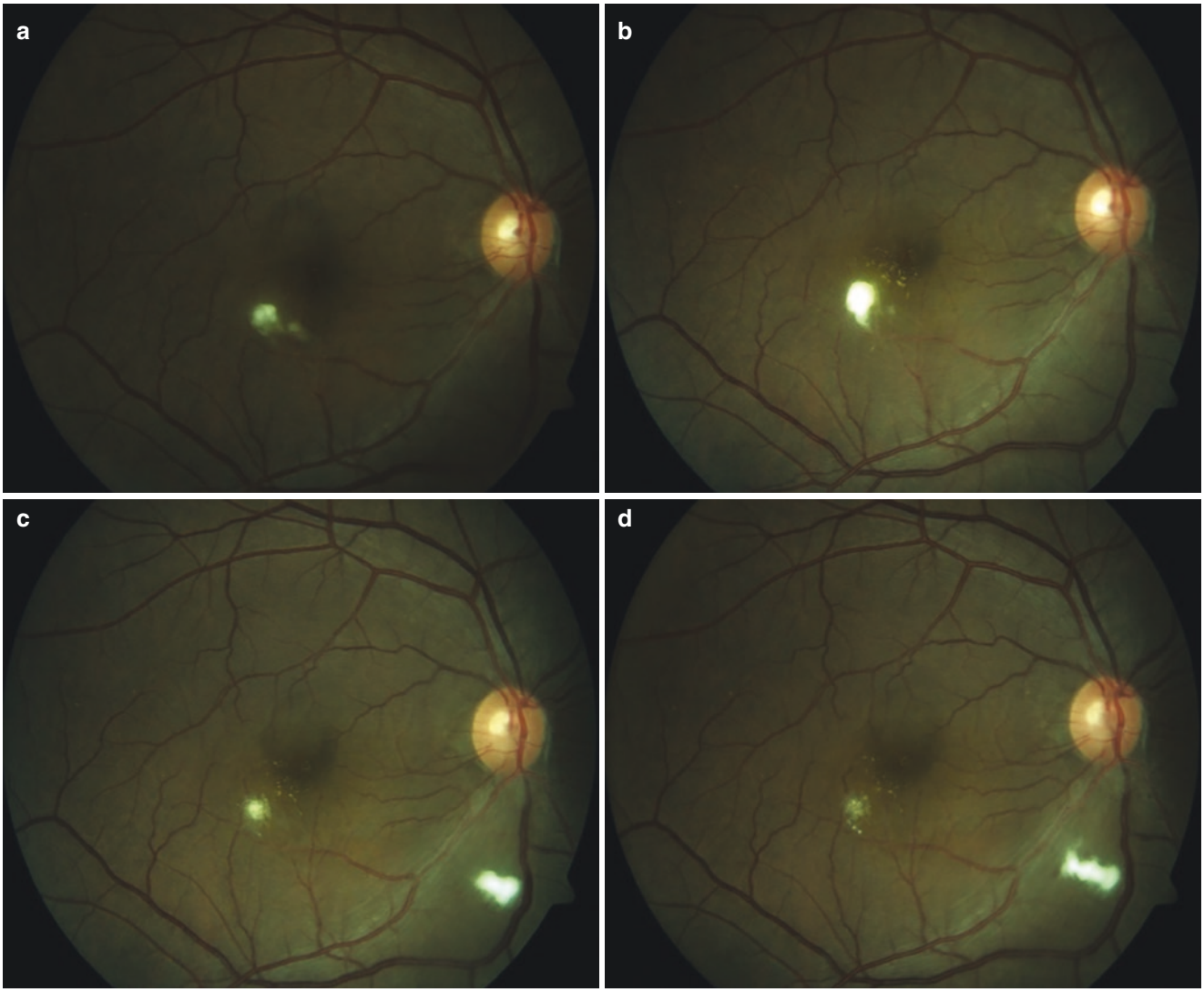

Fig. 23.9 Serial color fundus photographs show intraocular migration of granuloma. This case shows continuous (**a**, **b**) and discontinuous migration (**c**, **d**)

eosinophilia is a cardinal feature, patients with ocular toxocariasis do not typically exhibit high serum eosinophil counts (Paul et al. 2009). Historically, no confirmatory, or even suggestive, laboratory test supported a clinical diagnosis of ocular toxocariasis prior to the advent of enzyme-linked immunosorbent assays (ELISAs) (Rolda'n et al. 2010). Today, the standard diagnostic test is an indirect ELISA for excretory/secretory *T. canis* antigens. An ELISA titer ≥0.250 is usually considered positive, affording a sensitivity and specificity of 92.2% and 86.6%, respectively (Jin et al. 2013). The serum immunoglobulin E (IgE) level plays a supportive role in the diagnosis of ocular toxocariasis. However, eosinophilia is usually absent in ocular toxocariasis, in contrast to the patients with systemic toxocariasis. A recent study found that 69.6% of patients diagnosed serologically and clinically with ocular toxocariasis had elevated IgE levels but that only 11.6% exhibited eosinophilia (Ahn et al. 2014b).

Intraocular Assays

ELISA-mediated detection of anti-*Toxocara* antibodies in ocular fluid may assist in the diagnosis of ocular toxocariasis (Alabiad et al. 2010; Sharkey and McKay 1993; Shields 1984). However, the cutoff value remains controversial; the ELISA-positive rate was only 33% among patients with ocular toxocariasis when the serum cutoff level was used (Ahn et al. 2014b). Remnant *Toxocara* organisms were occasionally evident in vitrectomy specimens obtained during surgery (Maguire et al. 1990). Currently, the detection rates

afforded by vitreous cytology or biopsy remain unclear; further work is required to define optimal cutoffs.

Molecular Analysis

Efforts have been made, via PCR, to detect *Toxocara* DNA in the aqueous or vitreous humor. A few reports detected *T. canis* eye infections using molecular methods (Olave et al. 2016; Van De et al. 2013). However, in general, *T. canis* may not shed tissue into the vitreous.

Management

We know little about the pathogenesis, diagnosis, or optimal treatment of human toxocariasis. Thus, minimizing human exposure to *Toxocara* species is important. Reductions in raw meat consumption should reduce both systemic and ocular diseases. Management of ocular toxocariasis must reflect the severity of inflammation and the presence of any retinal comorbidities that might trigger permanent visual impairment. No consensus on optimal treatment has yet emerged. It is imperative to reduce inflammation, eliminate the infective organisms, and address vitreoretinal sequelae. Individualized approaches must be tailored to the visual manifestations associated with, and the severity of, intraocular inflammation and modified by reference to clinical responses.

Anti-inflammatory Therapy

Anti-inflammatory corticosteroids are used to treat both ocular and systemic inflammation, and may reduce the vitreoretinal sequelae causing vision loss secondary to ocular toxocariasis. Systemic, periocular, and topical corticosteroids reduce intraocular inflammation and improve inflammation-associated vitreoretinal complications. Cycloplegics prevent the development of anterior and posterior synechiae in inflamed anterior segments.

Anti-helmintic Therapy

The results of a few controlled trials of anti-helmintic drugs used to treat systemic toxocariasis have been published. However, any role for such drugs in patients with ocular toxocariasis remains controversial; it is not clear that anti-helmintics kill intraocular *Toxocara* larvae. Albendazole (400 mg twice daily for 7–14 days) is often prescribed. Thiabendazole (50 mg/kg/day for 3–7 days) is recommended for patients resistant to albendazole, but liver status should be closely monitored because of its liver toxicity.

Others

Surgery is indicated in cases with structural complications, including a dense or opaque vitreous membrane, retinal detachment, an epiretinal membrane, or a macular hole. In a recent study, 32 of 101 patients (31.7%) required surgery to remove epiretinal membranes (n = 19), to treat a vitreous opacity (n = 9), and/or to remedy retinal detachment (n = 2). Surgery was successful in 68.4%, 88.9%, and 50% of such patients, respectively (Ahn et al. 2014b). Choroidal neovascularization can be combined with retinal granuloma due to ocular toxocariasis. Repeated intravitreal injections of anti-VEGF agents can be efficacious for regressing CNV (Yoon and Woo 2018).

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Ocular Cysticercosis

24

Kalpana Babu

Introduction

Cysticercosis is the most common ocular tapeworm infection. It is caused by *Cysticercus cellulosae*, the larval form of the pork tapeworm, *Taenia solium*. Human becomes infected by drinking contaminated water or eating food containing the eggs of *Taenia solium* (Chatterjee 1976; Duke-Elder 1978; Kaliaperumal et al. 2005). The most common form of systemic involvement is neurocysticercosis. Ocular and adnexal cysticercosis represents 13–46% of systemic disease (Duke-Elder 1978; Kaliaperumal et al. 2005). Cysticerci can remain quiescent in the eye for up to 5 years. Cysticercosis has a worldwide distribution (Kaliaperumal et al. 2005; Madigubba et al. 2007). It is common in India, Mexico, South East Asia, Sub-Saharan Africa and South and Central America. It is rare in Great Britain and the United States. Risk factors include poverty and poor sanitation, both of which promote faecal–oral transmission of disease. Although there is no gender or racial predilection, patients are relatively young, and the disease is usually unilateral. Involvement of the left eye seems to be more common than the right eye (Madigubba et al. 2007; Atul et al. 1995).

Pathophysiology

Taenia solium passes its life cycle in two hosts: Humans are the definitive hosts and the adult parasites live in the small intestine for several years. The pig is the intermediate host and is also the main host of the larva.

Human cysticercosis is caused by the ingestion of the pork tapeworm, *T. solium*, when contaminated food such as contaminated vegetables, fruits or water is consumed. The consumed eggs behave as if they are within the intermediate host and hatch in the upper intestines of humans. The embryo penetrates the gut, invades lymphatics and blood stream and travels to various organs like central nervous system, eyes and skeletal muscles. The embryo discards the hooks and forms a head or the scolex by invagination of its wall, transforms into larvae and encysts in these tissues which have a high metabolic turnover and good glycogen supply. They may remain quiescent or die inciting an immunological reaction due to the chemical toxins they release (Chatterjee 1976; Duke-Elder 1978). Autoinfection can also occur from faecal–oral contamination. It has been speculated that the cysticercosis enters the eye via the choroidal circulation, where the vessels have a larger flow rate. From the choroid, it migrates into the subretinal space and then into the vitreous cavity through a hole in the retina. This passage probably incites inflammation and results in the formation of a chorioretinal scar (Foster and Vitale 2001).

Clinical Features

Systemic Involvement

The most common systemic manifestation is neurocysticercosis (Fig. 24.1). It is the cause of epilepsy in 50% of partial seizures in adults. The patients may present with seizures, recurrent headaches and increased intracranial pressure or as a psychiatric disorder. Signs of meningoencephalitis may occur in case of multiple cysts. Subcutaneous nodules and inflammatory cells in the muscles may be seen (Chatterjee 1976; Duke-Elder 1978; Foster and Vitale 2001).

Ocular Cysticercosis

Ocular cysticercosis may affect any portion of the visual pathway from the orbit to the visual cortex. The common sites of ocular involvement include retina/subretinal space (41%), vitreous cavity (27%), subconjunctival space (21%), anterior segment (8%) and lids/orbit (4%) (Ziaei et al. 2011).

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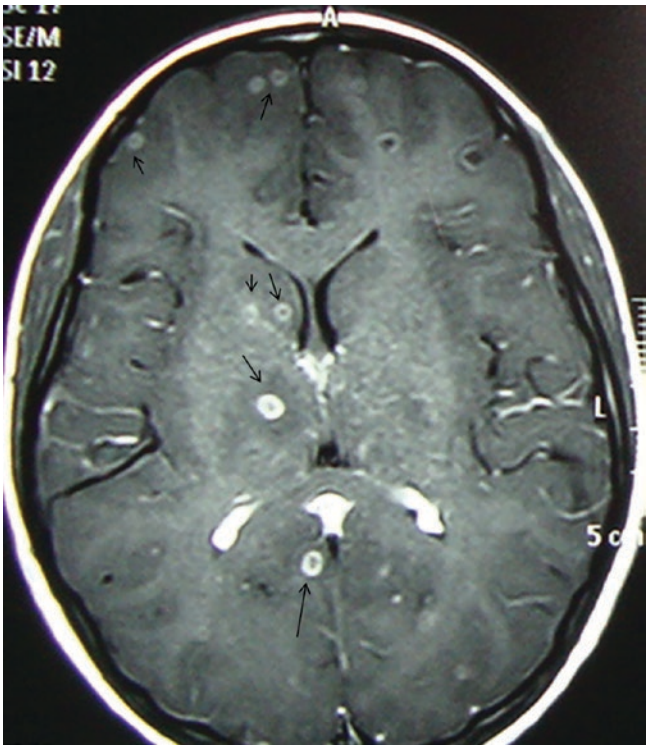

Fig. 24.1 CT scan of brain showing multiple ring lesions in neurocysticercosis (arrows)

The symptoms depend on the location and problems caused by the mass effect of the cyst or inflammation due to the dying parasite. Review of symptoms may reveal a history of epilepsy (Foster and Vitale 2001; Ziaei et al. 2011).

Intraocular cysticercosis may be asymptomatic or present with diminution of vision, floaters, pain, photophobia or red eye. Symptoms may occur for a few weeks or months before presentation. Visual acuity varies from a slight blur in vision in case of peripheral subretinal cysticercosis to hand movement in case of submacular cysticercosis. Cysts may be observed in the anterior segment, vitreous, subretinal and submacular locations (Figs. 24.2, 24.3 and 24.4) (Wender et al. 2011; Sharma et al. 2003; Mahendradas et al. 2007; Kruger-Leite et al. 1985). If the cyst is alive within the eye, it often induces a mild to moderate inflammatory reaction in the anterior chamber and/or the vitreous. It may be seen as spherical, translucent cyst with a scolex that undulates with evagination or invagination in response to the examining light. A dying parasite can lead to intense inflammatory reaction due to the liberation of chemical toxins, which can even lead to blindness and phthisis (Fig. 24.5). Retinal oedema, haemorrhages, subretinal exudates, sheathing of retinal vessels, exudative retinal detachment, retinal pigment epithelial disturbances and optic disc hyperaemia may also be seen. Optic nerve involvement is a very rare presentation. It usually presents with marked diminution of vision and field loss with or without proptosis. Papilledema or papillitis with a relative afferent papillary defect are common presenting signs (Sudan et al. 2005).

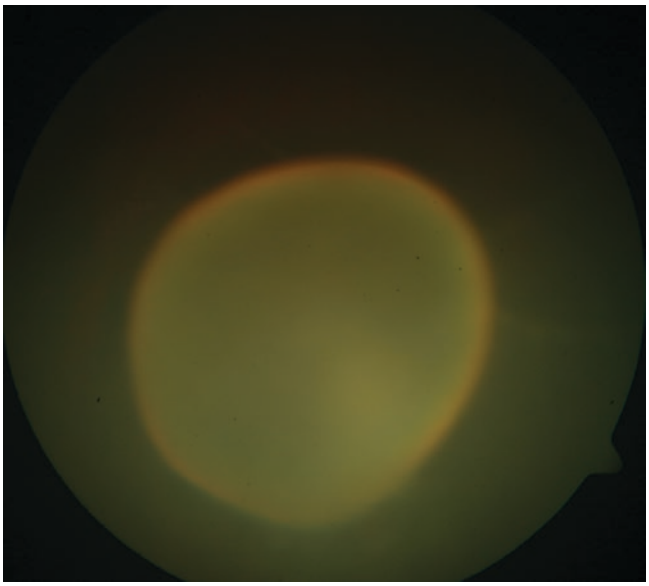

Fig. 24.2 Fundus photograph showing a cysticercus cyst in the vitreous

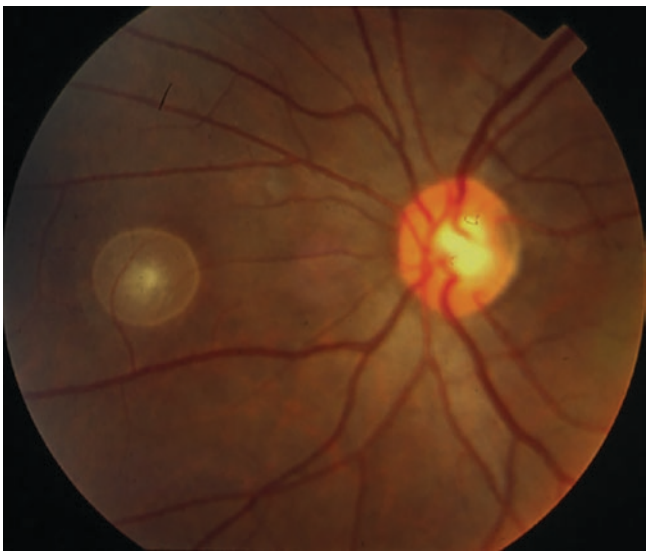

Fig. 24.3 Fundus photograph showing subretinal cyst

Subconjunctival involvement may be asymptomatic, present as recurrent conjunctivitis not responsive to topical antibiotics or a painful or painless swelling of the conjunctiva. The most common symptoms associated with orbital cysticercosis are diplopia (due to restrictive ophthalmopathy), recurrent pain and redness. Other presentations include gradually increasing non-axial proptosis, ptosis and lid nodules. Infection of the extraocular muscles usually causes problems due to the mass effect or the inflammatory response (Figs. 24.6 and 24.7). The most common muscle to be infected is the medial rectus (42%) followed by the superior rectus (18%), lateral rectus (15%), inferior rectus (13%), superior oblique and levator palpebrae superioris (5% each) and inferior oblique (1%) (Ziaei et al. 2011).

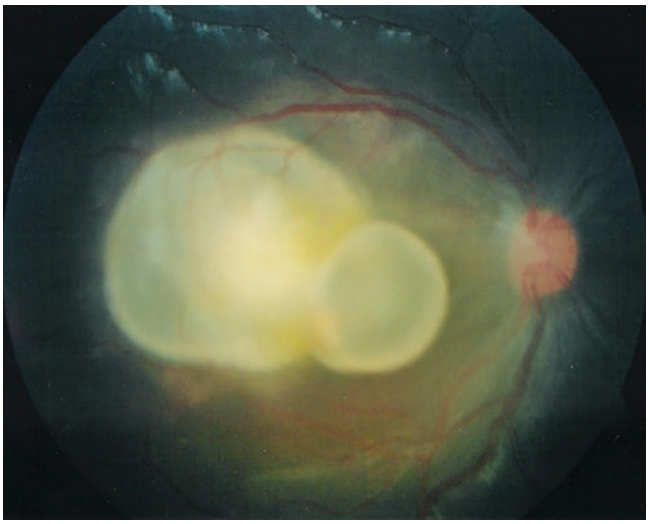

Fig. 24.4 Fundus photograph showing mushrooming of the cyst from the subretinal layer into the vitreous

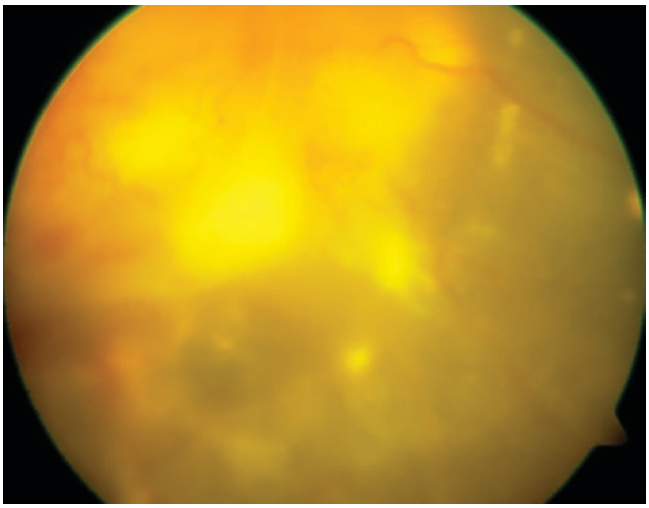

Fig. 24.5 Fundus photograph showing severe inflammation in a dead cyst

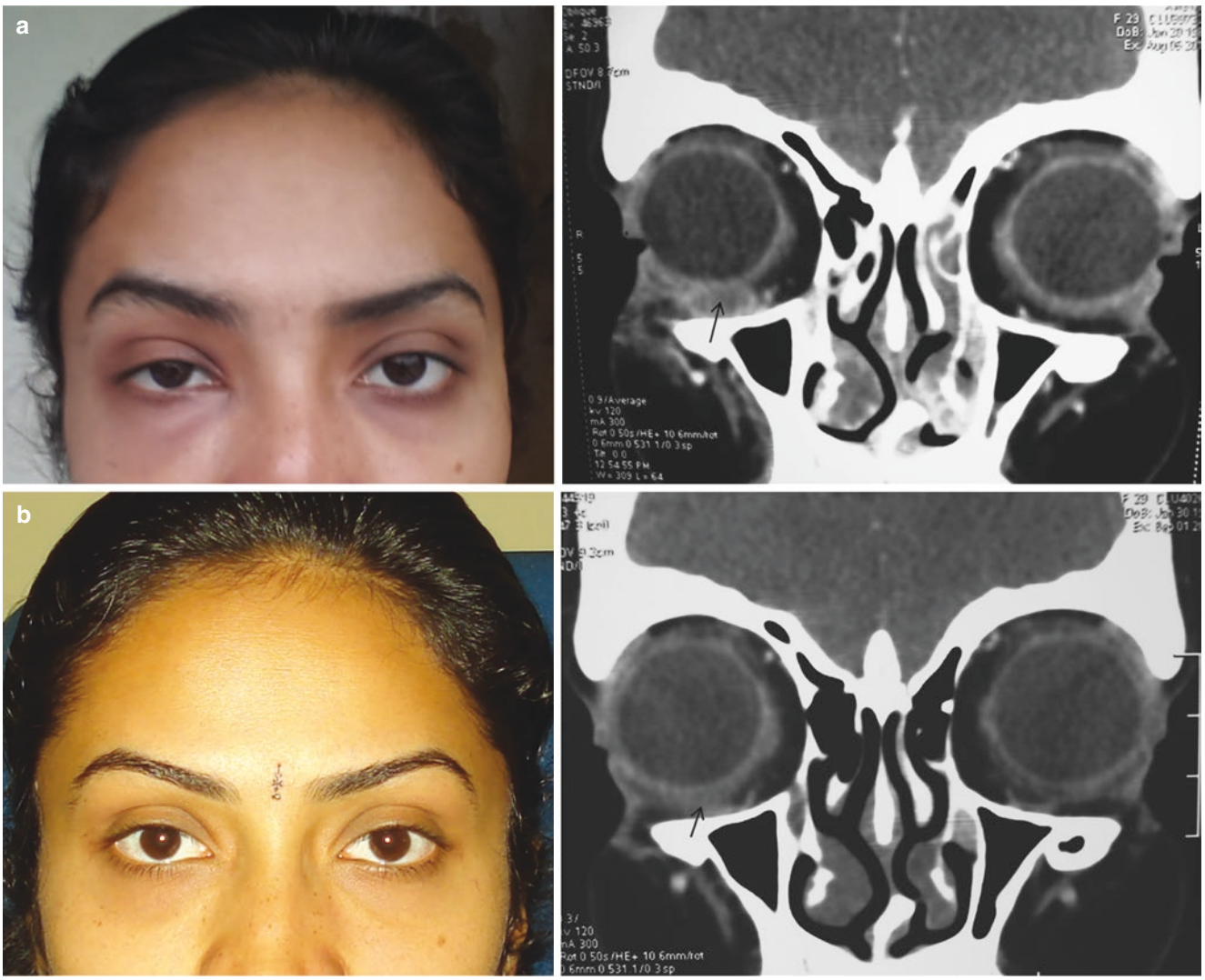

Fig. 24.6 External photograph and CT scan orbits showing ptosis in the right eye before medical treatment (**a**) and improvement after medical treatment (**b**). Arrow showing the location of cyst

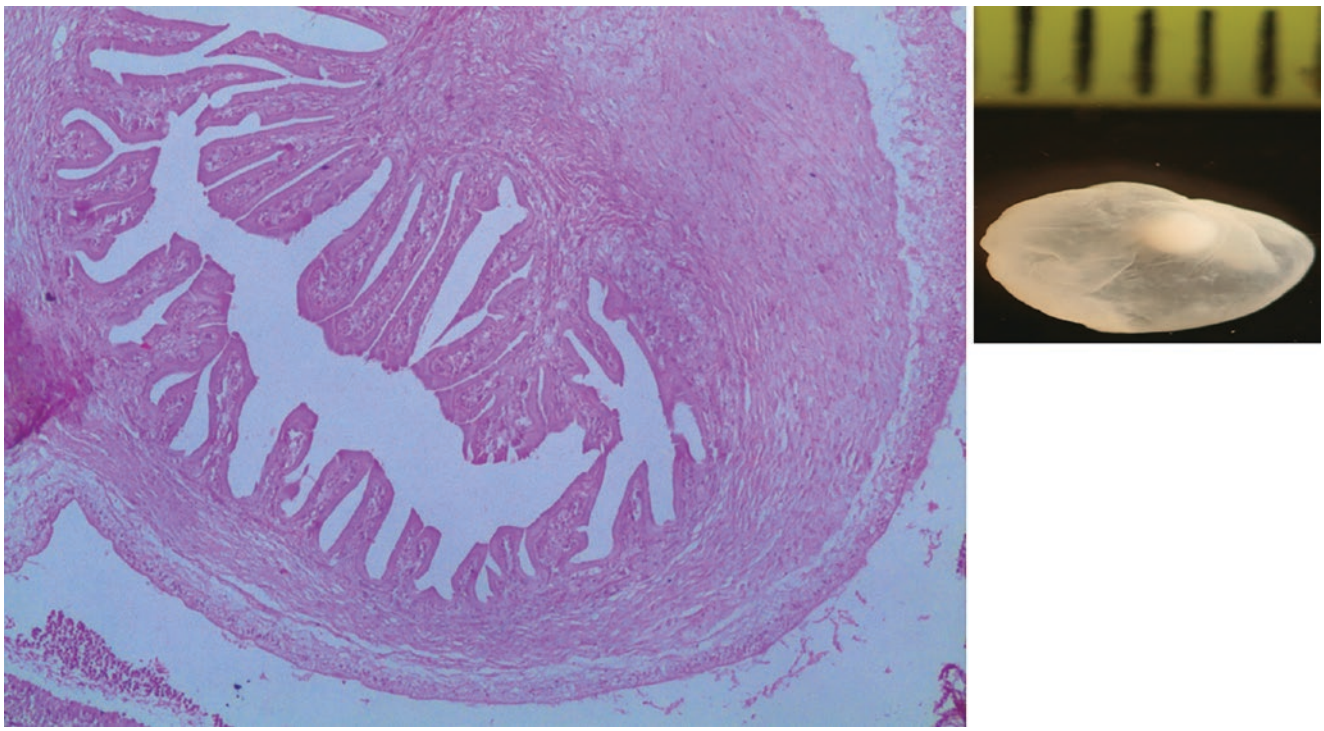

Fig. 24.7 Photograph of the excised cyst with pearly white scolex (inset) and microphotograph showing the cyst wall and branching body cavity of the *Cysticercus cellulosae*

Diagnosis

Diagnosis is usually on the basis of history including travel to endemic regions of the world, ingestion of raw or undercooked pork or known previous infections with this tapeworm. A history of relapsing subconjunctival or orbital inflammations, subcutaneous nodules or neurologic symptoms may indicate infection with this parasite (Ziaei et al. 2011). Laboratory findings include eosinophilia in 71% cases. Enzyme-linked immunosorbent assay (ELISA) for the cysticercosal antigen is available. It has sensitivities of 65–98% and specificities of 67–100% in neurocysticercosis depending on the specific test, cyst burden, location and phase of the infection. A positive test needs to be interpreted in the context of the clinical picture (Ziaei et al. 2011; Coker-Vann et al. 1981; Rosas et al. 1986).

Imaging is the most useful test because of the highly specific appearance of the encysted parasites. The 'Hanging drop' sign of a sonolucent cyst with well-defined margins in orbital cysticercosis and a central circular cyst with a highly reflective scolex within the cyst in intraocular cysticercosis on ultrasonography (B scan) are highly suggestive of cysticercosis. Imaging can also be used for follow-up examinations to note the regression of the cyst following medical treatment (Ziaei et al. 2011; Honavar and Sekhar 1998; Murthy et al. 1990).

On CT scans, the cyst appears isodense to the vitreous humour while on MRI, it appears isointense to CSF on T1- and T2-weighted images. A live cyst does not enhance with contrast while the dying cyst enhances in contrast due to the surrounding inflammatory reaction. CT scan cranium shows multiple ring lesions in neurocysticercosis.

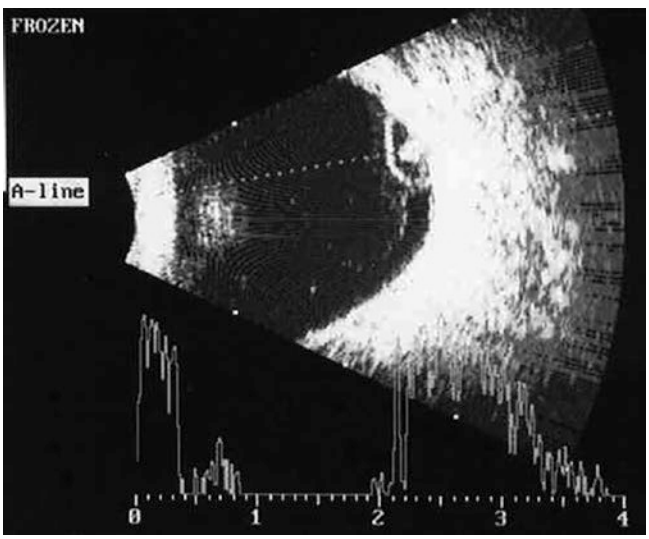

Fig. 24.8 Ultrasonography of the eye showing a globular cyst with high reflectivity inner wall and a high reflective echo corresponding to the scolex in the centre

Ultrasonography of the eye reveals a cyst-like structure with a high-amplitude echo corresponding to the inner wall of the cyst and the overlying retina. A dot-like echo corresponding to the scolex may be seen in the cyst (Fig. 24.8).

Differential Diagnosis

Dead cysts with ocular inflammation can mimic the 'headlight in the fog' appearance seen in toxoplasmosis. Ocular cysticercosis can also mimic retinoblastoma and Coats disease in children, diffuse unilateral subacute neuroretinitis and a choroidal tumour (Foster and Vitale 2001; Agarwal et al. 2003). Neurocysticercosis can mimic tuberculomas.

Management

The treatment for cysticercosis should be tailored to the symptoms and location of the cyst. For orbital cysticercosis, medical treatment is very useful (Ziaei et al. 2011). The first line of therapy includes oral albendazole given at the rate of 15 mg/kg body weight/day for a month, although different randomised clinical trials mention 1 month, 15 days and even 1 week (Garcia et al. 2002). This broad spectrum anti-helminthic acts by inhibiting glucose uptake of the parasite and interferes with its ATP production. Due to lack of energy production, the parasite becomes immobilised and eventually dies. Praziquantel, an alternative drug, has an inferior cyst elimination rate compared to albendazole (Garcia et al. 2002). It is recommended that oral corticosteroids at a dose of 1 mg/kg body weight along with cysticidal drugs are given to suppress the associated inflammatory response from the dying cyst. Surgical removal is usually contraindicated in orbital cysticercosis due to the extensive resections needed, the posterior location of most of the lesions and the likelihood of inducing a fibrotic reaction, which could further restrict the movement of the eye.

The treatment of intraocular cysticercosis is usually surgical removal of the intact cyst. Recent reports show more favourable visual outcome with the extraction of subretinal cysts with vitrectomy rather than via a sclerotomy (Wender et al. 2011; Sharma et al. 2003). Sharma et al. reported relative good postoperative outcomes with final visual acuity of 20/200 or better achieved in more than half of eyes in their series (Sharma et al. 2003).

The treatment guidelines of optic nerve cysticercosis are not well established due to the paucity of literature. Although cysticidal therapy with oral corticosteroid is the treatment of choice in most cases, the treatment needs to be individualised (Sudan et al. 2005). Cysticidal therapy may not be very useful in calcified lesions.

Prognosis

A successful outcome from the treatment of ocular cysticercosis requires death and removal of the organism and effective suppression of any inflammation. Cyst elimination rates of 92–95% have been reported in orbital cysticercosis. Complete recovery of ocular motility usually occurs within 3–6 months but may take longer (Ziaei et al. 2011). It depends on the chronicity of the disease and the sequelae of inflammation. Except few reports, good visual recovery has been reported even with optic nerve involvement (Sudan et al. 2005). Visual outcomes due to intraocular cysticercosis have been quite poor in the past. More favourable visual outcomes have been reported in recent years due to early presentation and diagnosis, improved surgical techniques of cyst removal and extraction of subretinal cysts with vitrectomy rather than sclerotomy (Sharma et al. 2003).

Conclusion

Cysticercosis is a parasitic infection caused by *Cysticercus cellulosae*, the larval form of *Taenia solium*. It can involve any part of the visual pathway including the orbits and adnexa. Diagnosis needs to be considered in patients coming from endemic regions and history of seizures. Diagnosis is confirmed by imaging and does not routinely require tissue biopsy. Treatment needs to be individualised and includes medical treatment with anti-helminthic drugs, oral steroids and surgically excision of an intact cyst.

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Diffuse Unilateral Subacute Neuroretinitis (DUSN)

25

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Introduction

Diffuse unilateral subacute neuroretinitis (DUSN) was first named by Gass in 1978 (Gass and Scelfo 1978) and was described as "unilateral wipe-out syndrome" (Gass 1996). Gass described 29 patients with features which included severe, insidious loss of peripheral and central vision, in association with vitritis, diffuse, and focal epithelial derangement with relative sparing of the macula, narrowing of the retinal vessels, optic atrophy, and subnormal electroretinographic findings (Fig. 25.1) (Gass and Scelfo 1978). Although the cause of the inflammation in DUSN was unknown, Gass believed the progressive unilateral visual loss was secondary to an inflammation of the retina, retinal vessels, retinal pigment epithelium (RPE), and the optic nerve (Gass et al. 1978). Although he suspected the involvement of a motile worm, it was not until 1983 that Gass and Braustein observed a subretinal nematode in two patients with DUSN (Gass and Braunstein 1983) and made the formal association (Nussenblatt 2004). In retrospect, cases of similar clinical descriptions were found as early as 1952 (Parsons 1952). The majority of cases reported were unilateral, however, rare bilateral cases have been reported (de Souza et al. 1999; Cortez et al. 2005).

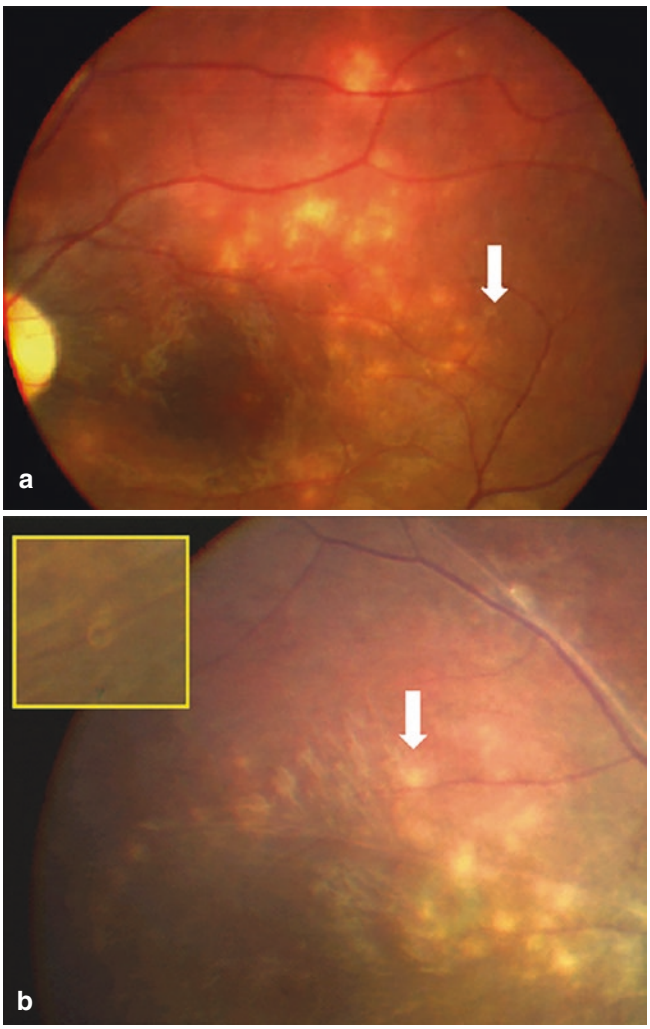

Fig. 25.1 (**a**, **b**) Fundus photographs demonstrating early stage findings of DUSN. There are crops evanescent, multifocal, gray-white lesions at the level of the outer retina in the superior fundus (arrow). The intraocular worm is seen in insert (**b**) as a motile, white worm

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This chapter reviews the pathogenesis, clinical features, differential diagnoses, and management options for diffuse unilateral subacute neuroretinitis.

Etiology and Mode of Transmission

Various parasites and nematodes have been reported as the etiologic agent of DUSN; however, most of these reports did not provide conclusive evidence (Arevalo et al. 2013). The smaller nematodes measuring 400–700 μm in size include *Toxocara canis* and *Ancylostoma caninum* were seen more commonly than the larger ones ranging from 1000 to 2000 μm in length, corresponding to *Baylisascaris procyonis* (Gass 1987). Rarely, *Thelazia*, nematodes of 4500–17,000 μm in size, were implicated in DUSN (Gass and Scelfo 1978; Kunavisarut et al. 2014). The smaller nematodes are endemic to the southeastern United States, the Caribbean islands, and South America, whereas the larger nematodes are found in the Midwestern United States. Trematodes, flatworms, have also been reported in DUSN.

Identification of the causative nematode in DUSN has been challenging as few were surgically extracted from the eye, and fewer were recovered intact (Arevalo et al. 2013). Blumenkranz and Culbertton performed a retinal biopsy via a transcleral approach but could not identify the organism (Blumenkranz and Culbertton 1985). Gass extracted a subretinal nematode transclerally after applying cryotherapy, although he could not identify the organism due to poor histologic details (Gass 1987). Therefore, traditionally, identification of the organism has been based on a combination of examination of morphologic features, serologic testing, and epidemiologic studies. More recently, newer techniques allow for the identification of nematodes through molecular studies and phylogenetic analyses (Poppert et al. 2017; Liu 2012). Polymerase chain reaction amplification and sequencing analysis of ribosomal ribonucleic acid and internal transcribed spacer regions 1 and 2 are used as target regions to differentiate between various parasites (Liu 2012). In the future, perhaps these techniques can be applied to intraocular fluid samples to help the identification of nematodes.

Toxocara canis

Toxocara is an infection in canine hosts accounting for the most prevalent human helminthic infection in industrialized countries (Hotez and Wilkins 2009). Humans acquire the disease via contaminated water sources and ingestion of infected raw meat. Gass initially hypothesized that *Toxocara* was a cause of DUSN (Gass et al. 1978), however ruled out this possibility based on negative serology in many patients. Additionally, the small size of the larval stage of *Toxocara* made it difficult to be seen biomicroscopically (Gass and Braunstein 1983). It is poorly understood why the clinical picture is different from that associated with ocular toxocariasis. Goldberg et al. described cases with evidence that low or nondiagnostic serum titers can be found in cases of *Toxocara* ocular larva migrans and may represent a false-negative test result (Goldberg et al. 1993; Searl et al. 1981; Wilson and Schantz 1991). Oppenheim et al. reported a case of *Toxocara* DUSN in which the patient's positive ELISA titer decreased fourfold over a 2-year period (Oppenheim et al. 1985). Therefore, a negative serologic test may be related to the timing of the serology in relation to the onset of the disease or the immune status of the patient.

Ancylostoma caninum

This worm is a parasitic infection of dogs in South America. *Ancylostoma ceylanicum* has been reported in dogs and cats in Southeast Asia, India, and Australia (Carroll and Grove 1986). *A. caninum* is a frequent cause of cutaneous larva migrans in the southeastern United States. Cutaneous larva migrans can be acquired through the fecal–oral route with dog feces contaminated with infectious eggs. Alternatively, larvae may enter through the skin, migrate through the blood stream to the lungs and trachea, and are then coughed up and swallowed into the gastrointestinal system. They attach themselves to the intestinal wall and begin to reproduce. Once eggs are shed into the environment through feces, the life cycle is complete (Arevalo et al. 2013).

In earlier reports, Gass and Braunstein suggested that the nematode less than 1000 μm in length was the dog hookworm, *Ancylostoma caninum* (Gass and Braunstein 1983). Later, de Souza et al. recovered an intact and motile organism via transvitreal approach (de Souza and Nakashima 1995). While parasitologists believed that morphologic features were consistent with a third-stage Toxocara larva, a photograph review by Bowman concluded that it was most likely *A. caninum* (Gass 1987). 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 (Gass 1987; Gass and Olsen 2001). In addition, the infective third larval stage of *A. caninum* is capable of surviving in host tissue for years without changing size or shape (Gass and Olsen 2001). In one case reported by Poppert et al., although the worm was destroyed during surgical extraction, it was identified through DNA sequencing and phylogenetic analysis of intraoperative fluids as *A. ceylanicum* (Poppert et al. 2017).

Baylisascaris procyonis

Baylisascaris procyonis is a nematode causing a parasitic infection of raccoons. In humans, it causes severe neurologic and ocular diseases, including visceral larva migrans, ocular larva migrans, and eosinophilic meningoencephalitis (Fox et al. 1985; Mets et al. 2003). *B. procyonis* can be detected in the serum and cerebrospinal fluid using indirect immunofluorescence assays. Goldberg reported ocular larva migrans and DUSN occurring without systemic evidence of infection (Goldberg et al. 1993).

In 1984, Kazacos suggested that the larger worm in patients with DUSN living in more northern climates was *Baylisascaris procyonis* (Kazacos et al. 1984). 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 (Kazacos et al. 1985). Additionally, the *B. procyonis* larvae may grow while in the eye and can account for the range of lengths of larvae seen (400–2000 μm), matching the larger nematode variant of DUSN (Kuchle et al. 1993). Although most patients have no history of raccoon exposure, most patients with large nematode DUSN are from the areas of the United States with raccoons commonly infected with *B. procyonis* (de Souza et al. 1999; Kazacos and Boyce 1989). Furthermore, large nematode DUSN occurred in the same regions where animal and human diseases due to *B. procyonis* have been recorded (midwestern and northeastern regions of the United States). Environmental contamination with raccoon fecal materials is common around suburban homes and barns. Accidental hand-to-mouth transfer of infective *B. procyonis* eggs may cause infection in humans (Goldberg et al. 1993).

Trematodes

Four cases of intraocular trematodes have been reported in the literature in association with DUSN (McDonald et al. 1994; Shea et al. 1973; Schweitzer et al. 2008). All of them were identified based on shape, size, and movement. McDonald et al. encountered two cases of human intraocular infection with *Alaria mesocercariae* in which the probable source of infection was ingestion of undercooked frog legs containing the trematode (McDonald et al. 1994). The worm in the first case was analyzed from fundus photographs, whereas in the second case, it was removed surgically from the vitreous cavity.

Clinical Features and Pathogenesis

Clinical characteristics can be classified into early and late stages. DUSN is most frequently seen in healthy children or young adults with no significant past ocular history. In the largest series of patients with DUSN described by de Amorim Garcia Filho et al., 69.4% of 121 patients were younger than 20 years of age (de Amorim Garcia Filho et al. 2012). Most patients presented in the late stage (92.6%) compared to 7.4% of patients presenting in the early stage. DUSN manifests as an intraocular inflammatory process characterized by multifocal chorioretinal lesions. The most common clinical features were subretinal tracks (91.7%), focal alterations of the RPE (89.3%), small white spots (80.2%), and optic nerve atrophy (76.9%). The pathogenesis of DUSN is believed to be a result of a local toxic effect on the outer retina caused by the worm, as well as a diffuse reaction in the inner and outer retina due to a toxin (Gass and Braunstein 1983; Arevalo et al. 2013b). Early and late stage findings outlined below correspond to an inflammatory reaction to the worm and its secreted toxins.

Early Stage

The chief complaint in symptomatic patients in the early stages is the presence of a central or paracentral scotoma (Gass and Scelfo 1978). Visual loss is severe at 20/200 to 20/400 or less in more than half of the patients and is usually irreversible (Gass and Braunstein 1983; de Amorim Garcia Filho et al. 2012). Patients with acute visual loss during early stages of the disease usually present with mild to moderate vitritis, mild optic disc edema, and recurrent evanescent, multifocal, gray-white lesions at the level of the outer retina. These lesions are typically clustered in only one segment of the fundus and fade within 7–10 days (Gass and Olsen 2001) (Fig. 25.1a). Less common clinical features include ocular discomfort, congestion, iridocyclitis, perivenous exudation, subretinal hemorrhages, serous exudation, and evidence of subretinal neovascularization (Gass and Olsen 2001). In approximately 25–40% of cases, a worm is visualized during the eye examination, and the most common location was in the posterior pole (17.3%) (Amorim et al. 2012; Stokkermans 1999). The intraocular worm is observed as a motile, white, glistening nematode that is tapered at both ends and varies in length from 400 to 2000 μm (Fig. 25.1b). It can be seen during any stage of the disease and often near the edges of active gray-white lesions. The worm can assume a coiled, S-shape, or figure of "8" configuration. The examining light may cause the worm to move by a series of slow coiling and uncoiling movements, and less often by slithering snake-like movements in the subretinal space (Gass 1987). Identification of the nematode was associated with younger age, the presence of multifocal yellow-white lesions, and vitritis (de Amorim Garcia Filho et al. 2012). The focal pigment epithelial changes can be explained by the location or the travel pattern of the worm. The longer worm has a greater

likelihood of leaving a tract of coarse clumping of RPE in the wake of its travels, whereas the shorter worm tends to leave focal, chorioretinal atrophic scars (Fig. 25.2) (Gass and Braunstein 1983). Focal chorioretinal white spots are thought to be an immune response to a secretion or excretion from the worm (Gass et al. 1978). The diffuse pigment epithelial changes are believed to be a toxic reaction (Barney 2002). The active gray-white evanescent lesions, which may be caused by substances left by the nematode in its wake, disappear in 1–2 weeks as the nematode travels elsewhere in the eye (Gass and Olsen 2001).

Late Stage

Visual acuity in late stages is profoundly decreased, with 80% or more showing vision 20/200 or worse (Barney 2002). The clinical picture of late stage disease is characterized by progressive optic atrophy and diffuse RPE changes in the peripapillary and peripheral retina over a period of weeks to months (Gass 1987; Arevalo et al. 2013b). Other signs which may be seen in DUSN includes afferent pupillary defect, mild or moderate vitritis, multifocal choroidal lesions, 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), and narrowing of the retinal arteries (Fig. 25.3) (Garcia et al. 2006; Gass and Olsen 2001). Retinal arteriole narrowing may vary by quadrant, and progressive ganglion cell loss leads to optic atrophy (Oréfice et al. 1998). Rarely, choroidal neovascularization can occur in the periphery in the late stage (Barney 2002).

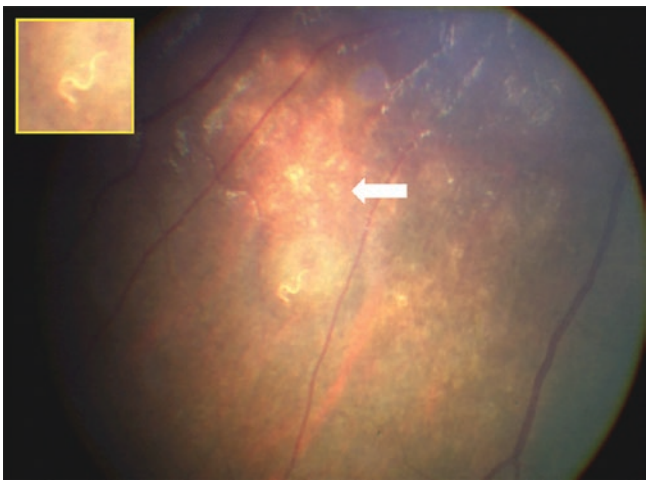

Fig. 25.2 The nematode (seen in the insert) may leave focal atrophic chorioretinal scars (arrow)

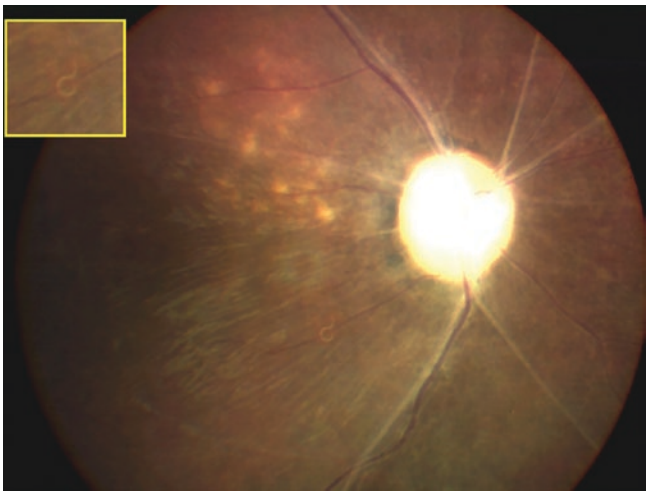

Fig. 25.3 This fundus photograph demonstrates the late stage of the disease with optic nerve pallor, narrowing of the retinal arteries, and focal as well as diffuse degenerative changes in the retina and retinal pigment epithelium. The intraocular worm is shown in the insert

Diagnostic Testing

The diagnosis of DUSN is clinical and depends on the ability to identify a worm in the retina (Arevalo et al. 2013). These cases are defined as confirmed DUSN. Eyes with early and late stage clinical features consistent with DUSN, but without identification of the worm, should be classified as presumed DUSN (de Amorim Garcia Filho et al. 2012). The diagnostic tests described below are nonspecific for the diagnosis of DUSN. The advent of phylogenetic analysis of ocular fluids may become useful in the future as a diagnostic tool in identifying the parasite.

Serology

Serologic testing, stool examinations, and peripheral blood smears are of little value in making the diagnosis of DUSN (Gass et al. 1978). Moreover, no serologic test exists for Ancylostoma (Gass and Olsen 2001). When a worm is identified in the eye of an otherwise healthy person, unless a peripheral eosinophilia is present, no further evaluation seems warranted to make the diagnosis.

Diagnostic Imaging

Fluorescein angiography: DUSN is characterized by early hypofluorescence of the focal gray-white lesions of active retinitis followed by late staining. There may be disc leakage as well as prominent perivenous leakage (Fig. 25.4). In more advanced stages of the disease, fluorescein angiography

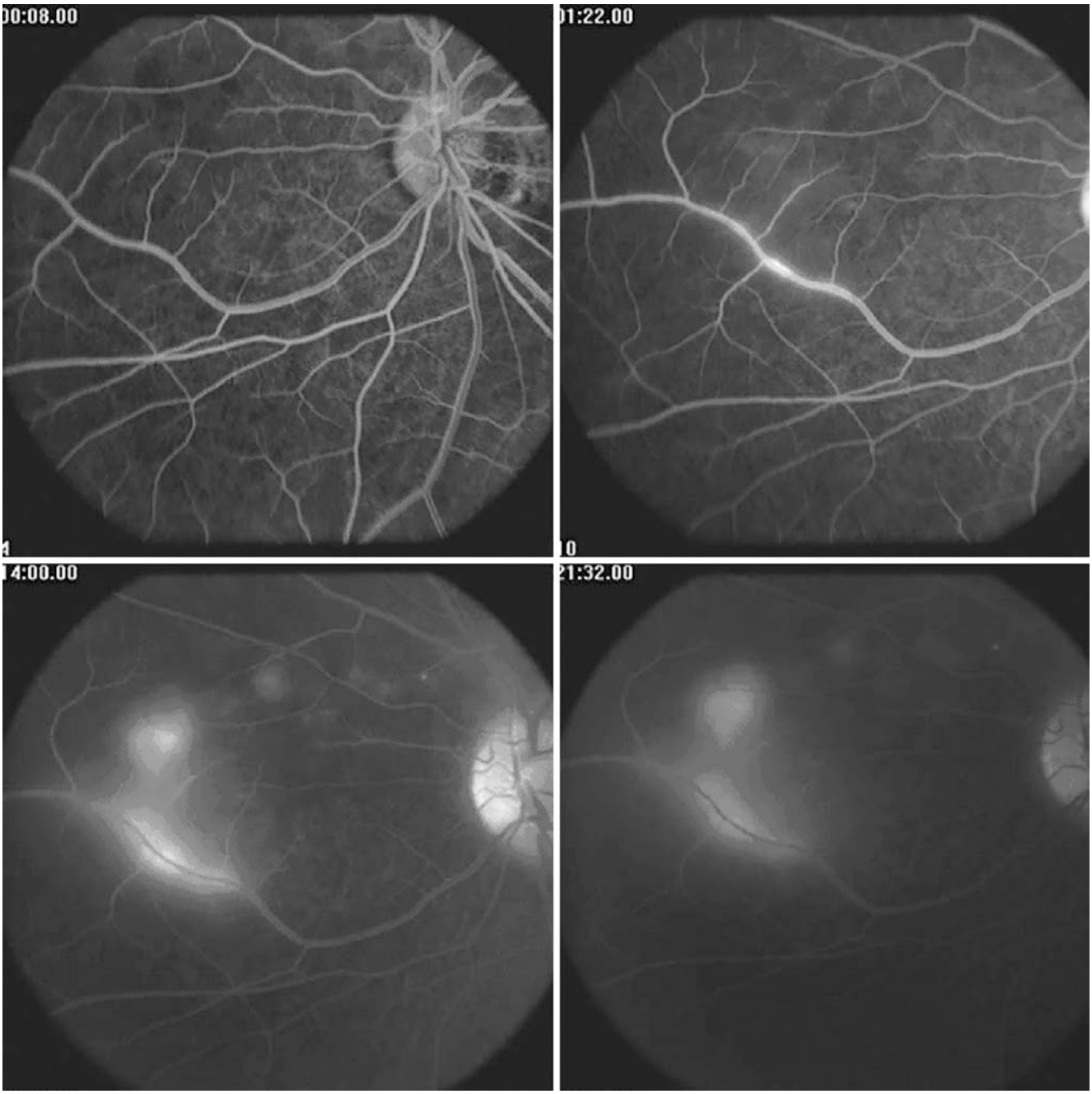

Fig. 25.4 Fluorescein angiogram performed on a patient with early stage DUSN showing areas of late leakage and staining and perivenous leakage inferiorly

shows increased background choroidal fluorescence due to progressively increased loss of RPE (Fig. 25.5) (Gass and Olsen 2001). These findings are nonspecific and may be found in other chorioretinal diseases.

Indocyanine green angiography (ICG-A): ICG-A demonstrates early hypofluorescent dark spots in DUSN. In the late phase, some lesions are persistently hypofluorescent and others become isofluorescent. These lesions suggest choroidal infiltration in DUSN, and late phase fluorescence may be related to degree of choroidal involvement. Persistently hypofluorescent dots are thought to be full-thickness lesions not allowing ICG to diffuse, whereas isofluorescent dots are likely partial-thickness lesions (Fig. 25.6) (Vianna et al. 2006).

Scanning laser ophthalmoscopy (SLO): Examination with SLO provides a high contrast image that may facilitate visualization of the nematode. Live video imaging with the SLO may also help document motility (Moraes et al. 2002).

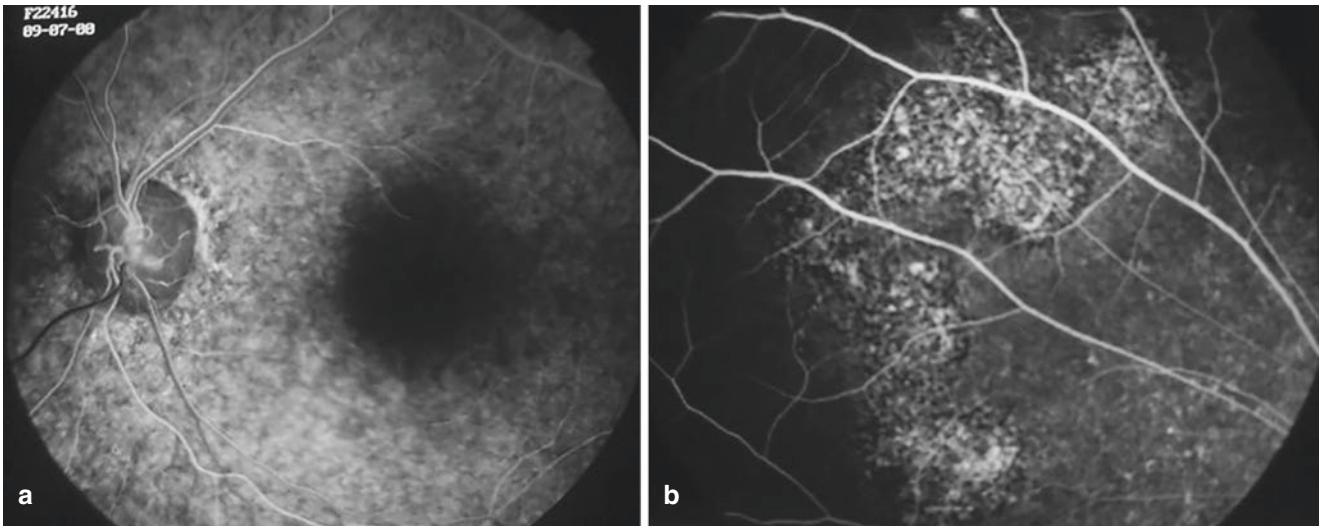

Fig. 25.5 (**a**) In the early stage, fluorescein angiography shows early hypofluorescence of the focal gray-white lesions of active retinitis with late staining. (**b**) In more advanced stages of the disease, angiography shows greater evidence of loss of pigment from the RPE and hyperfluorescence

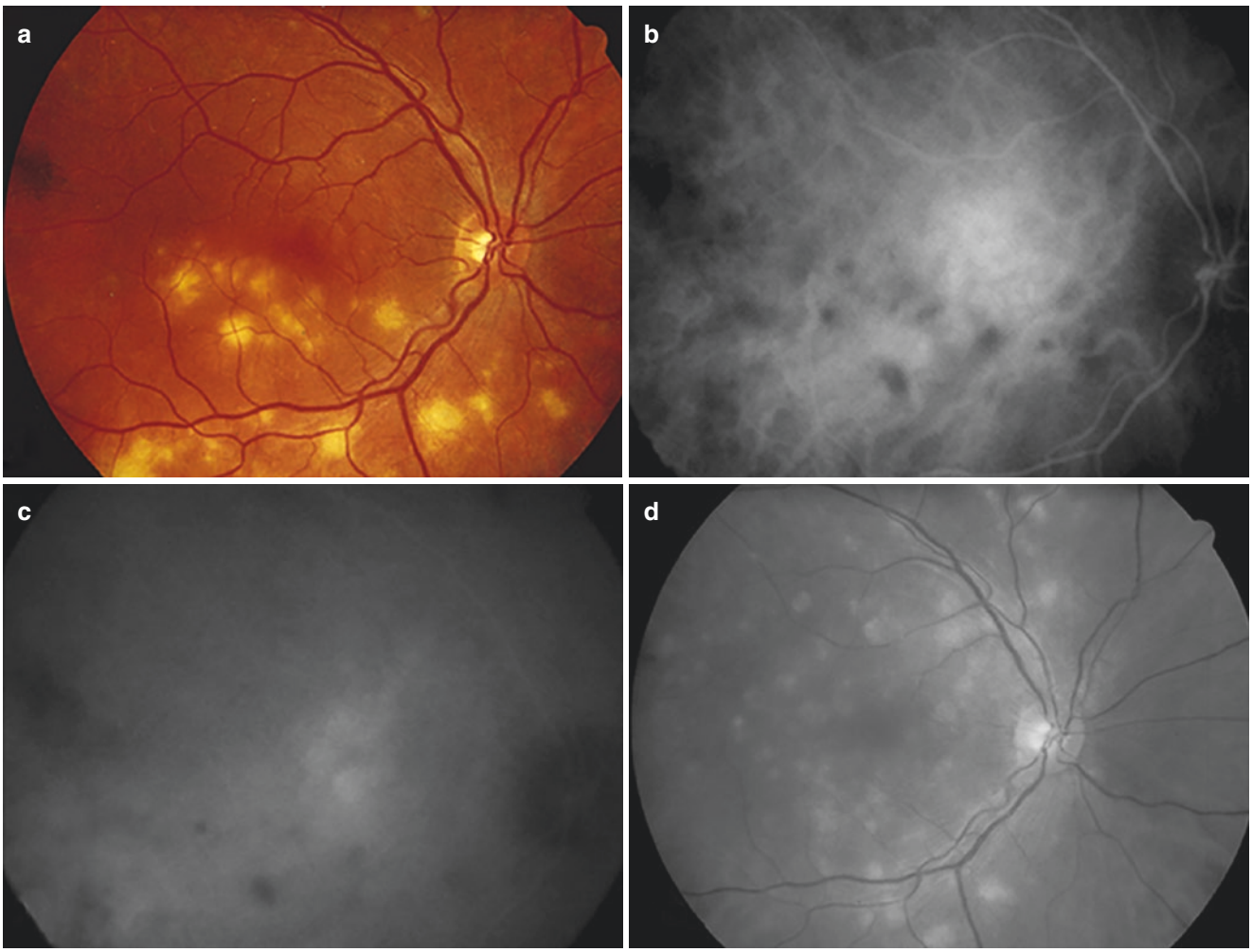

Fig. 25.6 Indocyanine green angiography performed on a patient with early stage DUSN. (**a**) The affected eye revealed multiple yellow-white subretinal lesions in the posterior pole. Early phase ICG-A shows hypocyanescence of the lesions, (**b**) whereas late phase ICG-A reveals hypofluorescent dots and hypercyanescence in the macular region (**c**). After 1 month, the superior subretinal lesions increased in number and became more evident (**d**) (Vianna et al. 2006 with permission)

Optical coherence tomography (OCT): OCT exhibits structural alterations caused by the parasite, affecting both the inner and outer retina. Previous studies reported a reduction in retinal nerve fiber layer (RNFL) thickness using the GDx nerve fiber analyzer corresponding to ganglion cell loss (Garcia et al. 2006). Recent studies using spectral-domain OCT also showed that RNFL in affected eyes was on average thinner than that of normal contralateral eyes. In the late stage, RNFL was thinner (mean 74.8 μm) compared to early stage disease (mean 96.5 μm), representing progressive atrophy. In the acute phase of the disease, it is possible to have transitory edema and an increase in RNFL thickness. Earlier studies using the Stratus OCT showed that there was a statistical significant correlation between decreased RNFL thickness and worse visual acuity (Fig. 25.7) (Gomes et al. 2009).

Furthermore, central macular thickness was decreased in the affected eyes compared to normal fellow eyes with loss of foveal depression in 75% of patients (Garcia Filho et al. 2011). On spectral-domain OCT scans, hyper-reflectivities can be identified in intraretinal and subretinal layers (Lima et al. 2016). These have been documented to correspond to the location of the parasite on fundus photographs, representing the worm itself or the inflammatory reaction surrounding it (Cunha et al. 2010). Kang et al. reported a case of a worm imaged in the sub-internal limiting membrane (ILM) space with adjacent sub-ILM fluid (Kang and Lee 2015). Photoreceptor disruption can be variably involved, with recovery reported after treatment (Tarantola et al. 2011). Finally, choroidal thickness was found to be similar in both affected and fellow eyes using enhanced depth imaging OCT scans (Berbel et al. 2014). DUSN has been reported using OCT angiography. In this case, the nematode was identified in two different locations at two different time points. Since it has no vascular system, an inactive worm may not be detected using the same technique (Kalevar and Jumper 2017).

Electrophysiologic Testing

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 has a very characteristic and reproducible negative electroretinogram where the b-wave of maximum combined response is flat, with below normal response and a decrease in the b/a ratio. The mechanism of this interesting phenomenon is explained by Oréfice et al. as being a consequence of a possible autoimmune, inflammatory, and/or toxic reaction to retinal bipolar cells (Garcia et al. 2006; Oréfice et al. 1998). The ERG in the

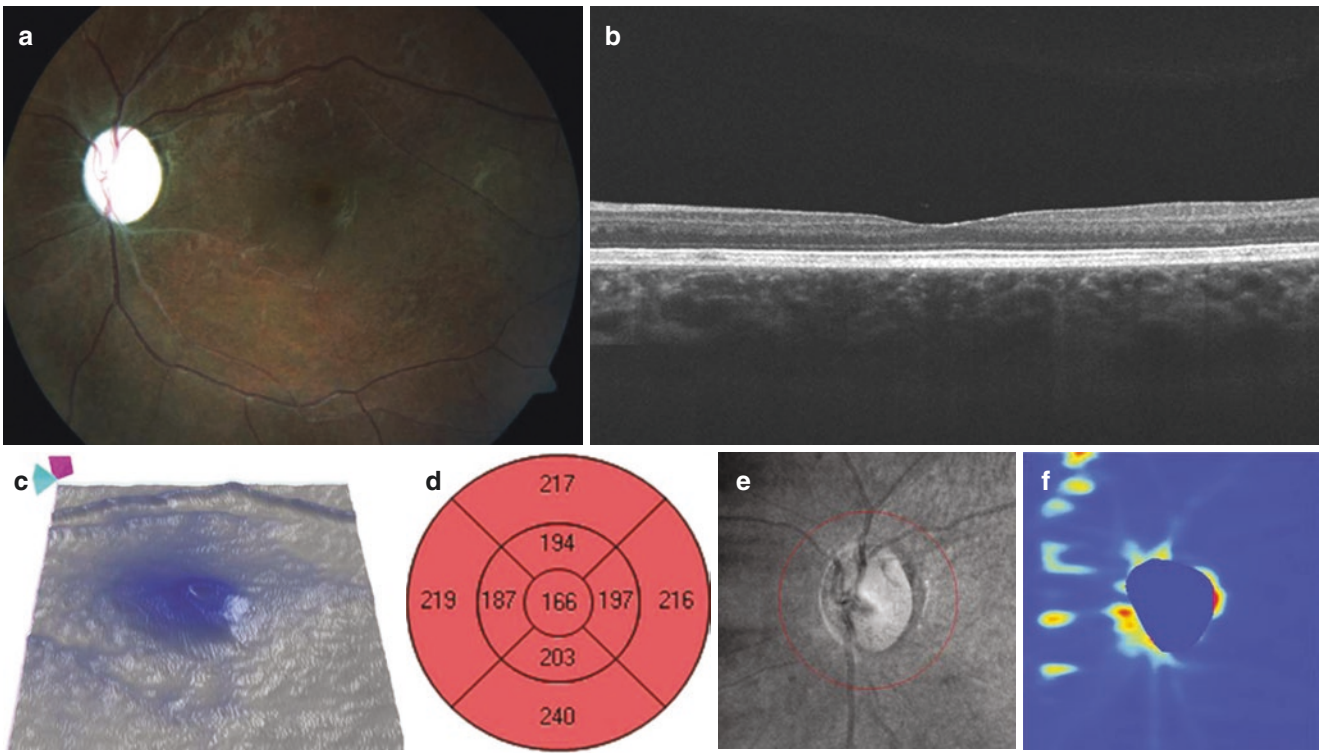

Fig. 25.7 Late stage Diffuse Unilateral Subacute Neuroretinitis. (**a**) Color fundus image of a 12-year-old boy with a visual acuity of 20/400 and a 6-month history of visual los. Optic nerve atrophy, retinal vessel narrowing and some degree of pigmentary changes can be seen. (**b**) High-resolution optical coherence tomography (OCT) through the fovea showing a thinning in the inner retinal layers. (**c**, **d**) OCT retinal thickness map (Cirrus, Carl Zeiss Meditec Inc., Dublin, CA) showing a diffuse retinal thinning. (**e**, **f**) OCT fundus image and retinal nerve fiber layer map displaying a reduction in retinal nerve fiber layer thickness

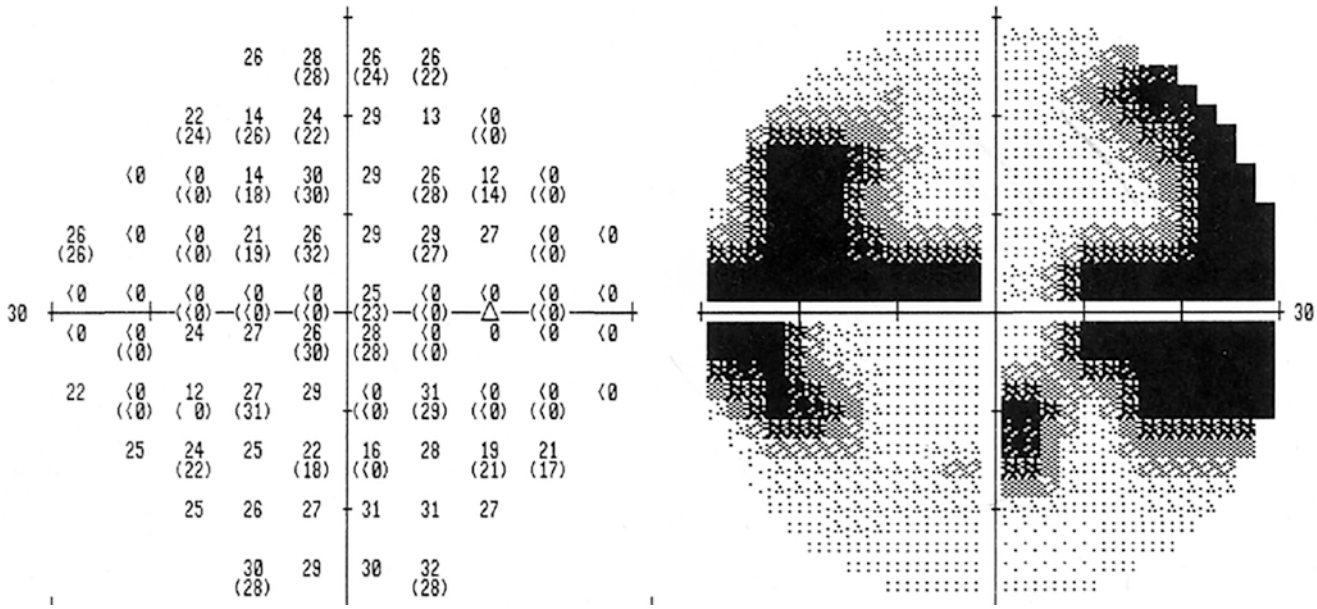

Fig. 25.8 A Humphrey visual field demonstrates central and paracentral scotoma which do not always correspond to active fundus lesions (courtesy of Eduardo Cunha de Souza, MD)

affected eye is usually abnormal even if tested in the early stage of the disease. The ERG is rarely completely extinguished, which differentiates it from an inherited retinal degeneration (Sabrosa and de Souza 2001). In addition, patients can have a normal electrooculogram (EOG) and abnormal ERG, suggesting a neuroepithelial disease (Stokkermans 1999). Multifocal electroretinography has been performed in DUSN showing decreased foveal response density, and increased parafoveal and perifoveal waveform amplitudes. In one case, 2 months after laser photocoagulation of a subretinal nematode, multifocal electroretinography showed full recovery consistent with visual acuity of 20/20 (Martidis et al. 2002).

Visual Field Studies

Gass and Olsen reported visual fields with various patterns that do not correspond to fundus changes (Gass and Olsen 2001) (Fig. 25.8). Recent studies report Humphrey visual fields that exhibit absolute scotoma corresponding to retinal areas previously affected by yellowish lesions (Vezzola et al. 2014).

Differential Diagnosis

Early signs and lesions of DUSN appear similar to other causes of focal chorioretinitis such as sarcoidosis, toxoplasmosis, histoplasmosis, multifocal choroiditis, serpiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy, and multiple evanescent white dot syndrome (Arevalo et al. 2013). The late stage of DUSN is often mistaken for posttraumatic chorioretinopathy, occlusive vascular disease, sarcoidosis, or toxic retinopathy (Gass and Olsen 2001).

Management

The current standard of care in the treatment of DUSN is a combination of oral anti-helmintics and laser photocoagulation of the nematode.

Laser Therapy

Visualization of the nematode is uncommon, as the light from biomicroscopic examination may cause the worm to migrate. Therefore, when seen, the worm should be treated with prompt photocoagulation. This leads to death of the nematode, decreases retinal migration by halting worm migration, and allows resolution of active chorioretinal lesions without causing significant intraocular inflammation. As the worm is motile, delays in treatment may lead to difficulty in locating the parasite (Venkatesh et al. 2005). The authors recommend a technique using a 532 nm green laser (EYELITE® Laser, Alcon Laboratories, Fort Worth, TX), with a 200 μm spot size, at a power of 200 mW, using confluent direct laser, with an average of 4–5 spots (Fig. 25.9). Improvement in vision and visual field may occur after laser treatment if performed early, however in late stages of the

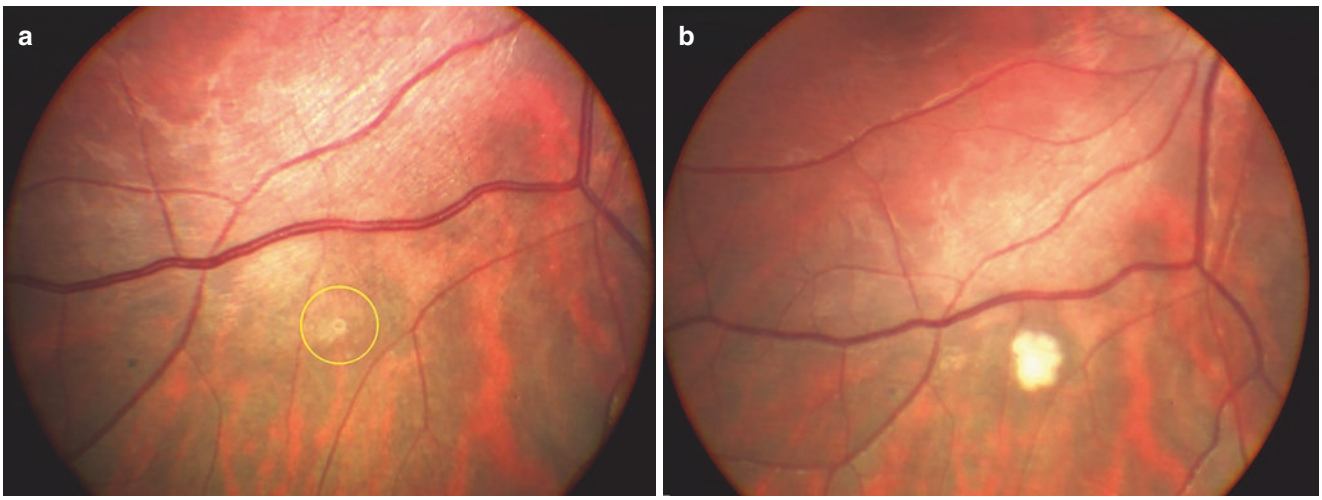

Fig. 25.9 This fundus demonstrates the nematode (yellow circle) along the inferotemporal vascular arcade in the right eye (**a**) before laser treatment and after laser photocoagulation (**b**)

disease, laser treatment does not reverse visual loss (Garcia et al. 2004; Garcia et al. 2005; de Amorim Garcia Filho et al. 2012). Laser treatment should be avoided to areas close to the foveal center, as it may cause a central scotoma and decreased vision. As nematodes have been documented to be photosensitive, low level of light or very light application of the laser may be used to lure the worm into the mid-periphery, where it may be destroyed with less collateral retinal damage. Intravitreal triamcinolone has been reported to expedite the clearing of media opacity due to severe vitritis eyes, to allow earlier visual identification of the nematode (Lima et al. 2016). Close follow-up is recommended to ensure inactivation of the worm (Micieli et al. 2016).

Medical Therapy

Oral anti-helmintics have been used with variable success for the treatment of DUSN. Gass et al. reported that thiabendazole may be effective in patients with moderate degrees of vitreous inflammation in association with a breakdown in blood–retinal barrier (Gass and Olsen 2001). However, in eyes without vitreous inflammation, oral anti-helmintic medication has not been shown to be successful. Laser can cause a breakdown in the blood–retinal barrier and may increase ocular penetration of oral thiabendazole. Therefore, in eyes where a worm cannot be identified and migrating evanescent lesions are found, moderately intense scatter photocoagulation can be performed in the vicinity of the white lesions to break down the blood–retinal barrier.

Alternatively, high-dose oral albendazole (400 mg/day) has been used in 12 patients who showed improvement in visual acuity, visual field, and ocular inflammation after treatment for 30 days (Souza et al. 2005). Worms were observed to become inactive in four patients in which worms were visible. No adverse drug side effects were observed in any of their cases during follow-up. Corticosteroids may be used in adjunct to decreased inflammation to a dying nematode, particularly when no parasite is seen (Padhi et al. 2017; Arevalo et al. 2013).

Surgical Therapy

Most cases can be managed medically, as the nematode can be destroyed by laser. However, in patients who are young and uncooperative, the nematode can be recovered via pars plana vitrectomy (de Souza and Nakashima 1995).

Summary

Diffuse unilateral subacute neuroretinitis is a rare unilateral inflammatory process characterized by an insidious and severe loss of central and peripheral vision associated with vitritis, multifocal chorioretinal lesions, and RPE loss. The most common parasites associated with DUSN include *Toxocara canis, Baylisascaris procyonis,* and *Ancylostoma caninum*. Clinical characteristics in early and late stages are similar to other infectious causes of posterior uveitis as well as white dot syndromes. Diagnosis remains clinical as serologic testing is often negative, and visualizing the motile worm is the most specific sign. Pathogenesis is poorly understood, but is speculated to be an autoimmune, inflammatory, or toxic reaction to the parasite. Laser photocoagulation offers the best chance for clinical resolution of the disease; however, the worm is only visualized in 25–40% of cases. In patients where the worm cannot be found, anti-parasitic

agents like thiabendazole and albendazole have been used with variable success. Vitrectomy has been used for the surgical extraction of nematodes. In the future, DNA phylogenetic analysis of parasites may offer further insights into the diagnosis and treatment of DUSN.

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Human Immunodeficiency Virus Infection and Cytomegalovirus Retinitis

26

Ian Y. Wong and Yong Tao

Introduction

Cytomegalovirus (CMV) retinitis is the most important blinding complication in patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS). Before the introduction of the highly active or combination antiretroviral therapy (HAART), the incidence of CMV retinitis was as high as 45.3 per 1000 person-years (Schwarcz et al. 2013).

Since around 1996, AIDS has been redefined as a chronic manageable condition through the introduction of HAART. The boost in immune system function following the use of HAART was able to reduce the incidence of CMV retinitis dramatically (Schwarcz et al. 2013). A recent 16-year cohort of 18,733 HIV/AIDS patients in the United States have reported an incidence of CMV retinitis in the pre-HAART era to be around 45.3 per 1000 person-years (Schwarcz et al. 2013). After the introduction of HAART during the years 1996–2000, the incidence has dropped to 8.8 per 1000 person-years. This figure further reduced to 1.5 during the period 2001–2008. Despite that, a recent report from Singapore reported an incidence of CMV retinitis among HIV hosts of 10.4 cases per 1000 person-years (Teoh et al. 2012). This has highlighted the geographical variation in the incidence of CMV retinitis among this group of susceptible individuals.

Therefore, it is of vital importance that ophthalmologists and physicians who treat AIDS patients be aware of the signs and symptoms of CMV retinitis, such that early detection be made possible and late complications such as retinal necrosis and detachment be avoided.

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Etiopathogenesis

The seroprevalence of CMV varies depending on the geographical location. Epidemiological studies have reported greater than 90% seropositivity among many Asian and South American countries and regions, including Brazil, China, India, etc. (Shigemi et al. 2015; Tabatabaee and Tayyebi 2009; Kangro et al. 1994). Seroprevalence tends to be lower among European countries such as Germany (Cannon et al. 2010), the Netherlands (Korndewal et al. 2015), and Iceland (Hassan et al. 2016). The seropositivity in the United States was also reported to be around 50.4%. According to a study by Canon and associates (Cannon et al. 2010), the seroprevalence increases with age and reaches a plateau beyond age 50 years. This may be a possibility why CMV retinitis is less common among susceptible patients in the pediatric age group.

Prior CMV infection is a prerequisite for the development of CMV retinitis. However, in most instances, active disease is a manifestation of end-organ reactivation of the virus, retina in the case of CMV retinitis, instead of primary infection (Jeon et al. 2012; Cheung et al. 2014). The risk increases when the CD4 cell count drops below 50/mm^3. Although differences do exist and have been reported, the clinical presentations of CMV retinitis in AIDS patients are in many ways similar or indistinguishable to that seen in patients with iatrogenic immunosuppression.

Clinical Features

CMV retinitis is in general a slowly progressive necrotizing retinitis that can affect anywhere in the retina (Iu et al. 2016). It can affect the periphery (Fig. 26.1), posterior pole (Figs. 26.2 and 26.3), or both (Fig. 26.4) and may be unilateral or bilateral. When in the posterior pole, affected retina appears whitish with prominent retinal hemorrhages (Fig. 26.2), resembling the classical description of "ketchup on cheese" (Figs. 26.5 and 26.6). The whitish retinal infiltrate

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through active retinitis areas may show thickened retina with intraretinal cyst formations (Figs. 26.6, 26.11, and 26.12). Optical coherence tomography angiography (OCTA) shows non-perfusion in areas of active retinitis as well as areas of necrosis after retinitis has resolved (Fig. 26.11). However, it should be noted that the diagnosis of CMV retinitis should always be a clinical diagnosis instead of an angiographical one.

It was believed that when CMV retinitis occurs in an AIDS patient, there is minimal or no inflammatory response. This was thought to be related to the lack of an active immunity in the host to mount such as response in reaction to the infective process. However, there have been reports to suggest that vitritis and anterior uveitis occur more commonly than expected and may be related to the widespread destruction of the retina in severely affected patients.

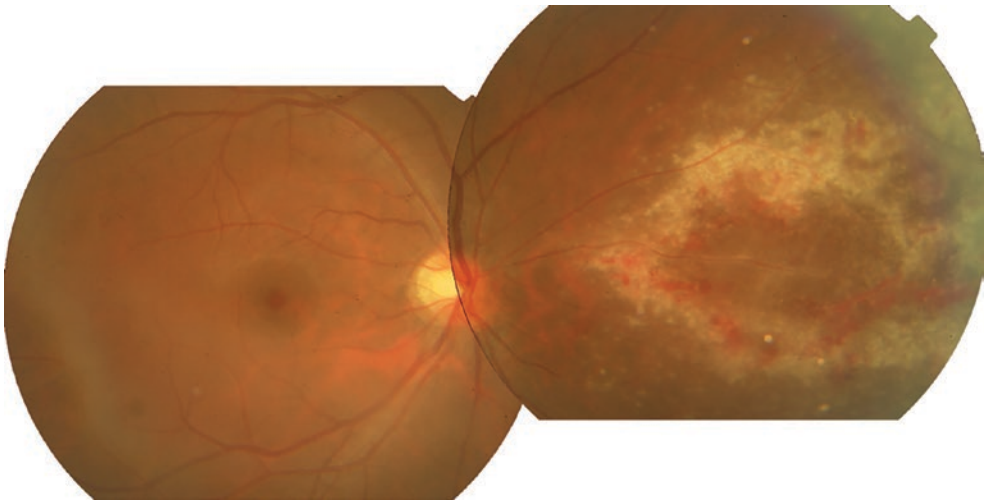


Fig. 26.1 Clinical photo of the right eye nasal peripheral retina with retinal hemorrhage and retinal infiltrates

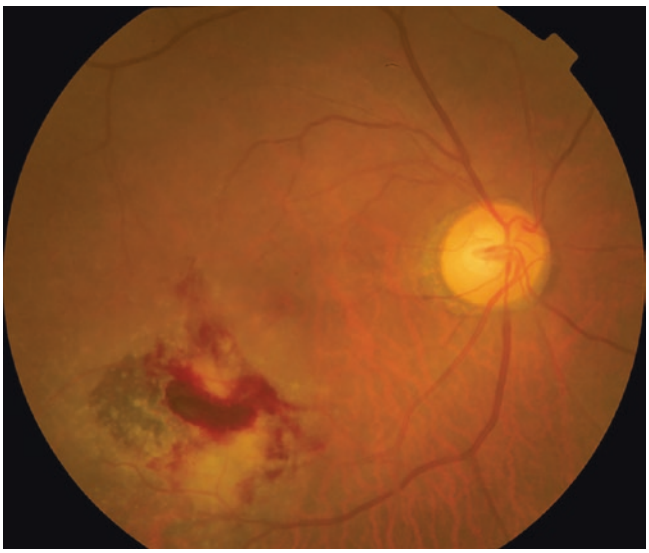


Fig. 26.2 Clinical photo of the right macula showing characteristic presentation of cytomegalovirus retinitis in the macula with a "cheese on ketchup" appearance

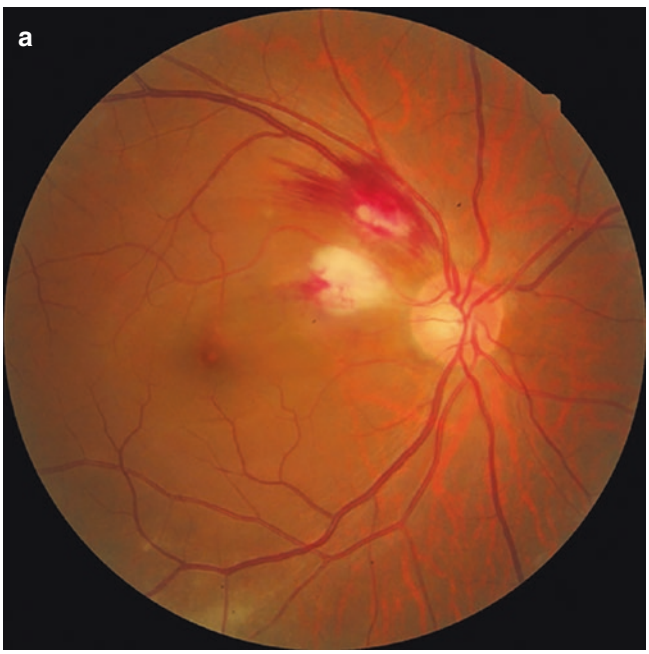
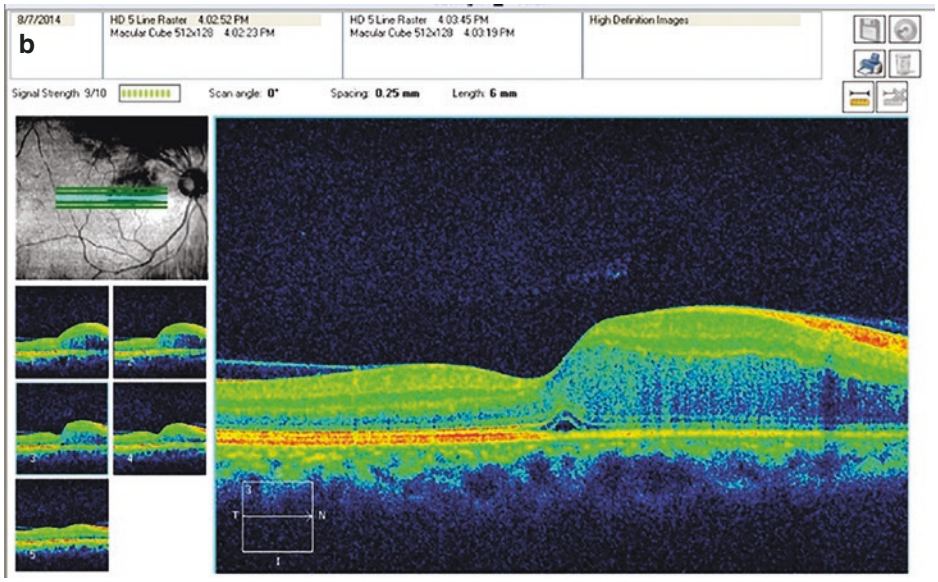


Fig. 26.3 (**a**) Fundus photo of the posterior pole showing retinitis and adjacent flame-shaped retinal hemorrhage. (**b**) Corresponding cross-sectional image on optical coherence tomography showed retinal thickening with small amount of subretinal fluid at the fovea (courtesy of Prof Koh-Hei Sonoda)

Fig. 26.3 (continued)



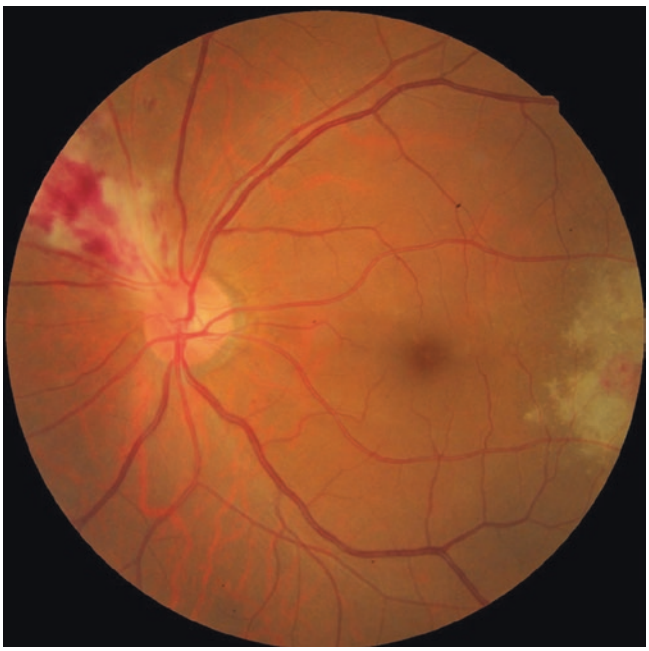


Fig. 26.4 Fundus photo showing cytomegalovirus retinitis with foci in both the macula and the area nasal to the disc (courtesy of Prof Koh-Hei Sonoda)

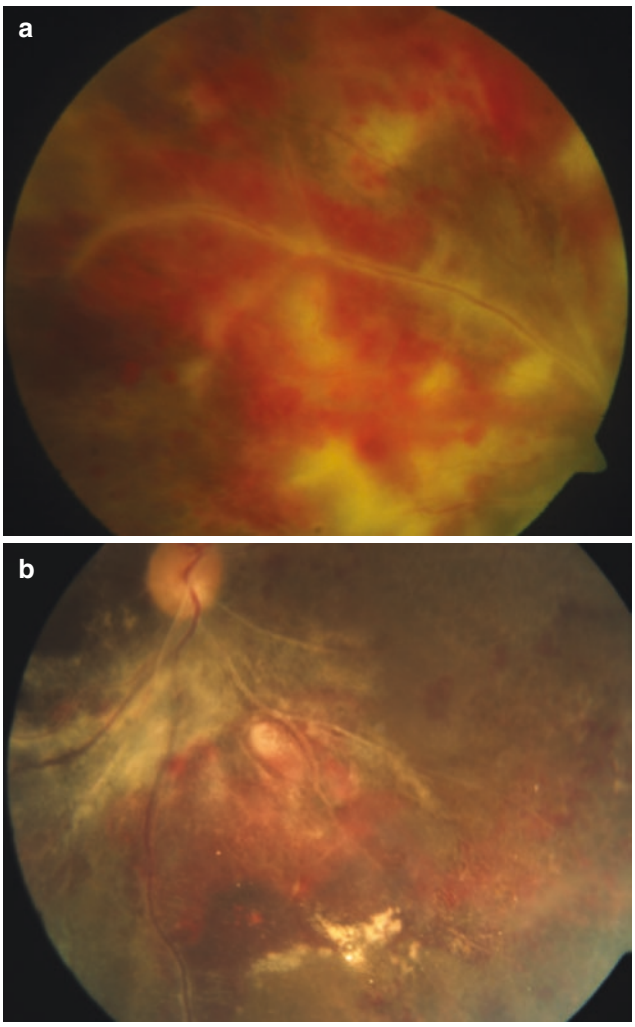


Fig. 26.5 (**a**) Typical presentation of cytomegalovirus retinitis with abundant retinal hemorrhage and infiltrate resembling the "cheese on ketchup" appearance. (**b**) Picture of the same patient following treatment showing resolution of the retinitis and the associated hemorrhage (courtesy of Dr. Jay Chhablani)

often demonstrates a brushfire configuration. In the periphery, CMV retinitis also appears as areas with whitish retinal infiltrate, but the pattern may be more of a granular appearance with or without prominent retinal hemorrhages (Figs. 26.7 and 26.8). Retinal vessels may be involved with a sheathing appearance. Frosted branch angiitis (Fig. 26.9) has also been reported in CMV retinitis. Fluorescein angiogram (FA) at this stage may show leakage where the retinitis is advancing, which may aid diagnosis in uncertain cases (Fig. 26.10). Optical coherence tomography (OCT) scans

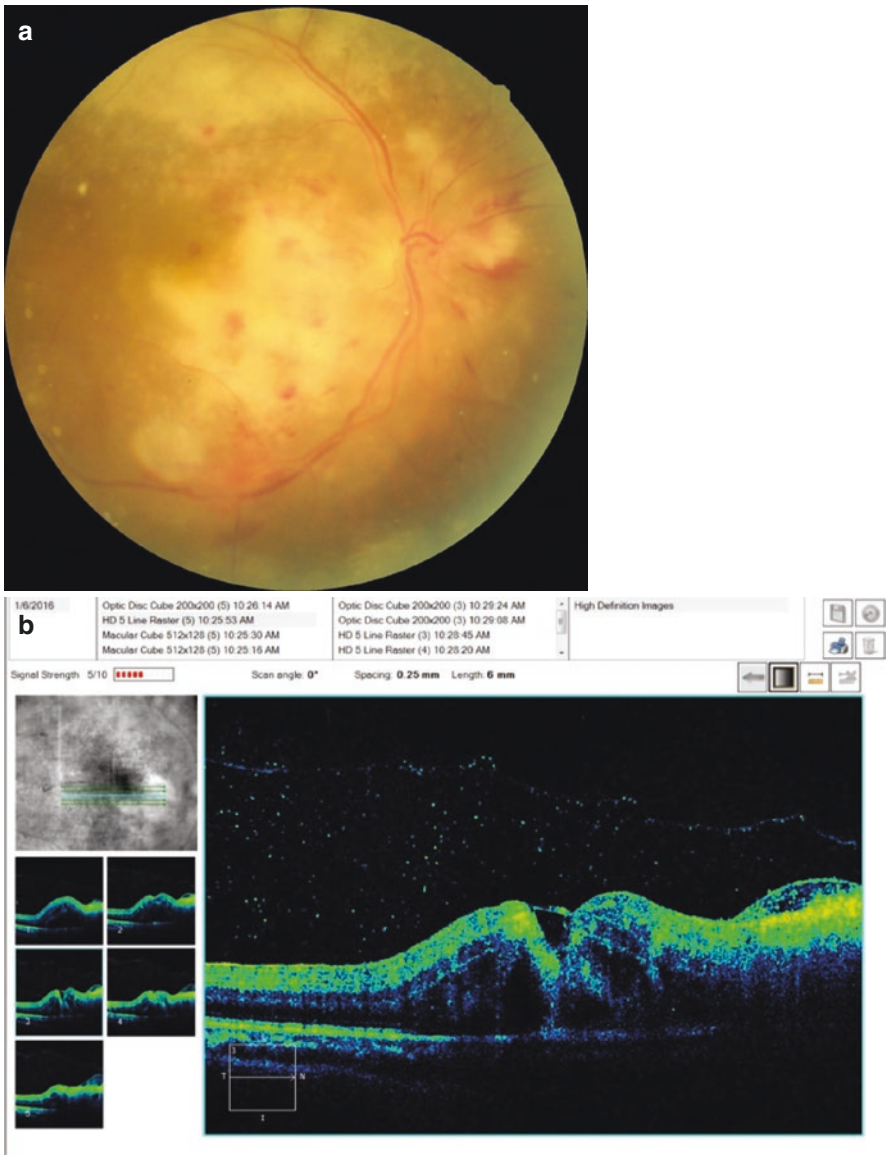


Fig. 26.6 (**a**) Fundus photo showing a diffusely involved macula with retinitis and retinal hemorrhage. (**b**) Corresponding optical coherence tomography showing thickened retina in an area with cytomegalovirus retinitis (courtesy of Prof Koh-Hei Sonoda)

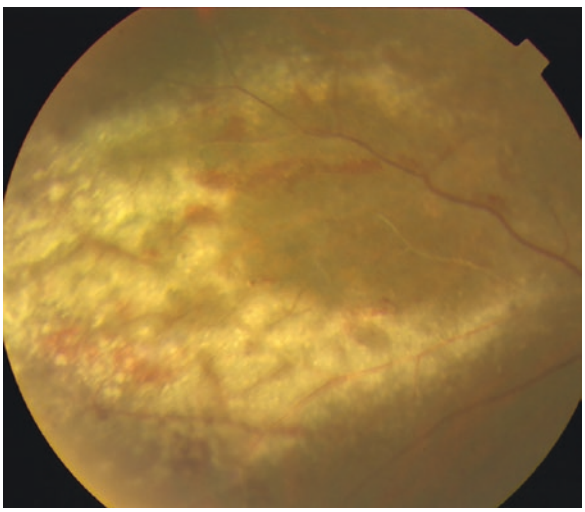


Fig. 26.7 Fundus photo demonstrating the "granular" appearance of retinal infiltrate in the periphery (courtesy of Prof Koh-Hei Sonoda)

As the retinitis progresses, areas left behind may show atrophic retina with sclerotic vessels. In the pre-HAART era, the incidence of retinal detachment in patients with CMV retinitis was around 33% per eye per year (Jabs et al. 1989; Gross et al. 1990; Kempen et al. 2001, 2003; Freeman et al. 1993). These detachments were associated with multiple retinal atrophic holes in areas of healed retinitis in the periphery (Freeman et al. 1992). Breaks form from necrotic areas which have been affected by the retinitis. These seldom present in the acute stage of the retinitis; rather, they usually present late, from weeks to months after initiation of anti-CMV treatment. It has been reported that the median time for retinal detachment to occur in an eye previously suffering from CMV retinitis was 18.2 months (Freeman et al. 1993). Risk factors for the development of retinal detachment include severe peripheral retinitis, severity of the retinitis when it was active,

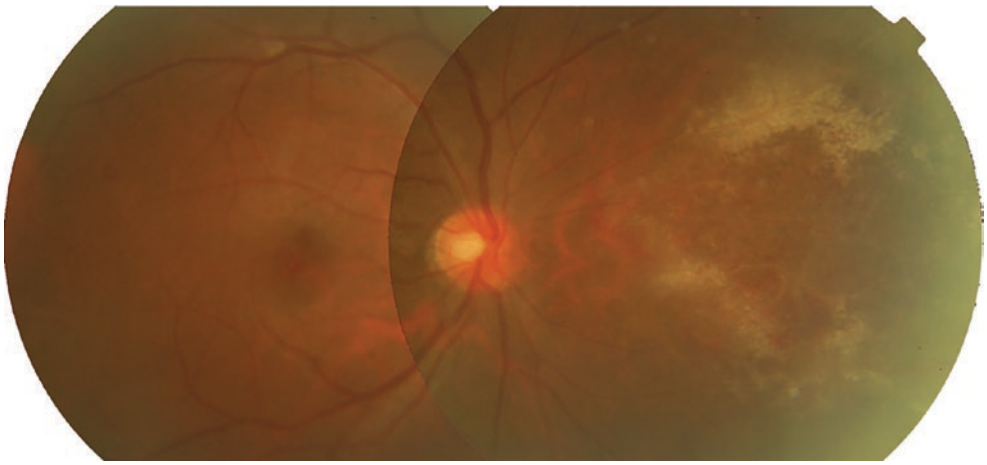


Fig. 26.8 Fundus photo demonstrating the "granular" appearance of retinal infiltrate in the periphery

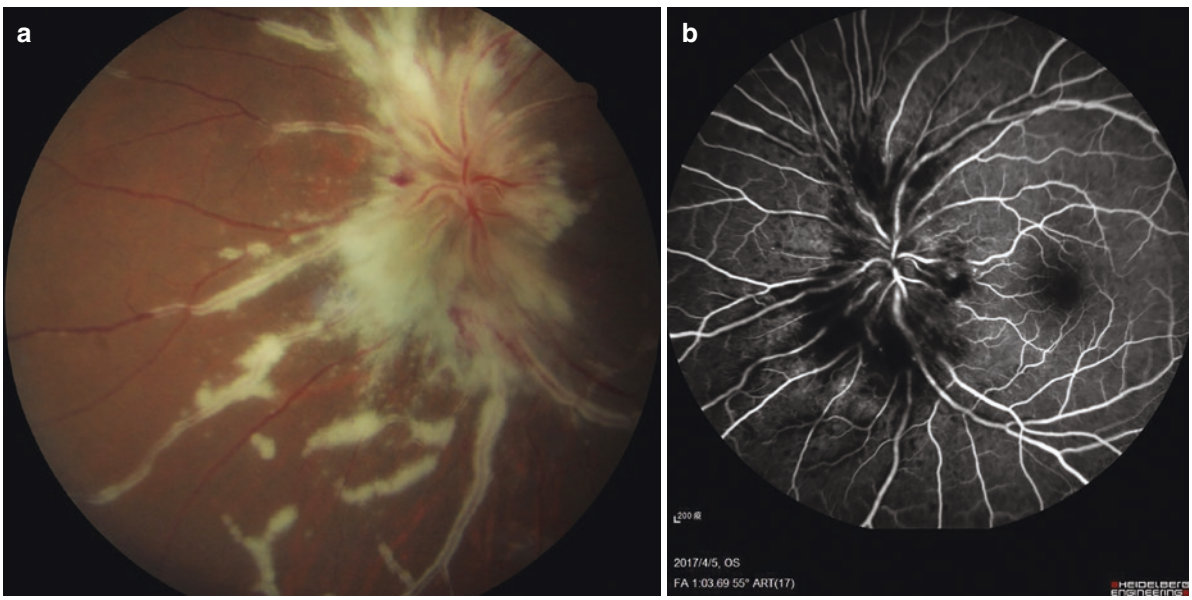


Fig. 26.9 (**a**) Peripapillary vessels with sheathing, resembling the classic description of "frosted branch angiitis." (**b**) Corresponding fluorescein angiogram showing the staining of involved blood vessel relative hypofluorescence in areas with dense retinal infiltrate (courtesy of Dr. De-Kuang Hwang)

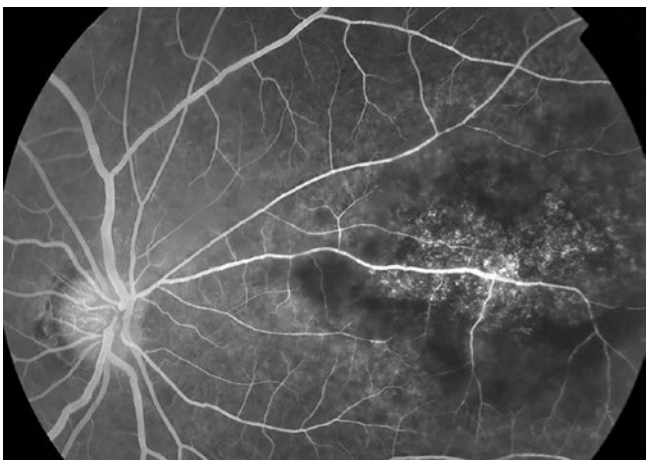


Fig. 26.10 Showing staining and leakage on fluorescein angiogram in the affected areas in a patient with cytomegalovirus retinitis

and involvement of the vitreous base by the disease (Freeman et al. 1993; Kempen et al. 2001; Holland et al. 1989). Fortunately, following the introduction of HAART, the risk of detachment from CMV retinitis has been much reduced (Kempen et al. 2001; Martin et al. 1994; Freeman 1999).

Immune recovery uveitis can occur following successful treatment of the underlying condition by HAART. This is thought to be a result of immune reconstitution in the host. The risk has been reported to be from 15.5% to 37.5% (Jabs et al. 2002; Arevalo et al. 2003). Clinical signs include iritis, vitritis, macular edema, and epiretinal membrane formation (Whitcup 2000; Karavellas et al. 2000; Newsom et al. 1998). Patients may suffer visual loss because of macular edema, hazy media due to vitritis, and cataract formation.

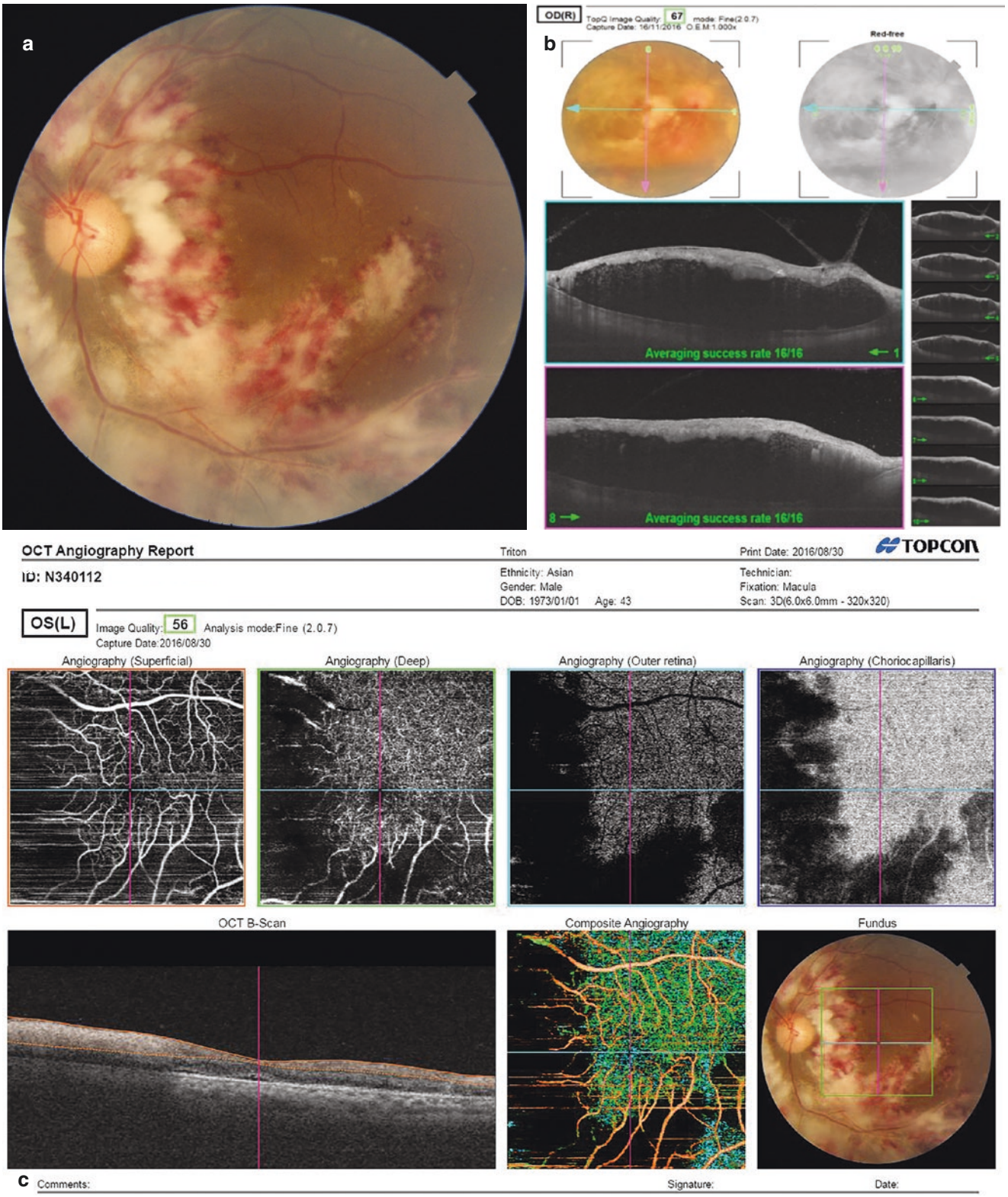


Fig. 26.11 (**a**, **b**) Cytomegalovirus retinitis patient with retinal thickening and intraretinal cystic changes demonstrated by optical coherence tomography. (**c**) Corresponding optical coherence tomography angiogram showed non-perfusion in areas of active retinitis (courtesy of Dr. Jay Chhablani)

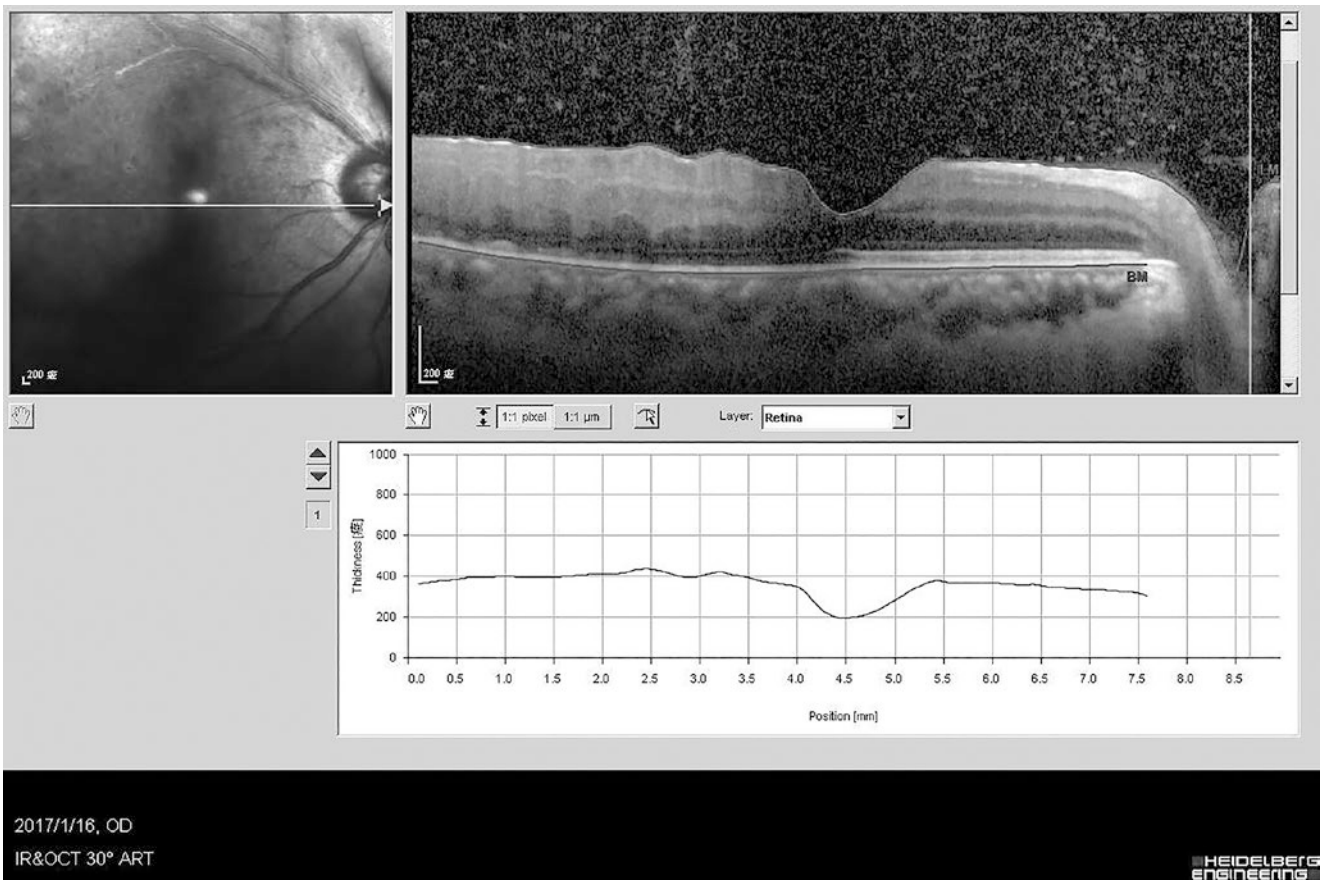


Fig. 26.12 Optical coherence tomography showing thickened retina in an area with cytomegalovirus retinitis (courtesy of Dr. De-Kuang Hwang)

Diagnosis

Diagnosis of CMV retinitis should be made based on clinical grounds. However, laboratory tests can aid the diagnosis in uncertain cases. It should be noted that in any patients with HIV of AIDS, especially those that have a CD4 cell count below 50/mm^3 (Kuppermann et al. 1993) that presents with retinal hemorrhage and retinitis, CMV retinitis should always be on the top of the differential list.

Blood CMV antigenemia may not be the most accurate test to correlate with ocular CMV retinitis. In this regard, polymerase chain reaction (PCR) tests for CMV on aqueous samples have a higher accuracy. In a recent study, PCR of the aqueous yielded significantly higher positive rates than testing for blood CMV antigenemia (Iu et al. 2016). Aqueous samples could easily be taken at the time of intravitreal injection of anti-CMV drugs when a paracentesis is performed into the anterior chamber. Alternatively, this could also be done at the slit lamp as a diagnostic procedure under aseptic conditions. Generally, the number of CMV DNA in aqueous by using real-time PCR is regarded as positive if it is above 500 copies/mL. In addition, as PCR is ultrasensitive in amplifying even only a trace amount of DNA, any procedural errors during PCR may lead to significant changes in terms of the results. Hence, the concentration of interleukin-8 (IL-8) in the aqueous is also another recommended marker for clinical diagnosis and monitoring. It can be safely performed by cytometric bead array (CBA) with flow cytometry on the aqueous aspirated during anterior chamber paracentesis at the time of intravitreal injections. It has been shown to be a good quantitative laboratory indicator of the activity of intraocular inflammation caused by CMV retinitis (Wang et al. 2014).

Management

Treatment of CMV retinitis in AIDS patients should be divided into ocular and systemic treatments. The United States Food and Drug Administration (FDA)-approved anti-CMV agents include ganciclovir, valganciclovir, foscarnet, and cidofovir. Intravenous ganciclovir is administered every 12 hours at a dose of 5 mg/kg for 2 weeks during induction phase and 5 mg/kg daily as maintenance (Au Eong et al. 1999; Stewart 2010).

Ocular treatment is most commonly in the form of intravitreal injections, which has the advantage of delivering the drug to the site of infection without causing systemic side effects. Disadvantages include the risk of intravitreal injections, the need for multiple injections, and also the inability to provide coverage for the contralateral eye and systemic viremia. Weekly intravitreal injections are performed initially, at a dose of 200 μg/0.05 mL (Henry et al. 1987; Miao et al. 2013; Wang et al. 2014). The aqueous levels of CMV DNA and IL-8 aid the clinician to decide the timing of cessation of intravitreal injections of antiviral agents. Foscarnet (2400 μg/0.1 mL) may be considered if the intraocular CMV DNA in the aqueous is persistently positive, and interleukin-8 increases after intravitreal injection of ganciclovir, as resistance to ganciclovir is a possibility (Boss et al. 2016; Lieberman et al. 1994). Systemic treatment has the advantages of providing coverage for CMV viremia and also protection for the contralateral eye, but patients may suffer from undesirable side effects; common ones include bone marrow suppression with ganciclovir, nephrotoxicity with foscarnet.

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Acute Retinal Necrosis and Progressive Outer Retinal Necrosis

27

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Introduction

Necrotizing retinopathies, including acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN), are a group of uncommon posterior segment complications associated with infections caused by the herpes virus. ARN was first described in 1971 by Urayama et al., Japanese ophthalmologists who termed the condition as Kirisawa uveitis and described it as acute unilateral panuveitis associated with optic neuritis and retinal panarteritis in healthy adults, with subsequent procession to diffuse necrotizing retinitis and/or subsequent rhegmatogenous retinal detachment (RRD) (Urayama et al. 1971). Standard diagnostic criteria for ARN were published by the American Uveitis Committee (Table 27.1) (Holland 1994).

PORN is reported as rapid progressive retinal necrosis with clinical features distinct from ARN. It was first described in 1990 in patients with acquired immunodeficiency syndrome (AIDS) (Forster et al. 1990). Clinically, it is characterized by multiple peripheral lesions in the outer retinal layer and with minimal or no inflammation in the aqueous and vitreous humor and no vascular inflammation, eventually progressing to full-thickness retinal necrosis and subsequent retinal detachment (Engstrom et al. 1994). PORN is also characterized by poor therapeutic responses to antiviral drugs due to immune dysfunction in the affected patients.

The prognosis of necrotizing retinopathies is poor in terms of visual acuity, even though treatment modalities such as antiviral therapy and vitrectomy have been established. Early diagnosis and treatment are essential to preserve vision because these conditions are rapidly exacerbated. Therefore, treatment is usually initiated before a definitive diagnosis is established through investigations for viral genes, which can be detected using polymerase chain reaction (PCR) (Sugita et al. 2013).

In the present chapter, we highlight the clinical features, diagnosis, and treatment of necrotizing retinopathies, including ARN and PORN.

Table 27.1 Clinical characteristics of acute retinal necrosis

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.	Evidence of occlusive vasculopathy with arterial involvement
5.	A prominent inflammatory reaction in the vitreous and anterior chamber

Etiopathology

ARN is caused by the members of *Herpesviridae* family, including herpes simplex virus (HSV) types 1 and 2 and varicella zoster virus (VZV). Primary infections by HSV and VZV are common in childhood, and these become latent in ganglion neurons. Although latent infections caused by these viruses are common, the precise mechanism underlying ARN development in healthy adults remains unclear. Some loci of the human leukocyte antigen class II have been associated with the development of ARN (Holland et al. 1989). Rochat et al. revealed some immune imbalance in ARN patients (Rochat et al. 1996), indicating that immune deficiency may be a cause for the onset of the disease. On the other hand, PORN is observed in immunocompromised host such as patients with AIDS, patients receiving immunosuppressive agents for autoimmune diseases or after organ transplantation, and patients receiving chemotherapy for malignant disease.

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Several techniques to diagnose the viral causes of ARN, such as antibody-based analysis of intraocular fluid or serum and viral culture, are available. In an electron microscopic analysis of retinal specimens from patients with ARN and PORN, viral particles morphologically consistent with VZV were detected in all layers of the affected retina (Duker and Blumenkranz 1991; Forster et al. 1990).

Of late, a PCR-based system has become available in the clinic for the detection of the genomes of various pathogens in a small volume of intraocular fluid. The sensitivity and specificity of this system for the detection of VZV and HSV in patients with herpetic retinitis are >95% (Wong et al. 2013). The Japanese ARN Study Group collated the clinical data of ARN patients with HSV-1, HSV-2, or VZV infection confirmed by the PCR system and has advocated a new diagnostic criterion of ARN (Takase et al. 2015). Moreover, quantitative PCR can be used to monitor the disease activity and evaluate the outcomes of treatment for ARN and PORN (Asano et al. 2004; Yin et al. 2007).

Clinical Features

Acute retinal necrosis (ARN): Patients with ARN initially complain of unilateral eye redness, ophthalmalgia, blurred vision, and/or vision loss. Ophthalmological examinations reveal acute unilateral iridocyclitis with granulomatous or fine keratic precipitates and, occasionally, folds in Descemet's membrane and/or posterior iris synechia in the anterior segment. The intraocular pressure is increased in 30% patients, although it returns to normal with a decrease in inflammation. In the posterior segment, vitreous opacity and multifocal, patchy, yellowish white lesions caused by inflammatory responses against VZV are observed in the peripheral retina (Fig. 27.1). With rapid progression of the disorder in the absence of antiviral therapy, the patchy lesions fuse and extend concentrically with occlusive periarteritis and necrotizing retinitis (Fig. 27.2). In the late stages of ARN, the necrotizing lesions in the retina become thin and atrophy. Then, vitreous traction and contractile membranes may be observed on the surface of the affected retina, leading to multifocal retinal breaks and subsequent RRD within a few months (Fig. 27.3).

In most cases, the optic nerve may be hyperemic and swollen because of optic neuropathy in the early stages

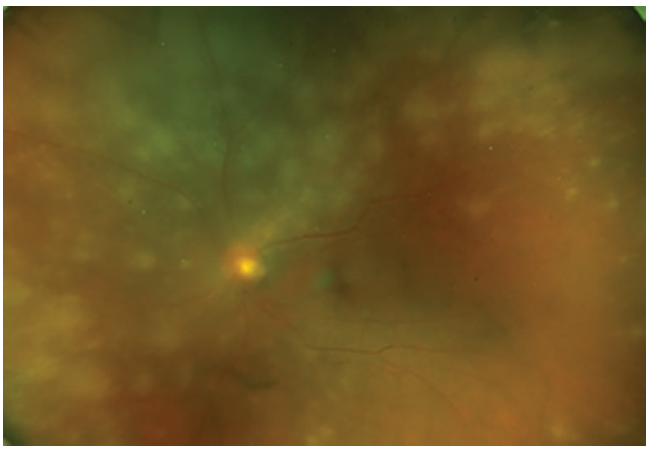

Fig. 27.1 Color fundus photograph showing multifocal, patchy, yellowish white lesions in the peripheral retina in a patient with acute retinal necrosis

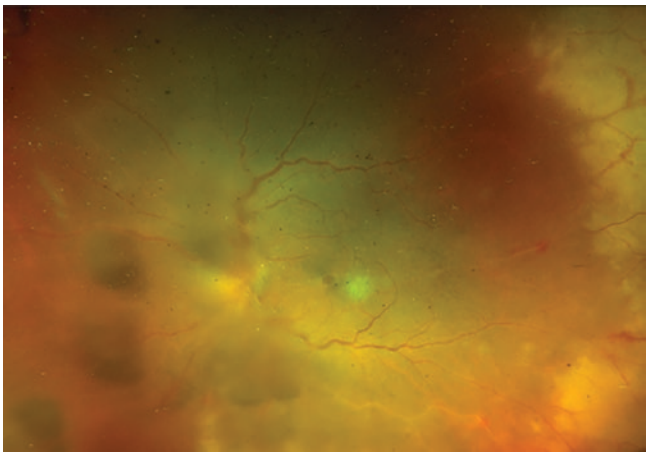

Fig. 27.2 Color fundus photograph showing fused yellowish white lesions with occlusive periarteritis and necrotizing retinitis in a patient with acute retinal necrosis

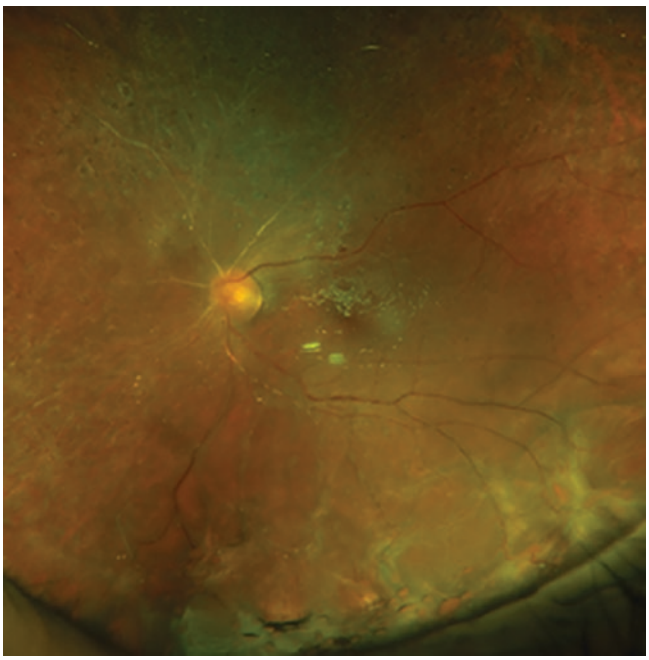

Fig. 27.3 Color fundus photograph showing rhegmatogenous retinal detachment with a retinal break in the lower peripheral retina with atrophic lesions in a patient with acute retinal necrosis

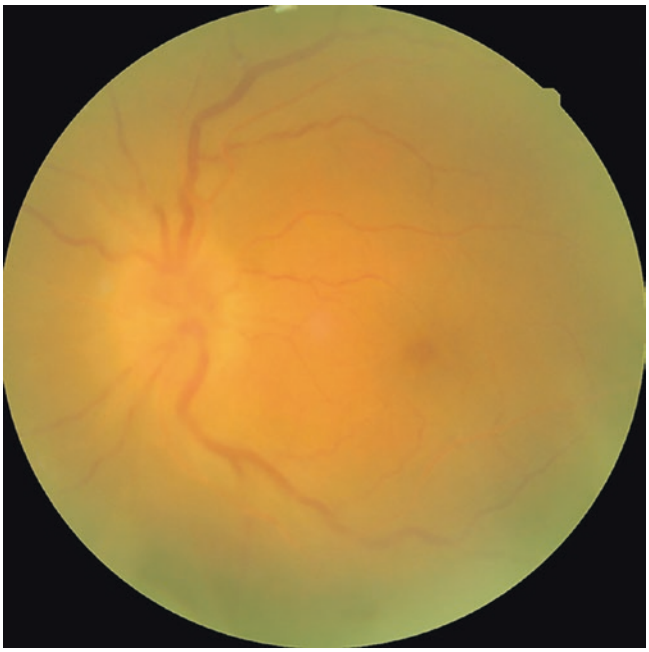

Fig. 27.4 Color fundus photograph showing optic nerve hyperemia and swelling and retinal artery occlusion around the optic nerve in patients with acute retinal necrosis

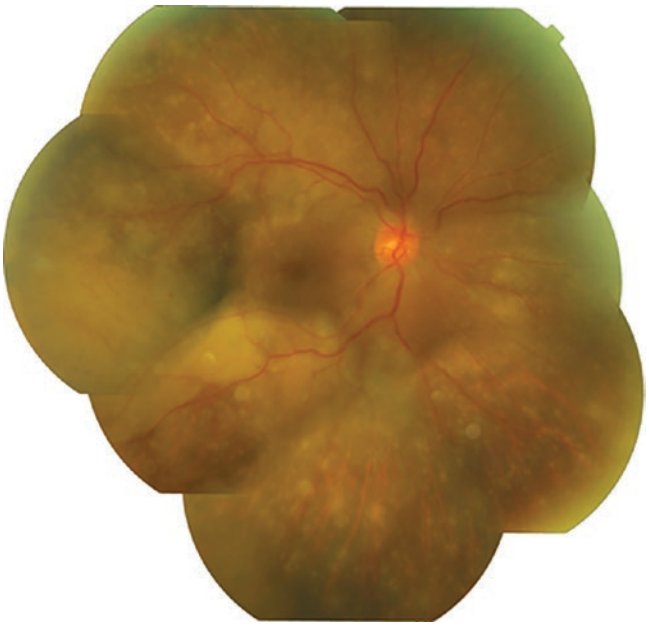

Fig. 27.5 Color fundus photograph showing optic nerve hyperemia and multifocal, patchy, yellowish white lesions without vasculitis and hemorrhage in the peripheral retina in a patient with progressive outer retinal necrosis

(Fig. 27.4), followed by atrophy in the late stages. Occlusion of the retinal arteries around the optic nerve is often observed. The extent of optic nerve damage is also considered as one of the most pivotal indicators of the prognosis of visual acuity (Iwahashi-Shima et al. 2013).

Finally, ARN can develop in the contralateral eye, usually within 6 weeks of onset in the affected eye, in approximately 30% patients; this can be prevented by timely antiviral therapy.

Progressive outer retinal necrosis (PORN): PORN is observed in immunocompromised hosts, such as patients with AIDS (CD4+ T-lymphocyte count $\leq 50/\mu L$) and patients with other conditions associated with immunosuppression. Symptoms include rapid and painless loss of central vision, floaters, and loss of peripheral vision. Ophthalmological examinations initially reveal multifocal, opaque, yellowish white lesions without granular borders, sometimes including areas of confluent opacifications, in the outer layer of the retina in the posterior pole or the periphery (Fig. 27.5) (Engstrom et al. 1994). There is no vasculitis, with minimal or no intraocular inflammation. However, vitritis and vasculitis have been reported to develop with an increase in the CD4+ T-lymphocyte count in patients with AIDS (Gore et al. 2012). Subsequently, the lesions rapidly spread through all retinal layers and progress in the macula, often leading to multifocal retinal breaks and subsequent RRD within several weeks. The visual outcomes are extremely poor despite available treatment options.

Fig. 27.6 Fluorescein angiography showing diffuse dye leakage in the peripheral necrotizing retina with vascular occlusion and staining in a patient with acute retinal necrosis

Fluorescein Angiography (FA) and Indocyanine Green Angiography (IA)

In patients with ARN and those with PORN, FA shows diffuse dye leakage in the peripheral necrotizing retina in the late phase (Figs. 27.6 and 27.7). Vascular occlusion and vascular staining are primarily obvious at the retinal artery with retinal arteritis in ARN patients (Fig. 27.8a). Vascular leakage from retinal vein is occasionally observed. IA shows vascular staining (Fig. 27.8b). On the other hand, FA does not show vascular occlusion and staining in patients with PORN (Fig. 27.7).

Optical Coherence Tomography for PORN

Optical coherence tomography shows perifoveal retinal thickening with decreased retinal reflectivity in the outer retina, which corresponds to macular edema in the initial stages (Fig. 27.9).

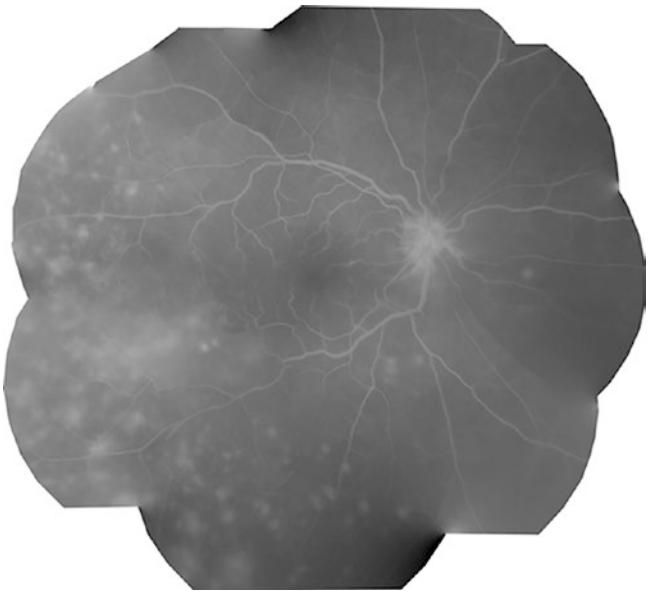

Fig. 27.7 Fluorescein angiography showing diffuse dye leakage in the peripheral necrotizing retina without vascular leakage and staining in a patient with progressive outer retinal necrosis

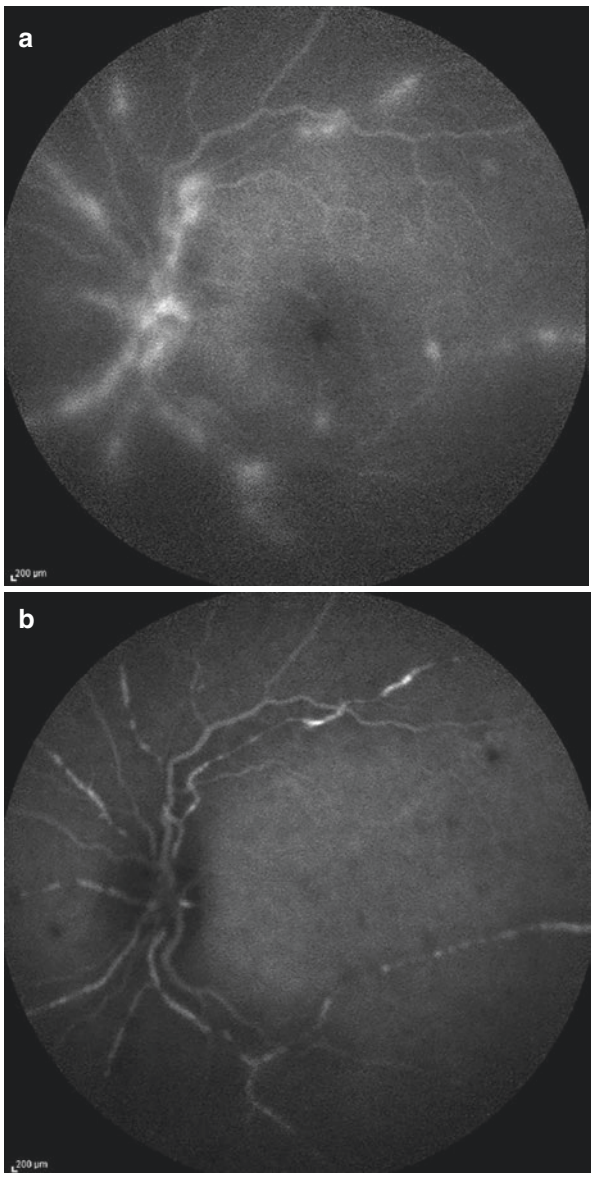

Fig. 27.8 Fluorescein (**a**) and indocyanine green (**b**) angiography show vascular occlusion and vascular staining for the retinal artery in a patient with acute retinal necrosis

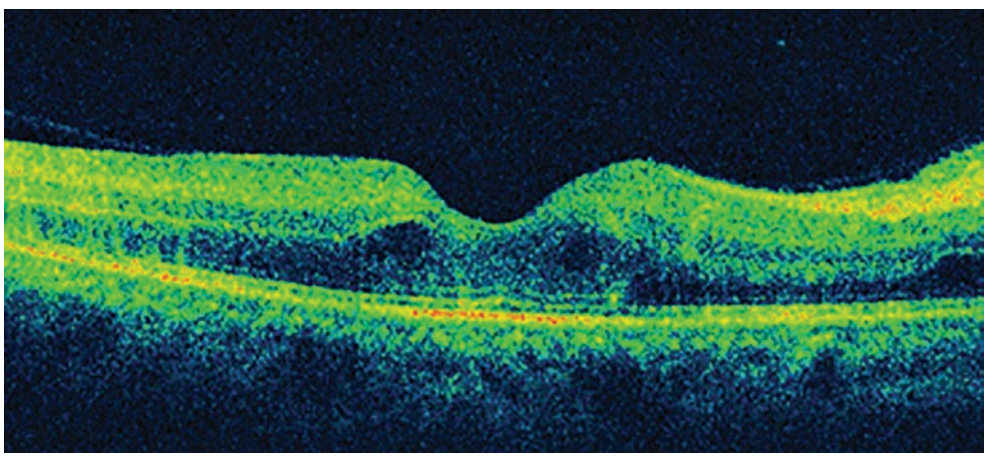

Fig. 27.9 Optical coherence tomography shows perifoveal retinal thickening with decreased retinal reflectivity in the outer retina, which corresponds to macular edema in a patient with progressive outer retinal necrosis

Management

Antiviral medication is crucial for the management of necrotizing retinopathies. In addition, a combination of vitreoretinal surgery such as vitrectomy or photocoagulation and antiviral therapy is required for the treatment of RRD in patients with ARN and PORN. Prophylactic laser photocoagulation or vitrectomy before RRD has been recommended for patients with ARN.

Medical Therapy

Antiviral drugs: Antiviral therapy is generally initiated before the confirmation of the diagnosis using PCR, because these conditions are rapidly exacerbated. Systemic administration of antiviral drugs can not only treat the affected eye but also prevent disease onset in the contralateral eye (Blumenkranz et al. 1986; Palay et al. 1991). Intravenous acyclovir is the standard initial antiviral agent for ARN, with an induction dose of 10 mg/kg three times a day for 7 days, followed by oral acyclovir 800 mg five times daily for 3–4 months (Wong et al. 2013). Because VZV often causes more severe manifestations and is less responsive to acyclovir, a higher doses of 15 mg/kg three times a day is recommended until the causative agent is detected (Kawaguchi et al. 2008). Valacyclovir, a prodrug to acyclovir, exhibits increased oral bioavailability compared with acyclovir and can be used instead of intravenous acyclovir in the induction phase.

However, the outcomes of intravenous acyclovir alone for the treatment of PORN are reportedly poor (Austin 2000). A combination of antiviral agents has been recommended for PORN because several studies have reported better outcomes with the combined treatment (Moorthy et al. 1997; Spaide et al. 1996) and the prevention of systemic adverse effects and the development of antiviral resistance (Jacobson et al. 1990). In addition, because responses to systemic administration of antiviral drugs are affected by the immune status in patients with PORN, immune recovery after highly active antiretroviral therapy can lead to safe discontinuation of antiviral therapy (Yin et al. 2007).

A combination of intravitreal injections of foscarnet (2.4 mg/0.1 mL per week) or ganciclovir (2 mg/0.1 mL two or three times a week) with systemic antiviral therapy has been reported to be successful for both ARN and PORN (Gore et al. 2012; Schoenberger et al. 2017; Wong et al. 2013).

Photocoagulation

With regard to ARN, several studies have reported that prophylactic laser photocoagulation of the normal retina at the margin of the necrotizing retinitis lesions is effective in preventing the onset of RRD (Cochrane et al. 2012; Lau et al. 2007; Meghpara et al. 2010; Sternberg et al. 1988). However, because of selection bias in these studies, the optimal strategy remains controversial (Schoenberger et al. 2017). With regard to PORN, laser photocoagulation has been reported ineffective in the prevention of RRD development (Engstrom et al. 1994).

Vitreoretinal Surgery

Vitrectomy combined with silicone oil tamponade and/or encircling scleral buckling is necessary to prevent the development of RRD. Prophylactic vitrectomy before the onset of RRD has been recommended for ARN patients, because the procedure can eliminate immune mediators and vitreous traction and allow for laser photocoagulation of the normal retina at the margin of the necrotizing retinitis lesion and silicone oil tamponade. However, because the anatomical outcomes and visual prognosis showed no differences between ARN patients who underwent prophylactic vitrectomy and those who did not, the usefulness of the procedure remains controversial (Hillenkamp et al. 2009; Iwahashi-Shima et al. 2013; Schoenberger et al. 2017).

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