Current Practices in Ophthalmology
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Uveitis

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Current Practices in Ophthalmology

Series Editor

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About the Editor

Phoebe Lin, MD, PhD completed her ophthalmology residency at the University of California San Francisco and a two-year fellowship in vitreoretinal surgery and disease at Duke University, where she was awarded a Heed Foundation fellowship and the Ron G. Michels fellowship. She then completed a one-year fellowship in uveitis and ocular inflammation at the Casey Eye Institute. Dr. Lin is currently an Associate Professor of Ophthalmology in the divisions of Retinal/Vitreous Diseases and Uveitis/Ocular Immunology at the Casey Eye Institute, where she participates in the education of surgical retina fellows, uveitis fellows, and ophthalmology residents, and also pursues independent research using animal models to identify novel therapeutic targets for uveitis. She has published over 70 peer-reviewed papers, book chapters, and other articles; is on the executive committee of the American Uveitis Society and the planning committee of the American Academy of Ophthalmology Uveitis subspecialty day meeting; and is an editor for the American Society of Retina Specialists publication, *Retina Times.*

Noninfectious Anterior Uveitis

1

Kristin Biggee

Introduction

Anterior uveitis encompasses a heterogenous group of disorders that can be divided into infectious versus noninfectious causes. It is defined anatomically by the Standardization of Uveitis Nomenclature (SUN) working group, as intraocular inflammation in which the predominant site of inflammation occurs in the anterior chamber. Anterior uveitis encompasses the previously used terms, including iritis, iridocyclitis, and anterior cyclitis. It can be further categorized based on degree of onset, duration, and course (Table 1.1) [1]. Further descriptors include laterality, inflammation of specific anterior segment structures, and/or the presence of granulomatous clinical entities. Categorization using the above terms can help clinicians determine different underlying diagnoses and treatment strategies.

Table 1.1 SUN working group descriptors of uveitis [1]

Category	Descriptor	Definition
Onset	Sudden	
	Insidious	
Duration	Limited	Less than 3-month duration
	Persistent	More than 3-month duration
Course	Acute	Episode includes sudden onset and limited duration
	Recurrent	Repeated episodes that are separated by 3 months or more of inactivity off treatment
	Chronic	Persistent uveitis with repeat episodes occurring within 3 months after discontinuing treatment

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Epidemiology and Demographics

Anterior uveitis has been reported as the most frequent anatomical subtype of uveitis among various groups and population studies [2–8]. Reports originating from tertiary care uveitis practices have calculated anterior uveitis in about 60% of cases, but are likely subject to referral bias, when compared to reports of up to 90% of cases found in community-based practices [2, 3]. Population studies conducted between 2004 and 2007 in Northern California, Hawaii, and the Veterans Affairs in the Pacific Northwest reported prevalence rates ranging from 54.5 to 81.7 per 100,000 persons [5–7]. A more recent study in 2012 looking at the prevalence of noninfectious uveitis among insurance claims from a large administrative database found that anterior uveitis accounted for 81% of adult cases (prevalence of 98 per 100,00 persons) and 75% of pediatric cases (22 per 100,000 persons) [8].

Females tend to have higher incidence and prevalence compared to males, but this can vary depending on underlying disease entity [5, 8]. For example, in human leukocyte antigen (HLA)-B27-associated anterior uveitis, which is the most common etiology of acute anterior uveitis, males are 2.5 times more likely to be affected than females [9]. Anterior uveitis can occur at any age, with more recent population studies finding peak rates in the elderly compared to earlier reports, which showed peak rates in middle age [4–8].

Clinical Findings and Complications

Common symptoms of anterior uveitis include ocular redness, pain, and photophobia. Blurred vision may be present depending on the degree of inflammation and possible associated complications. Patients may also be asymptomatic if there is a mild degree of inflammation or in certain underlying etiologies, such as some pediatric cases.

Findings on clinical examination include anterior chamber cells and flare. Anterior chamber cells and flare are graded on a level of 0 to 4+ based on the SUN working group grading scheme (Tables 1.2 and 1.3) [1]. There may be some retrolenticular cells in the anterior vitreous, although to a lesser extent compared to the anterior chamber. A hypopyon may be present and should be reported separately from cell grade. A fibrinous reaction may also occur in the anterior chamber, which sometimes causes a fibrin sheet to develop on the anterior lens capsule.

Keratic precipitates (KPs) can present on the corneal endothelium in various sizes, location, and degree of pigmentation (Fig. 1.1). Sizes vary between fine punctate KPs to larger white or tan mutton fat KPs, the latter being a clinical sign that has been used to categorize uveitis as granulomatous inflammation. Histopathology has shown accumulation of macrophages, lymphocytes, and plasma cells [10]. Due to the large variability in KP presentations, and debate whether the term

Table 1.2 SUN working group grading scheme for anterior chamber cells [1]

Grade	No. of cells per field of 1 mm × 1 mm slit beam
0	<1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

Table 1.3 SUN working group grading scheme for anterior chamber flare [1]

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens are clear)
3+	Marked (iris and lens are hazy)
4+	Intense (fibrin present)

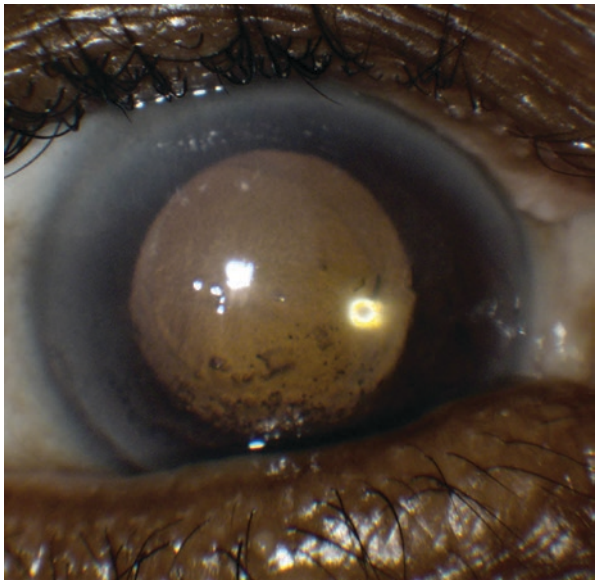

Fig. 1.1 Medium-sized pigmented keratic precipitates

granulomatous inflammation should be used without pathological confirmation, no consensus was reached in the SUN working group regarding KP description or their use in categorizing uveitis [1]. To date, there is no universally recognized standardization regarding their description.

The presence of iris nodules is another clinical sign that some use to categorize uveitis as granulomatous inflammation. Histopathology of nodules has shown collections of lymphocytic and plasma cells with areas of chronic granulomatous inflammation. However, not all iris nodules are necessarily true

granulomas [11]. Busacca nodules occur in the stroma, whereas Koeppe and Berlin nodules occur in the iris border and anterior chamber angle, respectively. In cases of noninfectious anterior uveitis, certain configurations of iris nodules may point to an underlying diagnosis such as sarcoidosis (granulomatous, irregular) or Fuchs' heterochromic uveitis (uniform, diffuse), as they have been reported in these conditions [12, 13].

Anterior uveitis can also present with associated endotheliitis or keratitis, causing corneal edema which is subtyped as a keratouveitis. Similar nomenclature can be used if there is associated anterior scleritis, subtyped as sclerouveitis.

Intraocular pressure is typically lower in noninfectious anterior uveitis, although ocular hypertension can occur as a complication from either steroid treatment or underlying uveitis. Ocular hypertension with an intraocular pressure over 21 was reported in 14.6% of noninfectious anterior uveitis cases in a recent large multicenter retrospective cohort study [14]. Mechanisms of uveitic ocular hypertension include possible associated trabeculitis or the accumulation of inflammatory cells and debris arising from other anterior segment structures blocking outflow of aqueous fluid in the trabecular meshwork.

Other complications arising in the anterior segment include posterior synechiae, peripheral anterior synechiae, and band keratopathy. Cataracts can occur as a complication of steroid treatment or underlying uveitis. If posterior synechiae or peripheral anterior synechiae reach 360°, then acute pupillary block glaucoma or acute secondary angle closure glaucoma can develop, respectively.

It is important to complete a dilated eye exam in all patients presenting with anterior uveitis to confirm the absence of inflammation in the vitreous or posterior segment and evaluate for associated complications. Posterior segment complications of anterior uveitis carry a risk for permanent vision loss and include cystoid macular edema, glaucoma, and hypotony maculopathy. Fig. 1.2 depicts some clinical signs of anterior uveitis and possible associated complications.

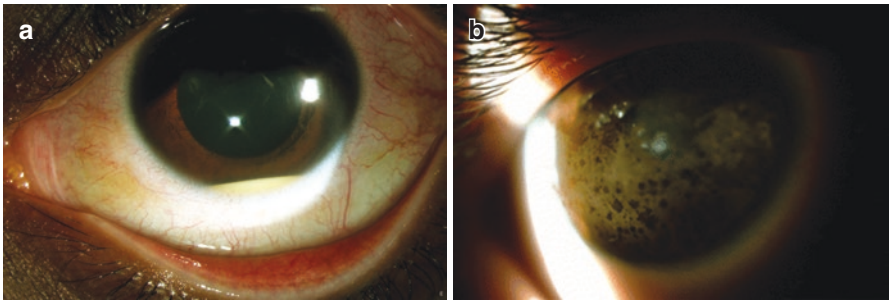

Fig. 1.2 (**a**) Hypopyon associated with drug-induced uveitis (Reproduced from Smith WM et al. [15]). (**b**) Band keratopathy associated with chronic uveitis (Reproduced without changes from Nascimento et al. [16]). (**c**) Posterior synechiae associated with recurrent anterior uveitis. (**d**) Cystoid macular edema associated with chronic anterior uveitis

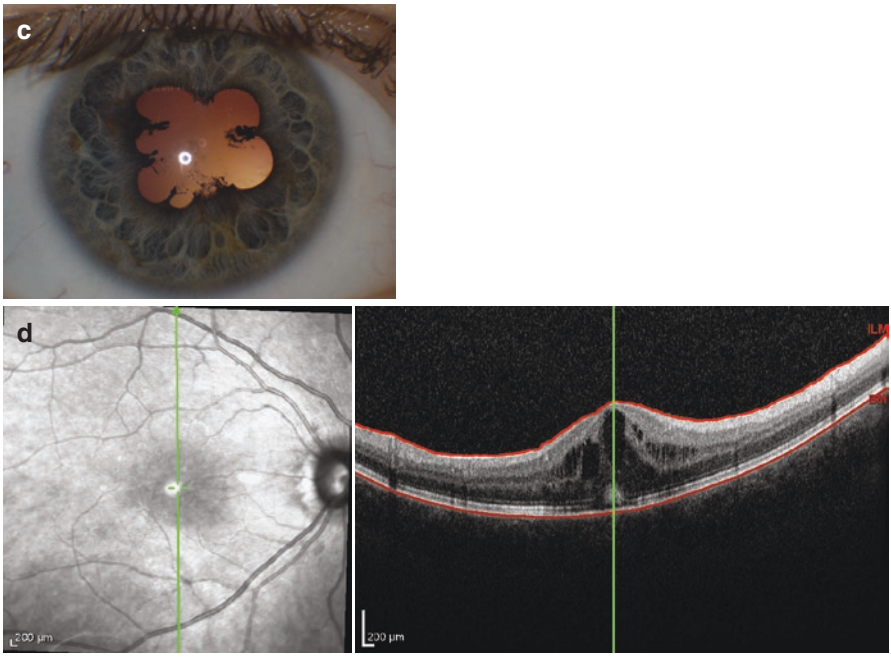

Fig. 1.2 (continued)

Differential Diagnosis and Workup

Anterior uveitis is most frequently noninfectious, as reported in 80% of cases in the Pacific Northwest Veterans Affairs Study and 90% of cases in a more recent claims-based analysis [6, 8]. All cases of anterior uveitis, however, should warrant investigation of possible infectious causes. Diagnostic testing for infectious causes should include at minimum a rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption test (FTA) or Treponema pallidum IgG test to screen for syphilis. Reverse serological testing for syphilis, starting with a treponemal test first, followed by reflex RPR titers is now recommended by the Centers for Disease Control. Tuberculin skin test with anergy panel (PPD) or serum quantiferon gold (QFG) should also be used to test for tuberculosis. Further details of ocular syphilis, tuberculous, and other infectious causes of uveitis are discussed in more detail in Chap. 2: Infectious Anterior Uveitis.

Noninfectious anterior uveitis can be further divided into idiopathic versus cases associated with systemic or known inflammatory causes. Idiopathic cases are predominant occurring in close to 90% of cases and considered a diagnosis of exclusion [8]. In the remaining minority of cases, associated systemic inflammatory causes include HLA B27-associated disease with or without seronegative spondylarthropathies, inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), tubular interstitial nephritis and uveitis (TINU), sarcoidosis, Behcet's

disease, Cogan syndrome, and Blau/Jabs syndrome, drug-induced uveitis, and occasionally, multiple sclerosis can present with anterior uveitis alone.

A complete medical history and thorough review of symptoms can alert providers to possible systemic associations. In rare cases, masquerade syndromes such as lymphoma, leukemia, or tumor can present with what appears to be an anterior uveitis [14, 17–20]. In the absence of infection, the presence of a hypopyon (Figure 1.2**a**) raises suspicion for possible HLA B27-associated disease, Behcet's disease, drug-induced uveitis, or masquerade syndromes [21–25].

As ocular sarcoidosis presents with anterior uveitis in close to 40% of cases, a chest radiograph (CXR) can be considered to further investigate for the disease. Ocular sarcoidosis most commonly presents bilaterally and has a high association with granulomatous KP and/or iris nodules. However, it has been associated with all subtypes of anterior uveitis. If suspicion is high for sarcoidosis, based on clinical history or ocular presentation, then a chest computed tomography scan (Chest CT), gallium scan, serum ACE level, or pulmonary function tests (PFTs) can also be considered. Biopsy of the lung, skin, or enlarged lymph nodes may result in a definitive diagnosis [26].

Other causes of anterior uveitis include trauma, ocular surgery, and lens-induced uveitis. Fuchs' heterochromic iridocyclitis and Posner-Schlossman are other ocular conditions usually associated with a variable degree of inflammation. Both conditions were previously categorized under noninfectious causes, but studies now show an underlying viral etiology (refer to Chap. 2) [27–29]. Fig. 1.3

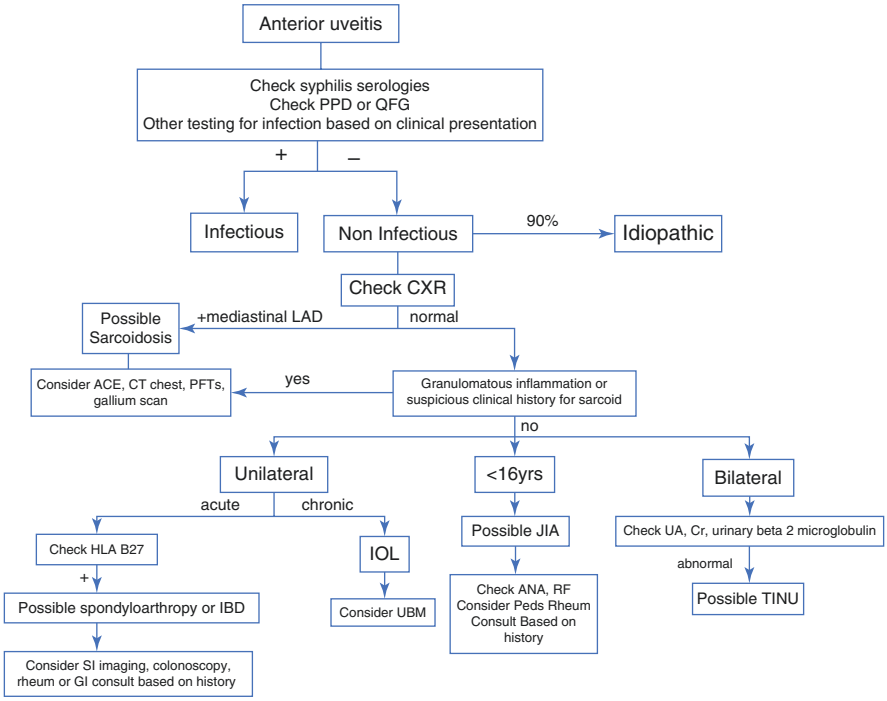

Fig. 1.3 Algorithm for workup of differential diagnosis in anterior uveitis

depicts a proposed algorithm for the workup and generation of a differential diagnoses for anterior uveitis.

HLA B27

HLA B27 is the most common systemic inflammatory association in noninfectious anterior uveitis, accounting for 50% of acute cases in an early landmark study [29]. More recent studies across variable racial groups report an association in 25–60% of anterior uveitis [21]. HLA B27 is a protein (antigen) located on cell surfaces that is present in approximately 8% of Caucasian populations and 1–5% of African, Arab, and Asian populations. Although there is a higher prevalence of HLA B27-associated anterior uveitis among Caucasian populations, it remains a common cause of anterior uveitis among all racial groups [21, 30].

HLA B27-associated uveitis typically presents with a sudden onset of unilateral anterior uveitis that is limited, lasting several weeks. It can be recurrent, sometimes alternating eyes, but rarely occurs simultaneously in both eyes. Hypopyon, fibrin, and synechiae formation are common [21, 30, 31]. Despite an often robust inflammatory response, prognosis is good, with a recent series reporting visual impairment in less than 5% [21].

The majority of individuals who are HLA B27 positive do not develop inflammatory conditions; however, a small percentage of individuals can develop seronegative spondylarthropathies, which include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease. A more recent classification system divides these diseases into axial and nonaxial disease [32]. Among cases of HLA B27-positive anterior uveitis, 50–70% can have associated seronegative spondyloarthropathy, and these patients are often unaware of this diagnosis [21, 30, 33].

Axial spondyloarthropathy causes inflammatory back pain due to sacroiliitis that is typically worse in the morning and improves with activity, and it is classically associated with ankylosing spondylitis. Around 90% of patients with ankylosing spondylitis are HLA-B27 positive [34]. Radiographs or MRI imaging of the sacroiliac joint can aid in the diagnosis. If left untreated, it may lead to significant spinal deformity. Associated peripheral arthritis or Achilles tendinitis can also be present [32–34]. Severe cases are infrequent, but can present with pulmonary fibrosis or cardiac dysfunction [35, 36].

Classic symptoms of reactive arthritis include arthritis, urethritis, and conjunctivitis or uveitis that is usually preceded by an initiating systemic infection within 4 weeks of symptoms. Other symptoms can include circinate balanitis, keratoderma blennorhagicum, sacroiliitis, nail pitting, enthesopathy, and oral ulcers [34, 37]. Seventy percent of patients are HLA B27 positive [34].

Symptoms of psoriatic arthritis include psoriasis and arthritis, often characterized by “sausage-like digits.” Nail changes are also common. Sixty to seventy percent of patients are HLA B27 positive. Inflammatory bowel disease is associated with HLA B27 in up to 70% of cases [34]. Compared to ankylosing spondylitis and reactive arthritis, anterior uveitis associated with psoriatic arthritis and inflammatory bowel disease is more likely to be bilateral and chronic and have an insidious onset [38].

Pediatric Noninfectious Anterior Uveitis

Although pediatric cases account for a small portion of noninfectious anterior uveitis and will also be covered in Chap. 9, it can carry a high risk of ocular complications and visual impairment. Many cases present without symptoms and a white appearing conjunctiva, resulting in delayed treatment. Ocular complications such as band keratopathy or cataract can often be present at the time of diagnosis [39].

The majority of cases are idiopathic; however, 30% have been associated with juvenile idiopathic arthritis (JIA), which includes a heterogenous group of chronic childhood arthropathies [8]. The most typical JIA-associated uveitis presents as a chronic bilateral anterior uveitis with insidious onset. It most commonly occurs in females with ANA positivity, RF negativity, and oligoarticular arthritis, with uveitis occurring in up to 30% of this subtype [39].

Anterior uveitis can also occur in other JIA subtypes. In the HLA B27-associated enthesitis or psoriatic arthritis subtypes, male gender and unilateral red painful eye are more common presentations [39]. Guidelines for uveitis screening in patients with JIA include ophthalmologic examinations every 3 months in high-risk subtypes who are less than 7 years old (i.e., ANA+, oligoarticular disease) and 6–12 months in other subtypes (see Chap. 9) [40].

Tubular interstitial nephritis and uveitis (TINU) is a rare cause of uveitis that most commonly occurs in adolescents and young females [41]. However, it has been reported among a variety of ages including older adults [42]. It typically presents with a bilateral anterior uveitis, but it can present with a variety of ocular manifestations. Clinical features include low-grade hematuria or proteinuria, elevated serum creatinine, and elevated urinary beta 2 microglobulin. The diagnosis can also be determined by kidney biopsy showing acute interstitial nephritis. Kidney and eye disease often progress independently [42].

Lens-Induced Uveitis

Lens-induced anterior uveitis includes phacoantigenic, phacolytic, and intraocular lens-related uveitis. Phacoantigenic uveitis comprises a zonal granulomatous response to lens proteins in the setting of a ruptured or compromised anterior capsule that is often associated with trauma. The inflammatory response is usually robust causing an acute red painful eye. Posterior synechiae and KP are also common [43].

Phacolytic uveitis involves a nongranulomatous inflammation that occurs in eyes with hypermature cataracts, in response to lens proteins leaking through an intact anterior capsule. On histopathology, lens-filled macrophages can be seen clogging the trabecular meshwork. In contrast to phacoantigenic uveitis, phacolytic uveitis typically does not present with KP [44]. In both phacoantigenic and phacolytic uveitis, definitive treatment includes lens removal.

Intraocular lens (IOL)-related uveitis includes uveitis–glaucoma–hyphema syndrome, which involves a nongranulomatous inflammation and presents with a

chronic or intermittent anterior uveitis. It results from an intraocular lens rubbing on the iris or ciliary body and can occur weeks to years after surgery. Anterior segment manifestations can include a mixture of white and red blood cells, hyphema, iris transillumination defects, pigment dispersion, a malpositioned or subluxed IOL, and/or elevated intraocular pressure [45]. It most commonly occurs in anterior or sulcus-positioned IOLs, but it has been reported in other scleral sutured or more posteriorly placed IOLs as well [46]. Definitive treatment includes removal or repositioning of the IOL.

Postsurgical inflammation should also be considered in pseudophakic eyes with chronic anterior uveitis. Inflammation may be prolonged in longer cases or those associated with iris manipulation or retained lens cortex [47, 48]. Anterior segment OCT or ultrasound biomicroscopy is useful to differentiate IOL-related causes. Definitive treatment may include removal of retained cortex. Also to keep in mind are indolent postoperative infectious processes such as due to *Propionibacterium acnes*.

Drug-Induced Uveitis

Drug-induced uveitis is a rare cause of anterior uveitis. Systemic and topical medications with strong evidence of association with anterior uveitis are listed in Table 1.4 [49, 50]. Reports of anterior uveitis associated with emerging metastatic melanoma immunotherapy treatments are also surfacing. Cases have been reported with the use of protein kinase inhibitors, such as dabrafenib, trametinib, and other immune checkpoint inhibitors, such as nivolumab, ipilimumab, and pembrolizumab [51–54]. A complete list of drugs reported in association with uveitis can be found at www.eyedrugregistry.com.

Pathophysiology

As noninfectious anterior uveitis is associated with a wide range of clinical manifestations and systemic associations, emerging knowledge regarding its pathogenesis is also heterogenous and likely multifaceted. Although the association between the HLA B27 and uveitis was discovered in 1972, its exact role in triggering an inflammatory response is still largely unknown. Theories exist regarding possible infectious triggers causing molecular mimicry, with self-peptides being identified in patients with ankylosing spondylitis [55]. Bacille Calmette–Guerin (BCG) is a known bacterial trigger for uveitis and reactive arthritis. In animal studies, BCG-injected rodents have developed subsequent spondyloarthritis, urethritis, and uveitis [30].

Associations with the gut microbiome is an emerging area of interest, as many cases of uveitis or reactive arthritis follow gram-negative bacillus gastroenteritis [56, 57]. Animal studies have now shown that HLAB27 does affect the gut microbiome in rodents [58]. Theories exist regarding possible increased gut permeability to bacterial antigens that could trigger inflammation either from direct antigenic

Table 1.4 Drugs with strong evidence of association with anterior uveitis [49, 50]

Route	Agent	Comments
Systemic	Rifabutin Cidofovir Bisphosphonates Sulfonamides Fluoroquinolones	
	Diethylcarbamazine	Antifilarial used to treat onchocerciasis
	Flubiprofen	Associated with TINU
	Chinese herb "Goreisan"	Associated with TINU
Topical	Metipranolol Brimonidine Prostaglandin analogues Cholinomimetics Antibiotics	
	Corticosteroids	Occurs upon withdrawal of drug in otherwise noninflamed eye, especially dexamethasone
Intraocular	Antibiotics Cidofovir Urokinase Plasmin/microplasmin Bevacizumab Ranibizumab Aflibercept Pegaptanib	
	Triamcinolone acetonide	Primarily due to incipients in certain formulations
Vaccine	Bacille Calmette–Guerin Influenza Hepatitis B	

exposure in ocular tissue or predispose to molecular mimicry or other alterations in the immune repertoire or response [59]. Other genes have also been associated with HLA B27 anterior uveitis, some affecting T-cell responses [30], which supports the notion of multiple factors likely at play.

Strides have also been made in identifying specific genetic and immune markers in other systemic diseases associated with noninfectious anterior uveitis. Sarcoidosis has been shown to involve a predominately CD4+ T lymphocyte-mediated process [60]. Behcet's disease has been associated with the HLA B51 haplotype and been shown to involve both T cells and neutrophils [61]. Sarcoidosis and Behcet's have both been associated with higher levels of interleukin 2 and interferon gamma [62]. JIA has been associated with several genes, and JIA with uveitis has been associated with HLA-A(∗)02:06 in a Japanese cohort [63, 64]. Inflammation involves a both T-cell and B-cell responses with high concentrations of tumor necrosis factor alpha, interleukin 6, and interleukin-1.

Treatment

The mainstay of treatment for noninfectious anterior uveitis includes topical steroids. Prednisolone acetate 1% is a common first-line agent, as it achieves and maintains a higher aqueous concentration, compared to topical dexamethasone and prednisolone phosphate. Lower potency topical steroids such at fluorometholone and loteprednol are considered ineffective in the treatment or prevention of anterior uveitis given their very low levels of absorption into the anterior chamber [65]. Topical steroid frequency should be dosed and subsequently tapered based on the level of anterior chamber cell and flare. Complications from ocular steroid treatment include elevated intraocular pressure, glaucoma, cataract, and increased risk of infection.

Difluprednate 0.05% is a higher potency topical steroid with greater levels of aqueous concentration compared to prednisolone acetate 1%. Two multicenter randomized controlled trials found topical difluprednate 0.05% to be noninferior to twice as frequent topical prednisolone acetate 1% in the treatment of noninfectious anterior uveitis. Pooled analysis from both studies showed a trend toward lower inflammation levels and better efficacy with difluprednate 0.05% versus prednisolone acetate 1%. However, difluprednate 0.05% carried a higher incidence of intraocular pressure increase [66]. Additional studies are needed to determine the difference of longer term safety profiles between the two drops regarding glaucoma and cataract formation risks.

Periocular steroid injections with dexamethasone or triamcinolone via a subconjunctival or subtenon approach have also been used in the treatment of anterior uveitis and achieve a higher aqueous concentration compared to prednisolone acetate 1% [65]. Subtenon injections can be given using 40 mg (1 ml/mg) of triamcinolone through either a superior or inferior transconjunctival approach or inferior transcutaneous approach. As both difluprednate 0.05% and periocular triamcinolone injections have higher potency with presumed higher risk of complications, their use is typically reserved for cases of recalcitrant severe anterior uveitis or those associated with cystoid macular edema that is not responding to frequent topical prednisolone acetate 1%.

Systemic steroids such as prednisone have also been used in cases of anterior uveitis. Due to frequently encountered systemic side effects, their use is typically reserved for short-term use in cases of bilateral severe or recalcitrant anterior uveitis. Their short-term use can also be considered in uveitis associated with steroid responsive glaucoma, as oral steroids carry less risk of intraocular pressure elevation compared to local therapy [14].

Topical cycloplegics are also used in the treatment of anterior uveitis to prevent or break posterior synechiae and peripheral anterior synechiae. They can also help alleviate photophobia by restricting iris/ciliary body movement in an acutely inflamed eye. Commonly used cycloplegics in order of decreasing potency include atropine, homatropine, and cyclopentolate.

Due to the risk of complications from steroid treatments, systemic steroid-sparing therapy should be considered in severe chronic or recurrent anterior uveitis,

in the development of intolerance or failure of steroid treatment [67], or when there are posterior complications such as cystoid macular edema affecting vision. The presence of bilateral disease may also be an indicator to consider steroid-sparing therapy.

In our group, indications for referral to a uveitis specialist for consideration of steroid-sparing therapy include the following:

- 1 or more episodes of severe uveitis per year
- 3 or more episodes of recurrent uveitis per year
- Persistent chronic anterior uveitis with grade 1 or higher anterior chamber cell that is unable to be improved with twice-daily prednisolone acetate 1% or less

Several studies have shown efficacy of steroid-sparing immunosuppressive therapy in anterior uveitis with the antimetabolites methotrexate, mycophenolate mofetil, and azathioprine, as well as the tumor necrosis factor (TNF)-alpha inhibitors infliximab and adalimumab. Reports of efficacy are also emerging among more novel biologic therapies, such as golimumab, anakinra, daclizumab, and tocilizumab. Rituximab and interferon alpha 2a have also shown treatment benefit in some cases [67]. Patients should be followed by a provider familiar with these medications, such as a uveitis specialist or rheumatologist, due to systemic risks of toxicity and the need for regular laboratory and clinical monitoring.

In HLA B27-associated cases, sulfasalazine is an anti-inflammatory agent that has also been shown to reduce frequency and severity of recurrent anterior uveitis and may be considered prior to the above immunosuppressive therapies [68, 69]. Sulfasalazine is dosed at 1000 mg orally twice daily. Patients should be counseled regarding risks of rash, serious allergic reactions, gastrointestinal upset, aplastic anemia, and liver, kidney changes. Laboratory monitoring should include baseline complete blood panel and comprehensive metabolic panel and should be repeated every 3 months. If sulfasalazine proves ineffective or patients are at high risk for visual impairment, TNF-alpha inhibitors such as infliximab or adalimumab have shown particular efficacy against HLA B27-associated diseases and could be considered over antimetabolites in this subtype [67].

In the absence of HLA B27-associated disease, antimetabolites are usually the first-line agents for steroid-sparing therapy in anterior uveitis. If one antimetabolite proves ineffective or a patient develops intolerance, then they can be switched to a different antimetabolite agent. Methotrexate has shown good efficacy against ocular and systemic sarcoidosis. Due to its known safety history in children, it is also often chosen to treat pediatric cases. Azathioprine is often chosen in Behcet's-associated uveitis, as there is a randomized placebo-controlled study demonstrating its efficacy in this disease entity [70]. Studies comparing efficacies of methotrexate, mycophenolate mofetil, and azathioprine in uveitis show no significant differences. However, higher rates of side effects and intolerances have been reported with azathioprine [67]. Patients taking methotrexate or mycophenolate should be counseled regarding the risk of fetal toxicities. Alcohol consumption should be avoided in methotrexate due to its higher risk of liver toxicity compared to other antimetabolites.

If antimetabolites prove ineffective, then TNF-alpha inhibitors such as infliximab and adalimumab can be used solely or in combination with antimetabolite agents. Patients should be counseled regarding risks of serious systemic infections, serious allergic reactions, anemia, and possible increased malignancy risks such as lymphoma. Lesser studies exist in other biologic agents. Tocilizumab is an interleukin 6 inhibitor whose efficacy in refractory anterior uveitis has been reported in cases associated with macular edema, Behcet's, and JIA and may prove to be another alternative treatment choice in these subtypes [71, 72].

Other agents such as T-cell inhibitors (i.e., cyclosporine, tacrolimus) and alkylating drugs (i.e., cyclophosphamide) also have reported efficacy against anterior uveitis used solely or in combination with antimetabolite drugs [67]. However, due to their associated systemic risks and toxicities and the relative safety and tolerability of biologic agents, their use in anterior uveitis has diminished.

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Infectious Anterior Uveitis

2

K. Matthew McKay and Nicholas J. Butler

Introduction

As with all forms of intraocular inflammation, the vast majority of patients with anterior uveitis (AU) have an underlying autoimmune or autoinflammatory predisposition. However, an important minority of patients presenting with AU will have an undisclosed infection, either localized to the eye(s) or the sequela of hematogenous spread of systemic infection. Differentiating infectious from immunological causes of uveitis is of utmost importance, given the significant differences in the approach to treatment. More so, corticosteroid therapy, especially peri- or intraocular steroid injections, without concomitant and appropriate antimicrobials may lead to disastrous outcomes in infectious uveitis. History, exam findings, the immune function of the host, and geography are all important elements in determining the risk for various pathogens. In the following discussion, we review the epidemiological considerations, diagnostic approach, and important etiologies and treatments of infectious AU.

Epidemiology and Demographics

AU is the most commonly encountered subtype of intraocular inflammation globally [1–3]. Among epidemiological surveys with sufficient detail to classify AU by etiology, the point prevalence of AU observed among consecutively referred patients

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ranges from 35 to 60%, and 7–34% of these cases have an associated infection [4–12]. Undoubtedly, this underestimates the true prevalence of infectious AU, as each of these studies determined that a majority, or significant minority, of AU eluded classification (i.e., undifferentiated, formerly idiopathic, in 30–74%). As molecular and other diagnostic techniques improve and become more widely available, it is probable that an infectious origin will be discoverable in a significant percentage of these as yet undifferentiated AU patients.

Given the high degree of variability in seroprevalence and risk for a given infection based on geographical, socioeconomic, demographical, and other determinants, the ubiquity of herpes viruses as the major cause of infectious AU worldwide seemingly defies the odds. In fact, herpes viruses are implicated in 50–100% of all new referrals with AU in whom an infectious cause is identified, irrespective of the continent of origin of the patient [4–12]. When further classified, herpes simplex virus (HSV)- and varicella zoster virus (VZV)-associated AU far outnumber that for other *herpesviridae*, namely cytomegalovirus (CMV) [4, 5]. The influence of geography and other demographical considerations are more apparent for AU associated with *Mycobacterium tuberculosis* (TB), the second most common infectious association in most studies, ranging from 0 to 38%. Ocular TB with isolated AU was seen in 0% of new referrals in Germany [7] and North Africa [8], 8% in Spain [4], 12% in Australia [6], and between 18 and 38% in surveys from Asia [5] and the Middle East [9–11]. Other important ocular pathogens are reported as a cause of infectious AU only sporadically, namely syphilis in 2–12% [4–6], Lyme disease in 9% from a single study in an endemic area of Germany [7], and leprosy in 2% from a tertiary eye institute in Singapore [5].

Over the past 10–15 years, we have come to understand that two important causes of AU, namely Fuchs uveitis syndrome (FUS) and glaucomatocyclitic crisis (GCC), also known as Posner-Schlossman syndrome (PSS), have an infectious etiology in the vast majority of cases. Specifically, rubella virus (RV) has been strongly associated with FUS, through isolation of the viral genome with polymerase chain reaction (PCR) and/or detection of specific antibody production against rubella in aqueous samples from patients with the clinical phenotype [13, 14]. In the United States, FUS has become less common since the implementation of the rubella vaccination program in 1969, though globally it remains an important cause of infectious AU [15]. For GCC, CMV has been most implicated, though other herpes viruses may have a lesser role [16, 17]. Considering then that the majority, if not all, of FUS and GCC represent active viral intraocular infection, the proportion of infectious AU cases increases to 8–45% of all AU referrals worldwide [4–12]. Generally speaking, the proportion of herpetic AU far exceeds that of FUS, which accounts for 0–19% of infectious AU in most series [4–6, 8, 11, 12]. However, in studies from Germany [7] and Iran [10], the proportion of infectious AU attributable to FUS significantly exceeds that of herpetic AU, at 52% and 63%, respectively, while in Turkey [9], the proportion of FUS is comparable to herpetic AU (42% vs. 47% of all infectious AU). Fewer patients with infectious AU are classified as having GCC or PSS, accounting for 0–16% of all infectious AU [4–12]. Predictably, the percentage of PSS is highest in Singapore, reflecting the high seroprevalence for CMV in this region [5].

Less is known regarding the demographics of infectious AU patients. Infectious AU disproportionately affects an older population as compared to undifferentiated or immune-mediated AU (median age: 60 years vs. 45 years) [5], which appears in large part to stem from the contribution of herpetic AU [3, 4, 7, 10]. There are conflicting data regarding the influence of gender on infectious AU. Bajwa et al. [12] found a threefold risk of herpetic AU in females as compared to males in multivariate analysis [odds ratio: 3.03, 95% CI (1.32, 7.71)], while others have found that male gender may be a risk factor for this disease [11]. For FUS, there is more agreement that men are disproportionately affected [7, 11]. Regarding racial differences, at least one group found herpetic AU to be nearly eightfold more common among Caucasians as compared to African Americans [12].

Diagnostic Approach

As with all ocular inflammatory disease, the workup of a patient with infectious AU starts with a meticulous history and examination. Keeping in mind the above epidemiological and demographical considerations, a ranking of pretest probabilities for various infectious etiologies can be formulated. Since herpetic AU predominates regardless of geography, inquiring about a history of cold sores, vesicular rashes, and/or history of shingles is critical and may raise or lower one's suspicion. For other possible pathogens, geographic variance of distribution carries much more weight. For instance, chikungunya virus-associated AU, while not reported in North America, has increasing relevance in India [18–21] and, less so, Brazil [22]. The likelihood would increase further if the patient has a recent history of fever and arthralgia. Other ubiquitous pathogens, like syphilis and TB, should always be considered in the differential diagnosis, and exposure history (unprotected sex or men who have sex with men for syphilis and migration from an endemic area and/or contact with homeless, imprisoned, or hospitalized individuals for TB) may similarly raise or lower pretest probabilities. Lyme disease also has a highly variable distribution of endemicity worldwide, being highest in North America, Europe, Australia, and parts of Asia [23]. Given the high rates of serological false positives, a detailed history regarding tick bites or exposures and/or symptoms concerning for systemic Lyme infection (erythema chronicum migrans rash, myocarditis, cranial neuropathies, arthritis, neurological disease) should be elicited [24]. Though atypical for syphilis, TB, or Lyme disease to cause an isolated AU, all are known for their protean manifestations. These select infectious etiologies, by no means exhaustive, illustrate the application of historical elements—geography, contacts, exposures, and other risk factors—in considering the role of specific pathogens in any new patient with AU. Regarding examination findings, any patient with unilateral acute, recurrent, or chronic AU associated with ocular hypertension should have an extensive search for an infectious etiology. Most, if not all, of these patients should undergo ocular fluid analysis, if they fail to respond to an empiric trial of appropriate antiviral therapy and topical steroid. A more detailed review of specific examination findings associated with various pathogens is presented in the etiology section of this chapter.

The next steps for investigating a patient for infectious causes of AU occur in the clinic with ancillary testing. Of the various modalities available to the clinician, in vivo confocal microscopy (IVCM) may provide the most valuable information. Wertheim et al. [25] provided the initial data on the diagnostic potential for IVCM in 33 prospectively enrolled uveitis patients (42 eyes), by imaging keratic precipitates (KPs). They found that, in comparison to slit lamp biomicroscopy, the IVCM morphologies of KP are far more heterogeneous than previously understood; more so, a distinctive classification of IVCM findings may differentiate infectious uveitis ("infiltrating" and/or "dendritiform" KP) from noninfectious ("smooth-rounded" and/or "globular" KP) causes. Others have subsequently repeated this work, finding infectious uveitis most commonly associated with KP having the following IVCM descriptors: "infiltrative," "infiltrating," "dendritiform," and "dendritic" [26–29]. Conversely, the IVCM characteristics of noninfectious KP were "globular," "multiple globular," "stippled," and "smooth-rounded" [27, 29], in keeping with the original study [25]. Underscoring the potential usefulness of this technology, the sensitivity, specificity, and positive predictive value of IVCM in identifying infectious uveitis have been estimated at 84%, 93%, and 97%, respectively [27]. The high degree of subjectivity in the interpretation of these images may introduce a lack of uniformity and confound the results, though investigators have determined that masked graders can be highly concordant, with an average Kappa value of 0.81 [28].

Looking at specific uveitic entities, investigators in Turkey found that 86% of FUS eyes had "dendritiform" KP with IVCM images taken during an active period [26]. This pattern in FUS patients appears to be highly consistent irrespective of treatment or disease duration, as found in a series of 13 consecutive FUS patients from France [30]. These patients had infiltrating KP with dendritic form when imaged with confocal, further described as a central hyperreflective core with branching pseudopodia which occasionally made connections to adjacent KP. Others have found similar findings for FUS patients from various geographic regions [29, 31]. In one series of 40 eyes with FUS, "dendritiform" KPs were the primary confocal morphology in 85% of eyes and primary or secondary morphology in 97.5% of eyes [31]. They further found that FUS patients have significantly more endothelial cell loss compared to age-matched controls. At least one study of FUS patients found somewhat less consistency in the morphology of KP with IVCM, noting "globular" pattern in 34 eyes, "dendritiform" in 31 eyes, "infiltrating" in 31 eyes, "stippled" in 27 eyes, and "cruciform" in 19 eyes [32]. Notably, even in this series with more variance, "dendritiform" and "infiltrating" predominate when grouped together. In looking at all of these studies, the close agreement between the IVCM findings of KP associated with FUS and infectious uveitis in general provides further support for an infectious etiology in FUS.

A final diagnostic application for IVCM in infectious AU may have enough specificity to obviate ocular fluid analysis in some cases. In patients with PCR-proven CMV endotheliitis with or without active AU, the pathognomonic histology finding of CMV-infected cells, namely "owl's eyes," has been demonstrated with IVCM imaging of KP, usually in regions of coin-shaped configuration [33–35]. These are

swollen endothelial cells with highly reflective nuclei and a surrounding halo of low reflectivity, as imaged with confocal. The over-sized nuclei stem from intranuclear viral inclusion bodies in actively infected cells, a finding that has high specificity but low sensitivity for CMV infection [36]. With IVCM images of the cornea, however, the sensitivity of this finding may be markedly increased, as the images can be directed exactly to the site of pathology (cluster of KP arranged in a circle, i.e., "coin-shaped"). Indeed, in a consecutive series of six patients with CMV endotheliitis, investigators demonstrated owl's eye endothelial cell morphology with IVCM in 100% of cases [34]. Importantly, these features disappear with treatment, implying that confocal, in addition to providing diagnostic information, is useful for making management decisions in CMV-associated AU and endotheliitis, potentially indicating when antivirals may be successfully suspended [34].

Employing anterior segment spectral domain optical coherence tomography (AS-sdOCT), investigators have identified increased reflectivity of the posterior corneal stroma and endothelium, along with irregular thickening of the endothelium, in patients with CMV endotheliitis [35, 37]. These features normalize with proper therapy. The hyperreflectivity, though, persists for some time even after clinical findings (corneal edema, KP, anterior chamber inflammation) have resolved, supporting a role for AS-sdOCT in disease monitoring and determining the need for ongoing therapy [35, 37]. Recently, Rose-Nussbaumer et al. [38] demonstrated a statistically significant difference in the Fourier-domain OCT reflectance of various white blood cells, allowing in vitro differentiation of neutrophils, monocytes, lymphocytes, and red blood cells. They applied these parameters to active uveitis patients and found in vivo differences in the predominant inflammatory cell type in various uveitic entities, suggesting diagnostic potential for differentiating infectious AU from other causes.

Even less has been published regarding the potential benefit of other ancillary testing for infectious AU. Endothelial cell loss, as determined by specular microscopy, is associated with viral AU and correlates with viral load in CMV-related AU, which may have important implications in disease monitoring [39]. However, others have failed to find a significant difference in endothelial cell density, size, or coefficient of variation between infectious and noninfectious uveitis [40]. Ultrasound biomicroscopy (UBM) may have limited applications for infectious AU. In chronic uveitis associated with TB, UBM may disclose iris and ciliary body nodules with hypoechoic centers [41]. In 24 Chinese patients with FUS that had UBM, 18 had echographic evidence of pars plana and vitreous base exudates [42]. Lastly, near-infrared autofluorescence of the iris may detect early cases of FUS, prior to the development of overt heterochromia or in cases in which heterochromia is more subtle or nonexistent [43]. This may have clinically meaningful potential, if it directs the clinician away from prolonged, and generally unhelpful, topical, and/or systemic steroid exposure in these subtle FUS cases.

To secure a definitive diagnosis of infectious AU, though, the sine qua non is ocular fluid analysis. Rates of PCR positivity are variable, likely depending upon pretest probabilities for any given cohort. In a series of 11 Japanese patients with clinically suspected viral uveitis, ten patients had positive PCR results for

herpetic viruses [44]. Seven of these patients had AU only and all seven were PCR positive. Others have found rates of DNA detection closer to 40%, in AU patients suspicious for infection [45, 46]. On the lower end, investigators in the United States found only 6 of 53 (11%) aqueous samples positive for viral DNA in consecutive AU patients with persistent activity despite therapy or clinical features suspicious for a viral cause [47]. Iris atrophy and pigmented KP significantly increased the likelihood of PCR positivity. In infectious AU, herpes virus DNA is detected in approximately 80–100% of PCR-positive cases [44–47]. Multiplex PCR may have utility in screening, but real-time (quantitative) PCR (RT-PCR) may confirm viral replication within the eye (i.e., active infection) [48]. Though PCR has particular utility in the setting of presumed viral AU, DNA from other types of infectious agents may be successfully identified. Of 53 aqueous samples from patients with granulomatous uveitis, 20 (38%) were positive for TB DNA with PCR [49].

The Goldmann-Witmer coefficient (GWC) indicates intraocular antibody production against a particular infectious agent, by comparing the ratio of pathogen-specific antibody to total antibody in the aqueous versus peripheral blood. Though not available in the United States, GWC testing is employed routinely in Europe and other parts of the world and substantially increases the diagnostic yield of ocular fluid analysis when paired with PCR. Of 30 human immunodeficiency virus (HIV)-negative patients with AU, PCR detected herpetic DNA in 8 of 30 (27%) cases, while GWC determined a viral cause in 15 (50%) patients [50]. Both tests were positive in only three patients, all of whom had CMV. Five patients had GWC confirmation of RV, while no PCR assay detected rubella DNA. Others have similarly found that GWC has superior sensitivity compared to PCR for suspected viral AU [45, 51, 52]. Aqueous fluid analysis yielded a herpetic virus in 16 of 42 (38%) French patients with possible viral AU, with GWC outperforming PCR by nearly threefold [51]. Specifically for virus detection, the superiority of GWC over PCR in AU patients is exactly opposite that for posterior uveitis patients, in whom PCR has better sensitivity [51]. This may stem from the fact that herpetic retinitis tends to present more acutely and fulminantly. Aqueous sampling within 2 weeks of symptoms may increase PCR positivity, while GWC generally becomes positive later and remains so for up to 4 months [50, 51]. GWC requires less volume as compared to PCR. For immunocompromised patients, PCR likely has a higher yield [52]. In general, diagnostic paracentesis of the anterior chamber is very safe, even in a pediatric population when performed with anesthesia [52], but some have reported significant complications [47].

In rare instances, older methodologies, such as tissue culture and histologic study, may identify the infectious etiology of anterior segment inflammation. In such cases, patients most often present with a chronic, smoldering AU, and culture of aqueous aspirates, if positive, demonstrates slow-growing bacteria, such as mycobacteria [53], *Corynebacterium* species [54], *Actinobacillus actinomycetemcomitans* [54], and, in the author's personal experience, *Propionibacterium acnes*. More invasive sampling of iris nodules or granulomas, with fine-needle aspiration or surgical iridectomy, has secured an infectious diagnosis as well [55–58].

Finally, after all clinic-based ancillary testing and aqueous sampling as indicated, the patient should be sent for general laboratory and radiological investigation. The usual noninfectious etiologies should be considered and ruled in or out with appropriate testing, which is beyond the focus herein. The value of serologic testing for any particular infection depends on the seroprevalence of positivity in the population. For herpetic AU, in particular HSV and VZV, serology generally has little value in Western populations, except to rule out these etiologies, as the vast majority of adults have been previously exposed. While in Asian locales, the seroprevalence of HSV is closer to 60%, increasing the clinical utility of a positive serologic result. Conversely, the seroprevalence for CMV in the Western countries ranges from 40 to 50% [59, 60], while 90% or more of Asian populations are positive [50, 60]; thus, the presence of CMV IgG would have more clinical relevance in a Western, non-Asian patient with AU. The use of the laboratory is somewhat different for possible bacterial AU. As for all patients with uveitis, screening for the presence of syphilis IgG is indicated in any new patient with AU. Directed testing for TB and Lyme disease should be performed in the context of the patient's risk for each infection, taking into account their travel to or migration from endemic areas, their exposures, and any associated systemic symptoms.

Viral Etiologies

Herpetic Anterior Uveitis (HAU)

There are eight members of the human herpesvirus (HHV) family, many of which have been implicated in ocular inflammatory disease [61]. Epstein–Barr virus (EBV or HHV4) involvement in AU is controversial, and evidence suggests that active viral replication does not occur in the eye [62]. Similarly, the evidence for implicating herpes family viruses HHV6-8 is still undetermined. On the other hand, HSV, VZV, and CMV are well-established causes of AU and have the potential to present similarly [63]. The clinical presentation of viral uveitis is thought to be determined by the interplay of the virus, the host's genetic makeup, and the immune status of the affected patient [17]. With the advent of PCR, antibody detection in the aqueous humor, and increased recognition of unique clinical characteristics, there is potential for greater specificity in definitive diagnosis of viral uveitis.

HSV1/HSV2 (HHV1/HHV2)

HSV 1 and 2 are incurable herpesviruses typically transmitted through oral-to-oral or sexual contact, respectively. Infections are common and generally asymptomatic. While more likely during an active flare, transmission is still possible with asymptomatic infection [64]. After establishing latent disease in the trigeminal or other sensory ganglia, reactivation can occur along nerve fibers at any time. Patients affected by HSV-related eye disease are predominantly middle-aged and female

[63, 65–67]. Unilateral disease is present in the majority [66, 68], but up to 19% of cases may be bilateral [69]. Previous studies have demonstrated that patients with atopic disease are more likely to have bilateral involvement and are more susceptible to developing HSV-related ocular disease [70–72].

The onset of HSV AU is acute, with symptoms, signs, and severity that can vary widely. Commonly reported clinical features accompanying the anterior chamber inflammation include medium to large granulomatous KP, which accumulate in the central corneal endothelium [66]. These KPs are typically flat and grayish and disappear with treatment. There are reports of nongranulomatous, fine KP as well [67, 73]. High intraocular pressure (IOP) is seen in 46–90% of patients [45, 63], presumably related to virus-associated trabeculitis with aqueous outflow impairment. Keratitis is present in an estimated 33–41% [68, 74]. These patients often have reduced corneal sensation. While the presence of keratitis associated with anterior segment inflammation supports a clinical diagnosis of viral, especially HSV-related AU, its absence does not rule out this etiology, posing a diagnostic challenge. Notably, prior to the use of PCR-guided diagnosis, there were no reports of HSV AU without keratitis in the literature. Similarly, iris atrophy is present in about 40–50% of patients and, in the setting of AU, is considered pathognomonic for a herpetic association [67, 73]. However, iris atrophy may be absent, especially early in the disease course. A series of patients with AU, sectoral iris atrophy, and absence of keratitis tested by aqueous humor PCR demonstrated HSV to be the causal agent in 83% [45]. The atrophy was noted to be progressive with each subsequent flare and characterized by defects at the iris pigment epithelium with scalloped, well-defined edges seen under transillumination. Of the patients in that series, 90% also had a distorted, dilated pupil, which was consistent with another report of pupillary dilation in 9 of 13 patients with HSV keratouveitis [75]. In this series, almost 60% of the 13 patients developed posterior synechiae (PS), another common feature of herpetic AU. Other clinical features, such as conjunctival injection and ocular pain, are common, reported in 43% and 57% of patients, respectively, in PCR-proven HSV-associated AU [66]. A history of recurrent fever blisters may be a helpful clinical feature suggestive of herpetic etiology. A hallmark of HSV-related ocular disease is a high rate of recurrence. Epidemiological estimates report a recurrence rate after initial episode of 27% at 1 year, 50% at 5 years, 57% at 10 years, and 63% after 20 years [76].

VZV (HHV3)

VZV causes primary infection in the form of varicella or chicken pox. Through axonal and likely viremic spread, it establishes latent infection in sensory ganglia where reactivation classically leads to a dermatomal rash (i.e., zoster or shingles). Over 95% of immunocompetent individuals over 50 years of age are seropositive for VZV and at risk for development of herpes zoster (HZ) [77]. Risk factors include increasing age, female sex, white race, and immunocompromised status [78]. Involvement of the ophthalmic division of the trigeminal nerve (V1) with a

characteristic vesicular rash, also known as herpes zoster ophthalmicus (HZO), poses particular risk for ocular involvement. It is estimated that 10–20% of cases of HZ involve the V1 distribution [79]. Approximately 30–50% of these will have ocular involvement, with 43% developing iridocyclitis [80, 81]. Although dermatologic findings are helpful, not all patients will present with a rash (zoster sine herpete).

Similar to HSV, VZV-associated AU presents acutely and varies in its symptoms, signs, and severity. Disease tends to be monophasic and of short duration, though recurrent disease does occur [80]. The most common ocular manifestations of VZV are keratitis, uveitis, and conjunctivitis [81]. Keratitis is estimated to be present in 31% [68], comparable to that in HSV AU.

There are additional clinical features that may assist in the diagnosis of VZV AU in the absence of keratitis and dermatitis. VZV-associated AU commonly presents unilaterally and with both granulomatous and nongranulomatous patterns of inflammation [73, 82]. It is also more common in patients over 50 years of age. In one study, the mean age of VZV AU was 65, whereas the mean age of HSV AU was 34 [45]. Similar to HSV AU, conjunctival redness is reported in about 60% of VZV AU cases, significantly more common than observed among CMV-associated AU patients [66].

Differentiating HSV- from VZV-associated AU on clinical grounds is challenging. In one series of patients with PCR-proven herpetic AU, VZV-associated disease was more likely to present with severe intraocular inflammation, high viral load in the aqueous humor, high aqueous flare grade, segmental iris atrophy, and elevated IOP [66]. However, in a separate series of patients with AU, sectoral iris atrophy, and absence of keratitis, only 17% were found to have VZV by aqueous humor PCR, while the remaining 83% were positive for HSV [45]. Quantitative analysis of anterior chamber viral load by RT-PCR has demonstrated that degree of iris atrophy and pupil distortion correlate with viral load in VZV-associated AU [82].

CMV (HHV5)

CMV transmission through mucous membrane contact or parenteral exposure can result in latent infection in nucleated cells of the blood and bone marrow. In immunocompromised individuals, CMV reactivation is associated with retinitis. CMV-associated AU, on the other hand, is seen more often in immunocompetent hosts, an association not recognized until the advent of diagnostic PCR [61]. There is a great deal of overlap between the clinical presentation of HSV-, VZV-, and CMV-associated AU, with some distinguishing features to consider. Anterior segment involvement of CMV appears to affect predominantly middle-aged men, though age range varies considerably [17, 83–85]. While medium to large KPs are predominant in HSV- or VZV-associated AU, a greater percentage of patients with CMV infection and AU will present with small KP. In one series, 39% of CMV-associated AU patients had medium to large KP and 44% had small to fine KP [66]. Endotheliitis with coin-shaped lesions (cluster of small KP arranged in a circular configuration) or linear KPs are characteristic of CMV-related ocular disease [84]. There is

evidence for significantly lower endothelial cell count in patients with CMV AU, in comparison to those with VZV AU [66]. Similar to HSV- and VZV-associated AU, iris atrophy is commonly observed. However, in the setting of CMV infection, diffuse iris atrophy appears to be more common than segmental [17, 85]. Other characteristic features of CMV AU include milder symptoms, milder anterior segment inflammation, and lower aqueous flare grades, as compared to those with either HSV or VZV. The vast majority of patients have ≤2+ cells in the anterior chamber [17, 85]. In one series, CMV AU patients had significantly less ocular pain and conjunctival injection compared with both VZV AU and HSV AU patients [66]. Finally, CMV is associated with severely elevated IOP, which frequently does not respond to topical corticosteroids alone [86].

CMV has been implicated as a causative organism in previously idiopathic PSS, and less commonly in FUS [87]. Indeed, Chee et al. found that 52% of 67 eyes with PSS and 42% of 36 eyes with FUS were PCR positive for CMV [87]. Unlike in PSS, CMV positivity in FUS was associated with important clinical differences. Patients with CMV-positive FUS were significantly older (median age: 65 years versus 49 years), more likely to be male (80% versus 43%), and more frequently observed to have nodular endothelial lesions (60% versus 9.5%), as compared to CMV-negative FUS patients. FUS patients who were age 57 or older were 16 times more likely to be CMV positive. Another series examining 104 patients from Singapore with AU and elevated IOP demonstrated CMV presence by PCR in 22.8%, accounting for about one-third of eyes with clinical PSS or FUS in this group of patients [17]. Based on this remarkably high percentage, it would seem that CMV is a relatively common cause of hypertensive uveitis, at least among Asian patients. Taken together, these studies suggest that manifestations of CMV-related AU occupy a spectrum of disease from acute, monophasic or recurrent, AU to chronic AU and can fulfill clinical criteria for PSS or, less commonly, FUS. Definitive diagnosis is elusive, without molecular testing of aqueous fluid (and possibly IVCM findings of coin-shaped lesions, as discussed above), but essential, given the significant differences in antiviral agent for CMV versus other herpes viruses.

Rubella

The ocular manifestations of RV, best-known in relation to congenital rubella syndrome caused by in utero infection, include cataracts, microphthalmos, iris abnormalities, and pigmentary retinopathy [88]. The association with postnatally acquired infection and subsequent AU, often with clinical features meeting criteria for FUS, has only recently been recognized. Classic features of FUS include stellate KP, iris atrophy and/or heterochromia, cataracts, and absence of PS. RV-associated AU tends to affect younger patients with a chronic course, leading to early cataracts and glaucoma [74]. In one series of 30 RV-associated uveitis cases, average age at presentation was 32 years [89]. Cataracts, present in 77% at initial visit, affected 90% at 1-year follow-up. Additional findings included KPs in 90%, iris heterochromia or atrophy in 46%, and notably absent PS in 93%. In another study examining 57

patients with RV-associated AU confirmed by GWC, 23% had iris heterochromia [74]. The lack of complete concordance between the clinical findings of FUS and RV-associated AU underscores the fact that other infections, such as CMV, may less commonly induce FUS.

Definitive diagnosis of RV-associated AU requires analysis of aqueous fluid, typically demonstrating negative PCR and positive GWC testing. In one series of 30 cases, 27 were diagnosed by GWC and all were PCR negative [89]. Similarly, a study of 57 GWC-confirmed cases of RV AU found PCR positivity in only 12% [74]. In suspected cases of RV-associated AU, ocular fluid analysis for differentiation from herpetic causes is essential. While there are effective treatments for the latter, RV has no targeted antiviral therapy.

Human Immunodeficiency Virus (HIV)

HIV infection is associated with ocular inflammation through a number of mechanisms; the vast majority involve opportunistic infections. For years, it was suspected that HIV may be a direct cause of uveitis, though it was not confirmed until 2008 with the demonstration of elevated intraocular to plasma HIV-RNA ratio [90]. Subsequently, in a series of 40 HIV-positive patients with uveitis, three had a highly elevated intraocular to plasma HIV-RNA ratio and no other cause for the uveitis could be elucidated [91]. All three of these patients had bilateral AU, and the inflammation subsided with HIV therapy alone. Two of the three patients, upon subsequent retesting 3 months later, had undetectable HIV levels in their plasma and intraocular fluid. Of the 40 patients examined, proof of intraocular opportunistic infection was identified in 72.5%, and intraocular HIV was detected in 32%. Similarly, in another series, investigators found six patients (8 eyes) with AU, among a consecutive series of 56 HIV-positive patients with uveitis, all associated with an elevated intraocular to plasma HIV-RNA ratio and negative for other ocular infections [92]. No patients were on antiretroviral therapy (ART) at the time of testing, and four of six had a CD4 count greater than 200. AU was present in all and vitritis was present in four. Interestingly, four of the six patients had clinical features of FUS, including fine KP, absence of PS, and elevated IOP. After failing topical corticosteroids, they all responded to ART with complete resolution of inflammation after several weeks. While evidence is limited, high intraocular to plasma HIV-RNA ratio supports the presence of active intraocular replication, and the absence of other causative organisms implicates HIV as a direct cause of AU.

Ebola

The Ebola virus (EBOV) has gained increasing international attention, since the largest epidemic in history struck West Africa between 2013 and 2016. This epidemic resulted in greater than 11,300 deaths and greater than 17,300 survivors, the largest EBOV survivor cohort since the initial 1976 outbreak [93]. EBOV

hemorrhagic fever (EHF) is associated with a flu-like illness, gastrointestinal manifestations, hemorrhagic complications, and high mortality rate [94]. Among several ocular manifestations of EBOV, including conjunctivitis, conjunctival hemorrhage, episcleritis, and interstitial keratitis, uveitis is the most commonly encountered in EHF survivors, affecting an estimated 13.5–34% [95–98]. In one series of 341 patients who underwent eye examination during the recent Ebola outbreak, 46 cases of uveitis were observed, of which 78% were unilateral and 48% were AU [96]. While the risk factors for the development of uveitis in EHF are not well-defined, higher viral load at disease presentation has been observed [97]. Uveitis typically presents during the convalescent phase of the disease. One study found that the median time from Ebola Treatment Unit discharge to uveitis-associated ocular symptoms was 3 weeks (ranging from 0 to 17.2 weeks) [97]. Given this latent period, EBOV may persist in the immunologically privileged site of the eye. In direct support of this theory, viable EBOV was isolated from the aqueous humor in a patient with unilateral, nongranulomatous AU associated with IOP of 44 mmHg, presenting 9 weeks after the clearance of viremia [99]. Similarly, during the 1975 Johannesburg outbreak of the Marburg virus (a filovirus similar to EBOV), one patient was diagnosed with uveitis during the convalescent phase and Marburg virus was cultured from fluid on anterior chamber tap [100]. Diagnosis is most commonly established with RT-PCR. The timing of antibody formation varies by host, so serologic testing is minimally useful in the acute setting [101].

Dengue

Dengue virus, transmitted by the Aedes mosquito, is an emerging infectious disease of the *Flaviviridae* family found in tropical and subtropical regions. Prior to 1970, only nine countries had suffered severe dengue epidemics; presently, more than 100 countries worldwide have endemic dengue [102]. Acute infection with the dengue virus is characterized by flu-like illness with high fever (40 °C/104 °F), as well as retro-orbital pain, headache, arthralgias, and abdominal pain [102]. Bleeding diatheses related to thrombocytopenia are common. Ocular disease typically manifests as posterior inflammation with retinal hemorrhage, macular edema, foveolitis, retinal vasculitis, and optic neuropathy. Most series report only a small percentage of patients with uveitis [103], though ocular complications associated with dengue have historically been overlooked [104]. One series of 50 patients with dengue-associated ophthalmic complications reported the presence of isolated AU in 7.7% [104]. These patients responded well to topical prednisolone with resolution of inflammation after 1 week of therapy. Delayed presentation with AU has also been reported in patients 3–5 months after infection, likely representing a hypersensitivity reaction as opposed to active intraocular viral replication [105]. Diagnosis can be made by PCR detection of dengue viral DNA in the serum during the acute phase of illness. After this period, serologic testing for IgG and IgM is the preferred method. IgM will be present in 80% of patients by day 5 and 99% by day 10 of infection [106]. While dengue virus does not seem to be a common cause of AU, there has

been a 30-fold increase in global incidence of dengue virus in the last half century including outbreaks in the southern United States and Hawaii [107, 108]. With the increased frequency of these outbreaks likely to continue, related cases of AU may become more common as well.

Chikungunya

Chikungunya virus is a mosquito-borne, RNA virus, belonging to the alphavirus genus of the family *Togaviridae*. The associated febrile illness is characterized by flu-like symptoms, abrupt onset of fever, severe arthralgias, headache, and rash similar to the illness associated with the dengue virus [109]. Clinically, providers can often differentiate this disease from that of dengue by the absence of thrombocytopenia with chikungunya [110]. There are a range of anterior and posterior inflammatory manifestations of chikungunya, but in contrast to dengue, AU is the most common, affecting an estimated 27% of patients presenting for eye care [19]. Pigmented KPs were a notable feature in these patients. On average, ocular symptoms develop approximately 1 month after onset of systemic symptoms and do not coincide with the febrile illness [19]. Serological testing of AU patients from endemic areas may be diagnostic. IgM levels peak 3–5 weeks after onset of illness and remain positive for 2 months. Similar to dengue, testing within 1 week of onset should include PCR testing for the direct detection of viral RNA [109].

Bacterial Etiologies

In terms of frequency of association and overall impact, bacterial causes of infectious AU pale in comparison to the viral causes discussed above. Nevertheless, important bacterial infections must be considered for all patients with undifferentiated AU, particularly, the great imitators: syphilis, TB, and, to a lesser extent, Lyme disease.

In general, patients with a bacterial uveitis present with isolated AU less commonly than posterior or panuveitis (for syphilis and TB) or intermediate uveitis (for Lyme), though exceptional case series exist. In most case series of ocular syphilis patients, isolated AU comprises 0–33% of cases [111–118]. However, in one study of 22 consecutive syphilitic uveitis patients from Singapore, nearly 50% of all patients had AU alone [119]. Most likely, these series underestimate the true incidence of isolated AU in patients with syphilis, as a significant percentage of patients with secondary syphilis have been found to have subclinical, asymptomatic AU when systematically screened [120]. Syphilis patients without HIV coinfection are more likely to present with isolated AU [112, 113, 115]. For presumed ocular TB, a similar range of patients (between 0 and 29%) present with isolated AU [121–126]. In some series, though, closer to half of all patients with presumed ocular TB had only AU [49, 127]. The data for Lyme disease are more limited. Similarly, only a minority (10–17%) of patients with ocular Lyme present with only AU [128–130].

Unlike for viral AU, there are few specific, and no pathognomonic, ocular findings for bacteria-associated AU. Chronic, uni- or bilateral granulomatous AU with large, mutton-fat KP has been classically described for both syphilis [131] and, perhaps more so, TB [126, 132, 133]; however, exceptions abound. Indeed, for both syphilis- and TB-associated AU, insidious, nongranulomatous disease may predominate [119, 121, 127]. In secondary syphilis patients with AU, conspicuously dilated iris vessels have been noted [131]. In comparison to other uveitic causes, iris nodules or granulomas are a fairly common finding in syphilis and TB patients with associated AU [114, 122, 126, 134]. Iris nodules may occasionally be noted in the angle of ocular TB patients, associated with peripheral anterior synechiae [132]. While not reported in the context of syphilis- or Lyme disease-associated AU, hypopyon may infrequently be seen in TB-associated AU [135, 136]; more rarely, the hypopyon may be darkly pigmented, perhaps stemming from pigment dispersion in the setting of iris necrosis [137, 138]. Lastly, PS may have some morphological specificity in ocular TB. Numerous investigators have described broad-based PS in TB-associated AU patients [122, 139], often involving two or more continuous quadrants [121, 123]. For AU patients, both extensive PS (two or more quadrants) and anterior scleritis are significantly associated with latent TB, in comparison to matched controls [123]. From limited reports, AU associated with papillitis [140, 141] or cotton wool spots [142] may raise the pretest probability for ocular Lyme. Certainly, AU in the context of cranial nerve palsy, especially cranial nerve seven, strongly suggests systemic Lyme infection [143].

As with other causes of AU, anterior segment complications, such as PS and cataract, are more frequently encountered in patients with ocular syphilis or TB involving only the anterior segment [113, 127]. Syphilis-associated AU patients generally present with better visual acuity, as compared to those with posterior disease [113]. Still, some authors have reported no difference in the visual prognosis for syphilis patients with AU alone versus those with posterior involvement, likely due to the higher rates of cataract progression with AU [114]. Aside from glaucoma, most complications associated with AU are reversible and do not induce irretrievable vision loss. As such, the visual prognosis for syphilis-, TB-, and Lyme disease-associated AU is generally favorable, given timely and directed therapy.

Treatment and Outcomes

The treatment of infectious AU involves targeting the underlying infectious etiology, suppressing the intraocular inflammation, and mitigating the development of ocular complications. For some viral infections, such as rubella, dengue, EBOV, and chikungunya, no targeted therapy exists. It should be mentioned, though, that rubella infection can be prevented with vaccination, and evidence has shown decreased rates of FUS since introduction of widespread vaccination [15]. On the opposite end of the spectrum, but equally straightforward in terms of therapeutic options, bacterial infections associated with AU have well-defined treatment protocols with specific antimicrobials: intravenous penicillin for syphilis, multidrug therapy for TB,

and oral doxycycline or intravenous ceftriaxone for Lyme disease. But for the vast majority of infectious AU cases, those stemming from herpetic disease, management approaches are more nuanced and less standardized. As such, the following section focuses on the evidence for various treatment strategies for the most common causes of infectious AU—specifically HSV, VZV, and CMV.

HSV1/HSV2 (HHV1/HHV2) and VZV (HHV3)

Acyclovir (ACV) is a safe and inexpensive antiviral therapy and is highly specific for the alpha herpesvirus family (including HSV1, HSV2, and VZV). It has demonstrated efficacy in controlling a number of herpesvirus infections, including orofacial [144, 145], genital [146, 147], and ocular HSV-related disease [148]. It achieves high concentration in aqueous humor, essentially rendering topical antiviral therapy unnecessary [149]. While it remains the systemic therapy of choice for HSV and VZV AU, clear evidence of its therapeutic value is still somewhat lacking. The Herpetic Eye Disease Study (HEDS) group specifically examined the effectiveness of oral ACV 400 mg PO five times per day for the treatment of HSV iridocyclitis, in addition to topical trifluridine and topical steroid [150]. Though this study was underpowered, there was a trend toward lower rate of treatment failure in the ACV-treated group. The true effect of ACV addition may have been diluted by the co-administration of topical antiviral therapy. Stronger evidence exists for the effectiveness of prophylactic therapy with ACV in the prevention of recurrent HSV-associated AU. The HEDS found decreased recurrence rate of ocular HSV by 45% with oral ACV at a dose of 400 mg PO twice daily [148]. The positive effect of therapy was not sustained after discontinuation, demonstrating the potential importance of long-term prophylaxis. Similarly, ACV therapy has been shown to be effective in VZV-associated dermatologic and ocular disease. When appropriate therapy is initiated promptly after the onset of dermatitis, lower incidence and severity of ocular manifestations, such as dendritiform keratopathy, stromal keratitis, and uveitis, have been demonstrated [151]. Further, more prompt resolution of skin manifestations, reduction of viral shedding, and attenuation of pain during the acute phase of the disease have been reported.

For HSV AU, ACV therapy for active disease should be initiated at a dose of 400 mg PO five times per day with twice daily dosing reserved for prophylaxis as necessary. Alternatively, valacyclovir (vACV), an esterified prodrug of ACV with significantly greater bioavailability, may be used, if minimizing the total number of pills per day may improve therapeutic compliance. For active disease, vACV 500 mg PO three times daily is standard, with 500 mg PO daily for maintenance therapy as needed [152]. Standard antiviral therapy for active VZV AU consists of oral ACV 800 mg PO five times daily for 7–10 days. Alternatively, vACV 1000 mg PO three times daily or famciclovir 500 mg PO three times daily is acceptable. For chronic VZV AU, or in the setting of frequently recurrent disease, prophylactic therapy with either ACV 800 mg PO BID or vACV 1000 mg PO daily may be attempted, though a lack of consensus exists and more frequent dosing may be needed [67].

Maintenance therapy should be initiated in patients with difficult to control disease or frequent recurrences. Stromal keratitis is the form of the disease most likely to cause permanent vision loss because of progressive corneal scarring [148]; thus, HAU patients with associated keratitis are most likely to benefit from prophylactic therapy. There is no clear guideline for when to initiate prophylactic antiviral therapy in patients with isolated HSV AU, though some recommend doing so for patients with two or more recurrences per year [45]. Others maintain prophylactic ACV for a minimum 2 years after the initial episode with a tendency toward lifelong therapy [73]. Regarding VZV, the herpes zoster vaccine has been shown to be effective in decreasing incidence of herpes zoster and is generally recommended for individuals aged 60 and older [78]. Vaccination is associated with a greater than 50% reduction in incidence of herpes zoster, having a major impact on the burden of ocular disease [78].

In addition to oral antiviral therapy, first-line therapy for treatment of HSV- or VZV-associated AU should include a topical corticosteroid for control of intraocular inflammation. Steroid therapy such as prednisolone acetate 1% drops can be initiated at a dose of four to eight times daily depending on severity of inflammation, followed by a gradual taper. Topical cycloplegic agents, such as cyclopentolate 1% BID, should be utilized when the anterior chamber cell grade is 1+ or greater, to minimize PS formation.

Consecutive flares of HSV and VZV ocular disease can cause a cumulative detrimental effect on visual function. The two most commonly reported complications associated with all herpetic AU are glaucoma and cataract formation [68, 153]. In a comparison of HSV- and VZV-associated uveitis, HSV-associated disease had a higher rate of developing secondary glaucoma as compared to VZV (54% vs 38%, respectively) [73], though other reports cite rates of 18–31% for HSV-related disease [45, 63, 66, 68, 74]. Estimates of incidence of secondary glaucoma for VZV-associated uveitis range from 30 to 40% [152]. Cataract formation appears to occur at a similar rate between HSV and VZV with about one-quarter to one-third of patients affected [152]. HSV keratitis (perhaps more frequently than VZV) can cause permanent and progressive corneal opacities leading to vision loss [68]. With long-term follow-up, rates of legal blindness for eyes with HSV-associated uveitis approach 20% [68]. Visual outcome for VZV-associated uveitis is variable but appears to be relatively good with only 15% of patients in one series with final visual acuity decreased by more than two Snellen lines [80]. Vision loss in the majority of these patients was attributable to posterior segment pathology.

CMV (HHV5)

With molecular diagnostics, our understanding of CMV as a major cause of isolated AU in immunocompetent individuals has had a tremendous impact on the treatment paradigm for suspected viral AU, as ACV and vACV have poor activity against CMV. The ideal first-line therapy for CMV AU, though, has yet to be determined due to a lack of randomized trials. Systemic options include intravenous ganciclovir

or its oral prodrug valganciclovir. Local options for therapy include topical ganciclovir 0.15% or intravitreal ganciclovir injection.

Systemic ganciclovir therapy is initiated as an intravenous induction phase with a dose of 5 mg/kg of body weight twice daily, followed by once daily dosing as maintenance therapy. Oral ganciclovir is limited by its poor bioavailability of about 6% [154]. On the contrary, the bioavailability of oral valganciclovir approaches 60%. Oral valganciclovir can be administered at 900 mg PO twice daily for induction, followed by maintenance dosing of 900 mg PO once daily. The duration of induction therapy is variable, generally lasting at least 3 weeks, as employed in CMV retinitis, or longer as necessary to achieve complete quiescence of AU. Maintenance therapy may have to be continued for several months, years, or indefinitely, given the high risk for recurrence after cessation of therapy.

Ganciclovir and valganciclovir should be used with caution and only by clinicians with experience in its administration and monitoring. Comanagement with an internist is advisable for ophthalmologists lacking familiarity. Both medications are associated with a number of adverse events, including bone marrow suppression, especially leukopenia. Complete blood counts and metabolic panels should be checked frequently, especially during the induction phase, and renal dosing may be required. Ideally, definitive diagnosis of CMV as the causative organism should be established prior to therapy, given the high potential for adverse events with systemic valganciclovir. However, in cases of chronic AU associated with episodes of highly elevated IOP, a trial of valganciclovir may be warranted.

For topical therapy, ganciclovir gel 0.15% has been administered four to six times daily [83, 155]. Intravitreal injection is formulated at a concentration of 2 mg/0.1 mL and can be administered weekly [155]. Others have administered intravitreal ganciclovir as a one-time loading dose followed by oral valganciclovir [156]. Two other medications, cidofovir and foscarnet, also demonstrate potent activity against CMV, though their toxicity profiles limit their use [154]. Topical steroid therapy should be initiated for suppression of inflammation at the start of antiviral therapy at a dose commensurate with the degree of intraocular inflammation. Given the high prevalence of elevated IOP and glaucoma with CMV AU, topical IOP lowering therapy is frequently necessary, progressing to surgical intervention as required [86, 157].

While CMV AU generally responds to therapy initially, recurrence rates are high. One series of 24 PCR-proven CMV AU eyes demonstrated response in all of the 12 treated eyes; however, 78% of eyes relapsed within 8 months after stopping treatment [17]. These patients received a variety of treatment regimens. Four patients were initially treated with intravenous ganciclovir twice daily for 6 weeks, followed by oral ganciclovir for an additional 6 weeks. When valganciclovir became available, five patients received this therapy with 6 weeks of 900 mg BID dosing followed by another 6 weeks of 450 mg BID dosing. Three patients received local therapy with weekly intravitreal ganciclovir for 3 months, due to cost issues associated with systemic therapy. Likewise, from the same group, in a series of 27 PCR-confirmed CMV AU patients exposed to 47 treatment episodes, there was an initial response rate of 77% to antiviral therapy, but 75% recurred after cessation of

therapy [155]. Ganciclovir treatment was administered by a variety of routes: systemic, topical, and intravitreal. Only four of the systemically treated patients received intravenous ganciclovir with the remaining patients treated with oral valganciclovir. Systemic ganciclovir and intravitreal implant demonstrated good response rate, but also high rate of recurrence which persisted even after a second course of treatment. There is some evidence that the topical ganciclovir gel, while associated with more modest response rates, may also be associated with lower rate of recurrence with four times daily dosing for a minimum of 3 months [155]. In one study examining only topical ganciclovir gel in 15 patients with confirmed CMV AU, patients showed significantly improved mean time to recurrence postinitiation of treatment (nearly 13 months) compared with pretreatment (4 months) [158]. While another series did demonstrate fewer recurrences per year while on topical ganciclovir gel, it did not demonstrate faster time-to-quiescence or a statistically significant prolonged time to recurrence [83]. Long-term follow-up (>24 months) of 15 immunocompetent CMV AU patients (six of whom received systemic therapy and all received topical antiviral and corticosteroid therapy), demonstrated that the mean number of relapses per month decreased significantly before and after therapy from 0.23 to 0.03, without significant difference between topical therapy alone or in combination with systemic therapy [85]. A large series of 106 CMV-associated endotheliitis patients reported that systemic and topical antiviral therapy may be more effective than either therapy alone [84]. The high recurrence rate with all modalities of therapy, especially after cessation, may necessitate prolonged antiviral maintenance therapy.

High rates of secondary glaucoma and cataract formation are similarly seen in CMV AU. One series demonstrated an almost 70% rate of cataract development with long-term follow-up (>2 years) [85]. A chronic elevation of IOP was also seen in 87%, with the majority eventually requiring glaucoma surgery. High rates of surgical intervention have been observed in other series as well [157]. Through medical management and surgical intervention, good IOP control and disease quiescence can ultimately be obtained [85, 157].

Another frequent complication associated with CMV AU is corneal decompensation [84, 153]. Surgical intervention may be necessary. CMV AU is associated with endotheliitis [84, 159, 160] and subsequent reduction of endothelial cell density [66]. However, a history of associated endotheliitis is not necessary for corneal failure. In a review of 18 patients with CMV-associated AU, only one was observed to have associated endotheliitis; however, 23% developed bullous keratopathy [66]. Three of these patients required corneal surgery. In another review of 109 eyes of 106 patients with PCR-confirmed CMV endotheliitis, AU or PSS is previously diagnosed in almost half [84]. Corneal transplants had been performed in 26% of patients prior to the definitive diagnosis of CMV, and of those, 18% underwent transplantation during follow-up. Final visual outcome of CMV AU appears to be good, with one large series reporting long-term visual acuity better than 20/25 after 2 years [85]. In patients with CMV endotheliitis, the final visual acuity may be somewhat worse, with one series reporting mean best-corrected visual acuity of 20/50 after follow-up of greater than 2 years [84].

Conclusion

Irrespective of geography, AU is the most prevalent anatomic subtype of uveitis, and up to one-third of all new patients with AU have an associated infection. As the power and availability of molecular diagnostics of aqueous fluid increase, the proportion of patients with AU attributable to an infection will grow. Epidemiological and demographic considerations help to stratify a patient's a priori risk for any particular infection, but herpetic AU far outweighs all other infectious causes of AU worldwide. Still, bacterial masqueraders, specifically syphilis, TB, and less so, Lyme disease, should always be considered. Various examination findings may increase pretest likelihoods for a particular infectious association, especially unilaterality, iris atrophy, corneal changes (denervation and/or scarring), and elevated IOP. No examination finding, though, is pathognomonic for any one infectious AU, with the exception, possibly, of coin-shaped clusters of KP in CMV-associated AU with endotheliitis.

Additional ancillary testing in the clinic with IVCM and, to a lesser extent, AS-sdOCT has increasing diagnostic potential; in fact, the owl's eye finding on IVCM has high specificity for detecting CMV-infected endothelial cells and may obviate the need for aqueous fluid analysis. For a substantial number of suspected viral AU eyes, PCR and/or intraocular antibody testing for GWC calculation, as available, is critical. This information has significant therapeutic implications, as the treatment for CMV-associated AU differs from that for HSV- and VZV-associated AU. Further, PCR and GWC may help differentiate FUS associated with RV from CMV, impacting the available options for management.

Proper therapy of infectious AU begins with identifying the inciting infection and promptly initiating directed antimicrobial therapy. The inflammatory component should be aggressively managed with topical steroid. The course and outcomes vary significantly, depending upon a multitude of factors including the pathogen, host response, timeliness and efficacy of appropriate management, and the development of ocular complications. The most common complications of infectious AU include cataract, glaucoma, and corneal scarring and/or decompensation. Some complications, such as cataract, may be readily treatable with rapid reversal of any related vision loss, while glaucoma and corneal disease may have more permanent, sight-threatening implications.

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Noninfectious Intermediate, Posterior, and Panuveitis

3

Akshay S. Thomas

Introduction

Classification systems exist in uveitis based on the clinical course (acute, chronic or recurrent), etiology (infectious or noninfectious), laterality (unilateral or bilateral), histology (granulomatous or nongranulomatous), and primary anatomic location of inflammation. Classification based on the primary location of inflammation is critical in establishing a differential diagnosis and thereby treatment approach. Classification as intermediate, posterior, and panuveitis is based on the Standardization of Uveitis Nomenclature (SUN) [1] working group definitions. Based on their criteria, intermediate uveitis refers to ocular inflammatory disease in which the primary site of inflammation is the middle of the eye. This includes the anterior vitreous cavity, posterior ciliary body, peripheral retina, and pars plana. Posterior uveitis refers to those entities in which the primary site of inflammation is the retina and/or choroid. Panuveitis indicates that the anterior segment, vitreous cavity, and retina/choroid are all involved in the disease process. While many uveitic entities may present as one or more of the aforementioned anatomic classifications, this chapter stratifies various diseases based on their typical location of involvement.

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Intermediate Uveitis

Background and Epidemiology

Intermediate uveitis represents the most infrequent type of uveitis accounting for roughly 15% of cases [2–4]. Estimates of disease prevalence are sparse, but regional reports from the United States have described this figure to be between 2 and 3 per 100,000 persons [5, 6]. There does not appear to be a racial or gender predilection in idiopathic intermediate uveitis, but this does not hold true to those cases of intermediate uveitis with an underlying systemic disease, or in the case of a subtype of intermediate uveitis found in children, called pars planitis which has a male-to-female ratio of 2:1. Idiopathic intermediate uveitis overall incidence peaks in the third and fourth decade of life and is bilateral in roughly 80% of cases [7, 8].

Common Symptoms

Patients with intermediate uveitis may only have symptoms of photopsias, floaters, and blurry vision. Photophobia, eye pain, and redness which are almost ubiquitous in active anterior and panuveitis are infrequent in adults with intermediate uveitis. Given the limited symptoms, the general prevalence of intermediate uveitis may be underreported.

Exam Findings

Clinical examination may reveal anterior chamber cell which usually represents spillover from the vitreous cavity in adults. Examination of the vitreous cavity may reveal vitreous cell and haze (Fig. 3.1). Inflammatory cells in the vitreous cavity may coalesce to form snowballs. On histopathologic examination, snowballs are granulomas of the vitreous [9]. Inflammatory exudates called snowbanks may develop on the pars plana and peripheral retina (Fig. 3.2). Histologic evaluation of snowbanks reveals fibroglial cells, blood vessels, lymphocytes, and vitreous collagen [10]. Active snowbanks have a fluffy appearance while inactive snowbanks have a fibrotic and smooth appearance. Special attention should be given to examination of the inferior vitreous cavity and pars plana, as gravitational accumulation of inflammatory mediators makes this the most commonly affected location in intermediate uveitis. Intermediate uveitis is often accompanied by cystoid macular edema (CME), the most common cause of vision loss in these patients, and peripheral retinal vasculitis. The peripheral retinal vasculitis is most often a periphlebitis and can be appreciated clinically as perivascular sheathing. Peripheral nonperfusion as a result of peripheral retinal vasculitis may result in retinal neovascularization, vitreous hemorrhage, and even tractional retinal detachment. Exudative retinal detachment can occur in cases with extensive snowbanks. Another potential complication that often gets missed in pars planitis is retinoschisis, typically in the inferior quadrants, either due to an exudative process from an active snowbank, a tractional process, or both [11].

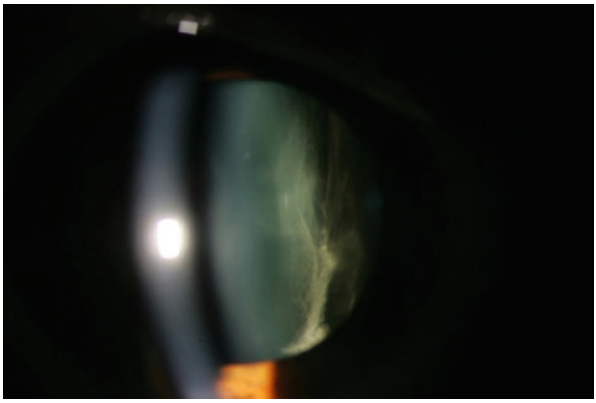

Fig. 3.1 A patient with intermediate uveitis showing vitreous opacities

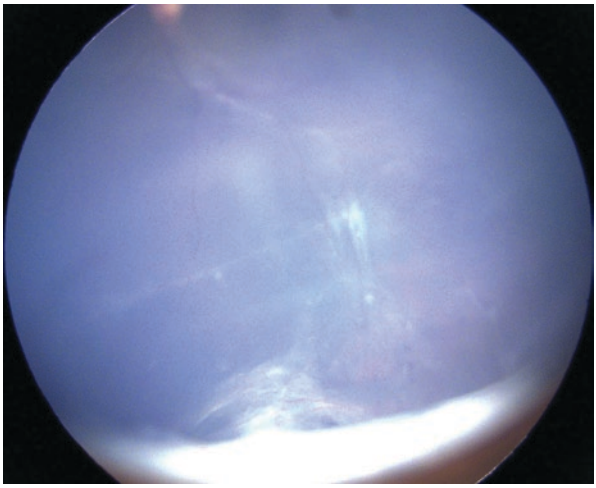

Fig. 3.2 A teenager with pars planitis. Note the smooth, fibrotic snowbanks. There is also a less clearly visualized area of tractional retinal detachment

Key Diagnostic Tests

While intermediate uveitis is a clinical diagnosis, multimodal imaging is important in following disease activity and response to therapy.

In cases where extensive media opacities hinder adequate examination of the retinal periphery, ultrasonography can help evaluate for the extent of vitreous opacities, the presence and location of pars plana exudates, cyclitic membranes, and/or the presence of a retinal detachment. A skilled ultrasonographer can also detect the presence and extent of macular thickening in cases where optical coherence tomography (OCT) is not possible [12]. OCT is critical in evaluating for cystic and noncystic thickening of the macula and can also detect vitreous cells and debris in the posterior vitreous. Monitoring changes in macular thickness on OCT is by far the most frequently employed ancillary imaging modality in intermediate uveitis. Fluorescein angiography (FA) is critical in detecting perivascular leakage suggestive of retinal vasculitis, quantifying the extent of peripheral nonperfusion and

evaluation for retinal neovascularization and angiographic CME. Given that many cases of intermediate uveitis involve the peripheral retinal vasculature, traditional fundus cameras which do not sample the far peripheral retina may miss cases of retinal vasculitis in intermediate uveitis. It is becoming more apparent that findings on ultra-widefield imaging such as peripheral vascular leakage (PVL) are associated with other signs of disease activity in uveitis such as CME, but there is no consensus as to whether asymptomatic PVL warrants treatment [13–16].

Differential Diagnosis and Critical Laboratory Workup

The differential diagnosis and associated workup for intermediate uveitis are listed in Table 3.1. Intermediate uveitis is most commonly idiopathic. Pars planitis is, by definition, a subgroup of intermediate uveitis in the presence of snowballs or snowbanks without an underlying systemic disease association, typically in a younger patient. As with most types of uveitis, a targeted review of systems to detect systemic symptoms associated with conditions associated with intermediate uveitis as listed in Table 3.1 is the key to identifying a potential cause and guide ancillary testing. Additionally, obtaining a thorough medical and social history is imperative.

Table 3.1 Differential diagnosis and associated workup for intermediate uveitis

Systemic disease	Workup
Infectious	
Cat-scratch disease	Serum Bartonella titers
Epstein-Barr virus (EBV)	Aqueous EBV PCR
Indolent endophthalmitis	Vitreous or aqueous cultures/PCR
Hepatitis C	Serum HCV antibodies
HTLV-1	Serum HTLV-1 antibodies
Lyme disease	Serum Lyme (*Borrelia burgdorferi)* antibodies
Syphilis	Serum antitreponemal antibodies
Toxocariasis	Aqueous toxocara antigen PCR
Toxoplasmosis	Aqueous/serum toxoplasma antibody titers
Whipple's disease	Referral to gastroenterology
Noninfectious	
Behçet disease	Clinical diagnosis
Inflammatory bowel disease	Referral to gastroenterology
Multiple sclerosis	Contrasted MRI of the brain, CSF studies
Pars planitis (idiopathic)	Diagnosis of exclusion
Sarcoidosis	Serum ACE and lysozyme levels, chest X-ray, CT chest
Masquerade syndromes	
Lymphoma (primary CNS or primary vitreoretinal)	Neuroimaging, diagnostic vitrectomy
Amyloidosis	Careful family history, tissue or vitreous biopsy
Retinal vascular disease with chronic dehemoglobinized vitreous hemorrhage	Blood pressure measurement, HbA1c level, fluorescein angiography
Retinoblastoma	Ultrasound evaluation for intralesional calcifications, genetic testing, neuroimaging

The most common infectious causes of intermediate uveitis include syphilis, tuberculosis (TB), and lyme disease, for which an exposure history is helpful. Multiple sclerosis (MS) and sarcoidosis are the most common systemic noninfectious disease associations of intermediate uveitis. Identifying the latter diagnoses might require a neurological, respiratory, and dermatologic review of systems questions, respectively. Clarifying ethnic background is also useful in the diagnosis of sarcoidosis. Masquerade syndromes such as intraocular lymphoma (which is discussed in more detail later) can present with isolated vitritis and should be considered in the appropriate demographic group, typically in patients >65 years old.

A focused laboratory and radiologic workup is indicated in all intermediate uveitis patients, guided by a thorough review of systems. Regardless of systemic findings (or lack thereof), all patients with intermediate uveitis should undergo testing for antitreponemal antibodies, quantiferon gold testing or tuberculin skin testing, and a chest X-ray to evaluate for syphilis, TB, and sarcoidosis. Additional testing for sarcoidosis in adults including serum angiotensin-converting enzyme (ACE) levels, serum lysozyme levels, and/or a CT scan of the chest may be warranted.

Associations have been found between the HLA-DR15 allele and pars planitis [17]. HLA DR15 is also associated with MS, suggesting a common predisposition to both entities in patients harboring this allele. In the presence of any neurologic symptoms, MRI imaging of the brain to evaluate for demyelination is warranted. Given recent trends in the neurology literature regarding early intervention and improved outcomes in patients with MS [18, 19], consideration should be given to neuroimaging even in asymptomatic patients with intermediate uveitis.

Treatment

The treatment options for noninfectious intermediate uveitis are numerous and include topical steroids and nonsteroidal anti-inflammatory agents (NSAIDs), periocular and intravitreal steroids, long-acting steroid implants, oral steroids, and steroid-sparing immunomodulatory therapy (IMT). The treatment algorithm for intermediate uveitis depends on if the disease process is unilateral or bilateral, the degree of vitreous opacities, and the presence of CME [20].

Treatment of infectious intermediate uveitis requires the appropriate systemically administered antibiotic(s), although an anterior spillover component could be treated with topical steroids and cycloplegics if necessary. Avoidance of local steroid depots in the setting of confirmed or suspected infectious uveitis should be emphasized, as these can result in irreversible loss of vision without concomitant treatment of the infectious process. Infectious intermediate uveitis will be covered in detail in Chap. 4.

Situation 1: Unilateral with Inactive/Minimally Active Disease

If there are minimal vitreous opacities, no CME, good vision, and no evidence of retinal neovascularization, close observation may be adequate. If there is mild smoldering CME, initiation of topical steroids (prednisolone acetate 1% or difluprednate) and topical NSAIDs with a slow taper of the steroids is reasonable.

Situation 2: Unilateral with Active Disease

In such patients, starting with a posterior-subtenons kenalog (PSTK) injection (40 mg/1 mL) is appropriate. The patient should be evaluated in a few weeks to assess their intraocular pressure and response to therapy.

If a patient has had a good response to local steroids, a PSTK injection or intravitreal triamcinolone acetonide (IVTA) injection can be given when there is active disease. If an IVTA is performed, care should be taken not to do the injection through an area of snowbanking. If the patient is requiring ≥3 local steroid injections a year, they may be a good candidate for a long-acting steroid implant. The most commonly used long-acting steroid implant is the fluocinolone acetonide (Retisert) sustained delivery system [21]. If such a surgically placed implant is planned, cataract extraction at the same time should be considered in phakic patients [22] and concomitant tube shunt surgery in those with glaucoma [23]. In those patients who are hesitant to undergo surgery, injection of the dexamethasone intravitreal insert (Ozurdex) [24] or an injectable fluocinolone acetonide implant [25] (not FDA approved for uveitis) may be considered.

If a patient has not had a good response to local steroid injection and there are prominent snowbanks, cryotherapy of the snowbanks with peri-procedural oral steroids can be considered [26]. If there are no significant snowbanks present or there has been a suboptimal response to cryotherapy, a diagnostic and therapeutic vitrectomy can be considered. Studies have shown that a vitrectomy may have a modest effect on severity of CME, improvement of vision, and FA features by removing the milieu containing the various inflammatory mediators [27–30]. In my experience, vitrectomy is usually reserved for cases of significant vitreous opacities obscuring the visual axis, particularly in the amblyogenic age range, or if there is suspicion for an infectious etiology or masquerade syndrome. When performing a vitrectomy, I would typically limit myself to a core vitrectomy for diagnostic and therapeutic purposes while leaving the peripheral vitreous which could serve as a catchment area for future intravitreal steroids.

If there is peripheral retinal neovascularization present, laser photocoagulation to the area of nonperfusion should be performed. In those patients who have persistent disease activity despite the above algorithm or in those who defer surgical intervention, treatment with oral steroids and possibly IMT as described in situation 4 is appropriate.

Situation 3: Bilateral with Inactive/Minimally Active Disease

A similar protocol can be applied to each eye as noted in Situation 1.

Situation 4: Bilateral with Active Disease

In addition to local therapy for treatment of CME in each eye as indicated in situation 2, oral steroids are warranted in those with bilateral active noninfectious intermediate uveitis. Steroids are usually started at 60 mg daily or 1 mg/kg/day and tapered slowly. I would typically keep the patient at the initial dose of steroids for 2 weeks and then taper by 10 mg every 1–2 weeks until the patient was at 20 mg/day. If the patient did not flare at this dose, I would taper the steroids by 5 mg every 1–2 weeks until they are at 10–15 mg/day and then subsequently taper by 2.5 mg every 1–2 weeks followed by a slow taper with 1 mg reductions over several months. The maximal safe long-term maintenance dose of oral steroids is debatable, but most clinicians would ideally aim for disease quiescence at a dose of ≤5 mg/day. If

disease quiescence cannot be obtained at this low dose of oral steroids, the patient will likely need systemic IMT or bilateral long-acting steroid implants.

When considering initiation of IMT for any form of uveitis, it is critical to be aware of the side effect profile and the laboratory monitoring needed with each agent (Table 3.2). If uncertain or unable to perform such monitoring, co-management with a rheumatologist is critical. Methotrexate is a reasonable first-line agent in

Table 3.2 Select immunomodulatory agents, their potential side effects, and required laboratory monitoring

Agent	Potential complications	Laboratory monitoring	Supplemental treatment
Corticosteroids	Reflux, GI ulcers, vascular fragility, fluid retention/weight gain, reduction in bone density, fat redistribution, muscle loss, hyperglycemia, hypertension	Blood pressure, weight, glucose every 3 months, lipids annually, bone density within first 3 months and then annually	Calcium 1500 mg daily, vitamin D 800 IU daily
Methotrexate	GI upset when taken orally, hepatotoxicity, pneumonitis, bone marrow suppression	CBC, liver function tests every 6–8 weeks	Folic acid 1 mg/day
Mycophenolate mofetil	Diarrhea, nausea, neutropenia, infection	CBC, basic metabolic panel monthly	None
Azathioprine	GI upset, hepatotoxicity, bone marrow suppression	CBC every 4–6 weeks, basic metabolic panel every 12 weeks	None
Cyclosporine	Hypertension, nephrotoxicity, gingival hyperplasia, GI upset, tremor, hirsutism	Creatinine monthly, CBC, liver function tests, magnesium level every 12 weeks	Home blood pressure monitoring
Cyclophosphamide	Hematuria, hemorrhagic cystitis, increased malignancy risk, sterility, alopecia	CBC and urinalysis every 1–4 weeks	Mesna
Adalimumab	Nausea, headache, rash, GI upset, TB reactivation	Yearly TB skin test or quantiferon gold	None
Infliximab	Infusion reactions, TB reactivation, increased risk of demyelination, increased risk of malignancy, drug-induced lupus, congestive heart failure, elevated liver function tests	Liver function tests every 3–6 months, yearly TB skin test or quantiferon gold	None
Rituximab	Infusion reactions, reactivation of hepatitis B, progressive multifocal leukoencephalopathy	CBC, platelet count every 2–4 months	None
Tocilizumab	Infusion reactions, dyslipidemia, elevated liver enzymes, abdominal pain, neutropenia, thrombocytopenia, demyelination	Lipids, neutrophils, platelet count, liver function tests 4–8 weeks after initial treatment then every 3 months	None

GI gastrointestinal, *TB* tuberculosis, *CBC* complete blood count

intermediate uveitis [31]. In those who have flared with an oral steroid taper, the oral steroids should be increased in dosage while methotrexate therapy is being added, as this medication will take several weeks to become therapeutic. If there is a suboptimal response to methotrexate, other medications such as azathioprine or mycophenolate mofetil can be substituted [32]. While TNF-alpha inhibitors such as adalimumab (the only FDA-approved biologic for the treatment of noninfectious uveitis) [33, 34] and infliximab can be very effective in managing intermediate uveitis, their association with exacerbating demyelinating disease needs to be considered in these patients who may already be at an increased risk of such disease [35]. At the very least, if TNF-alpha inhibitors are being considered, the patient should undergo neuroimaging to rule out preexisting demyelinating disease and testing to rule out TB if not already recently performed. Other immunosuppressive agents such as cyclophosphamide, chlorambucil, and cyclosporine may be considered, but their significant side effect profile and limited data regarding their efficacy make them third-line IMT in intermediate uveitis.

Clinical Outcomes

Patients with noninfectious intermediate uveitis can very often have an excellent visual outcome with many maintaining a visual acuity of 20/40 or better [6]. Critical to preserving vision in such eyes (and all eyes with uveitis) is aggressive control of inflammation. While patients with uveitis may have poor vision from band keratopathy, cataracts, vitreous hemorrhage, epiretinal membranes, and retinal detachment, the most common cause of permanent visual impairment is chronic CME [6]. Unchecked inflammation can additionally lead to progressive fibrovascular proliferation along the ciliary body and hypotony. By the time an eye with uveitis is hypotonous, visual prognosis is guarded and surgical and therapeutic options are far more limited.

Posterior Uveitis

Background

Posterior uveitis represents a large spectrum of inflammatory diseases which can lead to permanent vision loss from retinal pigment epithelium (RPE) and retinal atrophy, optic atrophy, retinal and choroidal neovascularization (CNV), and/or CME. While retinal vasculitis and CME commonly occur in posterior uveitis, their presence in the absence of chorioretinal lesions does not qualify as a posterior uveitis. Posterior uveitides may be classified based on a number of features (Table 3.3) including whether they are of infectious or noninfectious etiology, whether they typically feature vitritis, whether they feature a prominent retinal arteritis or phlebitis, and whether they fall under the spectrum of a white dot syndrome. The more

Table 3.3 Noninfectious diseases that can present as a posterior uveitis with associated clinical features

Disease	Vitritis typically present?	Prominent arteritis, phlebitis, both or neither?
White dot syndrome spectrum		
Birdshot chorioretinopathy	Yes	Phlebitis
Multifocal choroiditis panuveitis	Yes	Phlebitis
Punctate inner choroiditis	No	Neither
Multiple evanescent white dot syndrome	Yes	Neither
Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)	Yes	Neither
Acute retinal pigment epitheliitis	No	Neither
Acute macular neuroretinitis	No	Neither
Serpiginous choroiditis	No	Neither
Acute zonal occult outer retinopathy	No	Neither
Collagen vascular disease		
Systemic lupus erythematosus	No	Arteritis
Polyarteritis nodosa	No	Arteritis
Churg-Strauss syndrome	No	Arteritis
Granulomatosis with polyangiitis	No	Both
Relapsing polychondritis	No	Both
Others		
Sarcoidosis	Yes	Phlebitis
Behçet disease	Yes	Phlebitis
Inflammatory bowel disease	No	Both
Multiple sclerosis	Yes	Phlebitis
Sympathetic ophthalmia	Yes	Both
Vogt-Koyanagi-Harada syndrome	Yes	Both
Susac syndrome	No	Arteritis

common causes of posterior uveitis include sarcoidosis, syphilis, and tuberculosis, but infectious etiologies will be covered in Chap. 4. In this section, we will cover the white dot syndromes, posterior uveitis associated with systemic inflammatory conditions, and Susac syndrome. It is important to note that many of the entities listed as a posterior uveitis may meet the clinical criteria for panuveitis; however, the degree of vitritis and/or iridocyclitis is not typically as severe as the degree of chorioretinal inflammation.

Birdshot Retinochoroiditis (BRC)

Background and Epidemiology

BRC is a rare entity which accounts for 1.5% of uveitis patients referred to tertiary referral centers and between 6% and 8% of posterior uveitis patients [36]. There is a slight female preponderance and onset is typically in the fifth to sixth decades of life. This disease is bilateral and predominantly affects Caucasian patients. There is a strong association between BRC and the HLA-A29 allele with this allele being present in 95% of BRC patients [37].

Common Symptoms

BRC has an insidious onset. Patient may complain of floaters, photopsias, blurry vision, nyctalopia, dyschromatopsia, and/or photophobia.

Exam Findings

The diagnostic criteria for BRC are summarized in Table 3.4. Typically, there is low-grade (if any) anterior chamber inflammation. Findings such as keratic precipitates (KP) or posterior synechiae should prompt suspicion for an alternate diagnosis though fine KPs have been described in BRC [38]. Additional findings include anterior vitreous cells, mild–moderate vitreous haze, and bilateral cream-colored ovoid choroidal lesions with indistinct borders (Fig. 3.3). The choroidal lesions are usually about 500–1500 microns in diameter with their long axes oriented radially from the optic nerve head. The choroidal lesions can be subtle, are often asymmetric between the eyes, and tend to be more numerous in the peripapillary retina as well as nasally and inferiorly. With time, these lesions may coalesce in a linear pattern along retinal veins. Additional variably present findings include optic nerve swelling, epiretinal membrane (ERM), CME, choroidal CNV, perivenous sheathing, nerve fiber layer hemorrhages, and retinal neovascularization. Late changes include optic atrophy, vascular attenuation, macular scar formation, and chorioretinal atrophy (Fig. 3.3). It is important to note that patients may have symptoms for years prior to the development of typical birdshot lesions [39]. In such cases, ancillary testing may be critical for diagnosing BRC.

Key Diagnostic Tests

There are numerous imaging modalities that can help assess disease activity in BRC. OCT may show CME, ERM formation, or changes associated with CNV formation including subretinal fluid and subretinal hyperreflective material. In advanced cases, OCT may reveal outer retinal atrophy and choroidal thinning. Features of choroidal lesions have been described on enhanced depth imaging (EDI)-OCT as focal or diffuse areas of hyporeflectivity [40]. Given that active BRC

Table 3.4 Diagnostic criteria for Birdshot Chorioretinitis based on 2006 UCLA international workshop

Required characteristics	1. Bilateral disease 2. ≥3 Peripapillary birdshot lesions nasal or inferior to optic disc in at least 1 eye 3. ≤1+ Cells in anterior chamber 4. ≤2+ Vitreous haze
Supportive findings	1. HLA-A29 positivity 2. Retinal vasculitis 3. Cystoid macular edema
Exclusion criteria	1. Keratic precipitates 2. Posterior synechiae 3. Presence of infectious, neoplastic or alternate inflammatory disease that can produce multifocal choroidal lesions

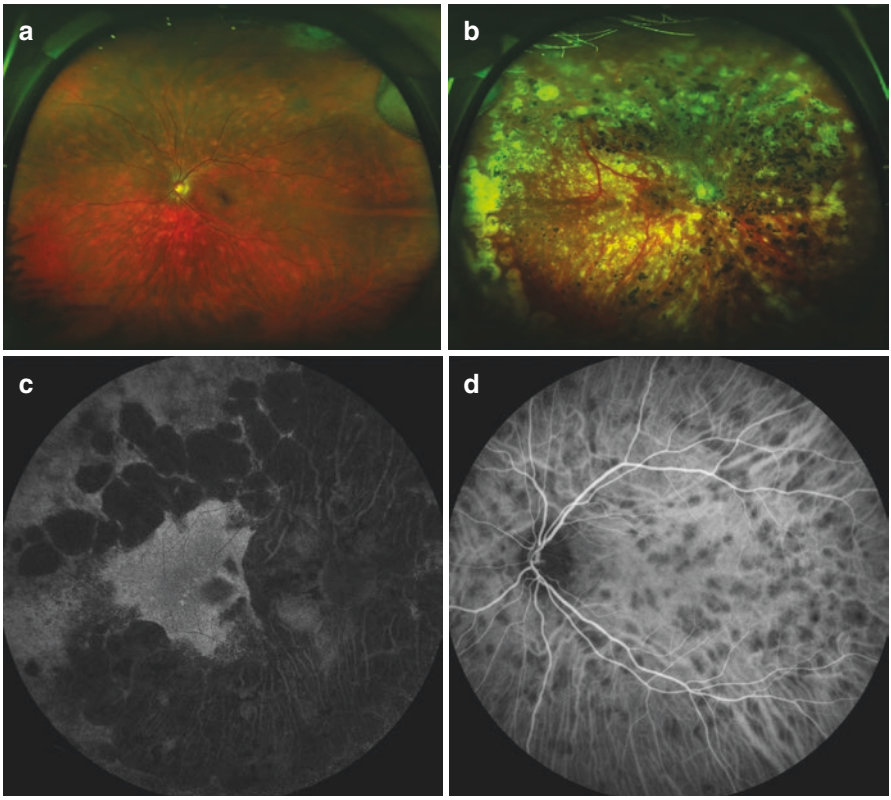

Fig. 3.3 Multimodal imaging in birdshot retinochoroiditis (BRC). (**a**) Classic hypopigmented ovoid lesions seen most numerous nasally in a case of BRC. Late BRC (**b**) characterized by diffuse chorioretinal atrophy. Fundus autofluoresence (**c**) showing confluent patches of hypoautofluorescence corresponding to areas of RPE atrophy. (**d**) ICG angiography showing numerous hypocyanescent choroidal lesions in BRC

typically features a larger vessel retinal vasculitis, perivascular thickening may be noted on OCT thickness maps independent of the degree of CME [41]. FA typically does not highlight birdshot lesions but can be useful in detecting perivascular leakage, papillitis, CNV formation, and rarely, retinal neovascularization. FA may reveal "quenching" where the dye disappears from the retinal circulation more quickly than in normal eyes. On indocyanine green (ICG) angiography, birdshot lesions appear as foci of hypocyanescence (Fig. 3.3). There are often more lesions evident on ICG than on clinical exam. Full-field electroretinography (ERG) is an important tool in monitoring disease progression in BRC [36]. ERG typically shows reduction in scotopic amplitudes prior to photopic responses, suggesting that rod dysfunction may occur prior to cone dysfunction. A delayed 30-Hz flicker implicit time is an early and sensitive sign of retinal dysfunction in BRC [42]. Fundus autofluorescence (FAF) patterns vary widely [43]. The most striking FAF finding is

confluent hypoautofluorescence in areas of RPE atrophy (Fig. 3.3). Visual fields are used to assess the mid-peripheral visual function in BRC patients and is an important component in disease monitoring.

Ultimately, there is no single imaging modality that completely reflects disease activity in BRC. Disease activity is usually determined using a combination of imaging modalities, functional tests, patient symptomatology, and clinical examination. In my experience, disease activity is usually measured by a combination of patient symptomatology, degree of vitritis, OCT findings (CME and perivascular thickening), and ERG/visual field changes if available. ERG and visual fields are typically done every 6–12 months depending on the suspicion for disease progression.

Differential Diagnosis and Critical Laboratory Workup

Other causes of posterior uveitis associated with depigmented fundus lesions such as sarcoidosis, tuberculosis, syphilis, sympathetic ophthalmia, and multifocal choroiditis with panuveitis (MCP) should be ruled out with antitreponemal antibodies, quantiferon-gold testing, a chest X-ray, careful history taking, and clinical examination. When clinical suspicion for BRC is high, testing for HLA-A29 positivity is reasonable. HLA-A29 positivity alone does not confer a diagnosis of BRC, as this allele is positive in roughly 7% of Caucasians. Rather, a negative HLA-A29 is helpful in ruling out the diagnosis of BRC with few exceptions.

Treatment

Given the rarity of this disease, no one treatment algorithm has been shown to be clearly superior. BRC follows a chronic recurrent course and oral steroids are typically employed during acute disease exacerbations as a bridge until steroid-sparing IMT becomes therapeutic or to achieve adequate disease quiescence to allow for placement of a Retisert implant. Oral steroids are started at a dose of roughly 1 mg/kg and tapered to the lowest effective dose to achieve quiescence with concomitant IMT or local therapy. Antimetabolites and biologics can effectively control inflammation in BRC [33, 34, 44]. In my practice, patients are typically placed on mycophenolate mofetil, azathioprine, or adalimumab either individually or in combination. While IMT may help achieve disease stability in terms of ERG, ICG, and visual field findings, these agents are variably effective in the management of CME. Thus, PSTK or IVTA injections, topical steroids, and topical NSAIDs may need to be employed as well. In cases of recurrent or recalcitrant CME, placement of a long-acting steroid implant should be considered.

Clinical Outcomes

Patients may experience a slow decline in vision despite treatment. In a large review of BRC patients published in 2005, a final visual acuity of 20/40 or better was reported in 75% of patients in the better seeing eye [36]. However, 9.8% of patient

were reported to be legally blind. As in many types of uveitis, chronic CME with secondary retinal atrophy is the leading cause of permanent vision loss in BRC.

Multifocal Choroiditis and Panuveitis (MCP) and Punctate Inner Choroiditis (PIC)

Background and Epidemiology

MCP and PIC are regarded by some as discrete entities and by others along the spectrum of the same disease [45–48]. They are presented here together to hallmark many of their similarities and differences. MCP and PIC both more commonly affect young myopic Caucasian women. The diseases are typically eventually bilateral and often asymmetric.

Common Symptoms

Both entities can cause blurry vision, photopsias, and metamorphopsia. MCP can additionally present with eye pain, photophobia, and floaters.

Exam Findings

The characteristic finding in MCP/PIC is the presence of a variable number of small whitish-yellow lesions measuring 50–200 microns in size in the acute phase. The lesions are initially sub-RPE and then seen at the level of the RPE and outer retina [47]. The lesions tend to be smaller and involve the posterior pole in PIC (Fig. 3.4). While the posterior pole is also commonly involved in MCP, there is a tendency to

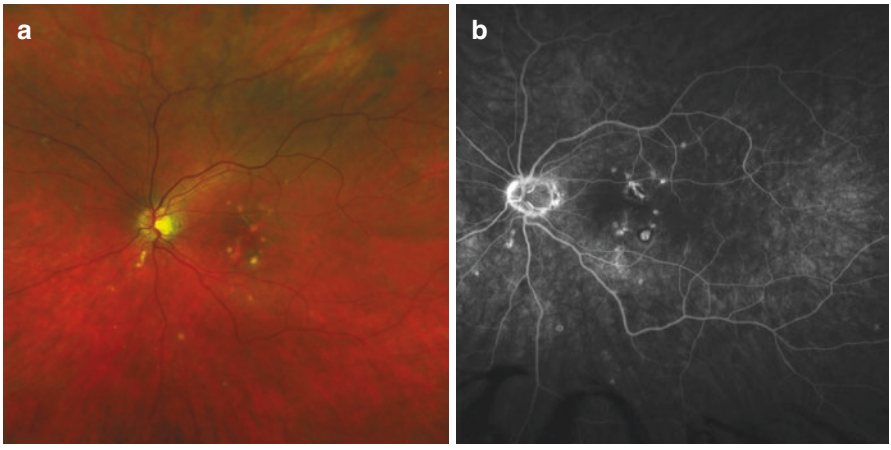

Fig. 3.4 Punctate inner choroiditis (PIC). Note that PIC lesions tend to cluster in the posterior pole (**a**). Fluorescein angiography reveals staining of PIC lesions and some areas of blockage from pigment deposition (**b**)

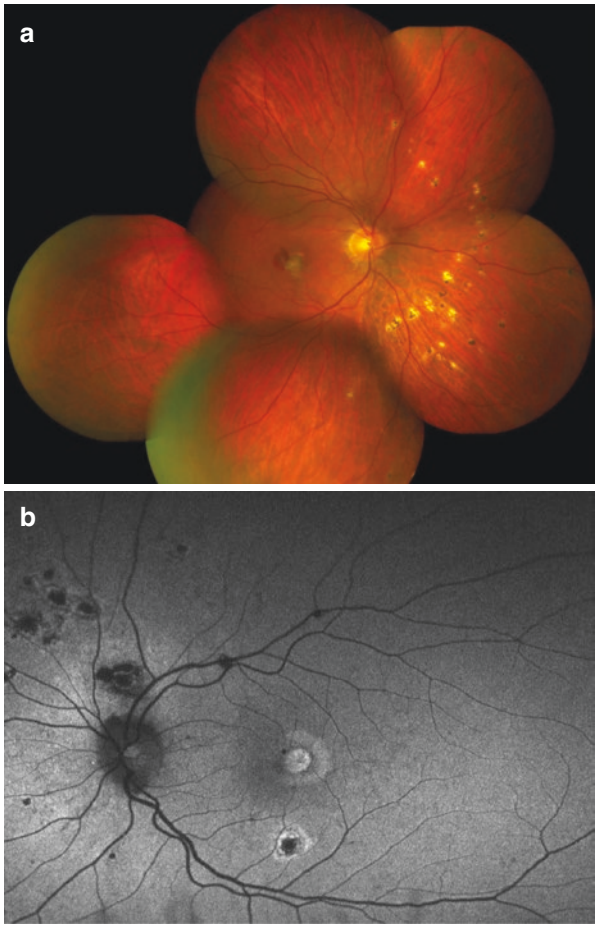

Fig. 3.5 Multifocal choroiditis and panuveitis (MCP). (**a**) Note that the lesions in MCP are not confined to the posterior pole. There is an area of foveal subretinal hemorrhage resulting from choroidal neovascularization. Autofluorescence (**b**) reveals punched-out areas of hypoautofluorescence, some with a rim of speckled hyperautofluorescence, likely representing an active lesion. There is also an area of hyperfluorescence over the fovea corresponding to a choroidal neovascularization

have a greater mid-peripheral involvement, with clustering of lesions nasally (Fig. 3.5). Confluent or clustered lesions may, on occasion, be associated with a localized neurosensory retinal detachment. Active lesions often have fuzzy borders. With time, these lesions evolve into punched-out atrophic chorioretinal spots with a ring of pigmentation along the edge of each lesion. These punched-out atrophic lesions can enlarge in size with time.

CME occurs in 10–20% of eyes. With persistent disease activity, new lesions, optic disc swelling, optic atrophy, and rarely disc neovascularization may occur [49]. CNV is common in MCP/PIC (occurs in 25–30% of cases) and may be associated with any of the chorioretinal lesions [50]. Complications associated with CNV including subretinal hemorrhage, subretinal/intraretinal fluid, and subretinal fibrosis (Figs. 3.5 and 3.6) can occur. At times, bridges of subretinal fibrosis may form between lesions. If such bridging fibrosis occurs between peripapillary lesions, the characteristic peripapillary "napkin-ring" fibrosis may be seen [51]. Subretinal

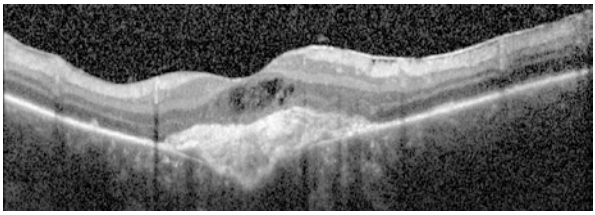

Fig. 3.6 Optical coherence tomography showing subretinal hyper-reflective material, corresponding to subretinal fibrosis and intraretinal fluid in a patient with multifocal choroiditis and panuveitis with choroidal neovascularization

fibrosis bridging between lesions—especially macular lesions—can lead to a clinical appearance termed "subretinal fibrosis and uveitis syndrome" (SFU). Some believe that SFU is a distinct entity from MCP/PIC and other believe that it is a severe phenotype of these uveitides [52].

There are certain features which are seen specifically in MCP, but not in PIC. Lesions may arrange themselves into peripheral linear streaks concentric to the ora in MCP which are referred to as Schlaegel lines. By definition, MCP is a panuveitis and so some degree of anterior chamber and vitreous inflammation and phlebitis is seen in active disease. PIC, on the other hand, is an isolated posterior uveitis and so iridocyclitis and vitritis are never seen.

Key Diagnostic Tests

Color fundus photos are important in MCP/PIC to evaluate for the development of new lesions over time with ultra-widefield imaging. OCT is useful for monitoring for CME and CNV. OCT findings through the lesions vary depending on the stage of evolution. Acute lesions may appear as drusenoid deposits between the RPE and Bruch membrane [47]. These lesions may resolve with treatment. With progression, the lesions spread to involve the outer retina. Atrophic lesions show outer retinal and RPE loss. FA of acute lesions show early hypofluorescence and late staining (Fig. 3.4). Chronic atrophic lesions may show a window defect centrally with blockage in areas of pigment deposition. FA may also show CNV formation which typically fluoresces in a pattern suggestive of classic CNV. ICGA may reveal many more hypocyanescent dots than clinically evident lesions. FAF may reveal spots of hyperautofluorescence corresponding to active lesions with photoreceptor loss but intact RPE. Atrophic lesions appear as patches of hypoautofluorescence (Fig. 3.5). In my clinical practice, comparing fundus findings to old photos, FAF and OCT are part of almost every follow-up visit.

Differential Diagnosis and Critical Laboratory Workup

Other causes of multifocal choroiditis resembling MCP/PIC include presumed ocular histoplasmosis syndrome (POHS), sarcoidosis, TB, syphilis, Vogt-Koyanagi-Harada syndrome (VKH), other white dot spectrum diseases, and nonuveitic entities such as myopic degeneration. Laboratory evaluation for sarcoidosis, TB, and syphilis should be performed. Differentiation of PIC or multifocal choroiditis without

panuveitis from POHS can be challenging, as the diseases share many common features. Inquiry into risk factors to histoplasma such as living in the Ohio-Mississippi River Valley or other endemic areas can potentially help separate the entities.

Treatment

MCP typically has a chronic recurrent course and PIC more often than not has a self-limited course. Treatment of MCP/PIC is directed at first ruling out infectious cause, followed by treatment of the inflammation and management of uveitic CNV. As the amount of vitritis and anterior chamber reaction in MCP is not typically fulminant (and is absent in PIC), evaluation for persistent disease activity often depends on evaluation for the development of new lesions. In MCP, if there is documented progression of disease, local steroids, and/or oral steroids are reasonable with transition to IMT if inflammation flares with tapering oral steroids. Such an approach is appropriate for PIC as well, if there is chronic recurrent inflammation with development of new lesions. Immunosuppressive therapy was found in a study of 122 eyes with MCP/PIC patients to reduce the risk of posterior pole complications (new and recurrent CNV) by 83% [53].

Macular CNV lesions are managed with antivascular endothelial growth factor (anti-VEGF) therapy [54–56]. CNV secondary to MCP/PIC can be treated with anti-VEGF injections on an as-needed basis as opposed to treating indefinitely at fixed intervals. That being said, given the risk of subretinal hemorrhage and subretinal fibrosis with undertreated CNV, patients having their CNV treated as needed should be educated on use of an amsler grid with strict return precautions in place. Furthermore, concomitant control of inflammation with IMT or steroids is usually required for optimal control of CNV with anti-VEGF agents.

Clinical Outcomes

Visual outcomes in MCP/PIC are variable and largely reflect the presence or absence of macular lesions with associated CNV. Brown et al. followed 68 eyes with MCP/PIC for a mean of 39 months and found that 66% maintained 20/40 or better vision with only 21% having 20/200 or worse vision [57]. Eyes with PIC generally have good visual outcomes and, on average, tend to do better than eyes with MCP [58, 59].

Multiple Evanescent White Dot Syndrome (MEWDS)

Background and Epidemiology

MEWDS is an uncommon, typically unilateral condition most often affecting young females. MEWDS was initially described in the 1980s [60] and has been reported in children as young as 10 years of age [61] and adults in their 60s [62].

Common Symptoms

Patients typically report acute onset unilateral blurry vision. Patient may also report photopsias and central/paracentral scotomas and/or an enlarged blind spot. About 50% of patients may report flu-like symptoms preceding ocular symptoms [60].

Exam Findings

Funduscopy in the acute phase may reveal multiple well circumscribed yellowish-white dots at the level of RPE and deep retina. The dots typically measure 100–200 microns in diameter and are concentrated in the macula. The dots are only present for a few weeks following which characteristic foveal granularity may be the only remaining clinical finding [63]. In rare instances, the dots may be replaced with chorioretinal scarring. Rarely, peripapillary pigmentary changes may be the presenting sign which may lead to peripapillary scarring [64, 65]. Additional findings not infrequently seen in MEWDS include mild disc swelling, mild perivenous sheathing, mild vitritis, and mild iridocyclitis. CNV has been rarely seen in MEWDS [66, 67]. While this disease is typically unilateral, bilateral cases have been reported. In bilateral cases, the eyes may be affected simultaneously or disparately [68].

Key Diagnostic Tests

Multimodal imaging has helped confirm that MEWDS primarily affects the photoreceptors. OCT through the lesions in the acute phase shows disruption of the outer retina (ellipsoid zone and interdigitation zone) with small hyperreflective projections into the outer nuclear layer.[68, 69] FA typically shows punctate area of hyperfluorescence in early frames which stain in later frames. The individual areas of staining classically appear to have a wreath-like configuration. ICGA may show several hypocyanescent dots more numerous than the dots evident clinically or on FA. FAF in the acute phase may reveal spots of hypoautofluorescence in the macula with dots of hyperautofluorescence corresponding to the lesions [69, 70]. Visual fields may show generalized depression, central/paracentral scotomas, or an enlarged blind spot. These visual field defects may persist for months following resolution of funduscopic findings as can photopsias [71]. ERG in the acute phase shows reduced a-wave amplitude consistent with photoreceptor dysfunction which typically normalizes in several weeks [72].

Differential Diagnosis and Critical Laboratory Workup

The differential diagnosis for MEWDS includes other white dot syndromes such as BRC, acute posterior multifocal placoid epitheliopathy (APMPPE), acute zonal occult outer retinopathy (AZOOR), and other entities such as sarcoidosis, syphilis, and lymphoma. Testing for syphilis and sarcoidosis is reasonable in a case of suspected MEWDS. The disc swelling often seen in MEWDS along with an enlarged blind spot and other visual field defects can be confused with a primary optic neuropathy [73].

Treatment

MEWDS is typically self-limited and no intervention is required. If CNV were to develop in MEWDS, anti-VEGF therapy would be reasonable [74].

Clinical Outcomes

Clinical outcomes are excellent in MEWDS with the large majority of patients having full visual recovery in several weeks. That being said, MEWDS can recur in the same or fellow eye. A chronic form of MEWDS has been reported with bilateral recurrent

disease [75]. There is the rare report in the literature citing successful use of IMT or systemic corticosteroids for management of chronic recurrent MEWDS [76].

Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

Background and Epidemiology

APMPPE is one of a handful of uveitic entities which present with placoid lesions involving the outer retina and RPE. APMPPE typically affects young adults and does not have a gender predilection. A number of systemic associations have been described with APMPPE most notably, CNS diseases including cerebral vasculitis, meningitis, encephalitis, and even stroke [77–80].

Common Symptoms

As the name suggests, patients present with an acute onset of symptoms including blurry vision, metamorphopsia, photopsias, scotomas, and spots in the vision. The disease is usually asymmetric with the second eye becoming involved a few days to weeks after the first. Patients may report a recent viral illness. Patients may also report concomitant malaise, headaches, and neck stiffness.

Exam Findings

Funduscopy during the acute phase reveals multiple, flat, yellowish-white lesions at the level of the deep retina and RPE. The lesions typically have indiscrete boundaries and measure 0.75–2 disc areas and are most abundant in the posterior pole (Fig. 3.7). Additional lesions typically develop in the weeks following onset of symptoms and so at any point, lesions at various stages of development may be noted. The lesions tend to clear centrally over several weeks leaving mixed areas of depigmentation and coarse pigment mottling. Acute lesions can have associated localized exudative subretinal fluid.

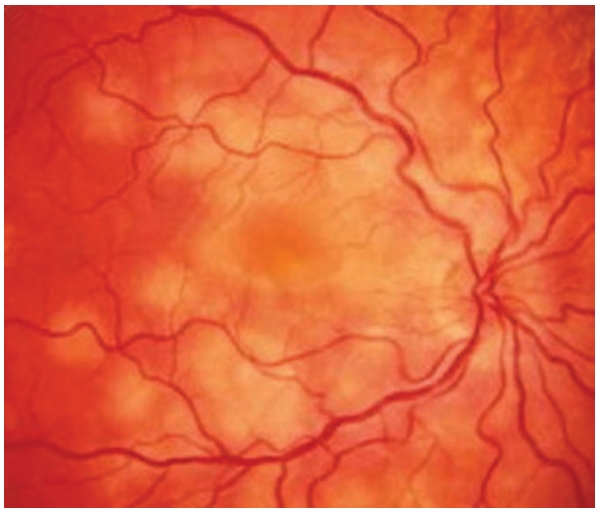

Fig. 3.7 A patient with acute posterior multifocal placoid pigment epitheliopathy showing multiple flat deep retinal/choroidal yellowish lesions

While vitritis and iridocyclitis are not prominent features of APMPPE, they may be present. Other infrequent findings include optic disc swelling, retinal vasculitis [81, 82], cystoid macular edema, exudative retinal detachment [83–85], and CNV [86].

Key Diagnostic Tests

OCT of acute lesions typically shows outer retinal hyper-reflectivity and subsequent outer retinal disruption. As the lesions heal clinically, outer retinal loss persists on OCT and RPE disruption develops [87, 88]. OCT may show a localized collection of subretinal fluid over the lesions which rapidly disappears [84]. FA of acute APMPPE lesions shows hypofluorescence in the early phase due to blockage or choriocapillaris flow voids with irregular staining of lesions in the late frames [89]. Subacute lesions may show hyperfluorescence secondary to window-defects corresponding to areas of RPE loss as well as hypofluorescence secondary to blockage from pigment deposition. ICGA typically reveals hypocyanescence of the lesions [90]. FAF typically shows hyperautofluorescence corresponding to areas of pigment deposition and hypoautofluorescence in areas of depigmentation from RPE atrophy [91].

Differential Diagnosis and Critical Laboratory Workup

The differential diagnosis for APMPPE includes other white dot syndromes, specifically those presenting with placoid lesions (serpiginous chorioretinopathy, ampignious chorioretinopathy, persistent placoid chorioretinopathy, and relentless placoid chorioretinopathy). These entities are discussed in detail later on in this chapter. Syphilis can present with a placoid chorioretinopathy and serological evaluation for this entity is necessary. Other entities such as sarcoidosis, TB, lymphoma, diffuse unilateral subacute necrosis, and metastatic disease to the choroid should be considered in cases with an atypical presentation or disease course.

Given the association with CNS complications, patients presenting with a headache, neck-stiffness, or other neurological symptoms should promptly undergo neuroimaging with referral to a neurologist. It should be noted that neuroimaging modalities such as MRA/CTA may not be able to detect subtle CNS vasculitis.

Treatment

Treatment is typically not necessary in cases of APMPPE and the disease generally does not recur though recurrent cases have been reported [92]. There are several reports on the use of oral steroids in the acute phase of APMPPE but the necessity of such therapy is questionable [93]. Most would agree that for APMPPE patients with CNS symptoms, initiation of systemic high-dose steroids is reasonable to help mitigate the potential CNS complications. In the rare instance of CNV development, anti-VEGF therapy is an effective treatment option [74, 94].

Clinical Outcomes

Patients with APMPPE usually have improvement in symptoms over a few weeks. A literature review of APMPPE patients reported that approximately 25% of patients end up with 20/40 or worse vision [93]. The same study additionally reported that 60% of patients have persistent visual symptoms. What is important to note from this study was that those with foveal involvement were significantly less likely to have complete visual recovery than those without foveal involvement. Ultimately,

patients may have continued improvement in vision up to 6 months following resolution of lesions but the outer retinal loss from APMPPE is not reversible [89].

Serpiginous Choroiditis (SC)

Background and Epidemiology

SC, another form of uveitis with placoid lesions, is most commonly seen in Caucasian patients without a gender predilection. While there do not appear to be any conclusive systemic associations, one study reported a higher prevalence in patients who were HLA-B27 positive. It is a chronic, progressive disease with onset most commonly between the fourth and eighth decades of life [95]. While both eyes are typically affected, disease activity may be asymmetric.

Common Symptoms

Patients typically do not experience symptoms until there is parafoveal involvement. At that point, they may experience blurry vision, metamorphopsia, and scotomas.

Exam Findings

There is usually minimal anterior chamber and only fine vitreous cells, if at all [96]. Funduscopy classically reveals bilateral asymmetric yellowish-gray lesions centered on the optic disc with pseudopodial or geographic extension in multiple directions (Fig. 3.8) [97]. Left untreated, the lesions continue to have centrifugal extension. The advancing edges of the lesion, which is where disease activity is typically confined, may appear fuzzy due to outer retinal swelling. In some cases, serous retinal detachment may be observed over areas of active disease [96]. CNV can occur at the edge of the inflammatory lesions in SC in about 15–20% of patients [98–100]. More infrequently, a periphlebitis, optic nerve swelling, or CME can occur [101, 102]. Subacute portions of the lesions can appear yellowish with course pigment clumping and scalloped edges corresponding to areas of choroidal, RPE, and outer retinal atrophy.

A separate variant of SC, called macular SC, can be rarely seen (Fig. 3.9). The lesions themselves are similar to those described above, but the macula is affected even before peripapillary involvement [103, 104].

Key Diagnostic Tests

OCT reveals outer retinal loss, RPE loss, and choroidal thinning in atrophic portions of the SC lesions (Fig. 3.8). The leading edge of the lesion, if active, may reveal outer retinal thickening, cystic changes, or subretinal fluid [105–109]. FA typically revealed blockage in early frames with staining of the edges of the lesions in later frames. Leakage associated with CNV, optic disc neovascularization [100], or periphlebitis may also be appreciated. ICGA shows striking hypocyanescence of an

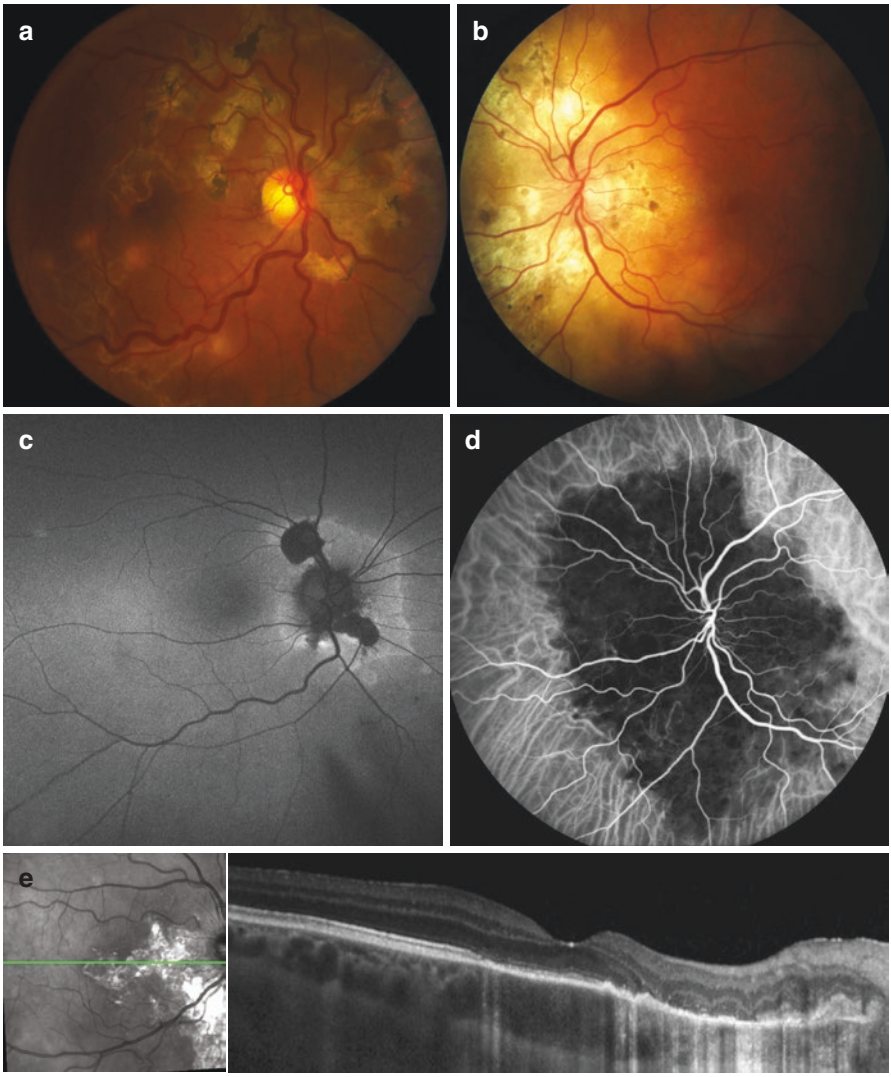

Fig. 3.8 Multimodal imaging in serpiginous choroidopathy (SC). (**a**) Variably pigmented peripapillary lesions with pseudopodial extension. (**b**) Another case of SC with a geographic pattern of spread. Note that the edges of the lesion are fuzzy, suggesting active disease. (**c**) Fundus autofluorescence in a case of SC showing peripapillary hypoautofluorescence corresponding to RPE atrophy with a surrounding area of hyperautofluorescence, suggesting active disease. (**d**) ICG angiogram corresponding to the patient seen in image (**b**). Note the deep hypocyanescence, suggesting choroidal involvement in the area of the lesion. (**e**) Near-infrared reflectance image and OCT line scan through a SC lesion. Note the outer retinal atrophy, RPE loss, choroidal thinning, and increased signal penetrance in an area of inactive SC. There is also EZ disruption in the fovea in an area of perhaps active involvement

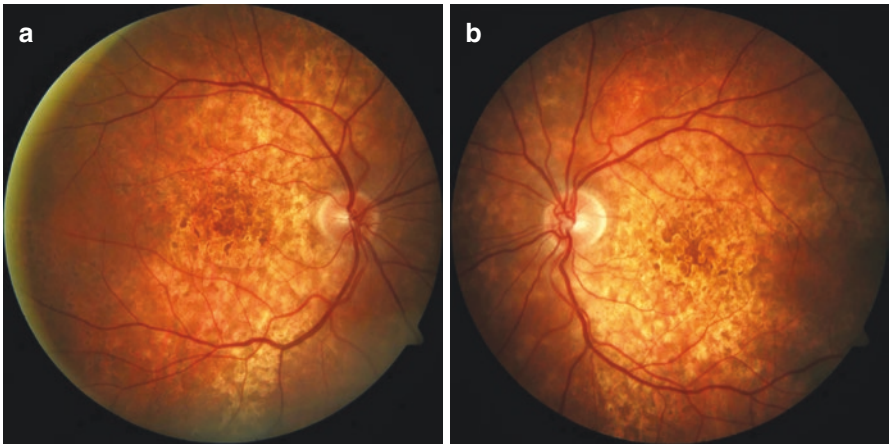

Fig. 3.9 Right (**a**) and left (**b**) eyes of a patient with macular serpiginous choroiditis. The pattern of pigmentary changes and atrophy is similar to typical serpiginous choroiditis except the macula is involved prior to significant peripapillary involvement

area larger than the visible extent of the lesions (Fig. 3.8) [110]. While many forms of choroiditis can show improvement in perfusion on ICG with time, SC tends to have minimal improvement in choroidal perfusion with time. FAF is perhaps the most useful tool in monitoring disease activity in SC. Areas of inactive disease show hypoautofluorescence corresponding to RPE atrophy. Active edges of the lesion, by contrast, appear hyperautofluorescent (Fig. 3.8) [111, 112].

Differential Diagnosis and Critical Laboratory Workup

Not many entities resemble the classic appearance of SC. There is however, a form of choroiditis related to TB (tuberculous SC or serpiginous-like choroiditis or multifocal serpiginous choroiditis) which may be indistinguishable from SC and must be ruled out. The key distinguishing features of tuberculous SC is that there tends to be more vitritis than idiopathic SC and tuberculous SC commonly features multifocal lesions involving the periphery [113]. Acute syphilitic posterior placoid chorioretinitis can also appear like SC, and must be investigated. Other entities which can cause a placoid maculopathy such as APMPPE, ampiginous choroidopathy, and placoid syphilis need to be considered. As with other white dot syndromes, sarcoidosis and lymphoma always need to be in the differential, especially in atypical cases.

Macular SC may be confused with AMD, macular dystrophies, and causes of choroidal ischemia including collagen vascular diseases and hypercoagulable states [104]. Judicious testing for these entities after careful clinical examination may be warranted. An entity closely resembling macular SC is another white dot syndrome named persistent placoid maculopathy (PPM). Patients with PPM usually have

bilateral macular whitish placoid lesions at the level of the RPE and outer retina. On examination, the lesions may be indistinguishable from macular SC, but there are some key differences in PPM: (1) Despite early foveal involvement, vision typically remains good unless CNV formation or atrophy develops; (2) FA shows early well-demarcated hypofluorescence of the lesion followed by partial filling in later frames; (3) The lesions fade over months to years without scar formation unless related to CNV [114].

Treatment

All cases of SC require treatment given its chronic progressive course. There is no single treatment regimen that has been shown to be superior to others given the rarity of this disease. Various forms of local and systemic steroids as well as IMT have been described. After infectious etiologies have been ruled out, patients are typically started on 1 mg/kg of prednisone to treat the acute lesions and IMT to prevent disease recurrence. The prednisone is slowly tapered to the lowest efficacious dose while the IMT becomes therapeutic. There are reports of successful management of SC with initial combination therapy of prednisone, azathioprine, and cyclosporine [115, 116], cyclosporine monotherapy [117, 118], and fluocinolone acetonide implant monotherapy [119]. In cases that fail to respond to the aforementioned regimens, consideration should be given to switching to more aggressive immunosuppression with alkylating agents such as cyclophosphamide or chlorambucil [120]. Given the serious potential side effects of alkylating agents, the decision to start such a regimen as well as subsequent monitoring should be done in concert with a rheumatologist. CNV, if present, can be managed with anti-VEGF agents.

Clinical Outcomes

Recurrent disease is generally the rule in untreated and undertreated SC. Active lesions typically heal in several weeks and recurrences can occur even years later. As affected areas do not completely recover RPE and photoreceptors, final visual outcome is a function of whether or not the fovea is affected. This is one of the challenges in managing SC, as the disease may often go undetected until the fovea is either involved or threatened in one eye. A study of long-term follow-up of patients with SC found that 25% of patients with SC had vision worse than 20/200 in their worse eye [121].

Ampiginous Chorioretinitis (ACR)

Background and Epidemiology

ACR, otherwise known as "relentless placoid chorioretinitis," shares feature of both APMPPE and SC (Table 3.5). This bilateral disease most commonly affects Caucasian patients and there are no conclusive systemic associations or gender predilection [122].

Table 3.5 Key differences between various forms of uveitis with placoid lesions

	APMPPE	Classic SC	Macular SC	Tuberculous SC	PPM	Ampiginous
Acute lesions	Flat yellow-white lesions each 1–2 disc areas in size mostly in the posterior pole fading over several weeks	Yellowish-gray lesions involving peripapillary region with pseudopodial extension fading over several weeks	Yellowish-gray lesion involving the macula and possibly sparing the peripapillary region fading over several weeks	Multifocal yellow-white serpiginoid lesions involving posterior pole and mid-periphery fading with treatment	Whitish flat lesions involving the macula fading over several months	Numerous yellowish-white lesions measuring 0.5 disc areas and involving the posterior pole and mid-periphery and post-equatorial fundus with continued growth and new lesions
Vitritis	Typically absent or mild	Typically absent or mild	Typically absent or mild	Typically significant	Typically absent	Typically absent or mild
FA features of lesions	Block early, stain late	Block early with staining of edges	Block early with staining of edges	Block early with staining of edges	Block early with partial filling of lesion	Block early, stain late
Disease course	Usually self-limited without recurrences	Chronic progressive	Chronic progressive	Progressive until TB treated	Chronic progressive	Chronic progressive
Treatment	Observation initially	Oral steroids + IMT	Oral steroids + IMT	Oral antimycobacterial therapy	Oral, local steroids	Oral steroids + IMT

APMMPE acute posterior multifocal placoid pigment epitheliopathy, *SC* serpiginous choroiditis, *PPM* persistent placoid maculopathy, *FA* fluorescein angiography, *IMT* immunomodulatory therapy

Common Symptoms

Patients commonly report blurry vision, metamorphopsia, scotomas, photopsias, and/or floaters.

Exam Findings

There is typically minimal, if any, anterior chamber and vitreous involvement. Funduscopy reveals bilateral numerous flat whitish lesions. The lesions are smaller than those of APMPPE, measuring roughly a half disc area each. The lesions may show continued growth and heal to form chorioretinal scars (Fig. 3.10). There is often active disease in both eyes simultaneously with lesions present throughout the fundus. With time, there may be >100 lesions in each eye which distinguishes this entity from other white dot syndromes with placoid lesions [123]. Subretinal fluid has been reported overlying lesions [123]. Interestingly, CNV has not been described in this entity, but it likely can occur.

Key Diagnostic Tests

Reports on OCT findings are limited, but described findings include outer retinal disruption, subretinal fluid, outer retinal hyper-reflectivity, and pigment epithelial detachment [124, 125]. Findings on dye-based tests are similar to APMPPE and SC with hypofluorescence in early frames with late staining on FA and hypocyanescence on ICGA. FAF typically shows hypoautofluorescence in atrophic lesions with an occasional margin of relative hyperautofluorescence (Fig. 3.10) [111, 125].

Differential Diagnosis and Critical Laboratory Workup

In addition to APMPPE and SC, other white dot syndromes such as MCP and BRC should be considered. It is important to rule out syphilis, sarcoidosis, and TB which

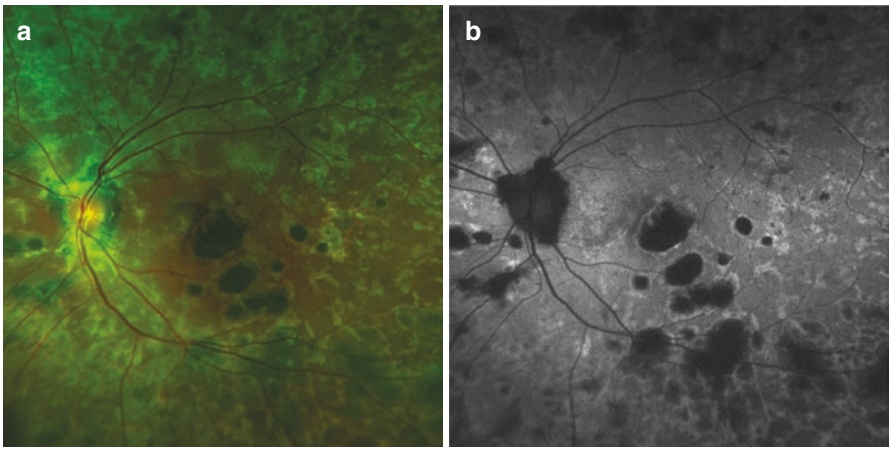

Fig. 3.10 A patient with ampiginous chorioretinopathy showing multiple lesions in various stages of evolution (**a**). Fundus autofluorescence shows hypoautofluorescence with a rim of hyperautofluorescence for many of the lesions as well as smaller hyperautofluorescent lesions temporally (**b**)

can take on a variety of fundus features some of which could resemble ACR. Lymphoma should also be suspected in atypical cases and neuroimaging should be employed when appropriate.

Treatment

Given the rarity of this entity, there is no consensus on an appropriate treatment regimen. Use of local steroids, oral steroids, azathioprine, cyclosporine, mycophenolate mofetil, and cyclophosphamide has been described [122, 123, 126]. A treatment approach similar to SC given the progressive nature of this disease may be considered.

Clinical Course

This is a chronic progressive disease with relapses reported months to years after disease onset. Given the rarity of this disease, long-term visual outcome data is limited. In a study of 26 eyes of 16 patients with ACR, the authors reported stability or improvement of vision in 24/26 eyes with treatment and worsening in 2 eyes due to subretinal fibrosis [123].

Acute Zonal Occult Outer Retinopathy (AZOOR)

Background and Epidemiology

AZOOR is a rare entity causing acute onset dysfunction of a region of outer retina. It most commonly affects young myopic women without a clear racial predisposition [127]. Patient may often report a preceding viral illness though no conclusive systemic association exists at this time.

Common Symptoms

Patients typically report acute onset of unilateral photopsias and scotomas in their vision. Patients may report progressive enlargement of the scotoma with time or the development of new scotomas. Some may report blurry central vision and difficulty seeing with dim lighting [128]. Some may present with bilateral symptoms.

Exam Findings

In the acute setting, funduscopy may be unrevealing. The anterior chamber is usually quiet and there is minimal vitritis. A grayish-white line has been reported between involved and uninvolved retina in the acute phase which disappears within a few weeks [128]. The initially involved retina is usually contiguous with the optic nerve progressing in a centrifugal fashion, but widespread involvement with skip areas or centripetal spread starting near the ora can also be seen [129]. With time, the areas of involved retina will show chorioretinal atrophy with pigment clumping resembling bone spicules as well as vascular attenuation (Fig. 3.11). CME, CNV, periphlebitis, and optic disc swelling are rarely seen [130].

Fig. 3.11 A patient with acute zonal occult outer retinopathy (AZOOR) showing patches of chorioretinal atrophy (**a**) emanating from the optic disc. On autofluorescence (**b**), there is hypoautofluorescence in regions of atrophy and relative hyperautofluorescence of the macula

Key Diagnostic Tests

OCT through a chronic lesion will reveal RPE disruption, outer retinal loss, and variable inner retinal thinning. OCT through an area corresponding to the grayish-white line previously mentioned may show subretinal hyperreflective material with preserved outer retinal architecture [128, 131, 132]. FA may be initially normal. As chorioretinal atrophy develops, a window defect will be seen in the area of involvement. ICGA may show hypocyanescence in the area of a chronic lesion due to choriocapillaris loss [128]. The transition zone between normal and abnormal retina in AZOOR is best appreciated with FAF (Fig. 3.11). A "trizonal" appearance of AZOOR on FAF has been described that reveals hypoautofluorescence of the chronic area of involvement corresponding to RPE loss and choroidal atrophy, surrounded by a ring of speckled hyperautofluorescence corresponding to the transition zone and then normal FAF in uninvolved retina [128]. ERG amplitudes are typically depressed with a delayed 30-Hz flicker in all affected eyes and may be helpful in early diagnosis [133]. Visual field testing typically reveals scotomas most often extending to the physiologic blind spot and other times extending from the periphery. Occasionally, some improvement in the extent of visual field loss may occur [133].

Differential Diagnosis and Critical Laboratory Workup

Given the prominence of the visual field loss with enlargement of the physiologic blind spot, optic neuropathies need to be ruled out, especially in the acute setting where fundus examination may be unremarkable. Once pigmentary changes occur, the fundus findings can resemble sectoral retinitis pigmentosa or diffuse unilateral subacute neuroretinitis (DUSN). Presence of bilateral disease, however, essentially rules out DUSN. The outer retinal loss and vascular attenuation can resemble

autoimmune retinopathy and may warrant testing for antiretinal antibodies. Because syphilitic outer retinitis and burned out serpiginous TB can look similar to AZOOR, it is usually prudent to test for both syphilis and TB in cases of suspected AZOOR, particularly prior to considering systemic immunomodulation.

Treatment

There is no conclusive data on whether treatment alters the clinical course of patients with AZOOR. There are reports of spontaneous remission of AZOOR [134]. There are limited reports regarding treatment of AZOOR with oral steroids and IMT [135]. One study reported rapid improvement of AZOOR treated with valacyclovir [136]. However, another study reported that IMT and antivirals did not appear to halt progression in a case of AZOOR followed up for 13 years [137].

Clinical Course

There is limited long-term data available on this rare entity. Some patients may have recurrences and bilateral involvement. In a study of 51 patients with AZOOR by Gass et al. followed up for a mean of 100 months, 76% developed bilateral disease and one-third had at least one recurrence [133]. The same study found that the visual field loss stabilized at 6 months from the time of diagnosis in 72%, progressed in 4%, and improved in 24%. On occasion, there may be improvement in retinal function of involved areas. A study of 38 Japanese patients with AZOOR reported recurrences in only nine patients with a mean follow-up time of 31 months [127]. Ultimately, visual outcomes are dependent on whether the area of chorioretinal atrophy involves the fovea. In the study by Gass et al., final acuity was 20/40 or better in 68% of affected eyes [133].

Other White Dot Syndrome Spectrum Conditions

Acute Macular Neuroretinitis (AMN)

AMN is an idiopathic condition, most commonly affecting young women [138]. Patients usually report a decline in vision and one or more paracentral scotomas. Some patients report a viral prodrome [139]. Funduscopy reveals one or more reddish-brown lesions which may be round or wedge-shaped. Other than these lesions, the remainder of the ocular exam is typically unremarkable. The lesions are most easily noticeable on near-infrared reflectance (NIR) imaging. FA and ICGA are typically normal in these patients. Advances in OCT have resulted in numerous additional reports of AMN as of late [140–142]. OCT imaging shortly after disease onset shows hyperreflectivity of the outer plexiform layer. Over the next few days, this hyperreflectivity resolves and the outer nuclear layer (ONL) and ellipsoid zone (EZ) become hyperreflective. As this hyperreflectivity subsides, thinning of the ONL, EZ, and interdigitation zone (IZ) ensues. These findings suggest that AMN is caused by ischemia of the retinal deep capillary plexus [140]. Other entities which could resemble AMN include prior central serous chorioretinopathy, outer retinal ischemia from retinal vascular disease, and photic injury. AMN may be unilateral or

bilateral and may recur. Most patients report an improvement in their scotomas though subtle funduscopic and OCT irregularities persist. AMN is a self-limited condition and no treatment has been proven effective.

Acute Retinal Pigment Epitheliitis (ARPE)

ARPE, also known as Krill disease, is a rare condition first described in 1972 in a series of six patients and typically affects young adults [143]. Patients commonly report unilateral blurry vision, scotomas, and occasionally, metamorphopsia. Some patients report a viral prodrome [144]. Funduscopy reveals discrete hyperpigmented spots surrounded by a hypopigmented halo clustered in the posterior pole. Iridocyclitis and vitritis are typically absent. The disease was typically thought to begin in the RPE, but recent studies with high-resolution OCT suggest that the disease begins in the IZ with subsequent RPE involvement [144, 145]. OCT through a lesion typically shows a hyperreflective elevation near the photoreceptor outer segments, causing an upward displacement of the external limiting membrane and disruption of the EZ, IZ, and RPE. FA may show window defects in early frames and late staining of the lesions [145]. The differential diagnosis for ARPE includes many of the other white dot syndromes. ARPE is a self-limited condition with resolution of symptoms, recovery of vision, and normalization of OCT morphology in several weeks.

Posterior Inflammation Associated with Systemic Inflammatory Conditions

There are a number of systemic inflammatory conditions which can feature an inflammatory process in the posterior portion of the eye, typically causing a retinal vasculitis or a posterior scleritis. These include collagen vascular diseases such as systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome, relapsing polychondritis, and the seronegative spondyloarthritides including inflammatory bowel disease (IBD). While a discussion of the systemic manifestations of each of these entities is beyond the scope of this text, these systemic inflammatory diseases share similar posterior segment findings. Disease-specific findings will be discussed as appropriate, but the focus of this section will be on the most common posterior segment manifestations of the aforementioned conditions—posterior scleritis and retinal vasculitis. While these diseases do not typically feature chorioretinal lesions required for designation as a posterior uveitis, they are on the differential for a patient presenting with posterior scleritis and/or retinal vasculitis, and thus, a discussion on this topic is warranted.

Patients may present with a complete lack of symptoms. If there is posterior scleritis, the patient may report severe pain. If the patient has sequelae of posterior scleritis or retinal vasculitis, symptoms may include blurry vision or scotomas. Systemic symptoms vary based on the underlying systemic inflammatory disease. As ocular symptoms may be the presenting finding in many of these disease processes, a detailed review of systems is critical in reaching a timely diagnosis.

Anterior segment findings such as episcleritis, scleritis, and peripheral ulcerative keratitis are more common in these conditions than posterior segment findings. Fundus findings may resemble hypertensive retinopathy with scattered cotton wool spots and hemorrhages as in lupus retinopathy (Fig. 3.12) [146, 147]. Retinal vasculitis can result in retinal vein and/or artery occlusions with their associated sequelae [148]. In SLE, presence of vaso-occlusive retinopathy is strongly associated with CNS lupus and antiphospholipid antibody syndrome [149, 150]. CME can also occur. Lupus choroidopathy, a result of choroidal ischemia, can result in serous retinal and pigment epithelial detachments (PED) [151]. Posterior scleritis, if present, can result in chorioretinal folds and serous choroidal and retinal detachments.

OCT may reveal inner retinal thinning in occlusive arterial disease or macular thickening in cases of CME or inflammatory vein occlusion. Serous PEDs may be seen if there is choroidal involvement. In cases of posterior scleritis, EDI imaging may show a thickened choroid and subretinal fluid. B-scan ultrasonography will show thickening of the ocular coats with collection of fluid in the posterior subtenons space. The hypoechoic signal of this fluid creates the characteristic "T-sign" on ultrasonography. FA may reveal perivascular hyperfluorescence in cases of retinal vasculitis (Fig. 3.12), vascular filling defects in cases of occlusive retinal vasculitis, choroidal filling defects and with multifocal spots of leakage resembling VKH in cases of posterior scleritis and inflammatory choroiditis, angiographic CME, and/or retinal neovascularization.

The differential diagnosis for an isolated retinal vasculitis or posterior scleritis is broad and includes all the entities in this category. Additionally, syphilis, sarcoidosis, and TB should be considered. For retinal vasculitis, entities such as Behçet disease and Susac syndrome are on the differential. For posterior scleritis with exudative retinal detachment, VKH and central serous chorioretinopathy should be considered. For patients with an isolated retinal vasculitis and/or posterior scleritis, laboratory testing for ANA and ANCA should be considered. Please note that this is

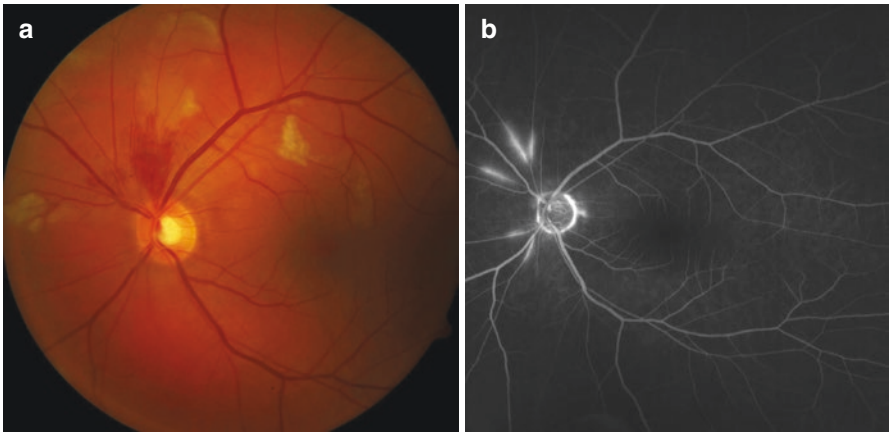

Fig. 3.12 A patient with lupus retinopathy. Funduscopy reveals multiple cotton-wool spots and a nerve fiber layer hemorrhage (**a**). Fluorescein angiography reveals periarteriolar hyperfluorescence consistent with an active retinal arteritis (**b**)

one of the few situations in uveitis category conditions where testing for ANA/ANCA is appropriate. Referral to a rheumatologist or gastroenterologist (for IBD) based on the patient's history, laboratory testing, and clinical suspicion is critical.

Treatment usually focuses on managing the underlying inflammatory condition and so, these patients are uniformly managed in concert with a rheumatologist or gastroenterologist (for IBD patients). It is important to note that while certain IMT regimens may effectively manage the patient's systemic symptoms, it is important to follow the patient regularly to see if there is resolution/stabilization of posterior segment findings. Many IMT regimens, for example, may be poorly efficacious at treating CME for which various forms of steroids, including long-acting steroid implants, may be necessary [152]. Additionally, scatter laser to areas of nonperfusion may be necessary in eyes with retinal neovascularization. While inflammatory CME is not typically treated with anti-VEGF agents, CME arising as a result of retinal vein occlusion may be treated as such.

Susac Syndrome

Background and Epidemiology

Susac syndrome is a rare clinical entity which features a triad of findings: (1) Multiple branch retinal artery occlusions (BRAO), (2) Hearing loss, (3) Encephalopathy. While Susac syndrome is not a classic posterior uveitis, in that there are no distinct chorioretinal lesions, it is on the differential diagnosis for an isolated retinal vasculitis and warrants discussion. Susac syndrome is an autoimmune microangiopathy as evidenced by the presence of antiendothelial antibodies in many patients with this condition [153, 154]. Susac syndrome more commonly effects females with a mean age of onset of 31.6 years [155].

Common Symptoms

Patients typically do not present with the full triad of symptoms [155]. Ocular symptoms include sudden vision loss or sudden development of scotomas. Neurological symptoms include headache, confusion, deficits in memory, trouble with concentration, personality changes, disorientation, stroke-like symptoms, and hearing loss.

Exam Findings

Funduscopy in patients with Susac syndrome may show focal or diffuse retinal arteriolar narrowing with only segmental blood flow (boxcarring) without any evidence of occlusive endovascular plaques. Arteriolar wall plaques, termed Gass plaques, are thought to be highly associated with Susac syndrome, but are not always seen. Anterior segment inflammation and vitritis are absent. Central retinal arteriolar occlusion has been described in Susac syndrome [156].

Key Diagnostic Tests

In cases of acute inflammatory BRAO, OCT will reveal inner retinal hyperreflectivity and thickening in the distribution of the occluded arteriole. With time, OCT will reveal inner retinal thinning in a similar distribution. Hyperreflectivity of the middle retinal layers referred to as paracentral acute middle maculopathy (PAMM) has also been

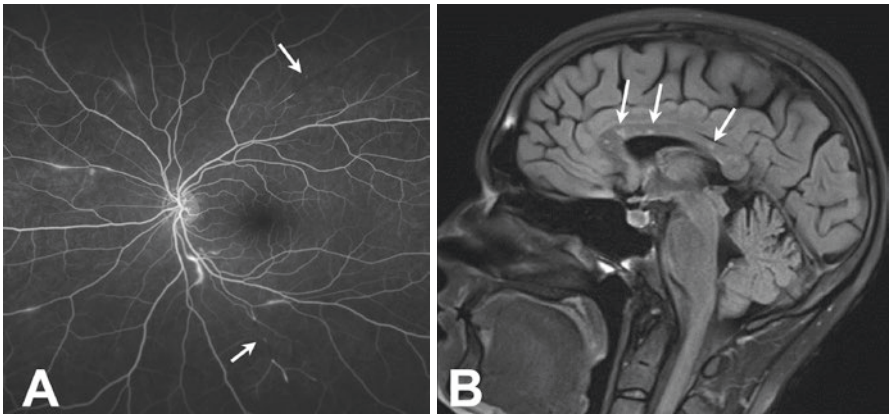

Fig. 3.13 A patient with Susac syndrome shows periarteriolar hyperfluorescence as well as arteriolar filling defects (arrows) on fluorescein angiography (**a**). MRI imaging (**b**) of the same patient showing lesions of the corpus callosum (arrows)

reported in Susac syndrome, but is nonspecific [157]. FA may reveal vascular filling defects in the distribution of the occluded arterioles (Fig. 3.13). There may additionally be multiple foci of periarteriolar hyperfluorescence indicative of an active vasculitis.

Differential Diagnosis and Critical Laboratory Workup

In the absence of encephalopathy and/or hearing loss, the differential diagnosis for an occlusive vasculitis, as seen in Susac syndrome, is broad and includes collagen vascular diseases, seronegative spondyloarthritides, Behçet disease, syphilis, sarcoidosis, and TB. The presence of neurological symptoms could make one consider MS. The presence of multiple BRAOs in a young patient could also concern the evaluating physician for hereditary or acquired hypercoagulability. Ultimately, the laboratory workup should be guided by thorough history taking, review of systems, and clinical evaluation. If there is concern for Susac syndrome, the patient should undergo an MRI of the brain and audiological evaluation. MRI may reveal supratentorial white matter lesions which characteristically involve the corpus callosum (Fig. 3.13) [155]. Audiological testing may reveal bilateral sensorineural hearing loss. Testing for antiendothelial antibodies can be considered but given that this test is not specific for Susac syndrome, testing is not mandatory.

Treatment

There have not been any prospective studies evaluating the optimal treatment strategy in Susac syndrome. A recent report based on a review of the literature and the authors own experience treating several patients with Susac syndrome, recommended a treatment algorithm based on the predominant site of involvement: the central nervous system (CNS), retina, or inner ear [158]. For Susac syndrome in which occlusive retinal vasculitis is the predominant symptoms, the authors recommended starting with a 3-day course of intravenous solumedrol, followed by a prolonged course of oral steroids and simultaneously starting intravenous

immunoglobulin (IVIG) therapy and mycophenolate mofetil. Should this regimen prove incompletely effective, mycophenolate should be substituted with rituximab. Use of cyclophosphamide may be necessary if treatment with rituximab yields inadequate inflammatory control. For CNS-predominant disease, the authors use a similar cocktail of medications with a lower threshold to initiate rituximab and cyclophosphamide based on the severity of CNS disease.

Clinical Course

Susac syndrome was once thought to be a self-limited disease. It is now known that the disease typically follows one of three patterns: (1) Monocyclic—Disease fluctuates in activity for a maximal period of 2 years and then does not recur; (2) Polycyclic—similar disease fluctuation as monocyclic, but relapses continue beyond a 2-year period; (3) Chronic continuous—disease remains continuously active for more than 2 years [159]. Given that the retinal damage following the BRAOs is not reversible, visual outcomes will depend on the degree of disease control and involvement of retinal blood vessels supplying the macula.

Panuveitis

Background

The panuveitides feature inflammatory involvement of all compartments of the eye—i.e., the anterior chamber, the vitreous cavity, and the choroid or retina. The noninfectious panuveitides typically feature bilateral involvement though the degree of involvement may be markedly asymmetric. Among diseases that classically present as a panuveitis, the most common noninfectious causes include sarcoidosis, VKH, sympathetic ophthalmia, and Behçet disease.

Sarcoidosis

Background

Sarcoidosis, a systemic granulomatous disease, is the most common identifiable cause of noninfectious panuveitis. In the United States, sarcoidosis more commonly affects African Americans than Caucasians. Interestingly, the prevalence of sarcoidosis among Black Americans is higher than that among the black population in Africa [160, 161]. Sarcoidosis most commonly affects young adults, typically presenting before the fifth decade of life. However, in sarcoidosis affecting Caucasian patients, usually those of Scandinavian-descent and Japanese individuals, the age of presentation can be bi-modal with a second peak at >50 years of age [162]. The etiology of sarcoidosis is unknown, though the HLA-DRB1 locus has been implicated as a possible contributing factor to the disease [163]. While intrathoracic involvement occurs most commonly in sarcoidosis, ocular involvement has been reported in as high as 50% of patients with sarcoidosis [164]. Additionally, between 5 and 10% of all patients with uveitis have biopsy-proven sarcoidosis [165, 166].

Common Symptoms

Sarcoidosis can affect any portion of the eye or ocular adnexa. For the sarcoidosis patient with panuveitis, ocular symptoms typically include blurry vision, light sensitivity, eye redness/pain, and floaters. Given that sarcoidosis is a multisystem disease, patients may have additional nonspecific symptoms including fever, fatigue, malaise, swollen lymph nodes, weight loss, cough, shortness of breath, chest pain, skin nodules which may be tender, and irregular heartbeats and palpitations, among others. Onset of systemic disease may be acute or insidious. Acute-onset disease tends to occur in younger patients and may presents in one of two ways: (1) Löfgren syndrome which is characterized by bilateral hilar lymphadenopathy, erythema nodosum, iritis, fever, anorexia, and arthralgias; (2) Heerfordt syndrome (uveoparotid fever) which is characterized by uveitis, parotitis, fever, and facial nerve palsy. Acute-onset disease tends to spontaneously remit within a few years [167]. Insidious-onset disease tends to occur in older patients and has a more chronic course.

Exam Findings

Sarcoidosis can present with a wide range of ocular findings which is why sarcoidosis is on the differential diagnosis for almost all types of uveitis. Evaluation of the ocular adnexa may reveal conjunctival nodules, lacrimal gland enlargement, or an orbital pseudotumor-like appearance [168]. The anterior segment may show scleral nodules, band keratopathy, mutton-fat (granulomatous) KPs (Fig. 3.14a), anterior chamber cell and flare, iris nodules at the pupillary border (Koeppe nodules), iris stroma (Busacca nodules), or near the angle (Berlin nodules). There may be peripheral anterior synechiae (PAS) with synechial angle closure, posterior synechiae or pigment on the anterior lens capsule (Fig. 3.14b). Examination of the vitreous cavity may reveal vitreous cell, haze, vitreous snowballs, or vitreous opacities having a "string of pearls" appearance. Funduscopic evaluation may reveal numerous findings. Retinal vasculitis which is most commonly a periphlebitis can be seen in ocular sarcoidosis. Yellowish perivenous sheathing with perivenous exudates referred to as "candlewax dripping" ("Taches de bougie") can be seen in severe sarcoid periphlebitis. An occlusive periphlebitis is uncommon, but, when present, can lead to retinal neovascularization and vitreous hemorrhage [169]. Arteriolar involvement is usually not seen in sarcoidosis. Multiple small pale-yellow choroidal infiltrates may be seen. They may appear as punched-out chorioretinal scars or active discrete infiltrates and are most commonly seen inferiorly (Fig. 3.14c). Large confluent choroidal infiltrates with pseudopodial extensions can also rarely be seen (Fig. 3.14d) [170]. Such large choroidal granulomas may be associated with serous retinal detachment. Subretinal yellowish-white granulomas can also occur. Granulomas of the optic nerve head may occur [171]. Additionally, disc swelling may be noted in sarcoidosis patients either due to active ocular disease or from papilledema secondary to CNS disease.

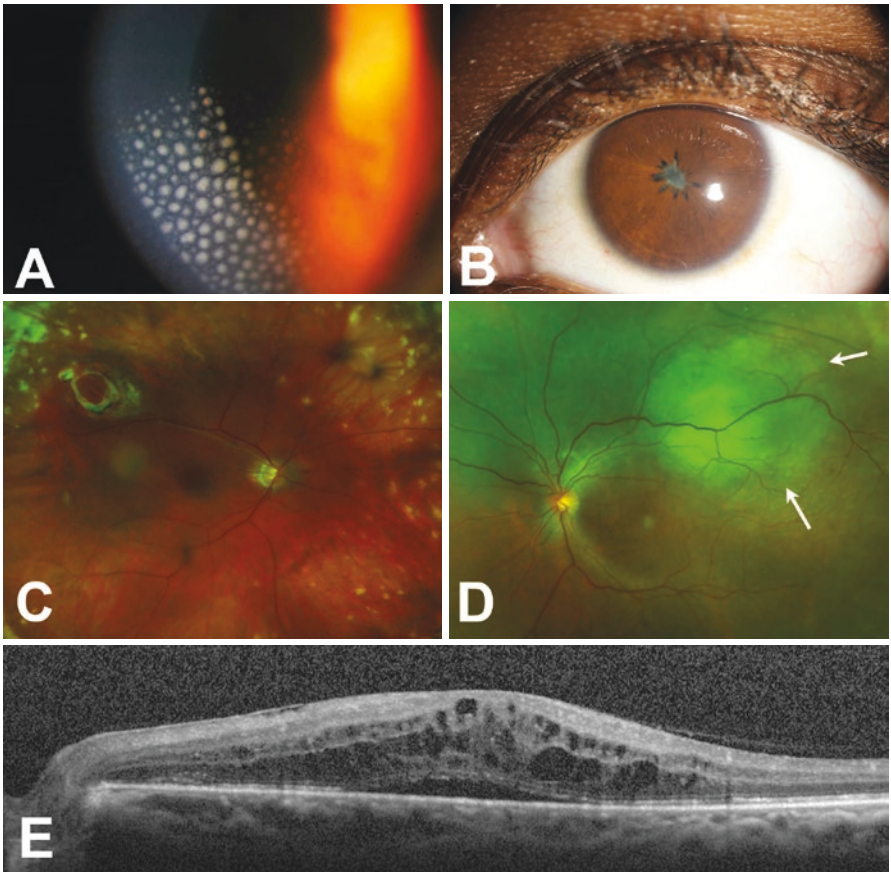

Fig. 3.14 Findings in sarcoidosis-related uveitis. (**a**) "Mutton-fat" keratic preciptates. (**b**) Posterior synechiae. (**c**) Multiple punched-out mid-peripheral chorioretinal lesions. (**d**) A large choroidal granuloma is evident along the superotemporal arcade (arrows). (**e**) OCT showing cystoid macular edema and subretinal fluid

Given the heterogeneity of findings which may be seen in sarcoidosis-related uveitis, the first international workshop on ocular sarcoidosis (IWOS) [172] reported seven ocular findings suggestive of ocular sarcoidosis:

1. Mutton-fat KPs and/or iris nodules
2. Trabecular meshwork nodules and/or tent-shaped PAS
3. Snowballs/vitreous opacities with string of pearls appearance
4. Multiple peripheral chorioretinal lesions which may be active or atrophic
5. Nodular/segmental periphlebitis and/or retinal macroaneurysm in an inflamed eye

6. Optic disc nodule/granuloma and/or solitary choroidal nodule
7. Bilateral disease

Key Diagnostic Tests

It should be noted that none of the IWOS criteria supporting ocular sarcoidosis are related to multimodal ocular imaging. Ocular diagnostic tests in cases of ocular sarcoidosis are therefore mainly for evaluating the degree of disease activity and response to therapy. OCT may reveal CME (Fig. 3.14e) and epiretinal membrane formation. OCT through a subretinal granuloma may reveal a subretinal hyperreflective lesion. EDI OCT through a choroidal granuloma may reveal a more homogeneous area compared to the surrounding choroid with increased signal transmission [173]. Large choroidal granulomas may appear as areas of irregular choroidal thickening with overlying subretinal fluid. FA may reveal perivenous hyperfluorescence, optic disc leakage, angiographic, CME, and/or retinal neovascularization. ICGA may have a number of patterns, but most commonly shows hypocyanescent lesions and hypercyanescent pinpoints [174, 175].

Differential Diagnosis and Critical Laboratory Workup

The differential diagnosis for the patient with sarcoidosis panuveitis includes TB, syphilis, VKH, toxoplasma panuveitis, intraocular lymphoma, among others. Pediatric sarcoidosis patients with uveitis can also present with an arthropathy and so juvenile idiopathic arthritis (JIA) and Blau syndrome need to be considered. The following laboratory evaluations are reported to be of value in supporting the diagnosis of ocular sarcoidosis per the IWOS: [172].

1. A negative tuberculin skin test in a patient who previously received the BCG vaccine or in a patient who previously had a positive tuberculin skin test
2. Elevated serum ACE and/or elevated serum lysozyme
3. A chest X-ray showing bilateral hilar lymphadenopathy (BHL)
4. Abnormal liver enzymes tests
5. CT chest showing BHL when the chest X-ray was negative

Anergy to a tuberculin skin test, but not quantiferon gold testing, has been reported in sarcoidosis and might be one method of providing supportive evidence [176]. It would be prudent to also rule out syphilis, given the heterogeneity of its presentation. An elevated serum ACE in sarcoidosis patients is secondary to high production of this enzyme in macrophage-dense granulomas. A study of 125 patients with sarcoidosis found that ACE was elevated in 60% of cases [177]. It should be noted that ACE is typically higher in healthy children than adults, and so, testing for ACE levels in children with suspected sarcoidosis may not be helpful. Additionally, patients taking ACE-inhibitors will have inaccurate measurements and so this test is not useful on such patients. Serum lysozyme also reflects macrophage activity and has been shown to be sensitive and specific for sarcoidosis [177, 178].

Evaluation of hepatic function was recommended by the IWOS, as the liver may be an occult site for granuloma formation. A "positive" liver function test is one in which the alkaline phosphatase levels are >3-fold the upper limit of normal or when two of the following three are >2-fold the upper limit of normal: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase. A chest X-ray showing BHL is present in as high as 89% of patients with systemic sarcoidosis [179, 180]. While a chest CT is not usually performed initially in the evaluation for sarcoidosis, when the clinical examination findings are highly suggestive of sarcoidosis, a chest CT might provide a higher sensitivity for detecting findings consistent with pulmonary sarcoidosis. It should be noted that mediastinal lymphadenopathy and pulmonary interstitial changes are also consistent with sarcoidosis. Additionally, some providers obtain an electrocardiogram or request their primary care physician to do so for all patients in whom there is suspected sarcoidosis, since the leading cause of sudden death in these patients is from an arrhythmia [181].

The IWOS developed four levels of certainty for the diagnosis of sarcoidosis, assuming that all other potential causes for uveitis had been ruled out: [172].

1. *Definite ocular sarcoidosis*: Those with biopsy-supported diagnosis and compatible uveitis.
2. *Presumed ocular sarcoidosis*: Those with compatible uveitis and radiographic evidence of BHL.
3. *Probable ocular sarcoidosis*: Those for whom biopsy was not performed and chest X-ray did not show BHL but three suggestive intraocular signs and two supportive laboratory tests were present.
4. *Possible ocular sarcoidosis*: Those for whom a lung biopsy was negative but four suggestive intraocular signs and two supportive laboratory tests were present.

Recent studies have shown that the IWOS criteria give high reliability in diagnosing ocular sarcoidosis and are used by many uveitis specialists in establishing the diagnosis of ocular sarcoidosis [182, 183]. Overall, once infectious causes of panuveitis have been ruled out, use of the IWOS criteria is a methodical way to reach a diagnosis of ocular sarcoidosis. Additional tests such as a high CD4/CD8 T-lymphocyte ratio in the vitreous of patients with sarcoidosis compared to those with nonsarcoid uveitis have also been adopted by some [184].

Treatment

Treatment of panuveitis in sarcoidosis follows a similar algorithm to treatment of bilateral active intermediate uveitis. That is, oral steroids with a slow taper are initiated. If disease activity recurs with tapering the steroids, IMT or bilateral Retisert implants may be needed. Management of the anterior component of the uveitis is typically augmented with topical steroids and cycloplegics and that of the intermediate and posterior components of the disease (including CME) with intraocular/periocular steroid injections. In terms of choice of IMT in patients with ocular sarcoidosis,

many agents including mycophenolate mofetil, methotrexate, azathioprine, and cyclosporine have been used with success [32, 185, 186]. In a large retrospective series, methotrexate was found to control uveitis in 66% of patients [187]. If there is an inadequate response to these mycophenolate or methotrexate, sometimes used in combination, one or both medications are substituted with azathioprine. There is no conclusive data on when to begin tapering off IMT in cases of quiescent ocular sarcoidosis. Much of what we know about tapering IMT in uveitis comes from the rheumatoid arthritis literature which suggests that if a patient has had quiescent disease for 2 or more years, it may be reasonable to slowly taper off IMT. Tumor necrosis factor-alpha inhibitors are likely to be effective in the treatment of antimetabolite-refractory ocular sarcoidosis, but have not been studied extensively. While adalimumab has shown efficacy in treatment and prevention of disease recurrence in noninfectious uveitis in a large randomized control clinical trial, only 10 patients in the treatment arm of the study had sarcoidosis-related uveitis [33]. In general, biologics are used with less frequency than antimetabolites in ocular sarcoidosis. Given that this is a multisystem disease, it is important to confer with the patient's rheumatologist, pulmonologist, and/or dermatologist about an optimal immunosuppressive regimen to manage all ongoing manifestations of the disease.

Clinical Course

A study by Karma et al. classified the course of ocular sarcoidosis into monophasic, relapsing, and chronic [188]. Those in the first two categories retained vision of 20/30 or better in 88% and 72% of eyes, respectively, while none with chronic inflammation retained such vision. Some have reported a worse visual prognosis for those with delayed presentation, glaucoma, posterior or intermediate uveitis, and others have found that the presence of CME portends a worse prognosis [189, 190]. Ultimately, aggressive control of inflammation with monitoring for and management of local and systemic side effects of therapy gives these patients the best opportunity to retain good vision.

Behçet Disease (BD)

Background and Epidemiology

BD is a multisystem chronic relapsing vasculitis most commonly seen in patients with heritage from countries along the Silk Road. The prevalence is as high as 420/100,000 in Turkey compared to only 0.64/100,000 in the United Kingdom [191]. BD most commonly presents in the third to fourth decades of life. The etiology is unknown, but there is a well-established association with the HLA-B51 allele [192]. Ocular manifestations occur in up to 70% of patients with BD and are bilateral in about 80% of cases [193].

Common Symptoms

Patients may be most symptomatic from the non-ocular systemic manifestations include recurrent oral aphthous ulcers, genital ulcers, and skin lesions. Cutaneous pathergy which features the development of a sterile pustule at the site of

venipuncture or injection is a characteristic, but not universal, finding in BD. Patients may exhibit dermatographia which is a hypersensitivity reaction featuring the development of erythematous lines following stroking of the skin. Vasculitis in BD can affect an artery or vein of any size and so, patients can present with chest pain from coronary arteritis or pericarditis, headache, strokes, nerve palsies, and confusion from CNS involvement, abdominal pain from GI ulceration, and joint pain.

Ocular symptoms in BD are secondary to either the acute anterior uveitis, retinitis, or retinal vasculitis. Ocular symptoms include redness, pain, photophobia, and blurry vision in one or both eyes.

There have been numerous diagnostic criteria for BD. The most recent and highly validated system is "The International Criteria for BD (ICBD)" [193] The ICBD, validated by the International Team for the Revision of the ICBD, suggests that if a patient scores ≥4 on the following scale, they are classified as having BD:

1. Recurrent genital or oral ulcerations (each 2 points)
2. Uveitis or retinal vasculitis (2 points for either)
3. Characteristic skin lesions (1 point)
4. CNS involvement (1 point)
5. Positive pathergy test (1 point)

This scoring system resulted in a sensitivity and specificity for identifying BD of approximately 94% and 92%, respectively.

Exam Findings

Anterior segment examination may reveal a nongranulomatous anterior uveitis with hypopyon formation. The hypopyon is characteristically transient and mobile in a relatively quiet eye ("cold hypopyon"). With multiple bouts of anterior uveitis, posterior synechiae, peripheral anterior synechiae, and synechial angle closure can occur. A variable amount of vitritis may be present, but is nearly universal in patients with active disease. The most common ocular finding in BD is an obliterative, necrotizing retinal vasculitis affecting both retinal arterioles and veins [194]. Subtler retinal vasculitis with retinal vascular sheathing, retinal vein, or arteriolar occlusion may be seen. Ischemia from retinal vascular occlusion may result in retinal neovascularization and vitreous hemorrhage. Patches of chalky white retinitis in areas of active retinal vasculitis may be seen (Refer to figures in Chap. 10). Papillitis may be seen which can lead to progressive optic atrophy. Additionally, retinal vascular leakage may result in CME and disc swelling. End-stage disease may be characterized by optic atrophy and white, sclerotic retinal vessels.

Key Diagnostic Tests

OCT may reveal diffuse thickening from vein occlusion, inner retinal thinning from arteriolar occlusion, chronic CME, or atrophy. FA may reveal perivascular hyperfluorescence (Fig. 3.15), disc hyperfluorescence, leakage in the macula, areas of nonperfusion and retinal neovascularization [195]. FA is a useful tool to follow patients with BD, as angiographic signs of activity may be present before overt clinical signs such as vascular sheathing.

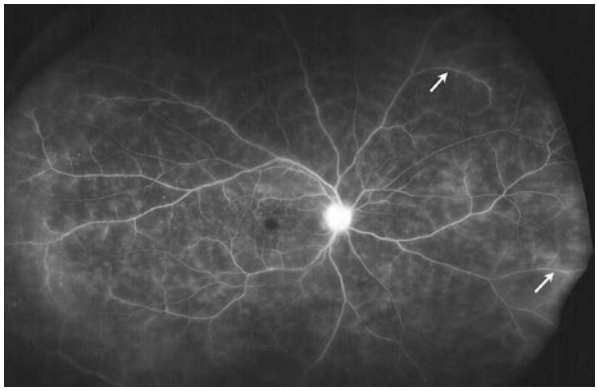

Fig. 3.15 Fluorescein angiography in Behçet disease showing optic disc hyperfluorescence, leakage along peripheral retinal vessels (arrows) as well as a diffuse capillaritis

Differential Diagnosis and Critical Laboratory Workup

For patients with panuveitis related to BD, other noninfectious causes of panuveitis such as sarcoidosis and VKH should be considered. Retinal whitening in BD can raise concern for herpetic acute retinal necrosis or toxoplasma panuveitis. Those with a hypopyon uveitis may be confused for an HLA-B27-associated anterior uveitis. Patients with prominent GI or articular symptoms and a mild uveitic phenotype may be misdiagnosed with a seronegative spondylarthropathy, particularly IBD-associated uveitis or a collagen vascular disease. In a patient presenting with panuveitis, serology and imaging to evaluate for sarcoidosis and syphilis are appropriate. In those with evidence of retinal necrosis, an anterior chamber tap for viral PCR and vitreous tap for toxoplasma titers can be considered.

Treatment

The treatment course for BD will depend on where the predominant site of inflammation is. For those with predominantly ocular symptoms, initiation of high-dose oral steroids (1.5 mg/kg) with a slow taper and azathioprine is recommended. Azathioprine has been shown in clinical trials and large retrospective analyses to result in fewer uveitis flares, less eye involvement, and less blindness than placebo [196–198]. There are additional reports involving a limited number of patients which have shown control of uveitis in BD using methotrexate, cyclosporine, infliximab, and adalimumab [199, 200]. Utilization of TNF-alpha inhibitors in particular has shown striking success in the treatment of BD. In Europe and elsewhere, interferon alpha 2a has also been successful in treating ocular BD. Finally, there have been reports of interleukin-1 inhibitors and tocilizumab (an interleukin-6 inhibitor) as treatment for treatment-refractory ocular BD [201]. As with other multisystem diseases featuring uveitis, therapeutic management needs to be done in concert with other specialists to ensure adequate systemic control and mitigate medication side effects.

Clinical Course

In an international study including over 1400 patients with BD, over 95% of patients had recurrent ocular disease with 23.3% of patients having vision worse than 20/200 in the better eye. Visual impairment is most often due to CME, ischemic maculopathy, optic atrophy, and glaucoma. While the visual outcomes reported may appear dismal, earlier diagnosis and new therapeutics may lead to improved visual outcomes.

Vogt-Koyanagi-Harada Disease (VKH)

Background and Epidemiology

VKH is a bilateral granulomatous panuveitis which features auditory, integumentary, and neurological involvement. VKH is more common among American Indians, Asians, Asian Indians, and Hispanic patients than Caucasians. It most commonly affects patients in their second to fifth decades of life, although pediatric VKH can also occur. The etiology of VKH is unknown, though an association has been shown to the HLA-DR1 and HLA-DR4 alleles [202, 203].

Common Symptoms

VKH is divided into four stages and has variability in symptoms based on the stage of the disease. The stages include:

1. *The prodromal stage*: In this stage, patients report a nonspecific flu-like illness. This stage typically lasts for 3–5 days and patients may experience headache, nausea dysacusis, meningismus, cranial nerve palsies, optic neuritis, hypersensitivity of the hair and skin to touch, photophobia, ocular pain, and tearing. Cerebrospinal fluid (CSF) analysis may show pleocytosis.
2. *The acute uveitic stage*: This occurs a few days after the prodromal stage and patients typically experience blurring of vision.
3. *The chronic uveitic or convalescent stage*: This stage occurs several weeks later. Patients may experience continued blurring of vision and may additionally report localized hair loss (alopecia), whitening of the eyelashes or hair (poliosis) and depigmentation of patches of skin (vitiligo) or fundus.
4. *The chronic recurrent stage*: This stage is characterized by smoldering panuveitis with recurrent bouts of anterior uveitis disease exacerbation. During such exacerbations, patients may experience a reduction in vision, floaters, light-sensitivity, and eye redness/pain.

Exam Findings

Ocular exam findings vary based on the stage of disease. During the *acute uveitic* stage of the disease, a bilateral granulomatous panuevitis may be present with KPs, anterior chamber inflammation, iris nodules (rarely), and vitritis. Funduscopy may

reveal blurring and hyperemia of the optic disc and choroidal thickening with focal serous detachments of the neurosensory retina (Fig. 3.16a). These areas of detachment may coalesce and form a large area of bullous detachment. The most commonly involved area is the peripapillary retina and posterior pole. Interestingly, the posterior findings are more common during the acute uveitic stage and only mild

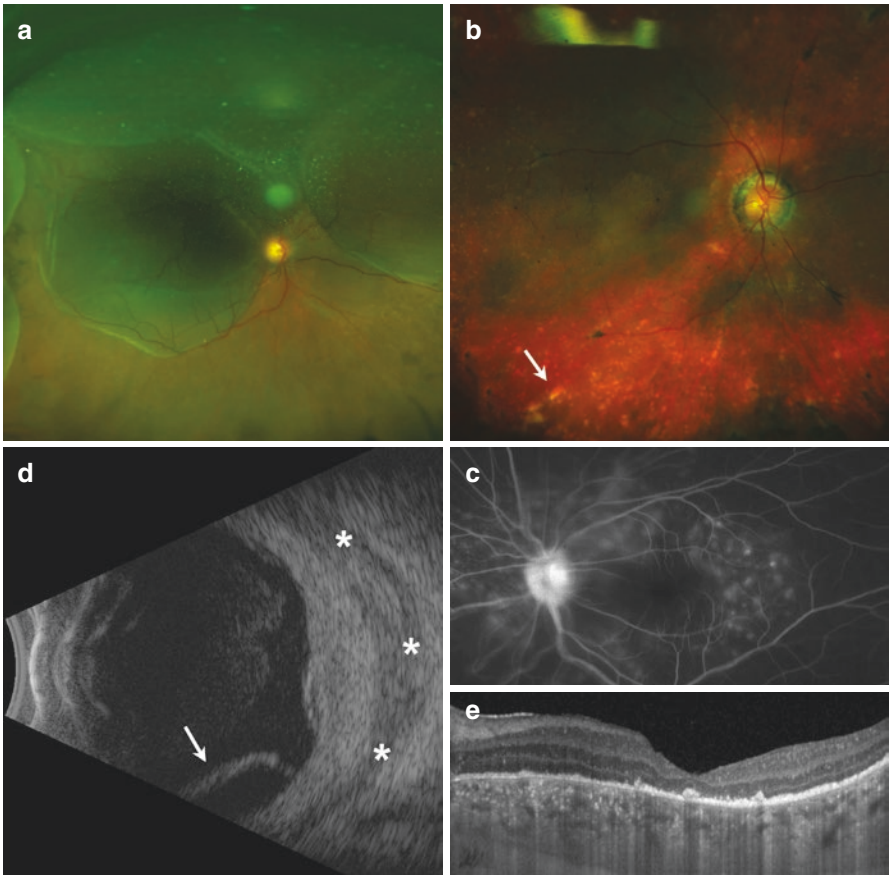

Fig. 3.16 Vogt-Koyanagi-Harada (VKH) syndrome and posterior scleritis. (**a**) Multifocal exudative retinal detachment in the acute stage of VKH. (**b**) Pigmentary changes and punched-out chorioretinal lesions (arrow) in a patient with VKH. (**c**) Fluorescein angiography showing multiple spots of leakage within an area of exudative detachment in VKH. (**d**) B-scan ultrasound in a case of posterior scleritis showing exudative retinal detachment (arrow), choroidal and scleral thickening and collection of fluid in the subtenons space (asterisks). All of these features other than the subtenons fluid may be seen in VKH. (**e**) OCT line-scan showing outer retinal loss, hyper-reflective foci, and significant choroidal thickening in VKH

anterior segment inflammation can occur during this stage. Inflammation of the ciliary body may lead to swelling and forward rotation of the lens-iris diaphragm, leading to acute angle closure glaucoma [204, 205]. Focal yellowish chorioretinal lesions can also be seen clinically (Fig. 3.16b), and correspond to the pathological Dalen-Fuchs nodules which are collections of sub-RPE (above Bruchs membrane) infiltrates consisting of leukocytes, epithelioid giant cells, and pigment.

The convalescent phase is marked by gradual resolution of serous retinal detachments and slow depigmentation of the choroid. This leads to an orange-red discoloration of the fundus, resulting in a "sunset-glow" appearance. Additionally, focal areas of RPE depigmentation or punched-out chorioretinal scars corresponding to resolved Dalen-Fuchs nodules may be seen. Other signs of RPE abnormality such as pigment clumping may occur. Loss of perilimbal pigmentation (perilimbal vitiligo or Sugiura sign) may be the first ocular sign of the convalescent phase.

During the chronic recurrent stage, posterior segment exacerbations are uncommon, but can occur. This stage features a smoldering anterior uveitis with acute exacerbation with the associated complications of posterior synechiae, PAS, synechial angle closure, and glaucoma. Additionally, posterior features of chronic uveitis such as CNV, subretinal fibrosis and optic atrophy may occur.

Of all the potential ocular findings in VKH, exudative retinal detachment and sunset glow fundus are the two most specific and most commonly seen findings in VKH [206]. With prompt treatment of acute disease, however, the sunset glow fundus may not develop.

Key Diagnostic Tests

OCT may reveal subretinal fluid, CME, pigment epithelial detachments over Dalen-Fuchs nodules, or retinal atrophy in chronic disease [207]. EDI OCT can show choroidal thickening which is an important diagnostic clue in VKH (Fig. 3.16e). FA may reveal hypofluorescent dots in the early phase corresponding to foci of choroidal inflammation which are shortly replaced by hyperfluorescent dots. In the later frames of the FA, a classic finding is multifocal areas of leakage with pooling into the area of exudative retinal detachment (Fig. 3.16c). In the later stages of disease, FA may show window defects in areas of RPE atrophy and evidence of CNV. FA additionally shows hyperfluorescence and leakage of the disc. ICGA may show hypocyanescent dots corresponding to foci of choroiditis [207]. FAF may reveal hypoautofluorescence in areas of RPE loss and hyperautofluorescence in areas of outer retinal loss with intact RPE [208]. B-scan ultrasonography is useful in detecting and following changes in choroidal thickening in VKH.

Differential Diagnosis and Critical Laboratory Workup

The extraocular manifestations of VKH are not uniformly present and thus diagnosis of VKH depends greatly on the ocular examination. The First International Workshop on VKH reported revised diagnostic criteria for VKH [209]. In addition

to no history of penetrating ocular trauma or surgery and no clinical/laboratory evidence of another uveitic entity, the following features must be present:

A. Complete VKH disease:
   1. Bilateral ocular involvement with characteristic early (subretinal fluid, characteristic FA findings, choroidal thickening on B scan) or late (ocular depigmentation, depigmented chorioretinal scars, pigment clumping, recurrent/chronic anterior uveitis) manifestations of disease.
   2. Neurological/auditory findings such as meningismus or tinnitus or CSF pleocytosis.
   3. Integumentary findings following onset of CNS and ocular disease such as alopecia, poliosis, or vitiligo.
B. Incomplete VKH disease: The ocular findings and either neurological/auditory or integumentary findings must be present.
C. Probable VKH disease: Only above ocular findings are present.

The differential diagnosis for probable VKH disease includes sympathetic ophthalmia, sarcoidosis, posterior scleritis, uveal effusion syndrome, and intraocular lymphoma.

Distinguishing VKH from sympathetic ophthalmia (SO) in the absence of CNS/auditory/integumentary findings can be challenging. SO, like VKH, is a chronic bilateral granulomatous panuveitis, but only occurs in patients with a history of penetrating trauma or intraocular surgery in one or both eyes [210]. While penetrating trauma is the most common cause of SO, intraocular surgery can also cause SO. The time separating the inciting incident and onset of SO is within 3 months in ~80% of some cases, but SO can occur years later. The eye with the prior surgery/penetrating injury (exciting eye) typically shows earlier and more severe inflammation than the fellow (sympathizing eye). The ocular findings can be indistinguishable from VKH including KPs, posterior synechiae, anterior chamber inflammation, vitritis, choroidal thickening, exudative retinal detachment with similar FA/ICGA features, Dalen-Fuchs nodules, optic atrophy, CME, and CNV [210]. Additionally, VKH and SO share similar HLA associations [211]. Thus, a history of no penetrating ocular injury or surgery is important in making the diagnosis of VKH.

Posterior scleritis can present very similarly to the acute uveitic stage of VKH with choroidal thickening and serous retinal detachment. Additionally, the FA features of multifocal spots of hyperfluorescence with leakage and pooling may be indistinguishable from VKH. Posterior scleritis, however, presents with a great deal of pain and a T-sign on B-scan ultrasonography, which do not occur in VKH (Fig. 3.16d).

Treatment

Despite the differences in VKH, SO, and posterior scleritis, the initial management is similar with high-dose (1.5–2 mg/kg/day) oral steroids. In all these entities, but especially in VKH, a slow taper of the oral steroids is critical, as recurrences in VKH are typically not as responsive to steroids. Studies have shown that steroids tapered over less than 6 months were much more likely to

result in disease recurrence in VKH [212]. In recurrent VKH, local steroid injections and addition of IMT or a long-term steroid implant are sometimes necessary [213]. Cyclosporine, azathioprine, infliximab or adalimumab, methotrexate, and cytotoxic agents have been shown to be efficacious in treating chronic VKH [214–217].

Clinical Course

Studies have shown that early treatment of VKH with high-dose corticosteroids with or without IMT can result in good visual outcomes with close to 70% of patients maintaining vision of 20/40 vision or better [218, 219] With recurrent inflammation, structural complications of chronic inflammation including cataract formation, glaucoma, CNV, and subretinal fibrosis can lead to poor visual outcomes.

Primary Vitreoretinal Lymphoma (PVRL)

Background and Epidemiology

PVRL is a subset of primary CNS lymphoma (PCNSL). PCNSL originates in the brain, meninges, spinal cord, or eye. Up to 25% of patients with PCNSL originating in the brain will have ocular involvement [220]. Among patients presenting with only ocular involvement, up to 90% will eventually have brain involvement [221, 222]. However, 15% of patients can have strictly ocular involvement. About 98% of PVRL are non-Hodgkin's large B-cell lymphomas [223]. While PVRL is not a uveitic entity, it can often masquerade as uveitis and so a discussion on this topic is warranted. PVRL typically presents in the sixth to eighth decades, though it can occur in younger patients who are immunocompromised. PVRL is bilateral in about 80% of cases, but can be highly asymmetric.

Common Symptoms

Patients may be asymptomatic or present with painless vision loss and floaters.

Exam Findings

Patients may have anterior chamber cells, KPs, and iris nodules. The vitreous cavity classically shows vitreous cells, vitreous haze, and condensations (Fig. 3.17). Funduscopy may reveal yellowish subretinal infiltrates (Fig. 3.18), sub-RPE infiltrates, and patches of RPE atrophy [224]. Exudative retinal detachment, perivascular infiltrates, and optic nerve infiltration or atrophy can also rarely occur [225].

Key Diagnostic Tests

OCT may reveal subretinal or sub-RPE hyperreflective material. FA can show areas of blockage from sub-RPE infiltrates or window defects in areas of atrophy. For patients with concern for PVRL, an MRI of the brain and orbits is critical which may reveal involvement of the brain parenchyma or meninges. Occasionally, cystoid macular edema can occur in the setting of PVRL.

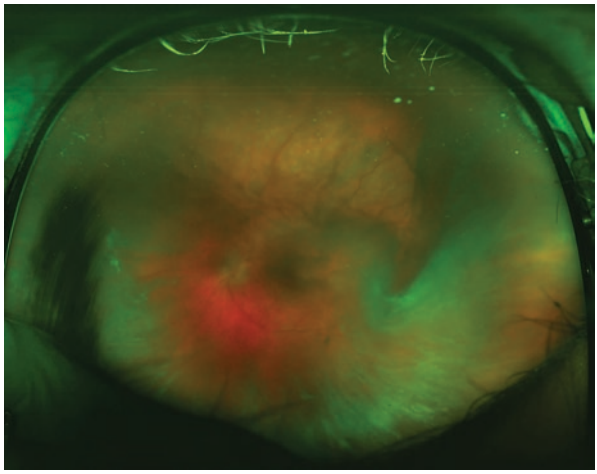

Fig. 3.17 Vitreous debris and haze in a case of primary vitreoretinal lymphoma

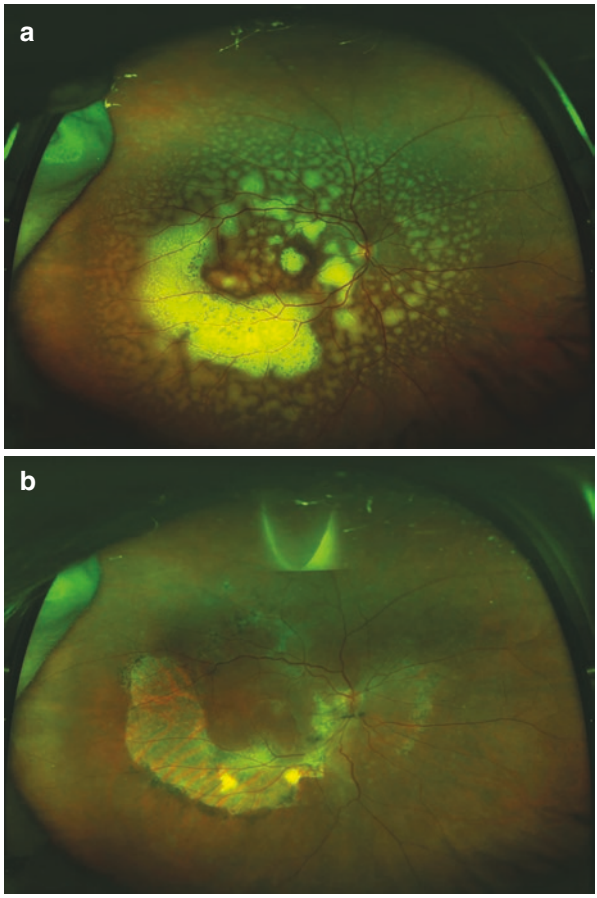

Fig. 3.18 Yellowish subretinal infiltrates in a patient with primary vitreoretinal lymphoma before (**a**) and after (**b**) systemic chemotherapy

Differential Diagnosis and Critical Laboratory Workup

In patients with a known history of PCNSL, the diagnosis of PVRL can be straightforward if the ocular findings are consistent. In patients without a known history of PCNSL, diagnosis of PVRL based on ocular examination alone can be a challenge, and one must maintain a high degree of suspicion. Additionally, as the vitreous cells in PVRL can be responsive to steroid treatment, this can further confound the diagnosis. In one study, the average time between onset of ocular symptoms and diagnosis of PVRL was 21 months [226]. Other causes of posterior uveitis and panuveitis such as syphilis, TB, sarcoidosis, and the white dot syndromes can closely resemble PVRL and are on the differential diagnosis. Subretinal and sub-RPE infiltrates can raise concern for metastatic disease from an alternate primary neoplasm. If laboratory testing is unremarkable for the aforementioned panuveitides and the patient fits the demographic for PVRL, the next step is neuroimaging. If neuroimaging is unrevealing, tissue diagnosis is necessary. For patients with a prominent vitreous component to their disease, a diagnostic vitrectomy is a reasonable approach. It is important to stop all forms of steroids prior to proceeding with a diagnostic vitrectomy, to maximize the diagnostic yield since it is thought that steroids can cause lysis of lymphoma cells. For patients with a prominent subretinal component, a subretinal aspirate may be performed. A chorioretinal biopsy can also be performed in such cases but especially for those with a prominent sub-RPE component. Regardless of the technique of biopsy performed, it is critical to have a discussion with the involved cytology and flow cytometry labs regarding appropriate tissue handling prior to performing the procedure.

Treatment

In cases of CNS involvement, treatment may involve external-beam radiation therapy (EBRT), systemic chemotherapy, or a combination of the two. In such cases, this treatment is also effective at managing the ocular disease. In cases of isolated ocular involvement, intravitreal chemotherapy (methotrexate and/or rituximab) and/or EBRT are the treatment options [227–230]. A sample intravitreal chemotherapeutic regimen for PVRL would be to inject methotrexate (400 μg/0.1 mL) twice a week for 4 weeks for induction followed by weekly injections for 4–8 weeks for consolidation followed by monthly injections for about a year. With a regimen similar to this, some studies have reported a 95% complete remission rate using less than 13 injections of methotrexate [231, 232]. Some studies have reported that rituximab may require fewer injections to achieve remission [227, 230]. In patients who cannot tolerate or come for multiple injections, EBRT may be a better option. In patients treated for CNS disease with systemic chemotherapy or whole-brain radiation therapy, isolated ocular relapses may occur. If neuroimaging confirms isolated recurrence in the eyes, such disease can similarly be managed with intravitreal chemotherapeutics.

Clinical Course

As mentioned previously, up to 90% of patients with PVRL may go on to develop CNS involvement. In a large series of 221 patients with PCNSL with PVRL, mean survival was 31 months [233]. The same study found that control of ocular disease did not conclusively improve survival.

Conclusion

Noninfectious intermediate, posterior, and panuveitis represent a large number of clinical entities. A systematic approach to diagnosis through careful history taking, clinical examination, multimodal imaging, and focused laboratory testing can help facilitate early diagnosis. Once the decision has been made to begin therapy, the uveitis should be managed aggressively to help prevent the development of irreversible complications such as optic atrophy, macular atrophy/scarring, and hypotony.

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Infectious Intermediate, Posterior, and Panuveitis

4

Mohsin H. Ali, Wenlan Zhang, and Dilraj S. Grewal

Cytomegalovirus

Microbiology

Cytomegalovirus (CMV) is an enveloped, double-stranded virus in the Herpesviridae family. There is a high prevalence of CMV in the general population, with one study reporting an overall seroprevalence of 58.9% in individuals aged 6 years or older [1]. The seroprevalence appears to increase with age (36.3% in 6–11 years old compared to 90.8% in individuals aged 80 years or older). There may be substantial variation in seroprevalence based on geographic location, racial and/or ethnic differences, and socioeconomic status [1, 2]. Primary infection leads to lifelong latency and the possibility of reactivation later in life. Reinfection with a different viral strain is also possible. Transmission occurs perinatally and sexually via contact with infected bodily fluids, such as saliva and urine, or via organ donation [3].

Epidemiology

In immunocompetent individuals, the primary CMV infection and reactivation may be asymptomatic or very mild, leaving laboratory testing for seropositivity potentially being the only indicator of exposure. In contrast, reactivation of this opportunistic infection in immunocompromised patients leads to symptomatic end-organ damage with high frequency. CMV retinitis, in particular, is the most common end-organ manifestation of the disease in severely immunocompromised acquired immunodeficiency syndrome (AIDS) patients [4]. The risk of developing CMV

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retinitis and the rapidity of progression are highest in patients with CD4+ T-cell lymphocyte count less than 50 per μL [4]. Other susceptible hosts include neonates and patients with a history of lymphoma, leukemia, solid-organ or bone marrow transplant recipients, systemic immunosuppressive therapy, primary immunodeficiencies, and intravitreal corticosteroid injections [5]. For example, in a study of bone marrow transplant patients with CMV viremia, 5.6% developed CMV retinitis [6]. Overall, the rates of CMV retinitis in non-AIDS patients are not well-established, but they appear to be less frequent than in the AIDS population.

In the pre-highly active antiretroviral therapy (HAART) era, 30% of AIDS patients suffered CMV retinitis during their lifetimes; however, this rate has been reduced by 75% in the HAART era [4]. The Longitudinal Study of the Ocular Complications of AIDS (LSOCA) study conducted in the HAART era reported a 4-year cumulative incidence of CMV retinitis in patients with CD4+ T-cell counts less than 100 cells/μL of 7% as compared to 25% in the pre-HAART era [7]. However, the same study reported cumulative 10- and 15-year rates of CMV retinitis in patients with CD4+ T-cell counts below 50 cells/μL of 34% and 44%, respectively [7]. Therefore, while the advent of HAART has led to a significant decline in the incidence of CMV retinitis, it remains a commonly encountered, potentially visually devastating condition in immunosuppressed individuals and the leading ocular opportunistic infection in AIDS patients [8].

Clinical Presentation

CMV retinitis is more commonly unilateral than bilateral [9]. Untreated unilateral CMV retinitis will commonly affect the fellow eye in the majority of patients [10]. Many patients with CMV retinitis will remain asymptomatic, while others may complain of decreased vision, scotomata, and floaters and photopsias. The anterior segment examination may reveal fine, stellate, keratic precipitates on the corneal endothelium, though the degree of anterior chamber and vitreous inflammation is typically mild if present. The fundus examination may be variable. Typically, there is full-thickness retinal necrosis which appears as creamy whitish or yellowish retinal lesions occurring as larger, confluent, or nonconfluent patches or as smaller, granular, satellite lesions (Fig. 4.1). These lesions may be present in the posterior pole, periphery, or both and often have a perivascular predilection. Additionally, intraretinal hemorrhages are typically present, located within the necrotic areas or at their leading edges (“brush fire” or “pizza pie” appearance). Frosted branch angiitis may also be seen. Independent of the frosted branch angiitis appearance, vasculitis and occlusive vasculopathy may also occur, manifesting as sclerotic, attenuated vessels, and angiographic nonperfusion. Papillitis, Kyrieleis plaques, or segmental retinal periarteritis, which are angiographically nonleaking, may also be seen [5, 11].

The clinical appearance of CMV retinitis has previously been subdivided into three variations: (1) classic or fulminant form, (2) indolent or granular form, and (3) exudative or perivascular form (also known as frosted branch angiitis) [11]. In the classic or fulminant form, there are areas of intraretinal hemorrhages within areas of whitish,

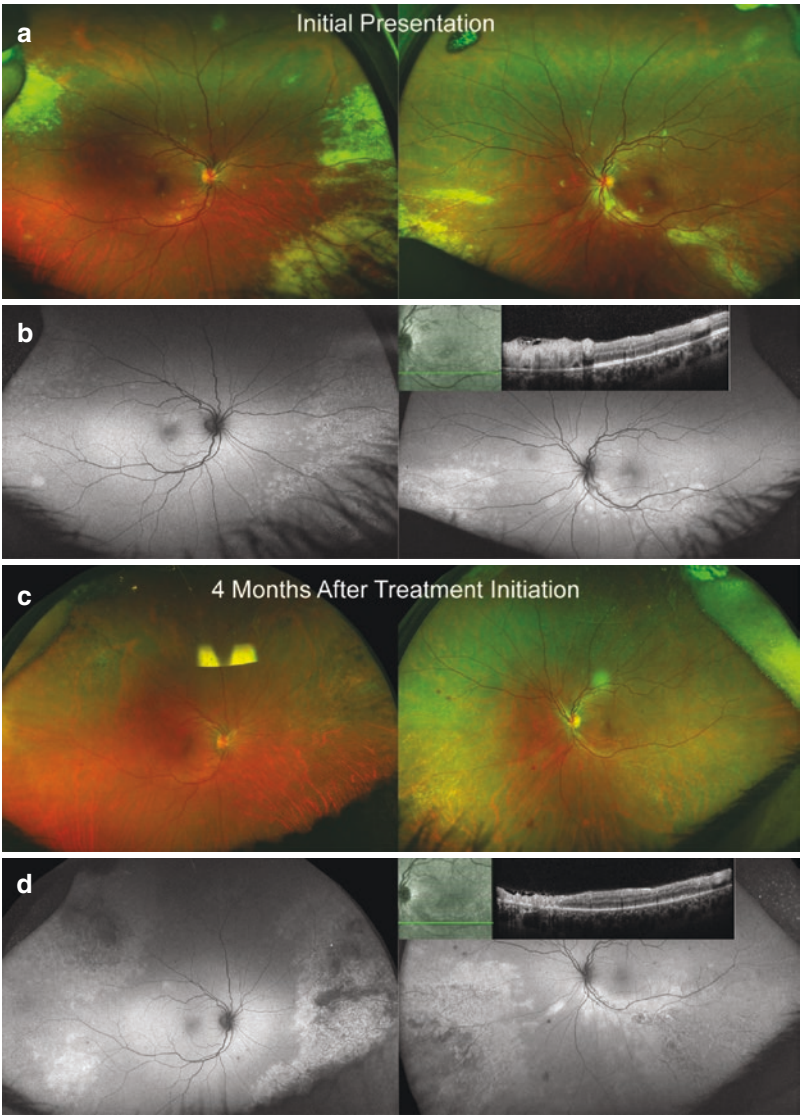


Fig. 4.1 CMV viral retinitis. (**a**) Optos wide-field imaging of right and left eyes in patient with newly diagnosed AIDS. Images show peripheral and posterior patches of retinitis with little vitritis and few intraretinal hemorrhages. Aqueous PCR was positive for CMV. (**b**) Corresponding optos fundus autofluorescence images with hyperfluorescence of lesions. Inset shows OCT of the left eye through an area of active retinitis at initial presentation with thickening and disorganization of the retinal inner layers near the inferotemporal arcade and focal pockets of subretinal fluid. (**c**) Optos images 4 months following course of intravenous ganciclovir and two intravitreal foscarnet injections each eye with peripheral atrophy and pigmentary changes consistent with healed retinitis. Area superior to optic nerve and superior arcade in right eye is reflection artifact on optos imaging. (**d**) Areas of hypoautofluorescence in patches of hyperautofluorescence. Inset shows corresponding OCT of the left eye 4 months following treatment with retinal thinning and atrophy with loss of the outer retinal layers

necrotic, edematous retina. In the indolent or granular form, smaller granular lesions as described above predominate, and other findings such as intraretinal hemorrhages, vascular sheathing, and retinal edema are less pronounced or absent. In the perivascular or exudative form, the classic "frosted branch angiitis" pattern of extensive perivascular sheathing is seen. The clinical presentation of CMV retinitis in AIDS patients and non-AIDS patients is often similar, though it has been suggested that non-AIDS patients may present with more significant intraocular inflammation and retinal vasculitis [12].

CMV retinitis may begin as what appears to be a small cotton wool spot. Therefore, clinicians must maintain a high degree of suspicion for such findings in immunosuppressed patients. In addition to the clinical examination, photodocumentation can be very helpful in monitoring lesion progression in both established and suspicious cases. Hyperautofluorescence of the leading edge of a lesion may be a harbinger of progression or reactivation [5]. Progression of a CMV lesion has previously been described as a greater or equal than 750 μm advancement of the lesion border (which accounts for 79% of retinitis progression), a new lesion (20% of progression cases), or both (9% of progression cases) [4]. Others have estimated a rate of lesion progression of 24 μm/day [5]. Increased progression of CMV retinitis has been associated with lower CD4+ T-cell count, higher HIV viral load, higher CMV viral load, newly diagnosed retinitis (compared to long-standing retinitis), and longer duration of AIDS [4]. Of these, lower CD4+ T-cell count was the strongest predictor of CMV retinitis progression [4].

With proper treatment, the retinitis will regress leaving behind areas of atrophic retina. Complications may include retinal breaks and rhegmatogenous retinal detachment (occurring in 3–8.7%) [12], cystoid macular edema, epiretinal membrane, neovascularization (of the retina, choroid, or optic disc), cataract formation, and optic atrophy [5, 9]. Immune recovery uveitis (IRU) occurs with immune reconstitution (increasing CD4+ T-cell counts in AIDS) and may result in iritis, vitritis, cataract, posterior synechiae, cystoid macular edema, and other inflammatory sequelae [9]. The risk of IRU may be higher in individuals with more severe CMV retinitis, those treated with cidofovir, and patients in whom HAART therapy was initiated prior to CMV induction therapy [9].

The diagnosis of CMV retinitis may be made on the clinical findings alone, but it may be aided by laboratory testing of the serum or intraocular fluids. It is important to note that CMV retinitis may still occur in the presence of negative serum testing. Polymerase chain reaction (PCR) testing has a high sensitivity and specificity for the diagnosis of intraocular CMV infection, both from aqueous samples (93% sensitivity, 99% specific) and vitreous samples (90% sensitive, 98% specific) [13]. Additionally, quantitative PCR analysis may be utilized to determine the response to treatment in select cases.

Management

The principles of CMV retinitis treatment include the following: (1) systemic antivirals; (2) intravitreal antivirals, if needed; (3) reconstituting the immune system, if

possible (e.g., beginning HAART therapy); and (4) continued monitoring in the quiescent phase for complications, such as retinal detachment, immune recovery uveitis, reactivation, and fellow eye involvement.

Systemic antiviral treatment is typically divided into an induction phase lasting 2–3 weeks and a maintenance phase. The dosing, duration, and choice of therapy may vary depending on multiple factors (such as renal function and comorbidities), but some general guidelines are listed below [5]:

- Oral valganciclovir
  - Induction: 900 mg twice daily
  - Maintenance: 900 mg daily
- Intravenous ganciclovir
  - Induction: 5 mg/kg twice daily
  - Maintenance: 5 mg/kg daily
- Intravenous foscarnet
  - Induction: 90 mg/kg twice daily
  - Maintenance: 120 mg/kg daily
- Intravenous cidofovir
  - Induction: 5 mg/kg weekly
  - Maintenance: 5 mg/kg every 2 weeks
- Others
  - Leflunomide
  - Letermovir
  - Maribavir
  - Brincidofovir
  - Artesunate

Systemic maintenance therapy may continue indefinitely (lifelong) especially in organ transplant recipients or at least until sustained immune reconstitution is achieved (e.g., greater than 6 months of CD4+ T-cell count greater than 100–150 cells/μL) [5]. Clinicians must also be aware of the possibility of drug-resistant strains of CMV. Mutations in the *UL97* viral gene confer low-level resistance to ganciclovir and valganciclovir, whereas mutations in the *UL54* gene confer high-level resistance to ganciclovir, valganciclovir, foscarnet, and cidofovir.

Intravitreal antiviral treatment may be administered with the medications listed below [5]. The induction phase of intravitreal therapy typically lasts until the progression of CMV retinitis has halted and ideally when signs of improvement become apparent. This can be done in combination with systemic antiviral therapy. Maintenance intravitreal injections are not necessary if adequate maintenance systemic therapy is being employed, but they may still be used depending on the location and extent of retinitis and the presence of resistance mutations. The intraocular sustained-release ganciclovir implant (4.5 mg) (Vitrasert, Bausch and Lomb, Rochester, NY, USA) which provided approximately 8 months of maintenance therapy is no longer available.

- Intravitreal ganciclovir
  - Induction: 2–4 mg/0.1 mL one to four times as needed (higher doses even up to 5–6 mg/0.1 mL have also been reported for the treatment of refractory, drug-resistant CMV) [14, 15]
  - Maintenance 2 mg weekly
- Intravitreal foscarnet
  - Induction: 1.2–2.4 mg 1–2 times weekly
  - Maintenance: 1.2–2.4 mg weekly
- Intravitreal cidofovir
  - Induction: 20 μg 1–8 times
  - Maintenance: 20 μg every 5–6 weeks

While intravitreal ganciclovir and foscarnet are generally well tolerated with minimal side effects, cidofovir has been associated with a high rate of anterior uveitis, cystoid macular edema, ciliary body atrophy and hypotony, and a higher rate of IRU [5].

It is important to realize that intravitreal antiviral injections do not prevent fellow eye involvement if injected unilaterally and do not address other organs where CMV-induced end-organ damage may be occurring or impending. Therefore, intravitreal therapy alone in the absence of systemic antiviral treatment is frequently reserved for select few cases such as in patients unable to tolerate or resistant to systemic antivirals.

In non-AIDS patients, reconstituting the immune system may involve withholding systemic immune suppression; however, this is often difficult given the patient's dependence on immunosuppression for other medical indications (e.g., transplant rejection). In AIDS patients, the goal of immune reconstitution with HAART is typically to reach a CD4+ T-cell count above 100 cells/μL. However, it must be noted that a higher CD4+ T-cell count (even greater than 200 cells/μL) is not fully protective against CMV reactivation and fellow eye involvement in AIDS patients, and therefore, careful vigilance remains prudent even after initiation of HAART therapy and apparent immune reconstitution; this may involve seeing patients for dilated fundus examinations every 3 months or even more frequently [16].

Necrotizing Herpetic Retinopathy (Including Acute Retinal Necrosis and Progressive Outer Retinal Necrosis)

Microbiology

Acute retinal necrosis syndrome (ARN) may be caused by varicella zoster virus (VZV), herpes simplex virus 1 or 2 (HSV 1/2), and less commonly by cytomegalovirus (CMV) or Epstein–Barr virus (EBV). By far, the most common causative organism in adults is VZV, which accounts for more than half of all affected patients in most studies [17–19]. In younger patients (e.g., younger than age 25), HSV—in particular, HSV2—may be more common than VZV [20]. Progressive outer retinal necrosis (PORN) is also most commonly caused by VZV.

Epidemiology

Acute retinal necrosis syndrome is a relatively rare condition, with an estimated annual incidence of 0.50–0.63 new cases per million population (based on nationwide surveys from the United Kingdom) [17, 21]. Studies have suggested that certain haplophenotypes may be associated with an increased immunogenetic predisposition of acquiring ARN [22]. A substantial number of patients (up to 60–90%) may have a history of prior or coexisting extraocular manifestations of VZV infection (such as zoster dermatitis) [11].

Clinical Presentation

The American Uveitis Society established clinical guidelines for the diagnosis of ARN in 1994 [22]. The defining clinical characteristics are summarized as follows:

1. Focal, well-demarcated areas of retinal necrosis localized to the peripheral retina (i.e., anterior to the vascular arcades)
2. Rapid, circumferential progression of necrosis in the absence of appropriate antiviral therapy
3. Occlusive vasculopathy
4. "Prominent" inflammatory reaction in the vitreous and anterior chamber
5. Other supporting clinical features that are supportive but not required for diagnosis include optic atrophy, scleritis, and pain

The inflammatory response accompanying ARN may consist of either granulomatous or nongranulomatous anterior uveitis, keratic precipitates, vitritis, retinal vasculitis, and papillitis. The areas of retinitis appear yellowish or whitish and, as mentioned in the American Uveitis Society guidelines, typically occur in the periphery (Figs. 4.2 and 4.3) after which they may ultimately coalesce and progress in a centripetal manner toward the posterior pole. There may be accompanying intraretinal hemorrhages and perivascular sheathing.

In contrast, patients with progressive outer retinal necrosis (PORN) typically do not exhibit a significant inflammatory response—and therefore, there is often a notable absence of anterior chamber or vitreous cell in the majority of patients, and only mild anterior chamber and vitreous cell (i.e., 1–2+ cell) and nongranulomatous keratic precipitate in a minority (one-third) of patients that do exhibit an inflammatory response [23]. The pattern of retinitis in PORN also differs from ARN. Retinitis in PORN typically begins as multifocal, discrete, outer retinal lesions in the posterior pole that ultimately progress to full-thickness involvement, including the inner retina, coalesce, and spread centrifugally [23]. As in ARN, there may be optic disc swelling, hyperemia, or atrophy, perivascular sheathing, and occlusive vasculopathy [23].

In general, ARN typically affects immunocompetent individuals, in contrast to PORN and CMV retinitis, which typically affect immunocompromised patients.

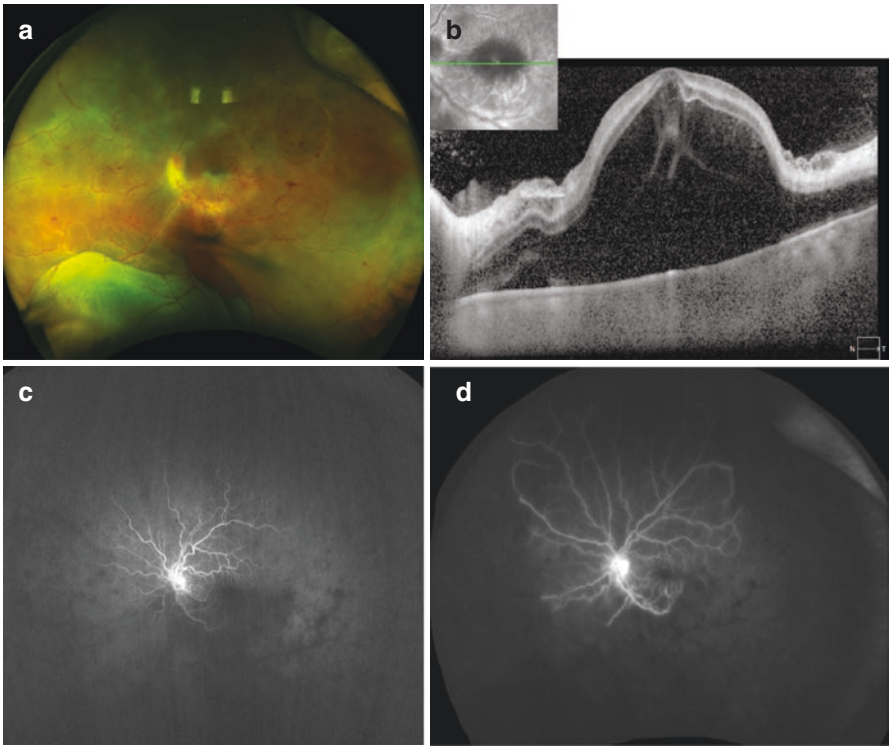


Fig. 4.2 HSV viral retinitis. (**a**) Optos image of left eye in patient with newly diagnosed HIV with aqueous PCR positive for HSV. Patient presented with unilateral rapidly decreasing vision with minimal vitritis, peripheral retinitis, diffuse retinal whitening, and vasculitis. There was an inferior retinal detachment with a small adjacent break in atrophic retina. (**b**) OCT through the macula with few vitreous cells, significant cystoid macular edema with subretinal fluid, and inner retinal thickening and disorganization. (**c**) Early fluorescein angiography with delayed arterial filling in a suspected central arterial occlusion. (**d**) Late fluorescein angiography with evidence of concurrent central venous occlusion and diffuse peripheral nonperfusion with perivascular and disc leakage

However, ARN and PORN may be better thought of as conditions across a spectrum of necrotizing herpetic retinopathy [24, 25]. Reports of patients with seemingly normal immune function with predominantly PORN-like clinical manifestations have been described [26].

It is important to note that the clinical presentation of ARN and PORN may be variable, perhaps owing to the etiological organism(s), the patient's immunophenotype, ocular and systemic comorbidities, or other factors [24]. As such, the American Uveitis Society's diagnostic guidelines for ARN intentionally include some degree of ambiguity to account for variable clinical presentations. For example, the degree of accompanying inflammation (described as "prominent") and the rapidity of progression (described as "rapid") are not clearly defined so as not to unduly restrict the diagnostic criteria. Accordingly, clinicians should maintain a low suspicion for necrotizing herpetic retinopathy when faced with any degree of the above-described clinical characteristics.

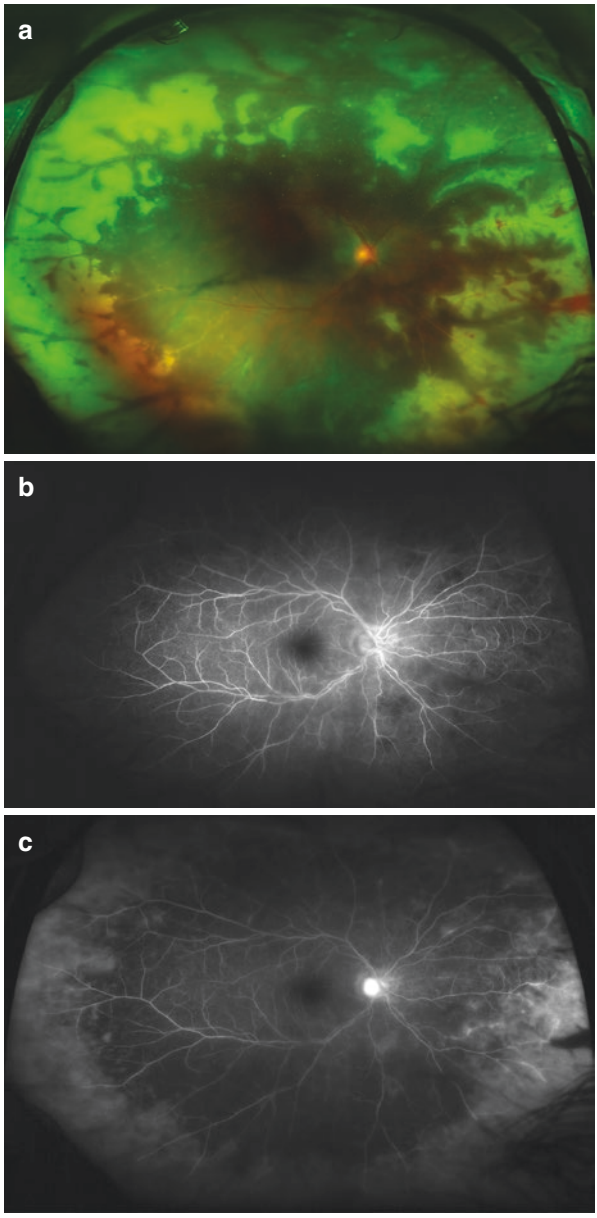


Fig. 4.3 VZV viral retinitis. (**a**) Optos image of right eye in patient with aqueous PCR positive for VZV. Exam showed mild vitritis with peripheral retinitis and vasculitis sparing the perivascular retina. (**b**) Midphase fluorescein angiography with blockage of retinitis lesions. (**c**) Late fluorescein angiography with late staining of retinitis and perivascular leakage

While the diagnosis of necrotizing herpetic retinopathy may be made based on the examination findings alone, it is often helpful to obtain identify the causative organism with aqueous or vitreous sampling and polymerase chain reaction (PCR) testing. Ocular fluid PCR in cases of clinically suspected ARN has a high rate of positive testing for VZV or HSV 1/2 (79–100%), and there is insufficient evidence to favor the superiority of obtaining positive results with either aqueous or vitreous

sampling [27]. It should be noted that awaiting PCR confirmation should not delay treatment in cases of clinically suspected ARN or PORN given the potential for rapid progression, vision loss, fellow eye involvement (which occurs in 59–70% of cases) [11], and systemic manifestations. PCR analysis of ocular fluids in patients who have already begun antiviral therapy may have a lower rate of virus detection, and therefore ocular fluid should ideally be collected for PCR testing prior to initiating antiviral treatment [27].

Management

The management of both ARN and PORN requires systemic antiviral treatment with or without the adjunctive use of intravitreal antivirals. Local intravitreal treatment alone is insufficient given the propensity for bilateral involvement and the possibility of coexisting systemic manifestations (e.g., encephalitis).

The systemic antivirals listed below may be considered. The dosing, duration, and choice of therapy are not standardized and may vary depending on multiple factors (such as renal function and comorbidities), and they may best be selected in collaboration with an infectious disease specialist. It is important to measure a baseline renal function, so dose adjustment can be performed as required.

- Oral valacyclovir (1000 or 2000 mg TID during induction period, followed by 1000 mg/day during maintenance phase)
- Oral acyclovir
- Oral valganciclovir
- Oral famciclovir
- Intravenous acyclovir
- Intravenous foscarnet
- Intravenous ganciclovir

The following intravitreal antiviral agents may be considered for adjunctive treatment along with systemic antivirals:

- Intravitreal foscarnet (typically 2.4 mg/0.1 mL)
- Intravitreal ganciclovir (typically 4 mg/0.1 mL)

In general, necrotizing herpetic retinopathy has been treated with intravenous antiviral therapy during an induction period typically ranging from 7 to 10 days or longer until noticeable disease quiescence is seen. This is often carried out using intravenous acyclovir, though the reported doses in prior studies have been variable (e.g., 1500 mg/m^2/day, 10 mg/kg q8hr, 500 mg/m^2 TID). Subsequently, a maintenance phase of oral antiviral therapy is typically employed (e.g., oral valacyclovir 1000 mg TID, oral acyclovir 800 mg 5×/day, or oral famciclovir 500 mg TID). The bioavailability of oral valacyclovir is higher compared to oral acyclovir (54–60% versus 15–30%), and it is therefore considered the preferred oral agent in the absence of other considerations such as cost and systemic comorbidities [27].

Serum antiviral levels as measured by area under the curve of orally administered valacyclovir 2000 mg QID have been shown to reach a similar concentration as compared to intravenously administered acyclovir 10 mg/kg q8hr [28]. Of note, the maximal concentration and time to peak concentration were superior with intravenous dosing. Orally administered antivirals likely also achieve therapeutically effective levels within the vitreous as well [27]. Given these considerations, a recent report by the American Academy of Ophthalmology has suggested that induction dosing with oral valacyclovir 2000 mg QID may be appropriate in ARN in the absence of other central nervous system involvement [27].

In addition to systemic antiviral treatment, during the induction period, there is likely additional benefit accrued from the use of adjunctive antiviral agents—in particular, two studies have suggested that adjunctive intravitreal foscarnet may increase the chance of visual acuity gain and decrease the risk of retinal detachment [27, 29, 30].

The robust inflammatory response may also need to be controlled typically with adjunctive topical and/or oral steroids. However, steroids should only be employed after initiating the appropriate antiviral therapy given their propensity to promote viral replication.

While necrotizing herpetic retinopathy is a treatable condition, it is important to recognize and counsel patients that the visual outcomes are generally poor. For example, 48% of eyes affected by ARN have a visual acuity below 20/200 at 6 months [27]. The poor visual outcomes may occur secondary to a variety of clinical sequelae such as retinal necrosis affecting the macula, optic neuropathy, and macular ischemia, among others. The most common cause of vision loss may be retinal detachment, which occurs in 26–85% of ARN patients [27]. There remains insufficient evidence to support prophylactic laser retinopexy or early pars plana vitrectomy as methods to reduce the risk of subsequent retinal detachment [27].

West Nile Virus

Microbiology and Epidemiology

West Nile virus (WNV) is a single-stranded RNA *Flavivirus* and is transmitted to humans via infected mosquitoes [9]. Despite its name, the virus has been reported in various geographic locations including North America, Europe, Africa, Asia, and Australia.

Clinical Presentation

Most WNV infections are subclinical (approximately 80%), though symptomatic patients experience systemic manifestations ranging from mild constitutional symptoms (e.g., fever, malaise, headache, myalgias, lymphadenopathy) to severe neuroinvasive disease that may consist of meningitis, encephalitis, paralysis, and a

poliomyelitis-like syndrome in rare cases [9, 31, 32]. These neurological symptoms only occur in less than 1% of patients [32]. Patients with severe meningoencephalitis are prone to WNV ocular involvement and may develop symptoms of blurred vision, floaters, visual field defect, redness, and pain occurring on average 10 days following the onset of systemic symptoms [9, 33]. They may have bilateral anterior chamber cell and flare, vitritis, multifocal chorioretinitis with deep, flat, creamy, whitish-yellowish lesions, retinal hemorrhages, vascular sheathing, occlusive vasculitis, and optic disc swelling [9, 31, 34]. Posterior segment involvement may occur in ~80% of patients, with most commonly encountered posterior segment findings being multifocal chorioretinitis (79.3%) and intraretinal hemorrhages (72.4%) [33]. The lesions comprising the chorioretinitis follow a linear or curvilinear pattern in relation to the retinal nerve fiber layer organization in the majority of cases (81.8%) [33].

Management

The diagnosis is suspected in the presence of the appropriate systemic findings and clinical history and may be confirmed with serological testing such as with enzyme-linked immunosorbent assay testing for WNV IgM. Most patients recover vision without treatment; though topical corticosteroids, oral corticosteroids, and ribavirin have been employed, the true efficacy of these treatments is not clear [9]. Other interventions such as intravitreal antivascular endothelial growth factor injections, panretinal photocoagulation, and vitrectomy are occasionally necessary in the setting of choroidal neovascularization, retinal neovascularization, and vitreous hemorrhage, respectively.

Toxoplasmosis

Microbiology

Ocular toxoplasmosis is caused by protozoan parasite *Toxoplasma gondii*, and humans most commonly acquire this infection postnatally via consumption of undercooked meats, most commonly pork, containing the bradyzoite form of *T. gondii* or via exposure to water and food contaminated with the oocyst form. Most epidemics of ocular toxoplasmosis are thought to be related to the latter mode of transmission. Additionally, humans may acquire the infection congenitally. The oocysts are produced solely in the intestinal tracts of felines, the definitive host of *T. gondii*, and exposure to felines (such as food or water contaminated with cat feces) is related to disease transmission.

Epidemiology

The seroprevalence of toxoplasmosis worldwide is generally quite high, though the rates vary markedly by geographic location, socioeconomic status, dietary habits, and religious practices [35, 36].

Clinical Presentation

Adults affected by toxoplasmosis retinochoroiditis may initially have a subclinical presentation with no symptoms or may experience decreased vision and floaters [37, 38]. Other patients may endorse a history of recurrent episodes of altered vision with spontaneous resolution. Patients are most commonly present with symptomatic infection in the second through fourth decades of life, with one study citing a mean age of initial presentation of 29.5 years [39, 40]. The majority of immunocompetent patients (72–83%) present with unilateral disease [37].

In immunocompetent patients, the classic presentation is a focus of retinitis situated adjacent to or arising at the border of a preexisting pigmented chorioretinal scar [37, 38]. Large lesions (e.g., larger than the diameter of the optic nerve head) accompanied by severe vitritis might exhibit the classic "headlight in a fog" appearance in which the headlight represents the focus of retinitis and the fog represents the severe vitritis. While vitritis is often a prominent feature, the degree of vitritis may range from mild to severe, and larger areas of retinitis are thought to be associated with more severe vitritis (Fig. 4.4). Other associated findings may include granulomatous or nongranulomatous anterior uveitis, keratic precipitates, retinal vasculitis (involving veins more commonly than arteries), and Kyrieleis plaques [37–39]. Elevated intraocular pressure, though not always present, is also a relatively distinctive feature of toxoplasmosis infection, similar to herpetic infections.

Several host, parasitic, and environmental factors, such as patient age, immune dysfunction, and parasite genotype, contribute to significant variations in disease manifestation leading to presentations different than the above-described classic features. Therefore, clinicians must maintain a high index of suspicion for toxoplasmosis retinochoroiditis in the setting of both classic and atypical clinical features of the disease. The following represent atypical manifestations of the disease: (1) clusters of smaller (e.g., 25–75 μm diameter), partial thickness, gray-white outer retinal lesions located in the posterior pole with minimal vitritis—a presentation which has been termed punctate outer retinal toxoplasmosis (PORT); (2) retinitis in the absence of a visible preexisting, inactive chorioretinal scar; (3) neuroretinitis; and (4) papillitis [37–39]. In addition, immunocompromised patients may present differently than immunocompetent patients and may have a more fulminant course, bilateral involvement, and multifocal and larger areas of active retinochoroiditis [37].

In certain patients, especially those who are immunocompromised, toxoplasmosis retinochoroiditis may be difficult to distinguish clinically from necrotizing herpetic retinopathy. Lack of hemorrhage, more densely yellow-white lesion color, distinct, smooth lesion borders, and prominent anterior chamber or vitreous inflammation may possibly favor the diagnosis of toxoplasmosis [41].

The diagnosis of ocular toxoplasmosis may be made on clinical grounds, but PCR analysis for the detection of *T. gondii* in ocular fluids (aqueous humor or vitreous) may be helpful, especially in atypical cases. The sensitivity of PCR for toxoplasmosis though lower than that of herpetic infections remains fairly high (~67%) [42]. Another useful diagnostic aide is the Goldmann-Witmer coefficient which compares the proportion of IgG in ocular fluid with the proportion of IgG in serum

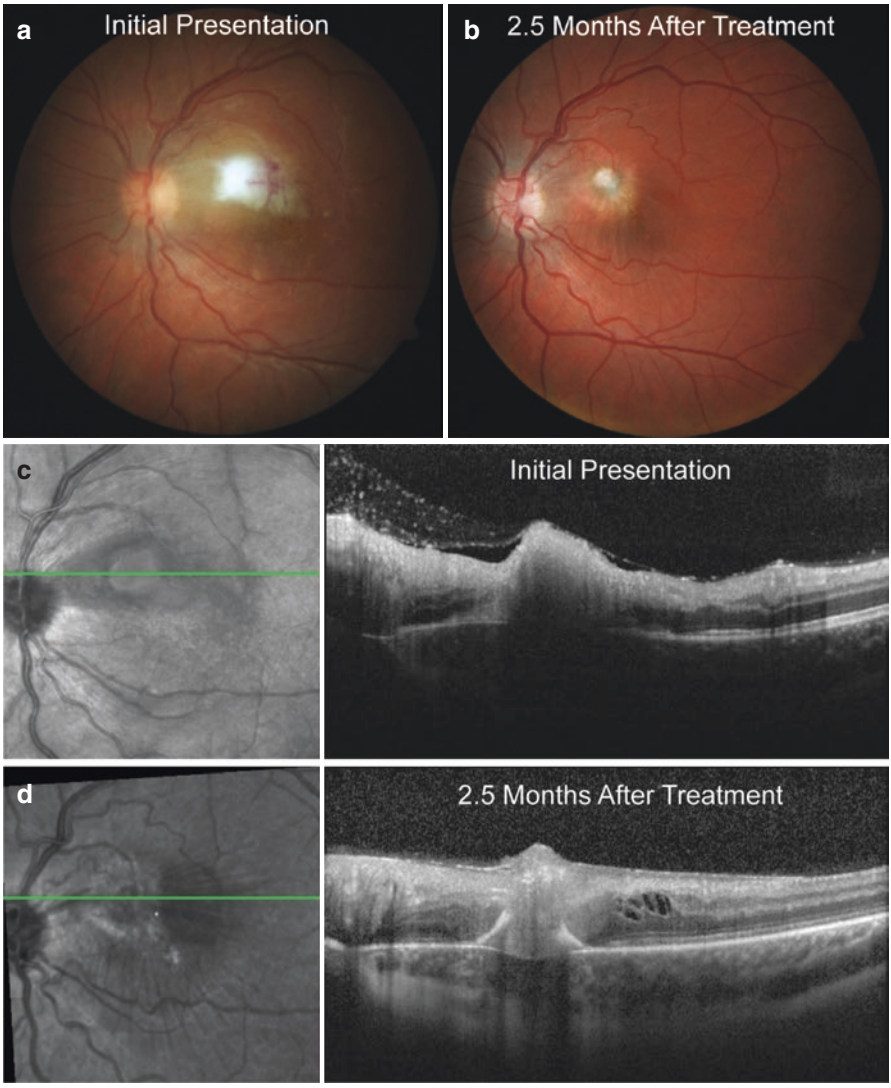


Fig. 4.4 Toxoplasmosis. (**a**) Fundus photo of left eye at initial presentation with white macular lesion, small intraretinal hemorrhage, and mild disc blurring. Aqueous sampling returned positive for toxoplasmosis and negative viral PCRs. (**b**) 2.5 months following atovaquone single-therapy treatment, there was consolidation of the macula lesion resolution of disc edema with an evolving epiretinal membrane. (**c**) OCT at initial presentation with few vitreous cells, full-thickness chorioretinal lesion corresponding to the white macular lesion with adjacent inner retinal thickening and disorganization. (**d**) Following treatment, there is consolidation of the chorioretinal lesion. There is an epiretinal membrane with mild nasal perifoveal cystic macular edema

samples of the same patient [37]. A ratio of at least three is often considered diagnostic. The Goldmann-Witmer coefficient may be positive at higher rates than PCR, and the complementary use of both diagnostic methods may increase the sensitivity of diagnosing disease.

Given the high prevalence of toxoplasmosis exposure in the general population in most geographic regions, serum serological testing for toxoplasmosis IgG and IgM is not considered to be beneficial in diagnosing active ocular toxoplasmosis infection; however, seronegativity may be useful to help exclude ocular toxoplasmosis. IgG typically appears within 1–2 weeks of active infection and remains detectable permanently, whereas IgM typically appears within a year of infection and IgM levels decline at a variable rate [37]. A rise in the IgG levels over a 3-week duration may be helpful as an indicator of recent infection [37].

Management

It is important to recognize that the majority of toxoplasmosis retinochoroiditis cases resolve without treatment within 1–2 months [37, 38]. Intuitively, one would assume that antimicrobial plus corticosteroid treatment-induced halting of parasite proliferation and associated inflammatory changes secondary to active toxoplasmosis chorioretinitis would be beneficial for such parameters as decreasing final lesion size, rate of complications, and duration of disease activity. However, a 2013 report by the American Academy of Ophthalmology (AAO) found a lack of level I evidence to support the routine use of antimicrobial or corticosteroid treatment for all cases of acute toxoplasmosis retinochoroiditis [43]. Despite this, most clinicians would likely institute treatment in cases with macular-involving, macular-threatening, or peripapillary lesions, prominent inflammation, and reduced visual acuity. Additionally, immunocompromised patients usually warrant treatment. The use of corticosteroids (typically prednisone or intravitreal dexamethasone and topical corticosteroids) should not be employed alone without appropriate antimicrobial coverage.

The same AAO report mentioned above found level II evidence to support the use of long-term prophylactic antimicrobial treatment to reduce the recurrence rate of chronic relapsing toxoplasmosis retinochoroiditis. Recurrent disease is an important consideration in many patients given the high rate of recurrence reported in previous studies (up to 79% over 5 years).

The following antimicrobials, individually or in combination, have been used in the treatment of acute toxoplasmosis chorioretinitis or the attempted prevention of recurrent episodes:

- Classic “triple therapy” with pyrimethamine (plus folinic acid), sulfadiazine, and prednisone
- “Quadruple therapy” with triple therapy combined with clindamycin

- Clindamycin
- Trimethoprim-sulfamethoxazole
- Azithromycin
- Spiramycin
- Atovaquone
- Intravitreal clindamycin

Toxocariasis

Microbiology and Epidemiology

Toxocariasis, the most prevalent helminthic infection in industrialized countries, is caused by the parasites *Toxocara canis* (dog roundworm) or *Toxocara cati* (feline roundworm) [44, 45]. The definitive hosts of these roundworms are canines and felines, respectively, and humans represent accidental or aberrant hosts that cannot further transmit the infection given that the *Toxocara* larvae are unable to mature into adulthood and shed eggs in humans [46]. In canines, the larvae may be transmitted transplacentally, accounting for a high prevalence of infection in puppies (reportedly greater than 80% in puppies younger than age 1 and less than 20% in dogs older than age 1) [44]. In contrast, *Toxocara* is not transmitted transplacentally, though transmammary transmission to kittens is possible [46]. The prevalence in cats varies between 10 and 75% [46]. In canines and felines, the larvae migrate to different organs, mature into adulthood, mate, and liberate eggs into the animals' feces [44, 46]. Humans then acquire the infection via ingestion of contaminated soil, exposure to contaminated hands, consumption of contaminated water or vegetables, and ingestion of infected raw or undercooked meat (particularly liver), or ingestion of raw animal blood [44, 46].

Clinical Presentation

Toxocara infection may result in visceral larva migrans or ocular larva migrans. Interestingly, ocular involvement is usually not seen when visceral larva migrans is present, and only 2% of patients with ocular involvement will recall a history of visceral larva migrans [44, 47, 48]. Patients with visceral larva migrans often have cough, wheeze, malaise, pruritic skin eruptions, tender skin nodules, hepatosplenomegaly, leukocytosis, and hypereosinophilia. Asthma, bronchitis, pneumonitis, and transient pulmonary infiltrates may be present. Very rarely, there may be cardiac and central nervous system involvement.

The ocular findings are unilateral in the vast majority of cases (~90%) and typically consist of retinochoroiditis involving the posterior pole or periphery [46]. This may manifest as a white or yellow-white retinal granuloma with varying degrees of overlying vitritis (Fig. 4.5) [45, 47, 48]. Prominent vitreous bands, retinal folds, retinal detachment, epiretinal membrane, macular edema, vasculitis, and papillitis

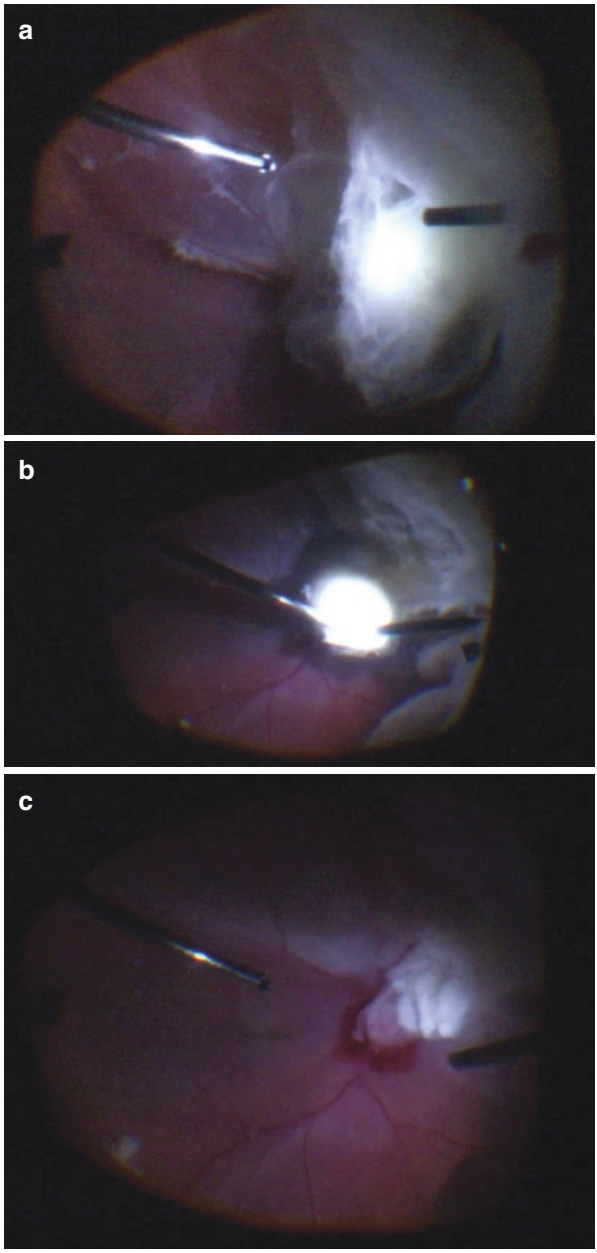


Fig. 4.5 Toxocara. (**a**) Intraoperative image of right eye in patient presenting with hand motion vision, significant anterior chamber cell reaction, vitritis, and endophytic vitreoretinal mass. Pars plana diagnostic vitrectomy was performed that eventually returned positive for Toxocara. Dense white membranes were seen overlying the retina with a dense round mass emanating from the optic nerve. (**b**) Membranes were carefully dissected from the mass surface. (**c**) Efforts to delaminate the mass from the retinal surface were unsuccessful as the mass was found to be full thickness through the retina. A combined tractional/rhegmatogenous retinal detachment repair was performed with instillation of 0.05 mL each of vancomycin, ceftazidime, and voriconazole at the end with silicone oil tamponade

may also be present [45, 47–49]. Anterior segment involvement, though less common, may include anterior uveitis, hypopyon, and keratic precipitates [49].

The diagnosis of ocular toxocariasis may be based on these findings in the appropriate clinical context, but certain laboratory markers may be useful. These include enzyme-linked immunosorbent assay (ELISA) for detection of anti-*Toxocara* IgG

in serum or intraocular fluid, Western blot of intraocular fluid (aqueous or vitreous), and calculation of a Goldmann-Witmer coefficient using intraocular fluid and serum IgG levels [45, 49, 50]. Eosinophilia and elevated serum total IgE levels may also be seen [45]. Clinicians should be aware of the possibility of false-positive ELISA results because of the possibility of cross-reactivity with other helminths [49].

Management

There is no established consensus regarding the best treatment for ocular toxocariasis. Studies have suggested that treatment with antihelminthic therapy (typically albendazole or mebendazole) in combination with corticosteroids (oral, intravitreal, or periocular) may aid in reducing the inflammatory response and risk of recurrences, but may not affect final visual outcomes [45, 49]. Additionally, vitrectomy may be required in cases of retinal detachment, epiretinal membrane, or persistent vitreous opacities.

Diffuse Unilateral Subacute Neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) is likely caused by a variety of different nematodes (class *Nematoda*), including *Toxocara canis*, *Ancylostoma caninum*, *Baylisascaris procyonis*, and others [46]. These organisms invade the subretinal space in their larval or adult forms, leading to a constellation of inflammatory changes related to the toxic effects of the nematode's wandering subretinal migratory behavior including transient and recurrent crops of gray-white outer retinal lesions, retinal pigment epithelial changes, vitritis, and papillitis [46, 51, 52]. More rare manifestations include retinal or subretinal hemorrhages, subretinal fluid, macular edema, perivascular sheathing or exudates, and choroidal neovascularization [46]. Ultimately, untreated cases may progress to widespread retinal pigment epithelial atrophy, retinal nerve fiber layer atrophy, optic nerve atrophy, and retinal vascular attenuation [46, 51, 52]. As implied in the name, the vast majority of cases are unilateral.

While the diagnosis may be suspected based on the above-mentioned constellation of findings, it can only be confirmed upon visualization of the nematode, which may have an S-shaped, coiled, or figure of eight configuration, smooth outline, and tapered ends [46]. The nematodes will exhibit photoaversion and migrate away from the examiner's light beam [46].

Treatment consists of photocoagulation of the worm, possible adjunctive use of corticosteroids, and possible antihelminthic therapy (e.g., oral albendazole) [46, 51, 52].

Cysticercosis

Ocular cysticercosis is caused by infection with the larval form of the pork tapeworm *Taenia solium*, which is transmitted to humans via ingestion of contaminated

food or water, retrograde peristalsis, or feco-oral autoinfection [53]. The encysted larvae of *T. solium* proliferate in the intestines and disseminate hematogenously to various organs, including the eyes, brain, and striated muscle, and develop into cysts [46, 53]. Ocular involvement consists of the formation of cysts in the orbit, lacrimal gland, extraocular muscles, conjunctiva, subconjunctival space, eyelid, anterior chamber, vitreous cavity, subretinal space, or optic nerve [46, 54]. The cyst may lead to localized inflammation, which may become particularly severe if the cyst wall ruptures. Extraocular disease can be treated with oral albendazole usually in combination with corticosteroids, while intraocular disease typically requires surgical cyst removal.

Syphilis

Microbiology

Syphilis is caused by infection with the spirochete bacterium *Treponema pallidum*. Acquired syphilis is most commonly contracted through sexual contact via infectious lesions, genital secretions, oral secretions, or small breaks in the skin. Vertical transmission leading to congenital syphilis may also occur transplacentally after the tenth week of pregnancy.

Epidemiology

According to data from the Center of Disease Control and Prevention, the rate of syphilis infection in the United States reached a historic nadir in the year 2000 at which time 5979 cases (2.1 cases per 100,000 population) of primary and secondary syphilis and 31,618 cases (11.2 cases per 100,000 population) of all stages of syphilis were reported [55]. However, since the year 2000, there has been a steady and consistent annual rise in the incidence of syphilis in the United States [55]. In 2016, there were 27,814 cases (8.7 cases per 100,000 population) and 88,042 (27.4 cases per 100,000 population) of all stages of syphilis reported [55]. It is estimated that syphilis accounts for approximately less than 1–2% of uveitis cases [56].

Clinical Presentation

There are four stages of untreated syphilis infection [56–58]:

1. Primary syphilis [56–58]: This stage manifests as a single, painless, indurated, nonpurulent chancre with regional lymphadenopathy. It typically occurs after a variable incubation period of 10–90 days. Given the painless nature of the chancre, the possible poorly visible location of lesions (e.g., anal area), and the spontaneous resolution within approximately 1 month, patients may progress through this first stage without disease detection.

2. Secondary syphilis [56–58]: This stage typically occurs 4–10 weeks following the development of the chancre. This stage is characterized by hematogenous dissemination of the spirochetes, which may result in maculopapular rash involving the palms and soles (affecting more than 70% of patients), fever, malaise, sore throat, arthralgias, and nontender lymphadenopathy, among others. Like the chancre of primary syphilis, the symptoms of secondary syphilis may resolve spontaneously, though may recur in approximately 25% of patients, most commonly within the first year.
3. Latent syphilis [56–58]: This stage represents a period of disease inactivity without symptoms.
4. Tertiary syphilis [56–58]: This stage may manifest as granulomatous inflammation (gumma) of the skin, mucous membranes, or virtually any other part of the human body and potentially life-threatening inflammation of the central nervous system or neurosyphilis (e.g., tabes dorsalis, meningitis, general paresis) and cardiovascular system (e.g., aortitis, aortic aneurysm, aortic valve insufficiency, coronary ostia narrowing). Approximately one-third of patients with latent syphilis progress to this stage.

The ocular manifestations of syphilis can occur at any stage of the disease process and can affect virtually any anatomical region of the eye, though there is no pathognomonic clinical sign of syphilis [59]. The complex, myriad presentations of ocular syphilis make syphilis a part of the differential diagnosis in many ocular disease states and make timely and accurate diagnosis particularly challenging.

The most common ocular manifestation of syphilis is considered to be uveitis. Although uveitis may affect patients in any stage, it is estimated to occur in approximately 2.5–5% of patients with tertiary syphilis. Syphilitic uveitis may be unilateral or bilateral, and it may be classified as anterior, intermediate, posterior, or panuveitis. A study of 95 eyes with ocular syphilis suggested the rates of ocular inflammation in various anatomic locations as follows: isolated anterior uveitis (15%), isolated intermediate uveitis (3%), isolated posterior uveitis including isolated papillitis and retinitis/chorioretinitis with or without papillitis (40%), and panuveitis (42%) (Fig. 4.6) [60]. In this study, posterior uveitis was more common in HIV-negative patients, and panuveitis was more common in HIV-positive patients (though another smaller study of 61 eyes found panuveitis to be the most common finding independent of HIV status and present in 45.9% of all cases) [60, 61]. The funduscopic appearance of retinal vasculitis was seen in 14%, anterior chamber inflammation >0.5+ cell was seen in 52% of patients (the vast majority of which was nongranulomatous), hypopyon was seen in 4%, and vitreous haze >0.5+ was seen in 49% [60].

In a study of 24 eyes of 14 patients with posterior segment-involving ocular syphilis presenting to a community-based practice in the United States, the following ophthalmic signs were most common: vitritis (63%), iritis (54%), keratic precipitates (54%), retinitis (54%), vessel sheathing (29%), disc edema (13), and serous retinal detachment (13%) [59]. In a separate study of 20 patients with posterior

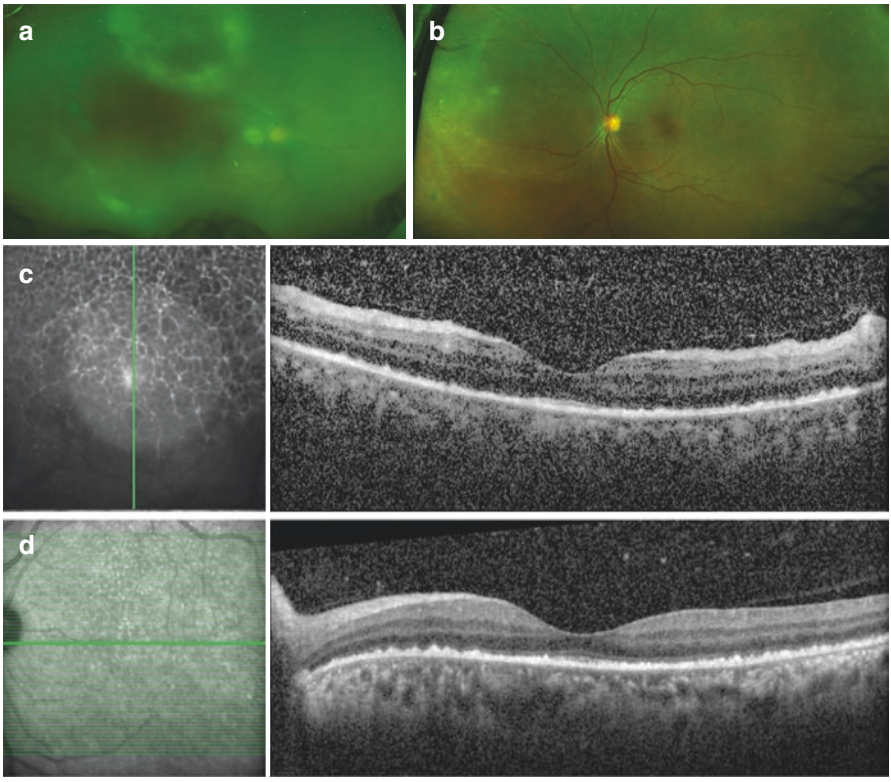


Fig. 4.6 Syphilis. (**a**, **b**) Patient with polysubstance abuse history, HIV, and hepatitis C presenting with 20/200 vision in the right eye and 20/60 vision in the left eye. Optos images of the right and left eyes show vitritis and small hypopigmented granular lesions. (**c**, **d**) OCT images of the macula show granular images on infrared images and multiple subretinal hyperreflective lesions at the level of the retinal pigmented epithelium suggesting placoid syphilis. *Treponema pallidum* antibody was reactive and RPR titer was reactive 1:256

segment-involving ocular syphilis presenting to a hospital-based practice in the United States, the following ophthalmic findings were most common: chorioretinitis (75%), panuveitis (15%), and vasculitis (10%) [62]. Other less common findings include retrobulbar optic neuritis and optic neuropathy.

Chorioretinitis in syphilis has been described as consisting of small (0.5–1.0 disc diameter), yellowish or grayish lesions typically located in the posterior pole and midperiphery [56]. A less common pattern of chorioretinitis has been termed acute syphilitic posterior placoid chorioretinitis (ASPPC) and presents as solitary, yellow or pale-yellow, placoid, circular, oval-shaped lesions in the posterior pole [63–65]. Optical coherence tomography (OCT) of these lesions may demonstrate loss of the outer retinal bands, including the ellipsoid and interdigitation zones, nodular thickening and hyperreflectivity of the retinal pigment epithelium, and punctate hyperreflectivity of the choroid [63, 66].

Laboratory Diagnosis

The diagnosis of syphilis is made via laboratory testing. Traditionally, a nontreponemal test (rapid plasma reagin [RPR] or venereal disease research laboratory test [VDRL]) is performed initially, with positive results prompting confirmation with treponemal-specific tests (*T. pallidum* particle agglutination [TP-PA] or fluorescent treponemal antibodies [FTA-abs]). While this traditional approach to syphilis screening has a fairly high predictive value, it can miss early primary and treated infection, because the initial nontreponemal tests (RPR and FTA-abs) may not be positive in the initial weeks following infection, and may decrease several years after infection in treated cases (as well as some untreated cases) [58, 67].

Nontreponemal tests may yield false-positive results in 1–2% of the population in the setting of conditions, such as lupus, infectious mononucleosis, malaria, leprosy, viral pneumonia, bacterial endocarditis, tuberculosis, pregnancy, injection drug use, and rickettsial infection [58, 67]. Treponemal tests may yield false-positive results in the setting of other spirochetal infections, malaria, and leprosy [58]. Human immunodeficiency virus may cause false-negative results with both nontreponemal and treponemal tests [58].

In recent years, a "reverse screening algorithm" has been encouraged by the Center for Disease Control and Prevention in an effort to enhance detection of early primary and treated infections. In this method, the initial screening is performed with syphilis IgG assays (e.g., enzyme immunoassays [EIA] or chemiluminescence immunoassays [CIA]). These tests are sometimes referred to as syphilis IgG in the literature. If positive, this prompts quantitative RPR testing which, if positive, would suggest past or present syphilis infection. In contrast, if the quantitative RPR is negative, this prompts a treponemal specific test (TP-PA) which, if positive, would also indicate past or present syphilis infection. If a patient has a positive EIA, negative RPR, and negative TP-PA and the clinical suspicion of syphilis remains high, it is prudent to repeat RPR testing in several weeks at which time conversion to a positive RPR would support past or present syphilis infection. Importantly, the laboratory testing cannot distinguish between prior and active infection, and clinicians must weigh the laboratory testing against the patient's history and clinical findings.

Patients with ocular syphilis should also undergo cerebrospinal fluid evaluation as well as human immunodeficiency virus (HIV) testing given the high risk of coinfection.

Management

Ocular syphilis, like neurosyphilis, is typically treated with intravenous penicillin G rather than with the intramuscular benzathine penicillin G typically used in primary, secondary, or latent syphilis. In instances where there is ocular syphilis without other central nervous system findings, it still remains most prudent to administer neurosyphilis-based treatment (i.e., intravenous penicillin G) [59]. The preferred regimen

is aqueous penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 h or as a continuous infusion for 10–14 days [56, 58]. The alternative treatment is procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times per day for 10–14 days [56, 58]. In penicillin-allergic patients, pretreatment desensitization is commonly done.

The Jarisch–Herxheimer reaction typically occurs within the first 24 h after the onset of treatment and results in symptoms such as fever, malaise, and myalgias. It is considered a hypersensitivity reaction in response to the large quantity of treponemal antibodies released into the systemic circulation. Typically, only supportive care is required for this.

Tuberculosis

Microbiology

Ocular tuberculosis is caused by the aerobic, acid-fast, rod-shaped bacterium *Mycobacterium tuberculosis*. The organism is contracted via inhalation of small airborne droplets. The bacilli initially infect the lungs resulting in pulmonary tuberculosis and may subsequently spread to regional lymph nodes and may hematogenously spread to other organs, including the eyes, resulting in extrapulmonary tuberculosis. Both in the pulmonary system and extrapulmonary sites, the bacilli may remain dormant without leading to clinically relevant disease (latent infection) [68]. In fact, it is estimated that 90% of patients who have contracted the mycobacteria never develop clinical manifestations, 5% develop disease within the first few years of exposure, and the remaining 5% develop disease many years after exposure [68].

Epidemiology

According to the World Health Organization's 2017 global tuberculosis report, the worldwide incidence of tuberculosis in 2016 was 10.4 million [69]. Fifty-six percent of patients with tuberculosis were from the following five countries (in descending order): India, Indonesia, China, the Philippines, and Pakistan [69]. Although the mortality rate has been declining, tuberculosis remains the ninth-leading cause of death worldwide—with an estimated 1.3 million deaths among HIV-negative patients and 374,000 deaths among HIV-positive patients worldwide [69]. The co-occurrence of HIV/AIDS and tuberculosis increases the risk of extrapulmonary tuberculosis—with an estimated 50% of patients with AIDS and tuberculosis having extrapulmonary involvement [68]. The risk of extrapulmonary involvement increases with lower CD4+ T-cell lymphocyte counts.

The prevalence of ocular tuberculosis is not well established; this is related to the inherent difficulty in confirming suspected cases with laboratory testing, varying global rates of tuberculosis over the years, and significant differences in tuberculosis rates across geographic territories.

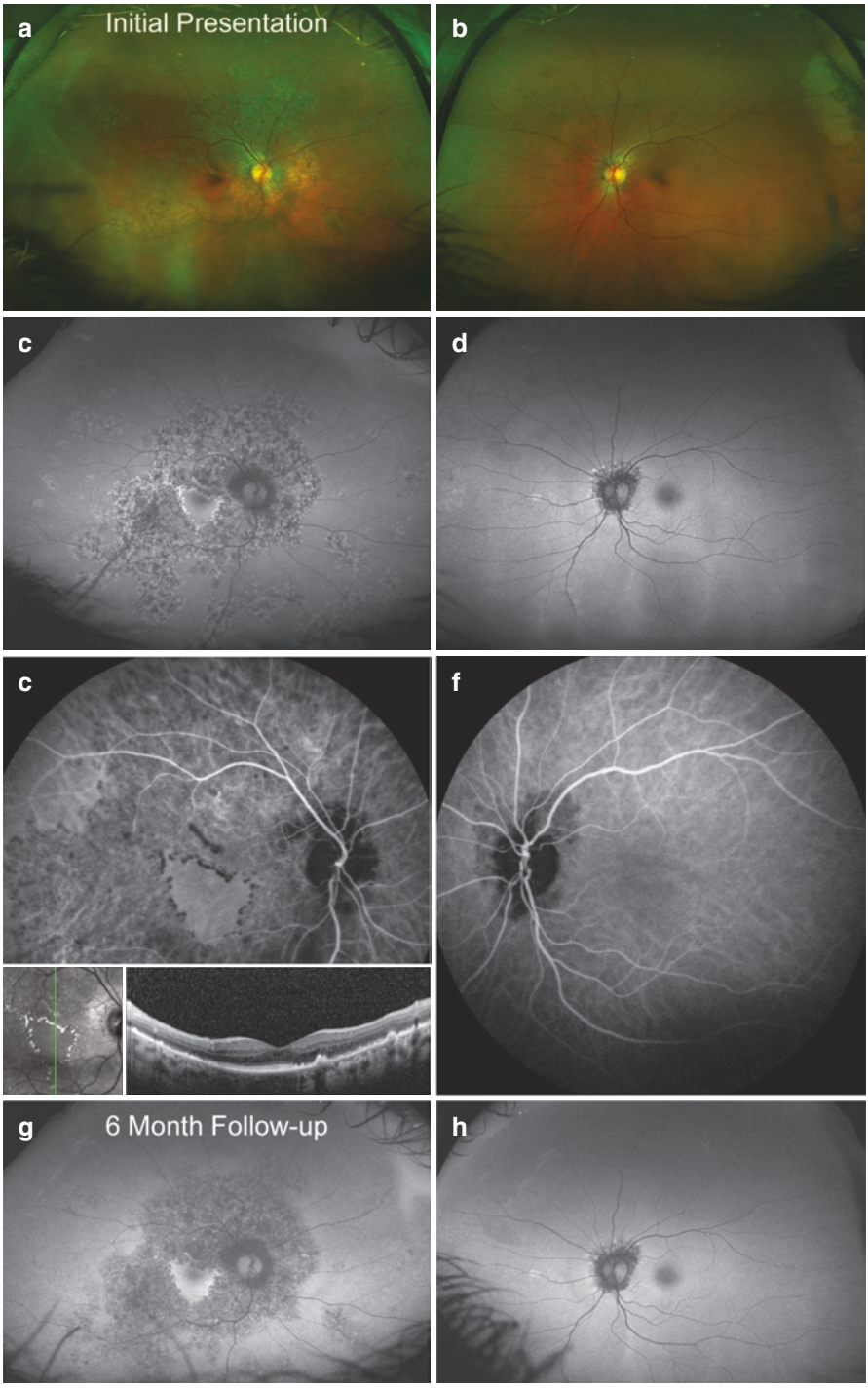
Clinical Presentation

Intraocular tuberculosis may have myriad clinical manifestations (without any specific pathognomonic findings) and may mimic many other infectious and noninfectious uveitides. The most common clinical findings are posterior uveitis (82.1% of patients), anterior uveitis (60.7%), panuveitis (57.1%), intermediate uveitis (39.3%), retinitis or retinal vasculitis (39.3%), and neuroretinitis or optic neuropathy (14.3%) [70]. Bilateral involvement is more common than unilateral involvement [68, 70].

Intermediate uveitis secondary to tuberculosis typically presents with vitritis as the most prominent feature, which may be accompanied by snowballs, snowbanks, vascular sheathing, cystoid macular edema, anterior uveitis, and retinochoroidal granulomas [68].

Posterior uveitis may manifest broadly as choroidal tubercles, subretinal abscess, and serpiginous-like choroiditis [68]. Choroidal tubercles are typically multiple, yellowish, whitish, or grayish-colored, small nodular elevations measuring ¼ disc diameter or smaller located in the posterior pole [68]. Choroidal tuberculomas, in contrast, are solitary, larger yellowish, whitish, or grayish-colored nodular elevations measuring 4–14 mm (or larger), which may be accompanied by overlying hemorrhage, retinal folds, or serous retinal detachment [68]. Subretinal abscesses arise from liquefaction necrosis of subretinal granulomas. These appear as yellowish, nodular elevations, possibly in association with overlying hemorrhage and choroidal neovascularization. Serpiginous-like choroiditis may appear in a multifocal or plaque-like pattern. The multifocal pattern presents as noncontiguous, discrete, multiple small yellowish, whitish lesions with indistinct borders that exhibit early hypofluorescence and late hyperfluorescence on fluorescein angiography and persistent hypocyanescence on indocyanine green angiography [68, 71]. These may eventually coalesce into confluent lesions over the course of approximately 1–4 weeks [71]. The plaque-like pattern presents as a larger confluent lesion with a leading active edge that exhibits early hypofluorescence and diffuses late hyperfluorescence of the leading edge, and it may appear more similar to serpiginous choroiditis (Fig. 4.7) [68, 71].

Fig. 4.7 Tuberculosis-associated serpiginous-like chorioretinitis. (**a**) Optos image of the right eye with diffuse atrophic and pigmentary changes in the posterior pole sparing the fovea with 20/40 vision. Quantiferon Gold testing was positive. (**b**) Optos image of the left eye with peripapillary atrophy and 20/25 vision. (**c**) Corresponding fundus autofluorescence of the right eye with patchy speckled hypo- and hyperautofluorescence covering nearly the entire posterior pole and several small discrete areas in the periphery but sparing the fovea. (**d**) Fundus autofluorescence with patchy speckled hypo- and hyperautofluorescence in the peripapillary area with few scattered areas of hyperautofluorescence nasally. (**e**) Indocyanine green angiography showing late hypocyanescence suggests choriocapillaris ischemia in the posterior pole sparing the fovea of the right eye. Inset shows OCT of the right eye with a ring of subretinal, retinal pigmented epithelium level, hyper-reflective deposits in the parafoveal involvement with attenuation of the outer retinal layers without fluid. (**f**) Late mild hypocyanescence of the left eye superior to the disc. (**g**) Six months following diagnosis and initiation of treatment for tuberculosis, there is resolution of hyperautofluorescence seen previously with areas of hypoautofluorescence sparing the fovea. (**h**) Resolution of hyperautofluorescence with remaining hypoautofluorescence


a
Initial Presentation
b
c
d
c
f
g
6 Month Follow-up
h

Eales disease, a retinal vasculitis typically characterized by recurrent vitreous hemorrhage, peripheral retinal ischemia, and retinal neovascularization without anterior chamber inflammation or vitritis most commonly occurring in young adult males, is thought to possibly be associated with tuberculosis exposure. It may represent an immune-mediated hypersensitivity reaction to tuberculous antigens. In contrast, retinal vasculitis that accompanies signs of active inflammation (e.g., vitritis and anterior uveitis) may be more indicative of active infection by tuberculosis bacilli rather than a hypersensitivity reaction [68, 71].

Diagnosis

Given the lack of distinct clinical features that may serve as pathognomonic indicators of ocular tuberculosis, other diagnostic tests are typically required. The Mantoux skin test is commonly employed and involves subcutaneous injection of purified protein derivative (PPD) and assessing for skin induration in 48–72 h. Varying degrees of induration may be positive depending on the patient's particular clinical history. Patients who have been vaccinated with the bacillus Calmette–Guérin (BCG) vaccine often have false-positive results with the Mantoux skin test, though this cross-reactivity is less likely to be seen 10 years or later after the BCG vaccine [68]. The interferon-γ release assay has similar sensitivity and higher specificity for the detection of tuberculosis and is not affected by a prior history of BCG vaccination [71]. Radiography or computer tomography of the chest is commonly employed to assess for pulmonary involvement. Analysis of ocular fluids or tissue (e.g., aqueous humor) may test positive for tuberculosis via polymerase chain reaction, acid fast bacilli staining on microscopic examination of smears, or culture in Lowenstein–Jensen media [68, 72].

Management

The management of the tuberculosis is becoming increasingly challenging with the emergence of drug-resistant strains. Rifampin-resistant tuberculosis (RR-TB) is defined by resistance to rifampin but not isoniazid; multidrug-resistant tuberculosis (MDR-TB) is defined by resistance to both rifampin and isoniazid; and extensively drug-resistant tuberculosis (XDR-TB) is defined by resistance to rifampin, isoniazid, fluoroquinolones, and at least one injectable drug (e.g., amikacin, kanamycin, or capreomycin) [69].

In general, intraocular tuberculosis requires systemic treatment similar to the regimen employed for pulmonary or extrapulmonary tuberculosis and typically involves a combination of the above-mentioned medications [70]. Additionally, systemic corticosteroids may be required to reduce the inflammation, though this may result in paradoxical worsening of the clinical findings. A Jarisch–Herxheimer-like reaction may also develop in some patients in response to systemic treatment [71].

Tick-Borne Diseases

Of the tick-borne diseases endemic to the United States, the following are known to exhibit posterior segment ocular manifestations (the causative agent is listed in parentheses): Babesiosis (*Babesia microti, B. duncani, B. divergens*), Ehrlichiosis (*Ehrlichia ewingii* and *Ehrlichia chaffeensis*), Lyme disease (*Borrelia species*), Powassan encephalitis (Powassan virus), Q fever (*Coxiella burnetii*), Rocky Mountain spotted fever (*Rickettsia rickettsii*), tick-borne relapsing fever (*Borrelia* species), and Tularemia (*Francisella tularensis*) [70]. Of these, Ehrlichiosis may cause optic neuritis and optic neuropathy, and tularemia may cause optic atrophy—and therefore, these will not be discussed further. While not discussed further in this chapter, of the global tick-borne diseases affecting other parts of the world, the following are known to exhibit posterior segment manifestations: Mediterranean spotted fever (*Rickettsia conorii*), Crimean–Congo hemorrhagic fever (Crimean–Congo hemorrhagic fever virus), and Kyasanur forest disease (Kyasanur forest disease virus) [70].

Lyme disease. Lyme disease, the most common tick-borne disease in the North America, is caused by the species of the spirochete bacteria belonging to the *Borrelia* genus *Borrelia burgdorferi, B. garinii, or B. afzelii.* In the United States, most cases are caused by *B. burgdorferi*, whereas in Europe most cases are caused by the latter two species [70]. Of note, *Borrelia burgdorferi* and *B. microti* (the parasite responsible for babesiosis) share the same primary reservoir host (white-footed mouse) and vector (deer tick, *Ixodes scapularis*), thereby leading to the possibility of coinfection with both Lyme disease and babesiosis in some patients [70]. Despite the transmission via deer ticks, it has been suggested that only about 25% of affected patients will recall having had a tick bite [70]. Systemically, the pathognomonic finding is the erythema migrans rash which is present in 90% of confirmed cases [70]. Other systemic manifestations include flu-like symptoms, lymphadenopathy, arthralgias, cardiac involvement (e.g., carditis, arteriovenous conduction block), and neurologic involvement (e.g., meningitis, cranial nerve palsies, radiculopathy, peripheral neuropathy). The posterior segment ocular manifestations may include the following: anterior, intermediate, posterior, or panuveitis, vitritis, retinitis, choroiditis, endophthalmitis, retinal vasculitis, cotton wool spots, macular edema, optic neuritis, papillitis, neuroretinitis, and papilledema [70, 71]. Given the varied ocular findings as well, the relative rarity of ocular involvement, and the inherent difficulty in definitively validating *Borrelia* infection, there are no established characteristic or pathognomonic ocular signs of this condition. Clinicians should remain vigilant for the possibility of Lyme disease when faced with a patient with any of the aforementioned possible ocular and systemic findings, travel to endemic areas, and history of possible exposure to ticks. The diagnosis of Lyme disease is particularly challenging. In general, a two-tier testing strategy is employed: first, an enzyme immunoassay or indirect immunofluorescence assay is performed, and second, equivocal or positive tests are confirmed using Western blot or immunoblot. However, it is important to note that false-positive results may occur, and therefore,

seropositivity in the absence of clinical findings is likely inadequate for diagnosis. Additionally, in early stages of the diseases, false negatives may occur (e.g., less than 50% of patients with erythema migrans have positive serological testing) [71]. Lyme disease is typically treated systemically with doxycycline, amoxicillin, or cefuroxime. As with syphilis, treatment for Lyme disease may lead to a Jarisch–Herxheimer reaction.

Babesiosis. Most cases of human babesiosis occur in the Northeast and upper Midwest of the United States, typically between the months of May and October, though cases have also been reported in other parts of the United States and the world [72]. The most common species responsible for human babesiosis is *Babesia microti*. As with Lyme disease, the primary reservoir host is the white-footed mouse and the vector is the deer tick, thereby leading to the possibility of coinfection with both babesiosis and Lyme disease in some patients. In addition to transmission via the deer tick (*Ixodes* scapularis), babesiosis may rarely be transmitted via transfusions of blood or blood products [72]. Posterior segment manifestations of babesiosis include nerve fiber layer infarcts, papillitis, retinal hemorrhages, and white-centered retinal hemorrhages [70]. Systemically, many patients are asymptomatic or develop symptoms of fever, malaise, fatigue, chills, headache, myalgias, arthralgias, photophobia, conjunctival injection, thrombocytopenia, and hemolytic anemia around 1–4 weeks after exposure [70, 72]. Immunocompetent or asplenic patients are at increased risk of fulminant disease with disseminated intravascular coagulation, hypotension, and end-organ damage [70]. The diagnosis of babesiosis can be established by the identification of babesia on blood smears with Giemsa or Wright staining, indirect immunofluorescent antibody assay, immunoblot assay, PCR assay, or intraperitoneal inoculation of a laboratory animal (e.g., hamster) with peripheral blood from the patient followed by blood testing in the hamster several weeks later [72]. Treatment options in immunocompetent patients include a 7- to 10-day course of azithromycin plus atovaquone or clindamycin plus quinine [72]. Immunocompromised patients may require more intensive therapy with longer courses of treatment and higher drug doses.

Powassan encephalitis. Powassan encephalitis is a very rare disease caused by a flavivirus—Powassan virus—which is endemic to the United States, Canada, Mexico, and Russia [73]. The primary reservoir hosts are woodchucks and foxes, and the vectors are deer ticks (*Ixodes* species) and the Rocky Mountain wood tick (*Dermacentor andersoni*) [73]. The systemic manifestations, occurring approximately 1–4 weeks after exposure, include fever, somnolence, nausea, myalgias, vomiting, headache, dizziness, and altered mental status. The central nervous system involvement can be varied, and seizures, hemiplegia, focal palsies or paresis, and coma, among others, may be seen [70, 73]. The posterior segment manifestations include optic disk swelling and retinal vascular tortuosity [70]. Ophthalmoplegia and nystagmus have also been described [70].

Rocky Mountain spotted fever. Rocky Mountain spotted fever (RMSF) is the most common rickettsial disease in the United States, though it is also endemic in Central and South America [74]. The majority of cases occur in the south Atlantic

and south central United States between the months of April and September [71, 74]. The causative bacterium, *Rickettsia rickettsia*, is transmitted via the American dog tick (*Dermacentor variabilis*), brown dog tick (*Rhipicephalus sanguineus*), and Rocky Mountain wood tick (*Dermacentor andersoni*) and infects vascular endothelial cells leading to tissue necrosis and obliterative vasculitis [70, 71, 74]. Systemic manifestations may include fever, headaches, myalgias, skin rash, abdominal symptoms, and conjunctival injection [71, 74]. The rash begins as a pink-colored macular rash on the distal extremities (wrists, ankles, forearms) and spreads centripetally, evolving into a maculopapular appearance and eventually a petechial appearance [74]. The rash may ultimately involve the palms and soles as well [74]. The posterior segment ocular manifestations of RMSF can be numerous and variable and include the following: vitritis, vasculitis, macular edema, optic disc edema, retinal artery occlusion, retinal venous tortuosity, cotton wool spots, intraretinal exudates and hemorrhages, neuroretinitis, optic neuritis, and ischemic optic neuropathy [70, 71]. Anterior segment manifestations include anterior uveitis. The diagnosis may be supported by serological testing via immunofluorescence antibody, immunohistochemistry, PCR, enzyme-linked immunosorbent assay, and cell culture. The treatment of choice is doxycycline (even in children).

Tick-borne relapsing fever. Tick-borne relapsing fever is caused by spirochetal infection with several *Borrelia* species, the two most common in the United States being *B. hermsii* and *B. turicatae.* The vectors are soft-bodied ticks of the *Ornithodoros* genus. The disease is endemic to the United States, central and South America, the Mediterranean, east Africa, and central Asia [70]. The ocular manifestations are not firmly established, but case reports have suggested the findings of conjunctivitis, iritis, and iridocyclitis, among others.

Endophthalmitis

Epidemiology and Microbiology

Endogenous endophthalmitis is acquired via hematogenous spread of infection to the eyes across the blood–ocular barrier. The reported incidence ranges from 0.04 to 0.4% [75]. It is most commonly seen in patients with a history of intravenous drug abuse, chronic indwelling catheters, immune dysfunction, diabetes mellitus, malignancy, prolonged hospital stay, and recent surgeries or hepatobiliary and gastrointestinal procedures [76]. The most commonly involved organisms include bacteria and fungi, with the latter being the more common cause in intravenous drug abuse patients [75]. Notable causative bacteria include *Klebsiella pneumoniae*, *Streptococcus* species, *Staphylococcus* species, *Pseudomonas aeruginosa*, *Escherichia coli*, *Neisseria meningitides*, among others (Fig. 4.8) [77]. Gram-negative organisms may predominate in Asian countries, while gram-positive organisms may predominate in Western countries [78]. The leading fungal causes are *Candida* and *Aspergillus* species [76].

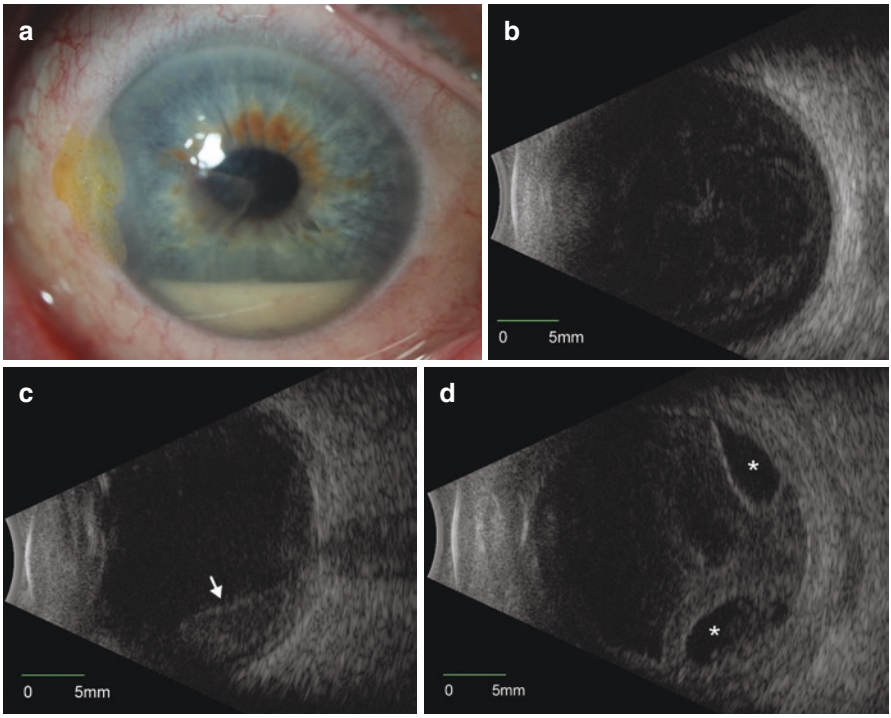


Fig. 4.8 Bacterial endophthalmitis. (**a**) Slit lamp photograph of right eye suspicious for bacterial endophthalmitis with conjunctival hyperemia, hypopyon, and corneal edema. Patient presented with hand motion vision postcataract surgery complicated by wound burn and wound leak despite corneal gluing. (**b**) Transverse B-scan ultrasound at 3 o'clock shows corresponding vitreous opacities and membranes with choroidal thickening and attached retina. (**c**) Vertical axial B-scan of postvitrectomized patient with postsurgical *streptococcal pneumoniae* endophthalmitis with layered hyperechoic material resembling a posterior hypopyon (arrow). (**d**) Transverse B-scan at 6 o'clock of patient presenting with endogenous *Klebsiella pneumoniae* panophthalmitis with two subretinal hypoechoic pockets suspicious for subretinal abscesses (asterisk)

Posttraumatic endophthalmitis after open globe injuries has an incidence ranging from 15 to 30% and is higher in the setting of retained intraocular foreign bodies [75].

Postintravitreal injection endophthalmitis has a reported incidence of 0.016–0.053% in the United States (where these injections are primarily performed in the outpatient, clinic setting). The rate of endophthalmitis has been shown to be similar after intravitreal injection of bevacizumab, ranibizumab, and aflibercept, but it appears to be higher after intravitreal injection of corticosteroids [75, 79]. Guidelines for appropriate intravitreal injection technique assembled by an expert panel suggest that the risk of endophthalmitis may be reduced by the use of povidone-iodine solution on the conjunctival surface at the intended injection site, avoidance of contact between the intended injection site and needle with the eyelashes or eyelid margin after the final application of povidone-iodine and until the completion of the injection, avoidance of extensive eyelid massage pre- or postinjection to avoid

Meibomian gland expression, the use of sterile or nonsterile gloves, and limitation of aerosolized droplet contamination by minimizing speaking (by both the physician and patient) or the use of surgical masks [80]. Steps that were deemed unnecessary include routine use of pre-, peri-, and postinjection antibiotic prophylaxis and use of a sterile drape [80].

Postcataract extraction endophthalmitis has a reported incidence of 0.012–1.3% based on a meta-analysis including nationwide surveys and large case series from different countries since the year 2000 [81]. Risk factors for postcataract endophthalmitis may include vitreous loss, posterior capsule rupture, poor corneal wound construction, hypotony, eyelid inflammatory disease, older age (e.g., above age 80), and diabetes mellitus [82]. The only intervention with category I evidence of reducing postcataract surgery endophthalmitis risk is use of povidone-iodine during the preoperative prep [82]. Recently, intracameral antibiotic administration during cataract surgery (e.g., cefuroxime, moxifloxacin, vancomycin) has been reported to reduce the risk of postoperative endophthalmitis [83–87]. Vancomycin usage has dropped significantly since its association with hemorrhagic occlusive retinal vasculitis was described. Analysis of microbiologic isolates from the Endophthalmitis Vitrectomy Study (EVS) resulted in an overall culture positivity rate of 69.3% with the vast majority of causative organisms being gram-positive bacteria (94.2%) [88]. Of the gram-positive bacteria, 70% were coagulase-negative micrococci (almost exclusively *Staphylococcus epidermidis*), 9.9% were *Staphylococcus aureus*, 9% were *Streptococcus* species, and 2.2% were *Enterococcus* species [88]. Gram-negative organisms (including *Pseudomonas*, *Proteus*, *Morganella*, *Citrobacter*, *Serratia*, *Enterobacter*, and *Flavobacterium* species) accounted for only 5.9% of isolates [88].

Postglaucoma surgery endophthalmitis has an estimated incidence of 0.7% following glaucoma drainage device implantation and a reported 5-year cumulative incidence of 0.45–1.7% following trabeculectomy [89, 90]. The risk of endophthalmitis may be lower with glaucoma drainage implants than with trabeculectomy. Risk factors for postglaucoma surgery endophthalmitis include younger age, diabetes mellitus, use of intraoperative antimetabolites (i.e., 5-fluorouracil and Mitomycin-C), inferior blebs, thin blebs, bleb leakage, blebitis, bleb manipulation, limbal-based peritomy, blepharitis, tube or implant erosion, and prophylactic topical antibiotic use [75, 82]. The most commonly isolated causative organisms include coagulase-negative *Staphylococci*, other *Staphylococcus* species, *Streptococcus* species, *Haemophilus influenza*, and *Pseudomonas aeruginosa* [75, 82]. Coagulase-negative *Staphylococci* appear to predominate in early-onset bleb-related endophthalmitis, while *Streptococcus* species appear to predominate in late-onset (more than 4 weeks postoperatively) bleb-related endophthalmitis and glaucoma drainage implant-related endophthalmitis [82].

Postpars plana vitrectomy endophthalmitis has a reported incidence of 0.058% based on a large prospective study from the United Kingdom between the years 2010 and 2012 (though various studies over have found rates of 0.03–0.84%) [82, 91]. Risk factors may include preoperative topical corticosteroid use and immunosuppression [91]. Other suspected risk factors include postoperative hypotony,

sutureless sclerotomy closure, and lack of tamponade agent (air, gas, or silicone oil) [82]. The most frequently implicated organism is coagulase-negative *Staphylococci*, though *Streptococci*, *Enterococci*, *Bacillus,* and *Pseudomonas* species have also commonly been reported [82].

Chronic or delayed-onset postoperative endophthalmitis (which occurs more than 6 weeks postoperatively) is typically associated with less virulent organisms, typically *Propionibacterium acnes* and fungal species [75]. *Propionibacterium acnes* should be suspected in the presence of whitish plaques or infiltrates seen within the capsular bag and smoldering low-grade inflammation for many months refractory to conventional topical steroid treatment.

Clinical Presentation

Patients affected by acute postoperative and posttraumatic endophthalmitis typically complain of significant pain, eye redness, and decreased vision. In general, patients would be expected to present approximately 3–7 days postoperatively. The clinical findings often include eyelid edema, globe tenderness, prominent conjunctival or episcleral injection, corneal edema, severe anterior chamber inflammation often with a hypopyon and fibrin formation, and vitritis (either seen via biomicroscopy or ultrasonographically). Patients with a history of a trabeculectomy may have findings consistent with blebitis including a mucopurulent, whitish infiltrate of the bleb or bleb leak. Patients with glaucoma drainage implants may have a prominent inflammatory reaction around the tube in the anterior chamber or visible exposure of the tube or plate (e.g., in the setting of tube or plate erosion).

Patients with endogenous endophthalmitis may present differently than those with exogenous endophthalmitis, though most will share the findings of eye pain, blurred vision, anterior chamber inflammation, hypopyon, and fibrin formation similar to exogenous cases. In contrast, endogenous cases may exhibit bilateral involvement (12–29% of cases), may present prior to or concurrently with manifestations of systemic illness, often lack a history of recent intraocular surgery, and may be more likely to have been initially misdiagnosed with noninfectious uveitis, conjunctivitis, acute glaucoma, or other diagnoses [76]. The extraocular foci of infection, in order of frequency, may include liver abscess, pneumonia, endocarditis, soft-tissue infection, meningitis, septic arthritis, orbital cellulitis, renal abscess, and brain abscess [78].

Management

The principles of endophthalmitis management include determination of the causative organism via ocular fluid sampling, administration of antimicrobial therapy, removal of any lingering source of infection, and rehabilitation of vision. Ocular fluid sampling should include either a vitreous or anterior chamber paracentesis for culture (specifically, for bacterial and fungal species), possibly polymerase chain reaction testing if available, and gram stain, potassium hydroxide (KOH) stain, or

calcofluor white stain. When *Propionibacterium acnes* is suspected, the lab should be alerted to analyze the culture for 14 days given the slower growth rate of the organism in culture media.

Intravitreal antibiotics should cover both gram-positive and gram-negative organisms, and antifungals should be administered in certain situations (such as trauma including contamination with organic matter and chronic, delayed-onset endophthalmitis). The following are potential intravitreal antibiotic doses:

- Vancomycin 1 mg/0.1 mL
- Ceftazidime 2.25 mg/0.1 mL
- Ceftriaxone 2 mg/0.1 mL
- Amikacin 0.4 mg/0.1 mL
- Voriconazole 0.1 mg/0.1 mL
- Amphotericin-B (0.005 mg/0.1 mL)

Amikacin, which was used in the Endophthalmitis Vitrectomy Study, has since been replaced by ceftazidime as the preferred first-line antibiotic for gram-negative coverage given concerns of macular infarction. Similarly, gentamicin is now rarely used given the risk of retinotoxicity and macular infarction. Intravitreal antibiotics typically remain at therapeutic levels within the vitreous cavity for several days following injection and therefore failure to achieve clinical improvement after the initial injections should prompt consideration of vitrectomy. It should be noted that vitrectomized eyes may have quicker antibiotic clearance relative to nonvitrectomized eyes and may potentially be at increased theoretical risk of retinotoxic effects of intravitreal antibiotics immediately after injection [92]. In aphakic eyes, the increased vitreous volume may lead to slightly decreased antibiotic concentrations [92].

Topical antibiotics are also typically prescribed, and occasionally fortified antibiotics are used, especially when there is a prominent ocular surface abnormality (such as infectious keratitis, blebitis, bleb leak, or glaucoma drainage implant exposure). Oral antibiotics are sometimes employed; oral fluoroquinolones, such as moxifloxacin and ciprofloxacin, are commonly chosen because of the likelihood of their increased intraocular penetration relative to other oral antibiotics [92]. Oral linezolid, which has primarily gram-positive coverage, has also been shown to have good intraocular penetration and may be considered in select cases [92]. In cases of endogenous endophthalmitis, in addition to intravitreal antibiotics, identification and treatment of the nonocular foci of systemic infection are necessary.

In addition to antibiotics, corticosteroids are often necessary to temper the robust inflammatory reaction that accompanies the infection (though there is no definite evidence to support the routine use of adjunctive steroid therapy) [93]. Frequent topical corticosteroids are often utilized. Though more controversial, oral corticosteroids, intravitreal corticosteroids (such as dexamethasone 0.4 mg/0.1 mL), or subconjunctival corticosteroids (such as dexamethasone 6 mg/0.25 mL) can be considered in acute, typical-appearing, presumed-bacterial endophthalmitis. Cycloplegia should also be used.

The Endophthalmitis Vitrectomy Study (EVS) evaluated the role of early vitrectomy (within 6 h of diagnosis) in patients with clear ocular media and postcataract

surgery or postsecondary intraocular lens implantation surgery [94]. Removal of approximately 50% of the vitreous was required, induction of posterior vitreous detachment was avoided, and silicone oil was not used. The EVS study suggested the benefit of early vitrectomy compared to intravitreal injections in patients presenting with light perception vision. Only 53% of patients achieved visual acuity of 20/40 or better; however, with advancements in vitrectomy instrumentation and techniques, more recent studies have suggested the possibility of improved visual outcomes compared to those in the EVS study [92, 94]. Additionally, the findings of the EVS study may not be generalizable to endophthalmitis occurring in settings other than postcataract surgery or postsecondary intraocular lens implantation, and most clinicians are more likely to proceed with initial vitrectomy in postglaucoma surgery and posttraumatic endophthalmitis. While the indications for initial or early vitrectomy remain controversial, it appears well established that endophthalmitis that fails to respond to initial intravitreal antibiotics or resolved infection with residual vitreous debris will benefit from vitrectomy.

Cases of *Propionibacterium acnes* may require partial or total capsulectomy or intraocular lens removal or exchange in addition to intraocular vancomycin injection.

Candidiasis

Microbiology and Epidemiology

Ocular candidiasis is caused by several different *Candida* species, including *C. albicans* (most common), *C. parapsilosis*, *C. glabrata*, *C. tropicalis,* and *C. krusei* [95, 96]. In recent years, ocular candidiasis has been reported to occur in 0.9–16% of patients with systemic candidemia [95–100].

Clinical Presentation

The ocular manifestations are broadly divided into *Candida* chorioretinitis and *Candida* endophthalmitis. Candida endophthalmitis is typically described as consisting of fluffy, white ball-like opacities in the vitreous cavity (Fig. 4.9), sometimes described as a "string of pearls" or snowballs [76, 98]. Candida chorioretinitis is described as whitish-yellowish, creamy, deep, choroidal, and/or retinal infiltrates without the aforementioned vitreous opacities [76, 96, 97]. Cryptococcal choroiditis, a rarely described entity, may also appear similarly (Fig. 4.10). The Infectious Disease Society of America recommends ophthalmological evaluation of all patients with candidemia within the first week of diagnosis. Some authors have also suggested that patients with candidemia with initially normal-appearing fundus

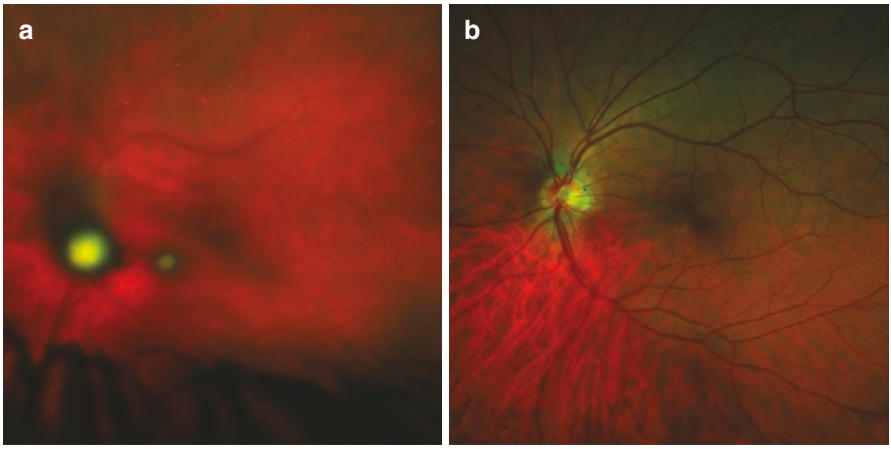


Fig. 4.9 Fungal endophthalmitis. (**a**) Suspected fungal endophthalmitis of left eye in patient with intravenous drug abuse history who presented with hypopyon, mild vitritis, and two small round yellow lesions in the vitreous overlying the optic nerve and macula. Vision was 20/640 at presentation. (**b**) Diagnostic and therapeutic vitrectomy was performed without positive cultures. Following empiric intravenous coverage with broad-spectrum antibiotics and antifungal, intravitreal injection of vancomycin, ceftazidime, and amphotericin B, vitritis resolved without additional lesions. Postoperative month 6 fundus photo depicts clear vitreous cavity without lesions, vision improved to 20/25

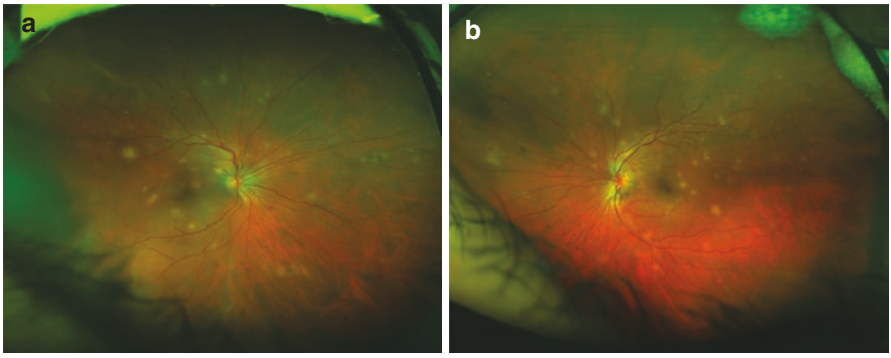


Fig. 4.10 Cryptococcal choroiditis. (**a**) Optos image of right eye with Cryptococcal choroiditis without evidence of vitritis, with multiple deep small creamy yellow lesions throughout the fundus. (**b**) Similar optos image of left eye. (**c**) OCT of the right eye shows an attached macula with a temporal macular lesion at the level of the choroid and retinal pigmented epithelium (RPE). (**d**) OCT of the left eye similarly shows an attached macula with two lesions at the level of the choroid and RPE with disruption of the ellipsoid zone and external limiting membrane

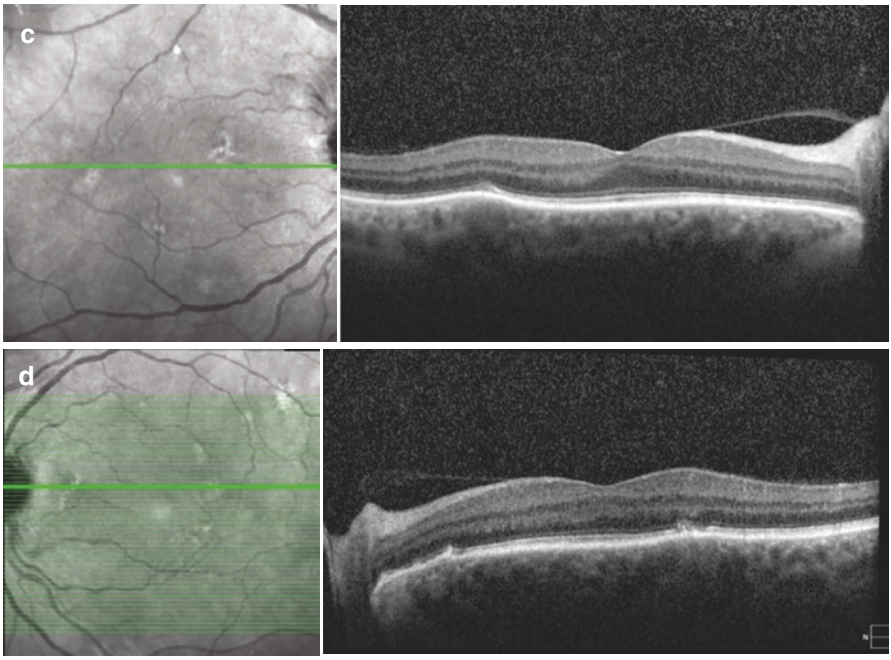


Fig. 4.10 (continued)

examinations be re-evaluated in approximately 2 weeks because of the potential that up to 13% of ocular candidiasis may be missed on the initial examination [95].

Management

Treatment of ocular candidiasis requires systemic antifungal therapy. Treatment with systemic fluconazole or voriconazole is preferred given their enhanced intraocular penetration relative to amphotericin and echinocandins (caspofungin, anidulafungin, and micafungin) [95, 97]. Patients with macular-involving *Candida* chorioretinitis or endophthalmitis are typically administered intravitreal voriconazole or amphotericin, and some require vitrectomy, while those with extramacular chorioretinitis can often be treated with systemic treatment alone.

Presumed Ocular Histoplasmosis Syndrome

Microbiology and Epidemiology

Ocular histoplasmosis syndrome is caused by the dimorphic fungus, *Histoplasma capsulatum* [101]. Humans acquire the infection upon inhalation of spores from contaminated soil. While histoplasmosis is the most endemic mycosis worldwide,

most reports of ocular histoplasmosis are from the United Sates. Histoplasmosis infection is particularly prevalent in the Mississippi and Ohio river valley which comprises a triangular shaped region connecting Eastern Nebraska, Central Ohio, and Southwestern Mississippi [101]. Tennessee is the state with the highest incidence of infection [101]. The overall incidence of ocular histoplasmosis is unknown.

Clinical Presentation

Infection by *Histoplasma* may lead to mild constitutional symptoms, though most patients remain asymptomatic while developing subclinical calcified pulmonary nodules and, if tested, positive histoplasmin skin reactions [101]. Ocular histoplasmosis comprises the following constellation of findings: (1) "punched-out" chorioretinal scars (so-called histo spots) located in the midperiphery or macula; (2) peripapillary atrophy which is typically pigmented; (3) absence of anterior chamber inflammation or vitritis; and (4) possible development of choroidal neovascularization and disciform scarring [101, 102]. A histoplasmosis skin test is available but rarely employed because of the possibility of false positives given cross-reactivity with infection by other fungal species and the very high prevalence of positive skin tests results in endemic areas [101].

Management

Choroidal neovascularization associated with ocular histoplasmosis syndrome is treated with intravitreal injection of antivascular endothelial growth factor with or without laser photocoagulation or photodynamic therapy. Smoking should be discouraged given the increased risk of choroidal neovascularization that accompanies this [101, 102].

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Diagnostic Testing in Uveitis

5

Ashlin Joye and John Gonzales

Introduction

The recognition of active uveitis is established upon slit lamp examination, dilated funduscopy, or ancillary imaging studies. Identifying the specific etiology, however, is not simple. Perhaps the most important step in this process is differentiating infectious from noninfectious processes. Differentiating an infectious disease from a noninfectious disease allows for a more precise diagnosis and can help direct therapy or inform prognosis. A thorough history and clinical exam can uncover helpful clues, which are important when combined with the clinical features of inflammation. These constellations of findings and history can then serve as the basis for making a directed approach of investigative studies. There is no "usual" uveitis workup. Rather, tests are ordered that will help include or exclude certain uveitic processes that the clinician is considering. It is of utmost importance, then, that the clinician understands the purpose and utility of each test ordered. This chapter recommends a basic diagnostic approach and discusses common laboratory tests used in the evaluation of various uveitic entities.

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Diagnostic Strategy

Numerous causes, complex mechanisms, and overlapping clinical features do not allow for a perfect diagnostic algorithm in uveitis. For this reason, recommendations are generally driven by expert opinion. These entail the utilization of medical history and clinical exam clues to formulate a more directed (or oriented) approach [1–7]. This approach is most likely to aid in diagnosis while avoiding impractical evaluation for rare conditions with low pretest probability, and limits the utilization of tests with low positive predictive value (PPV) [8]. It should be noted that differences in prevalence of uveitic entities in certain US or foreign populations will alter pretest probability and likely change the diagnostic strategy. Universally, however, a comprehensive medical, family, social, and travel history is necessary to uncover certain risk factors, as is a thorough review of systems to evaluate for signs of infection or systemic involvement [3]. Distinguishing clinical features is integral in developing an efficient diagnostic approach. This involves classifying the type of uveitis, including laterality (bilateral vs. unilateral), type of inflammation (granulomatous vs. nongranulomatous), and structural location (anterior vs. intermediate vs. posterior vs. panuveitis vs. scleritis) [1, 3, 4, 7]. Additionally, factors such as age, sex, and race of the patient can give important direction when considering etiology.

Note: Chest radiography, testing for tuberculosis, and syphilis serology should be included in all uveitis workups. This is due to the ability of sarcoidosis, tuberculosis, and syphilis to masquerade as almost any type of uveitis [1, 9].

Non-ocular Imaging (Table 5.1)

Pulmonary Imaging

Chest radiography is typically ordered during the initial workup of all uveitis patients; it is an important step when evaluating for pulmonary signs of tuberculosis and sarcoidosis, both of which can present with almost any combination of uveitic features. *Chest X-ray (CXR)* is safe and inexpensive, and can be performed expeditiously. It is widely used as the first-line screening tool when evaluating for features of pulmonary involvement in sarcoidosis or tuberculosis [1, 10]. *Chest computed tomography (CT)* is more expensive and exposes the patient to higher levels of radiation than CXR, but is more sensitive and specific than CXR when evaluating for concomitant pulmonary disease with uveitis [6, 10–12], particularly in females older than 50 years of age [10, 12]. High-resolution chest CT should be considered as a follow-up to a negative CXR when there is a persistently high index of suspicion for tuberculosis or sarcoid uveitis. It is important to note that sarcoid and TB uveitis presents frequently without signs of pulmonary involvement and absence of pulmonary signs does not necessarily exclude these diagnoses [10, 13].

Table 5.1 Overview of non-ocular imaging

Non-ocular imaging				
	Overview	When to order	Important entities	Utility
Pulmonary				
Chest X-ray (CXR)	Inexpensive, safe, lacks sensitivity	New uveitis patients	Sarcoidosis Tuberculosis	[a] [a]
Chest computed tomography (CT)	Expensive, more radiation. More sensitive and specific than CXR for TB and sarcoidosis	After negative CXR with high index of suspicion for sarcoidosis	Sarcoidosis Tuberculosis	[b] [b]
Cerebral				
Brain magnetic resonance imaging (MRI)	Safe but expensive and not recommended for routine use due to low specificity. Specific patterns of enhancement may suggest central nervous system involvement	To rule out MS before initiating anti-TNF therapy in intermediate uveitis, and in suspected primary vitreoretinal lymphoma (PVRL)	Multiple sclerosis PVRL	[b] [b]

Anti-TNF Antitumor necrosis factor-alpha
[a]Almost always useful
[b]Useful under given circumstances

Brain Imaging

Brain magnetic resonance imaging (MRI) has the potential to show manifestations of neurologic disease that may not be present on clinical exam. This is most useful when evaluating for demyelinating lesions in multiple sclerosis (MS), for as many as 10% of patients with intermediate uveitis eventuate to MS [14, 15]. However, routine imaging for periventricular white matter lesions consistent with MS should not be performed as a screening tool in patients with intermediate uveitis. Rather, MRI should be considered in cases of intermediate or anterior uveitis with neurological findings or symptoms consistent with MS, and to rule out demyelinating features before institution of anti-TNF-alpha therapy, as this may be associated with the development or progression of MS in those predisposed to developing it [15]. Behçet's disease (T1 iso-hypointense and T2 hyperintense lesions of the white matter, brain stem, basal ganglia, and thalamus) and Vogt-Koyanagi-Harada (hyperintense white matter lesions) with neurologic involvement may also show characteristic patterns of enhancement [16–18]. In cases of suspected primary vitreoretinal lymphoma (PVRL), MRI with gadolinium should be performed to evaluate for brain involvement, as this finding will affect the treatment regimen [19, 20]. In the setting of neurological symptoms or mental status changes elicited on review of systems, and typical clinical ophthalmic examination findings, obtaining an MRI can help expedite the diagnosis of MS or CNS lymphoma, given that occasionally these conditions manifest first in the eye. Despite these associations, brain MRI is typically

low yield in the inital uveitis workup and should be reserved for patients with signs of neurologic involvement that necessitate further characterization.

Infectious Testing (Table 5.2)

Ocular Fluid

Polymerase chain reaction (PCR) uses targeted primers to amplify a segment of DNA from a suspected infectious pathogen. As a directed test, one must specify the infectious agent(s) being sought, which will inform the appropriate primer to be used for genetic amplification. The number of tests is therefore limited by the sample volume and some pathogens are not routinely identified by standard laboratory testing protocols. PCR of ocular fluid can be helpful when establishing the causative

Table 5.2 Overview of infectious testing

Infectious testing				
	Overview	When to order	Important entities	Utility
Ocular fluid				
Polymerase chain reaction (PCR)	Targeted primers to amplify DNA. Number of pathogens tested is limited by volume	Unilateral, hypertensive uveitis consistent with infectious (such as viral) etiology	Herpes family viruses (EBV, CMV, HSV, VZV) *Toxoplasma gondii*	[a] [a]
Culture	Allows for culturing of pathogens and antimicrobial susceptibility testing	Suspected endophthalmitis, particularly following ocular trauma or intraocular surgery (exogenous), or systemic infection (endogenous)	Bacteria or fungus	[b]
Goldmann-Witmer coefficient (GWC)	Intraocular to serum antibody ratio. Indirect way of implicating local infection. May improve pathogen detection when paired with PCR	Consider in cases where clinical suspicion of infectious pathogen is high but directed PCR is negative	Difficult diagnoses	[b]
Metagenomic deep sequencing (MDS)	Novel molecular assay, indiscriminate amplification, and bioinformatics processing	Limited availability and expensive. Useful in research and elusive diagnoses	Elusive diagnoses of rare infectious pathogens	[b]
Tuberculosis (TB)				
Interferon-gamma release assay (IGRA)	Detects release of interferon-gamma from sensitized T cells after TB protein exposure. Minimal BCG interference	Consider as the first-line TB test in most cases of uveitis	Tuberculosis	[a]

Table 5.2 (continued)

Infectious testing				
	Overview	When to order	Important entities	Utility
Tuberculin skin test (TST)	Measures delayed T-cell response to TB purified protein. High false positives following BCG vaccine	May be used when IGRA not available or in patients from highly endemic regions	Tuberculosis	[b]
Syphilis				
Treponema specific	TP-EIA, FTA-ABS, and TP-PA. Detect Treponemal-specific antibodies. Sensitive and specific. Reverse sequence screening starts with TP-EIA	All unknown uveitis (TP-EIA is first test in reverse sequence screening algorithm)	Syphilis	[a]
Nonspecific treponemal	RPR or VDRL. Detect nontreponemal antibodies to cardiolipin and lecithin lipids that are released by damaged cells. Titer correlates with disease activity. Ordered following positive TP-EIA	RPR is second test in reverse sequence screening algorithm following positive TP-EIA	Syphilis	[a]
Cerebrospinal fluid (CSF) analysis	Nontreponemal testing of CSF in suspected ocular syphilis due to potential for CNS involvement	Provides a baseline marker to monitor response to neurosyphilis treatment	Syphilis	[b]
HIV	HIV status has important systemic and therapeutic implications in ocular syphilis	Should be determined in all cases of ocular syphilis (common coinfection)	Syphilis	[b]
Other				
Serology/PCR	Various serological/PCR testing can detect IgG (previous or chronic infection), IgM (acute infection), or pathogen DNA	May be useful in difficult diagnoses. Serum values must be correlated with ocular findings as positive results do not confirm infection in the eye	*Bartonella henselae* [b] Toxoplasma gondii [b] Herpes viridae [b]	

CMV Cytomegalovirus, *HSV* Herpes simplex virus, *VZV* Varicella zoster virus, *BCG* Bacillus Calmette-Guérin vaccine, *TP-EIA* Treponema pallidum enzyme immunoassay, *FTA-ABS* Fluorescent Treponemal antibody absorption test, *TP-PA* Treponema pallidum particle agglutination assay, *RPR* Rapid plasma reagin, *VDRL* Venereal disease research laboratory test, *CNS* Central nervous system, *HIV* Human immunodeficiency virus, *Ig* = Immunoglobulin

[a]Almost always useful

[b]Useful under given circumstances

pathogen in suspected infection and either anterior or posterior involvement [21–26]. Commonly tested pathogens include cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Toxoplasma gondii*. Ebstein-Barr virus (EBV) can also be tested.

Culture of aqueous or vitreous for bacteria and fungus may be important to perform particularly in suspected cases of endophthalmitis. A patient with a history of ocular trauma, intraocular surgery, or those who are immunosuppressed and at risk for endogenous endophthalmitis might prompt investigation for bacterial or fungal etiology. It is important to note that vitreous culture is much more sensitive for bacterial or fungal endophthalmitis, and if suspected, vitreous tap should be performed over an anterior chamber paracentesis, unless the vitreous is unable to be obtained safely [27]. Culture may determine the causative pathogen and antimicrobial susceptibility.

Goldmann-Witmer coefficient (GWC) is a ratio of intraocular antibody to serum antibody as measured by enzyme-linked immunosorbent assay (ELISA). The GWC is defined by X/Y; where X = specific antibody in aqueous or vitreous divided by total IgG in aqueous or vitreous; and Y = specific antibody in serum divided by total IgG in serum. A GWC > 4 is highly suggestive of local production of antibody against the suspected pathogen. Like PCR, the pathogen in question must be specified for the test. This test can complement PCR testing particularly when there is a high suspicion for a specific etiology, but directed PCR is negative. In such cases, it is possible that at the time of ocular fluid sampling, a sufficiently high enough pathogen load was not present for the PCR assay's sensitivity to detect. GWC could detect local antibodies for said pathogen, which would be an indirect way of implicating that particular pathogen [28, 29]. GWC, however, is not routinely done in many locations, including the United States.

Metagenomic-deep sequencing (MDS) is a novel molecular assay that indiscriminately amplifies all DNA or RNA (depending on the assay used) in a sample, and is followed by bioinformatics processing (removal of human, contaminant, and non-pathogenic DNA reads) and comparison to a known database of pathogens [30, 31]. It is capable of providing unbiased pathogen detection from the minute volumes frequently obtained from ocular fluid sampling, and may be particularly useful for detecting an elusive or rare causative pathogen [31]. MDS is currently exploratory, expensive, and not routinely available.

Tuberculosis

Interferon-gamma release assay (IGRA) is the preferred serologic testing for tuberculosis and most commonly in the form of QuantiFERON-TB Gold (utilizes ELISA) or T-SPOT.TB (Enzyme-Linked ImmunoSpot) (Fig. 5.1). IGRAs detect the release of interferon gamma from previously sensitized T cells upon re-exposure to specific *Mycobacterium tuberculosis* (TB) proteins. There is minimal interference from Bacille Calmette-Guérin (BCG) vaccine and other mycobacteria.

Fig. 5.1 An example of an interferon gamma release assay test, the QuantiFERON-Gold TB. The assay tubes are processed in the following order: Nil, Mitogen, and TB antigen

Mantoux tuberculin skin test (TST) measures the delayed T-cell-mediated (Type IV) hypersensitivity response to an intradermal injection of tuberculin purified protein derivative (PPD). Criteria for positive induration vary between populations with certain risk factors and immune dysfunction. Limitations include a high false-positive rate following BCG vaccine or nontuberculous mycobacteria exposure.

Although IGRA testing has been shown to be more sensitive and specific than TST in cases of non-ocular TB (sensitivity and specificity for IGRA of 92.3% and 84.6%, respectively vs. sensitivity and specificity for TST of 56.4% and 61.5%, respectively) [32], these results have not been demonstrated in cases of isolated ocular involvement. Ang et al. have demonstrated in multiple studies that IGRA may be less sensitive than TST in detecting ocular TB (36–91% vs. 72–96%), although it is more specific (75–82% vs. 51–73%) [33–35]. Discordance rates up to 26.5% between IGRA and TST testing leave us without a gold standard for detecting ocular TB, though a Bayesian analysis from Ang et al. suggests that the chances of ocular TB are highest with both positive IGRA and TST results [35, 36]. IGRA should be the initial test in populations with low rates of tuberculosis [35].

Note: TST can be useful in the diagnostic workup of sarcoidosis. See sarcoidosis biomarkers.

Syphilis

Treponema-specific testing includes the treponemal enzyme immunoassay (TP-EIA), fluorescent treponemal antibody absorption (FTA-ABS), and *Treponema pallidum* particle agglutination (TP-PA). These tests detect antibodies to Treponema antigens and are sensitive for detecting very early syphilis, prior treated syphilis, late and latent syphilis. Treponema-specific tests are more sensitive and specific than nontreponemal tests, though they frequently remain positive for life, and are therefore not useful in determining whether current active ocular inflammation is due to syphilis in the setting of previously treated infection.

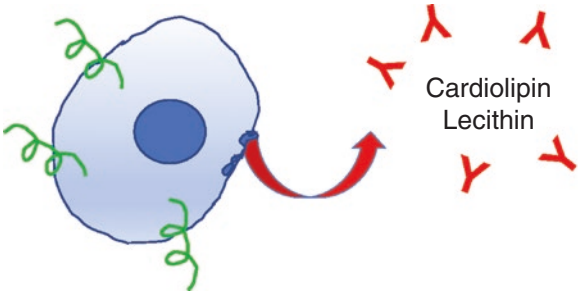

Fig. 5.2 Syphilitc cell damage. When Treponema pallidum (green spirochetes here) invades cells, damage to the cell wall releases cardiolipin and lecithin, which stimulates the production of antibodies (red) against these lipid products

Nontreponemal (nonspecific) testing includes the rapid plasma reagin (RPR) and venereal disease research laboratory test (VDRL). These tests detect antibodies to cardiolipin and lecithin lipids that are released from cells damaged by *Treponema pallidum* (Fig. 5.2). Titers correlate with disease activity and are reliably elevated during primary and secondary infection, although they may fall during latency, tertiary infection (during which you may have active uveitis), or following appropriate treatment. False-negative results may rarely occur during active syphilis due to the prozone effect, a phenomenon in which high antibody titers interfere with precipitation of antibody-antigen complex necessary for visualization of a positive test [37]. In such cases, the laboratory should be instructed to perform serial dilutions of the original sample, which may yield a true-positive result [37, 38].

Historically, nontreponemal tests were used for syphilis screening and followed with a treponema-specific test to confirm a positive result [38]. This method of testing is less sensitive, particularly during early and late syphilis when RPR titers are low. In 2008, the CDC recommended a more sensitive reverse-sequence methodology, which is more sensitive, but has a higher false-positive rate. This method begins with a treponema-specific test (TP-EIA) followed by reflexive quantitative RPR following a positive result. A positive RPR indicates a past or current infection, while a negative RPR would trigger TP-PA testing. A positive TP-PA indicates past or current infection, while a negative result suggests that syphilis is unlikely [38]. Figure 5.3 shows the reverse-sequence algorithm.

Ocular syphilis is considered a form of neurosyphilis, with accompanying cerebrospinal fluid (CSF) abnormalities in as high as 72% of patients [38–40], and the CDC currently recommends treatment with neurosyphilis therapy (10–14 days of IV penicillin) in all cases [41]. VDRL should be performed on CSF before treatment initiation to provide a baseline marker necessary to monitor adequate treatment response [38].

Note: High-risk activities that pose a risk for contraction of syphilis also include a risk for human immunodeficiency virus (HIV) *exposure. For this reason, HIV testing should be ordered in all cases of suspected ocular syphilis as coinfection can have important systemic and therapeutic implications* [38].

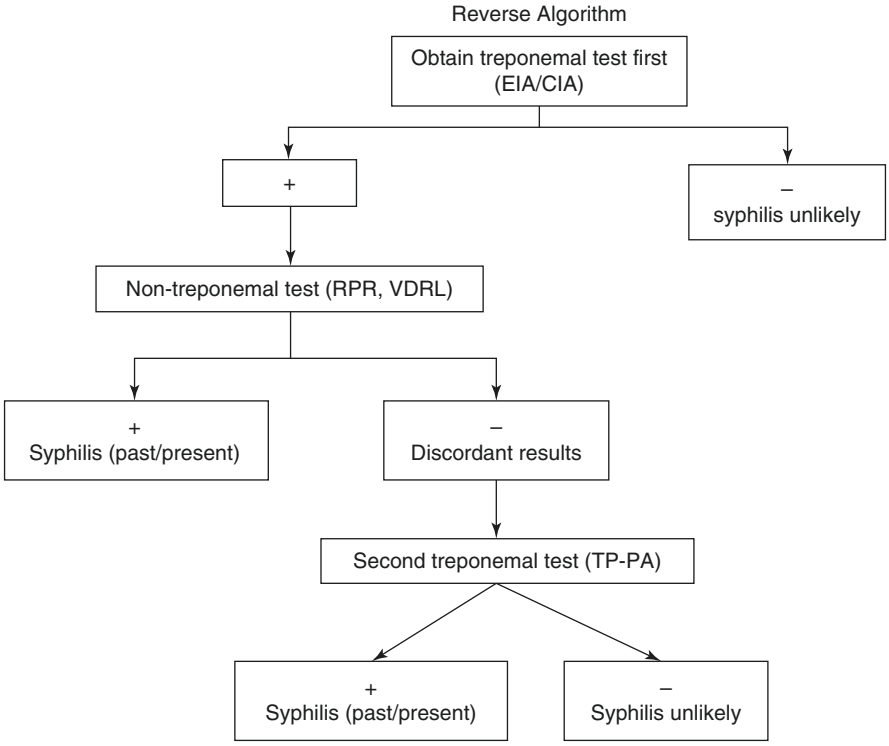

Fig. 5.3 Syphilis reverse screening algorithm. Adapted from Tong et al. [93]

Other Infectious Testing

There are various serological tests that measure the amount of a specific antibody in the serum. This can be in the form of *IgG (previous or chronic infection) or IgM (acute infection)*. PCR can also be used to detect pathogen DNA in the blood. Quantitative Ig titers and PCR can be useful in distinguishing active from latent or past infection, but serum values cannot confirm disease activity in the eye and should therefore be correlated with clinical findings. Some potentially useful infectious serology tests (aside from syphilis and TB tests discussed previously) include IgG and IgM for *CMV, HSV, VZV, Toxoplasma gondii, Toxocara, and Bartonella henselae* [42]. Ocular infection with *Toxoplasma gondii can frequently be diagnosed by clinical exam alone; however, PCR of ocular fluid or serologic testing for exposure with IgG and IgM may be warranted when the presentation is atypical* [43]. *Borrelia burgdorferi* (Lyme disease) serology has a low positive predictive value alone and should be avoided in the absence of systemic findings of Lyme disease and travel to endemic areas [44, 45].

Noninfectious Testing (Table 5.3)

Autoantibody Testing

Circulating serum autoantibodies are frequently associated with a variety of rheumatologic disease. While certain autoantibodies may confer some risk for the development of specific conditions, the relatively high prevalence of those antibodies in

Table 5.3 Overview of noninfectious testing

Noninfectious testing			
	Overview	When to order	Utility
Autoantibody			
Antinuclear antibody (ANA)	Autoantibodies directed against cell nucleus antigens. Detected via microscopic visualization of fluorescent patterns. ANA titers correlate with disease activity	Suspected JIA-associated uveitis or in cases where clinical or systemic findings of SLE exist	[b]
Rheumatoid factor (RF)	Autoantibodies against fc region of IgG detected by ELISA. Nonspecific marker of many rheumatologic conditions	Scleritis and JIA-associated uveitis	[b]
Anticyclic citrullinated peptide (anti-CCP)	Autoantibodies against cyclic citrullinated peptide (CCP). Gold standard diagnosis of RA due to high specificity, although less sensitive than RF	Scleritis associated with rheumatoid arthritis (RA)	[b]
Antineutrophil cytoplasmic antibodies (ANCA)	Autoantibodies against proteinase 3 (PR3) and myeloperoxidase (MPO). Cytoplasmic (C-ANCA) staining pattern is specific for granulomatosis with polyangiitis (GPA) and PR3 antibodies	Scleritis associated with granulomatosis with polyangiitis (GPA)	[b]
Human leukocyte antigens (HLA)			
HLA-A29	Associated with birdshot chorioretinitis (BSCR). Low specificity due to 8% prevalence in general Caucasian US population. Cannot confirm BSCR but negative result could rule it out	When evaluating white dot syndrome consistent with BSCR	[b]
HLA-B27	One of the strongest known HLA disease associations with seronegative spondyloarthropathies (JIA, ankylosing spondylitis, reactive arthritis)	Very important when evaluating young patient with uveitis (especially anterior) and joint pain	[b]
HLA-B51	Associated with Behçet's disease	Not included in current Behçet's diagnostic criteria	[c]
HLA-DRB1∗0102	Strongly correlated with tubulointerstitial nephritis and uveitis syndrome (TINU)	Not widely available and not recommended due to other accurate testing for TINU	[c]
TINU biomarkers			
Urine beta-2 microglobulin and serum creatinine	Elevated levels suggest loss of proteins/decreased glomerular filtration rate due to tubulointerstitial nephritis	Young patients with uveitis. Elevation of both levels has a 100% positive predictive value for TINU	[b]

Table 5.3 (continued)

Noninfectious testing			
	Overview	When to order	Utility
Sarcoidosis biomarkers			
ACE and lysozyme	Noncaseating granulomas in sarcoidosis actively secrete serum angiotensin converting enzyme (ACE) and lysozyme. However, a variety of pulmonary conditions can result in elevated levels ACE levels will be negatively affected in patients on ACE inhibitors	Suspected ocular sarcoidosis	[b]
Ocular fluid and tissue biopsy			
Histopathology/ cytopathology	Evaluation of molecular morphology. Biopsy of affected tissue in sarcoidosis shows noncaseating granulomas. Biopsy in PVRL may show large, atypical lymphocytes with prominent nucleoli and scanty basophilic cytoplasm	Gold standard for diagnosing pulmonary sarcoidosis or PVRL. Low yield of cells in the biopsy of suspected PVRL may limit sensitivity	[b]
Immunochemistry/ IgH gene rearrangement	Molecular techniques to detect monoclonality of leukocytes. Commonly done in the form of PCR to detect rearrangement of immunoglobulin heavy chain (IgH) of malignant cells	Suspected primary vitreoretinal lymphoma (PVRL)	[b]
IL-10/IL-6 ratio	B-cell lymphomas produce high levels of interleukin-10. Therefore, a high IL-10/ IL-6 ratio can support a PVRL diagnosis	Suspected PVRL	[b]
MYD-88 (L265P) mutation	The leucine to proline change at position 265 in the *MYD-88* gene is associated with PVRL	Suspected PVRL	[b]
CSF analysis			
Cytopathology/ Flow Cytometry	Cytopathology and flow cytometry of the CSF may be helpful to evaluate for central nervous system involvement in PVRL Pleocytosis (increased white blood cell count) in the CSF reflects inflammatory changes in the CNS	Suspected PVRL MS, VKH, Behçet's disease	[b] [b]
Oligoclonal bands	Large amounts of few Ig cell lines detected as characteristic immunoblotting patterns. Seen in MS, SLE, neuro-sarcoidosis, and neuro-Behçet's	Lumbar puncture is not routinely performed for uveitis diagnoses, but could be considered in cases of MS-associated uveitis, particularly if there are neurologic features present	[b]

JIA Juvenile idiopathic arthritis, *ELISA* Enzyme-linked immunosorbent assay, *CSF* Cerebrospinal fluid, *MS* Multiple sclerosis, *VKH* Vogt-Koyanagi Harada disease, *SLE* Systemic lupus erythematosus

[a]Always useful

[b]Useful under given circumstances

[c]Rarely useful

the healthy population limits the specificity of these tests. The only autoantibody test with proven utility is the antinuclear antibody (ANA) in uveitis associated with juvenile idiopathic arthritis (JIA) [46]. All others have limited positive predictive value and should not be ordered routinely.

Antinuclear antibodies (ANA) are autoantibodies directed against cell nucleus antigens and detected via microscopic visualization of fluorescent markers in characteristic patterns. ANA titers may correlate with rheumatologic disease activity. Despite being an important prognostic marker for many conditions, particularly connective tissue diseases such as systemic lupus erythematosus (SLE), the low positive predictive value (PPV) limits its use in uveitis [8, 47]. It is useful in the evaluation of juvenile inflammatory arthritis (JIA)-associated uveitis [46] or cases where there are systemic findings consistent with systemic lupus erythematosus (SLE) [47]. In most cases of uveitis (besides JIA), ANA is not ordered since SLE is usually associated with scleritis as opposed to uveitis. An exception occurs in the rare presentation of SLE-associated occlusive retinal vasculitis and/or ischemic choroiditis, which might prompt ANA testing, especially when patients also report other systemic symptoms or findings that are part of SLE clinical criteria.

Rheumatoid factors (RF) are autoantibodies directed against the Fc region of immunoglobulin G. These are detected via enzyme-linked immunosorbent assay (ELISA), and are a nonspecific biomarker found in multiple rheumatologic conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), SLE, and Sjögren's Syndrome. RF is also frequently positive in Hepatitis C cryoglobulinemia. There is low utility for RF testing in uveitis, although RF titers may predict progression from isolated ocular RA (which does not usually cause uveitis, but rather, scleritis) to systemic involvement [48].

Anticyclic citrullinated peptide (Anti-CCP) autoantibodies are less sensitive than RF but have emerged as the more specific gold standard for diagnosis of RA [49, 50]. Anti-CCP may be helpful in confirming the diagnosis in cases with ocular involvement such as RA-associated scleritis.

Antineutrophil cytoplasmic antibodies (ANCA) are autoantibodies against proteinase 3 (PR3) and myeloperoxidase (MPO) and detected by ELISA or indirect immunofluorescence of ethanol-fixed neutrophils. The perinuclear pattern (P-ANCA) is nonspecific, correlates with MPO antibodies, and can be associated with microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. Cytoplasmic pattern (C-ANCA) is highly specific for granulomatosis with polyangiitis (GPA) and usually correlates with PR3 antibodies [51]. ANCA testing may be considered in cases of scleritis consistent with GPA, and may predict progression from isolated GPA to systemic involvement [48].

Note: While ANA, ANCA, RF, and anti-CCP are not typically useful tests in uveitis aside from rare scenarios, these tests are useful in scleritis.

Serum antiretinal antibodies (ARA) may be found in autoimmune retinopathy, in association with nonparaneoplastic or paraneoplastic processes, including cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) [52]. Retina-specific antibodies are crucial in confirming the diagnosis of autoimmune retinopathy, and can be demonstrated using Western blot, immunohistochemistry, or

ELISA testing. However, ARA have also been found in association with various uveitic entities [53] including retinitis pigmentosa, Vogt-Koyanagi-Harada, Birdshot chorioretinopathy, and Behçet's, and as high as 62% of normal control sera [54]. Due to the rarity of autoimmune retinopathy and low specificity of ARA, the utility of ARA testing in uveitis is limited.

Human Leukocyte Antigens (HLA)

The HLA are a collection of genes encoding the major histocompatibility complex (MHC), antigen-presenting proteins integral to appropriate immune function (Fig. 5.4) [55]. HLA A, B, and C correspond to MHC class I, proteins found on most nucleated cells that present intracellular antigens to CD8+ T-cells. HLA DQ and DR (plus others) correspond to MHC class II; this class of proteins are found on antigen-presenting cells (APCs) such as dendritic cells, mononuclear phagocytes, and B cells, and present extracellular antigens to CD4+ T cells. Abnormal structure and function of either class of MHC proteins predispose carriers to immune dysfunction and autoimmune pathology. Despite disease association with certain HLA alleles, the positive predictive value of HLA testing in uveitis is very low (<0.50) and should not be included in routine screening [56]. Nevertheless, the use of HLA testing may prove useful in supporting or excluding a difficult diagnosis, and remains a powerful tool for researching pathogenetic mechanisms [56–59].

The *HLA-A29 allele* may be useful when evaluating a white dot syndrome consistent with birdshot chorioretinopathy (BSCR) [60–64]. Due to the 8% prevalence of the HLA-A29 allele in the US Caucasian population, its presence does not

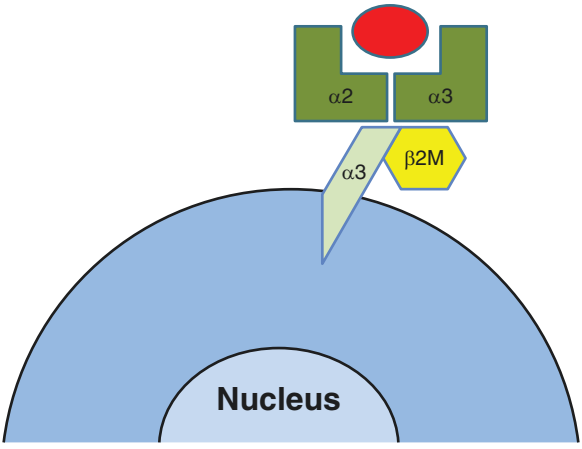

Fig. 5.4 Human leukocyte antigen (HLA) structure. HLAs are part of the major histocompatibility complex or proteins expressed on the surface of nucleated cells. The polymorphic alpha chains are encoded by the *HLA* gene. The beta-2 microglobulin (B2M) subunit is encoded by the beta-2-microglobulin gene. HLA (of the MHC class I genes) presents endogenous or exogenous peptides (red circle) to cytotoxic CD8+ T-cells

confirm BSCR, although its absence may exclude the disease since the presence of HLA-A29 in BSCR approaches 100% [65].

The *HLA-B27 allele* is strongly associated with the seronegative spondyloarthropathies, such as ankylosing spondylitis, reactive arthritis, and JIA, and remains one of the strongest HLA-disease associations [66]. Uveitis, particularly acute anterior uveitis, is a common finding in these seronegative spondyloarthropathies, and therefore, HLA-B27 may be helpful when evaluating a young patient with unilateral acute anterior uveitis and joint pain [67, 68]. It is important to note that the US non-Hispanic white population carries HLA-B27 at a prevalence of 7.5% [69]. The majority never develop signs of systemic inflammatory disease, and those with HLA-B27 develop acute anterior uveitis (AAU) at a cumulative incidence rate of 1% [70]. Conversely, greater than 50% of patients with AAU are HLA-B27 positive, and 30–40% of patients with ankylosing spondylitis develop at least one episode of AAU [70].

The *HLA-B51 allele* has been associated with Behçet's disease and related uveitis [71, 72]. However, current diagnostic criteria for Behçet's disease do not include the HLA-B51 allele and its absence in a patient suspected of having Behçet's disease should not preclude such a diagnosis if clinical features are compatible.

The *HLA-DRB1∗0102 allelic variant* is strongly correlated with tubulointerstitial nephritis and uveitis syndrome (TINU) [73, 74]. Testing is not widely available and not currently recommended, given that the positive predictive value of combining elevated urine beta-2 microglobulin and serum creatinine is high in cases of TINU (see below).

Urine Beta-2 Microglobulin and Serum Creatinine

Elevated levels of *serum creatinine and urinary beta-2 microglobulin* suggest renal tubule dysfunction (loss of proteins and decreased glomerular filtration rate) and may indicate tubulointerstitial nephritis. When evaluating a young uveitis patient for tubulointerstitial nephritis and uveitis syndrome (TINU), which typically presents with a bilateral anterior uveitis, a combined elevated urinary beta-2 microglobulin ($\geq$0.20 mg/L) and elevated serum creatinine (>0.74 mg/dL in those of age $\leq$15 years and >1.17 mg/dL in those older than 15 years) has been shown to provide a positive predictive value (PPV) of 100% and a negative predictive value of 97% [75].

Sarcoidosis Biomarkers

Elevated serum levels of *angiotensin-converting enzyme (ACE)* or *lysozyme* can be found in multiple pulmonary disease processes as a result of injury and increased metabolic activity [76]. The noncaseating granulomas in sarcoidosis actively secrete ACE and lysozyme [77], which may directly mediate inflammation. These markers are not specific to sarcoidosis, although elevation of one or both of these values is a

supportive investigational test according to the International Workshop on Ocular Sarcoidosis (IWOS) criteria [77]. It is important to note that patients on ACE inhibitors may exhibit low levels of ACE and these results should be interpreted with caution. It should also be noted that definitive diagnosis of sarcoidosis requires a biopsy demonstrating a sarcoid granuloma on histopathology.

Note: The tuberculin skin test (TST) is useful in the diagnostic workup of sarcoidosis. A negative TST, in a patient with the BCG vaccine or previously positive TST, indicates a suppressed delayed-type hypersensitivity and cutaneous anergy consistent with sarcoidosis; this is supportive investigation for diagnosis according to the IWOS criteria [77].

Ocular Fluid and Tissue Biopsy

When evaluating an eye with presumed noninfectious uveitis, it is important to keep in mind the possibility of a masquerade process. *Sarcoidosis* is capable of mimicking almost any type of uveitis, and *primary vitreoretinal lymphoma (PVRL)*, a subset of primary central nervous system lymphoma (PCNSL), is a notoriously lethal malignancy that can masquerade as a chronic anterior, posterior, intermediate, or pan-uveitis. In these cases, it may become necessary to obtain ocular tissue in order to rule in or rule out a diagnosis.

Histopathology/cytopathology/immunohistochemistry can be used to evaluate the molecular morphology. Biopsy of affected tissue (conjunctiva, choroid, and retina) showing *noncaseating granulomas* from an eye with a compatible uveitis meets definite ocular sarcoidosis criteria [77]. Vitreous samples or chorioretinal biopsy in PVRL may reveal *atypical lymphocytes* characterized by large irregular nuclei, prominent nucleoli, and scant basophilic cytoplasm [19, 78, 79]. Reactive lymphocytes may also be present. Visualization of atypical cells may be the most specific for confirming PVRL, but there can be a low yield of cells obtained during diagnostic sampling, thereby lowering sensitivity [79]. Immunohistochemistry can be used to identify B-cell or T-cell lineage.

Immunoglobulin heavy chain (*IgH*) or *T-cell receptor* (*TCR) gene rearrangement* is a molecular technique capable of detecting monoclonality of a specific B- or T-cell population in the sampled tissue or fluid [78, 80]. This is performed by way of polymerase chain reaction (PCR) to detect rearrangements of the *IgH* or *TCR* gene of malignant cells in suspected cases of PVRL in B- and T-cell lymphomas, respectively [79].

Interleukins (IL) are a class of inflammatory cytokines secreted by white blood cells. B-cell lymphomas produce large amounts of IL-10, whereas inflammatory cells typically secret IL-6. Therefore, since PVRL is typically of B-cell origin, a *high IL-10/IL-6 ratio* can support a diagnosis of PVRL [19, 78, 80].

Polymerase chain reaction (PCR) and next-generation sequencing techniques (such as MDS) are capable of detecting specific gene mutations that are associated with certain malignancies. There are many mutations of the gene *MYD-88* associated with the development of several types of lymphoma, and the *MYD-88* L265P

mutation in particular is present in an overwhelming majority of patients with PVRL [81–84]. The advantage of newer assays, such as MDS, is that both rare and common mutations associated with lymphoproliferative disorders can be detected with very minute ocular fluid volumes [83, 84].

Cerebrospinal Fluid (CSF) Analysis

CSF pleocytosis, or increased white blood cell count in the CSF, reflects inflammatory changes in the central nervous system (CNS). Certain CNS inflammatory conditions, such as Vogt-Koyanagi-Harada (VKH) disease [85, 86], multiple sclerosis (MS) [87, 88], and Behçet's disease [89], may manifest with both uveitis and CSF pleocytosis on lumbar puncture. Due to the nonspecificity of pleocytosis, routine lumbar punctures are not recommended for diagnosing uveitic entities. Additionally, fluorescein angiography findings alone may support a diagnosis of VKH without the need for lumbar puncture [85].

Oligoclonal bands, or large amounts of just a few immunoglobulin clonal lines, can be detected as a characteristic pattern of immunoglobulin G using immunoblotting techniques. This pattern can be seen in CNS infection or neuroinflammatory diseases such as multiple sclerosis [87, 88], SLE [90], neuro-sarcoidosis [90–92], and neuro-Behçet's [89, 90].

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Ophthalmic Imaging in Uveitis

6

Phoebe Lin

Fundus Photography and Multispectral Fundus Images

Fundus photography and/or pseudocolor multispectral fundus imaging has (have) several uses in the management of the uveitis patient including, but not limited to, documentation of vitreous haze; longitudinal documentation of quantity and location of choroidal and/or retinal lesions; and for correlation with other imaging or examination findings. For vitreous haze, clinical grading (rather than photographic grading) remains the standard method of grading, since the clinician, using either the 6-step NIH scale [1], or the 9-step Miami scale [2], can have good reliability [3] particularly within two steps in the grading scale, in addition to the fact that a person can mentally subtract out the degradation in fundus details caused by corneal or lenticular opacities. However, despite the inability of fundus photos to account for this mental subtraction of media opacity, photographic grading of vitreous haze is likely more reliable than clinical grading [2, 4]. For instance, the 9-step grading scale for photographic grading had very high agreement between clinician graders within 1 grade (rather than within 2 grades for clinical grading), with κ values averaging 0.91, which is considered near perfect [2], and with validation studies showing moderately strong correlation with clinical vitreous haze grading ($r = 0.51$, $p < 0.001$) [4]. Perhaps even more importantly, photographic vitreous haze score seemed to correlate with visual acuity of 20/50 or worse. Furthermore, an automated method to grade vitreous haze using an image-processing algorithm was developed by Passaglia and colleagues, which has substantial agreement with reader photographic grades for both NIH and Miami scales (κ 0.61 and 0.67, respectively) [5]. In the clinic, our practice still uses clinical vitreous haze grading in intermediate-predominant uveitis, via the NIH scale for convenience (fewer steps) but also because it carries slightly more favorable within 1-grade agreement [3] than the 9-step scale, and we prefer to

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utilize fundus photographs (typically standard 50° fundus photographs) as corroboration to decrease the chance of subjectivity in gauging response to treatment over time. The difference between photographic vitreous haze grading using standard fundus photography vs. ultra-widefield modalities that utilize multiple spectra to create a pseudocolor image (Optos® images) has yet to be fully determined, given that the only study comparing the latter to standard fundus photography found correlation, but did not attempt to perform standard vitreous haze photographic grading, and instead, only looked at the presence or absence of vitreous haze [6].

A second utilization for fundus photography is to more objectively locate new chorioretinal lesions in the fundus over time. With either standard fundus photography particularly with peripheral scans using the montage, and with ultra-widefield (UWF) imaging, this can be done, except for some limitations in the superior and inferior periphery in UWF imaging, which can be obstructed by the eyelids without gaze-directed image acquisition (Fig. 6.1). While not tested head-to-head, multispectral imaging might be able to identify outer retinal and choroidal lesions

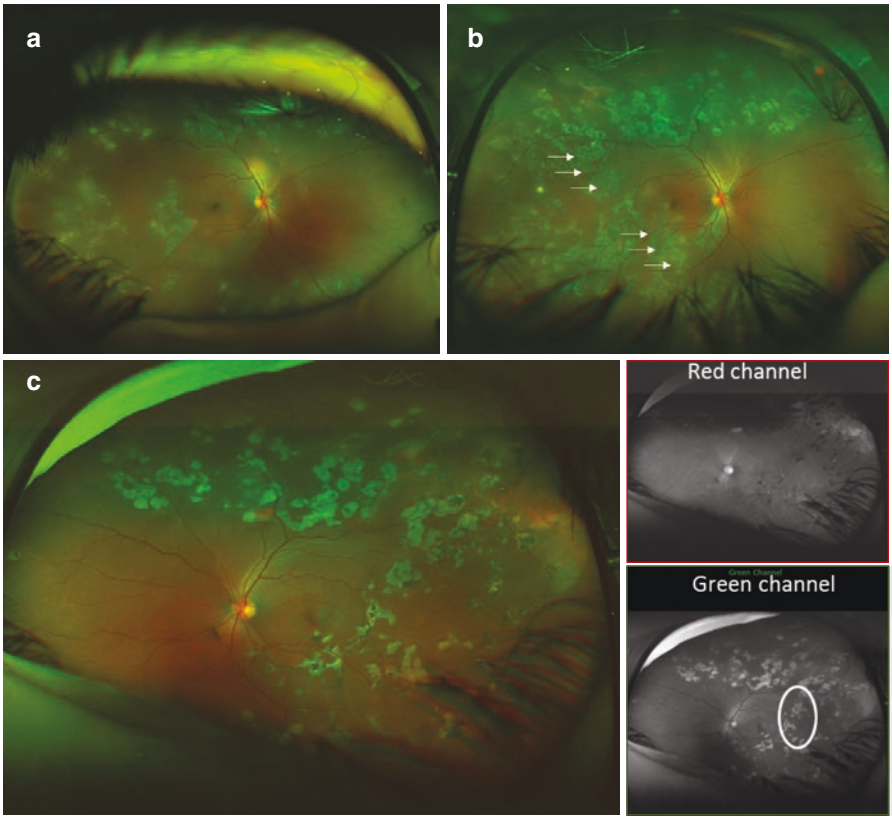

Fig. 6.1 Utility of fundus photography. (**a**, **b**) Documentation of new outer retinal lesions over time in a patient with relentless placoid chorioretinitis (new lesions designated by arrows). (**c**) Demonstration of split spectrum ultra-widefield images of the left eye of patient shown in **a** and **b**. The 535 nm laser image (green channel in lower right panel) reveals outer retinal/RPE level lesions (white oval) much more readily than the 632 nm channel (red channel shown in upper right panel)

even more easily than clinical examination, particularly in the periphery. Knickelbein and colleagues showed that split spectrum images from the 635 nm laser of the UWF imaging device were able to identify choroidal lesions much more readily than the 532 nm laser image [7]. The combined multispectral image therefore was able to identify choroidal lesions very easily. How this compares to ICGA including wide-field ICGA, in identifying choroidal lesions, has yet to be determined. The 532 nm split spectrum images, on the other hand, more easily identified lesions located in the outer retina or retinal pigment epithelium, above Bruchs' membrane, than the 635 nm images [7]. The latter was useful in identifying borders of primary vitreoretinal lymphoma, for instance. In our clinic, we obtain UWF imaging for posterior-involving uveitis patients at baseline and at follow-up. We find it useful to display the multispectral pseudocolor image as well as the split spectra images (532 nm and 630 nm) separately on our image viewing software (Fig. 6.1c).

Finally, fundus photography can also be very useful in correlating chorioretinal lesions seen on examination as well as correlating location of lesions seen on OCT or fundus autofluorescence.

Fluorescein Angiography (FA)

The utility of FA in uveitis is multifold, including assessment of retinal vascular leakage (Fig. 6.2), optic disc leakage, macular leakage in cystoid macular edema, areas of capillary nonperfusion or ischemia, and complications of inflammation such as retinal neovascularization (Fig. 6.2), choroidal neovascularization, or retinal arteriolar or vein occlusions. In addition, certain posterior uveitic lesions can have FA characteristics that are corroborative for the clinical differential diagnosis. For instance, in multiple evanescent white dot syndrome, typical lesions that are seen in the posterior pole are small hyperfluorescent lesions individually grouped in a wreath configuration. In acute placoid multifocal posterior pigment epitheliopathy (APMPPE), typical FA lesions are hypofluorescent in early frames and hyperfluorescent in late frames. It should be noted that other conditions including, but not limited to, multifocal choroiditis, tuberculosis, syphilis, toxoplasmosis affecting the outer retina, and sometimes, vitreoretinal lymphoma, can all have this "block early and stain late" FA pattern as well, particularly in the acute phase, and these FA findings are not pathognomonic for a single condition. On the other hand, serpiginous choroidopathy might have borders that are hypofluorescent early and stain later, whereas the central portion of the lesions might be hyperfluorescent from early frames due to window defect. Vogt-Koyanagi-Harada (VKH) disease often presents with multiple pinpoint hyperfluorescent spots, optic disc leakage, and/or pooling of fluorescein dye in areas of serous retinal detachment.

Retinal Vascular Leakage

Another advantage of FA is to identify whether retinal vascular leakage is venular or arteriolar-predominant, which might inform the differential diagnosis (covered in

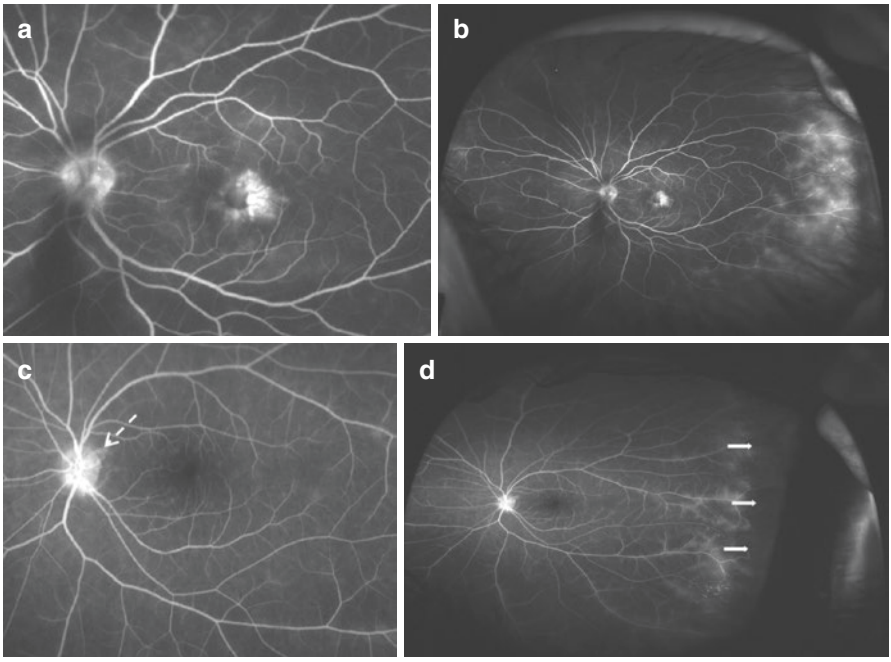

Fig. 6.2 Use of ultra-widefield fluorescein angiography in uveitis. (**a**) 50° FA image in a 41-year-old patient with panuveitis showing cystoid macular edema with minimal vascular leakage, while the same image including the ultra-widefield view (**b**) demonstrates significant peripheral vascular leakage. (**c**) 50° FA in a 24-year-old woman with pars planitis showing minimal retinal vascular leakage and neovascularization of the disc (dotted arrow), while the same image including the ultra-widefield view (**d**) demonstrates peripheral vascular leakage and significant peripheral capillary nonperfusion (white solid arrows)

Chap. 3). While most uveitis specialists agree that active inflammation can be assessed in some patients by the degree of retinal vascular leakage on FA, it remains to be determined what degree of residual leakage is tolerable, and would not necessarily lead to long-term complications such as retinal neovascularization or visual field loss, particularly, following a treatment response. Furthermore, currently, there is no widely used or validated imaging algorithm to quantitate retinal vascular leakage that might aid in the assessment of activity level. Ehlers and colleagues, however, have developed a fully automated software platform that can quantitate retinal vascular leakage area and microaneurysms on UWF FA images [8]. While this study was done in diabetic patients, one can imagine that the same software can be applied to uveitic patients with retinal vasculitis. It is unclear whether or not grading of leakage at a particular site can be assessed using this custom software, however. Techniques such as these may prove useful in the future for use as endpoints in clinical trials and for regular patient care if validated.

Also not yet fully elucidated is the relative significance of diffuse vascular leakage or capillary leakage compared with isolated peripheral vascular leakage (the

latter has been more commonly identified with the use of UWF FA) (Fig. 6.2). While Campbell and colleagues demonstrated that uveitis specialists were more likely to designate active disease and alter management when UWF FA was used compared with simulated conventional FA, due to the detection of PVL, they did not address whether or not this was clinically meaningful or would alter outcome, given that the study had no follow-up [9]. In another retrospective cross-sectional study, peripheral vascular leakage seen on UWF FA in uveitis patients was associated with other signs of active inflammation, such as macular edema and optic disc leakage [10]. However, in a follow-up study looking at PVL patients who either did or did not undergo treatment augmentation, when controlling for patients with CME, there appeared to be no impact on visual acuity at 1 year [11]. Given the latter study's retrospective nature, short one-year follow-up, and lack of correlation to functional testing such as visual field testing or ERG, it remains unclear whether or not isolated peripheral vascular leakage seen on UWF FA requires treatment [11]. Thus, it would be highly useful for the field of uveitis to better understand the clinical significance of retinal vascular leakage and for there to be improved, validated grading of retinal vascular leakage via FA imaging. In our practice, most patients with intermediate, posterior, or panuveitis obtain a baseline UWF FA and follow-up FA depending on the presence of retinal vascular leakage and/or suspected complications of retinal vasculitis or development of choroidal neovascularization. In the absence of quantitative means to assess retinal vascular leakage, we use qualitative means by comparing two images over time side by side at similar phases after fluorescein injection.

Cystoid Macular Edema

Finally, while FA has been used in the past to assess macular leakage and uveitic macular edema, with the advent of OCT, it is perhaps now used more to assess retinal vascular leakage, and only corroborate macular edema. From the multicenter uveitis steroid treatment trial (MUST) data, Kempen and colleagues found that OCT and FA had only moderate agreement in identifying uveitic macular edema, with OCT more frequently returning usable information (90.4% vs. 77%; $\kappa = 0.44$) [12]. Given the advantages in terms of safety and cost, OCT rather than FA is used for the initial evaluation of uveitic macular edema.

Indocyanine Green Angiography

Because indocyanine green dye is 98% protein-bound, it can better characterize choroidal pathology found in many uveitic entities since it passes through the large fenestrations of the choriocapillaris and into the choroidal stroma where it lingers. Thus, choroidal inflammatory infiltrates appear hypocyanescent due to the space-occupying lesions that prevent diffusion of the ICG molecule. Examples of this are found in cases of tuberculous choroidal granulomas, sarcoidosis, birdshot chorioretinopathy, and VKH, in which you will see multifocal hypocyanescent lesions.

Other findings that might be associated with uveitis include the following: hypocyanescence from choriocapillaris nonperfusion, which are more irregularly shaped and sometimes geographic in appearance, and hypercyanescence from leakage of choroidal vessels. While early classical birdshot lesions are not typically seen at all on FA, they are very characteristically seen as regularly spaced, multifocal hypocyanescent lesions on ICGA, and can make for early diagnosis of this condition prior to vision loss [13]. ICGA has been shown to be much more sensitive for birdshot chorioretinopathy than examination alone, as demonstrated by Reddy and colleagues [14]. Herbort and colleagues have also shown that in serpiginous choroidopathy (SC), severe choroidal nonperfusion on ICGA can delineate lesions to a larger extent than can be detected on FA, thus allowing for visualization of the active edge. These active edges on ICGA are said to correlate with the hyperreflective outer retinal areas seen on OCT usually adjacent to an older lesion which has already had RPE atrophy and some degree of choroidal atrophy. Aggressive treatment of these active edges can minimize underlying atrophy and can potentially restore visual function in these areas.

Fundus Autofluorescence

FAF was first described by Machemer in 1970 as pseudofluorescence emittance from the retina prior to fluorescein injection while performing an FA. Later, it was determined that the main fundus fluorophore-emitting autofluorescence was lipofuscin, originating from the RPE which accumulates byproducts from incomplete degradation of photoreceptor outer segments. There are two main autofluorescence systems utilized clinically. The Spectralis machine captures fluorophores stimulated at 488 nm (a blue laser), whereas the Optos machine utilizes a 532 nm laser (green laser) with slight differences in lesions that they are able to detect. Processes most likely to cause hyperautofluorescence include those that disrupt photoreceptor turnover and thus increase accumulation of lipofuscin in the RPE. Other situations in which a uveitic eye might display hyperautofluorescence include displaced luteal pigment from cystoid macular edema, infiltration with macrophages, which also contain lipofuscin, and unmasking of choroidal vessels once RPE and choriocapillaris have atrophied. Hypoautofluorescence, on the other hand, usually occurs when there is loss of RPE cells, but can also occur with increased RPE melanin content, presence of overlying subretinal fluid, with subretinal fibrosis, or with media opacities such as cataract, vitritis or vitreous hemorrhage.

Particularly with the use of UWF FAF, uveitis affecting the retina can be monitored quite effectively. For instance, in uveitis in which there is an outer retinal, RPE or full thickness retinal predominance, active borders of zonal or contiguous disease can be identified perhaps more easily than examination alone. In cases of syphilitic posterior uveitis, particularly syphilitic outer retinitis (SOR), the delineation of the active border is much more evident on UWFFAF than on examination alone or standard fundus photography, and hyperautofluorescent areas correlate very well with ellipsoid zone (EZ) changes on OCT where the latter could be obtained [15]. With

UWF FAF, the borders of active SOR far in the periphery are also well delineated, unlike with OCT alone. In acute zonal occult outer retinopathy (AZOOR), UWF FAF has demonstrated easy identification of both centripetal and centrifugal spread of AZOOR, and that autofluorescent abnormalities correlated well with perimetry, OCT in areas where it could be obtained, as well as electroretinography [16]. Another study describes a characteristic trizonal FAF appearance of AZOOR to include a normal zone of autofluorescence (Zone 1), a speckled hyperautofluorescent zone (Zone 2), and a hypoautofluorescent zone (Zone 3) thought to be associated with RPE and choroidal atrophy [17]. However, in acute rather than chronic or old AZOOR, both studies noted that areas involved were diffusely hyperautofluorescent. Many cases had a distinct ring of bright hyperautofluorescence at the border of hypoautofluorescent areas [16, 17]. In addition to AZOOR and syphilitic outer retinitis, FAF is useful in delineating active borders in serpiginous choroiditis, new lesions in relentless placoid chorioretinitis, multifocal choroiditis, punctate inner choroiditis, and sarcoid panuveitis, as well as delineating active borders most easily for herpetic viral retinitis [18–20].

In serpiginous choroidopathy, a relatively large case series demonstrated that active borders (defined as lesions with characteristic FA findings with one border later progressing) had an indistinct hypoautofluorescent area outside a well-delineated hyperautofluorescent border, whereas the transitional portions of the lesion (nonleading edge) appear to have mixed hypoautofluorescence, an intensely hyperautofluorescent intermediate border, and a well-delineated hypoautofluorescent border [21]. Completely inactive lesions were diffusely hypoautofluorescent and well delineated [21]. The indistinct hypoautofluorescent areas in active lesions are likely due to outer retinal and/or RPE edema, as has been described on OCT as outer retinal hyperflective lesions. This description is different than in our experience, in which we see diffuse hyperautofluorescence outside lesions containing distinct hypoautofluorescent borders with brightly hyperautofluorescent middle portions (Fig. 6.3). This difference can perhaps be due to different FAF machines being utilized with the Carreno study utilizing Spaide autofluorescence filters at excitation wavelength of 585 nm, and with our group using Optos autofluorescence image acquisition (532 nm). Our inactive lesion findings, however, are similar, in that they are diffusely hypoautofluorescent and well delineated. In our practice, patients with choroidal or retina-involving uveitis receive UWF FAF or standard Spectralis FAF at baseline and at follow-up in addition to color or multispectral imaging.

Optical Coherence Tomography

Clinicians treating all anatomic subtypes of uveitis have found immense utility in spectral domain OCT (SD-OCT) for the following: to identify and quantify cystoid macular edema (CME); to identify and monitor resolution of fluid (subretinal fluid, intraretinal fluid, sub-RPE fluid); to monitor retinal structural involvement (ellipsoid zone disruption, full-thickness or outer retinal infiltration, inner retinal layer

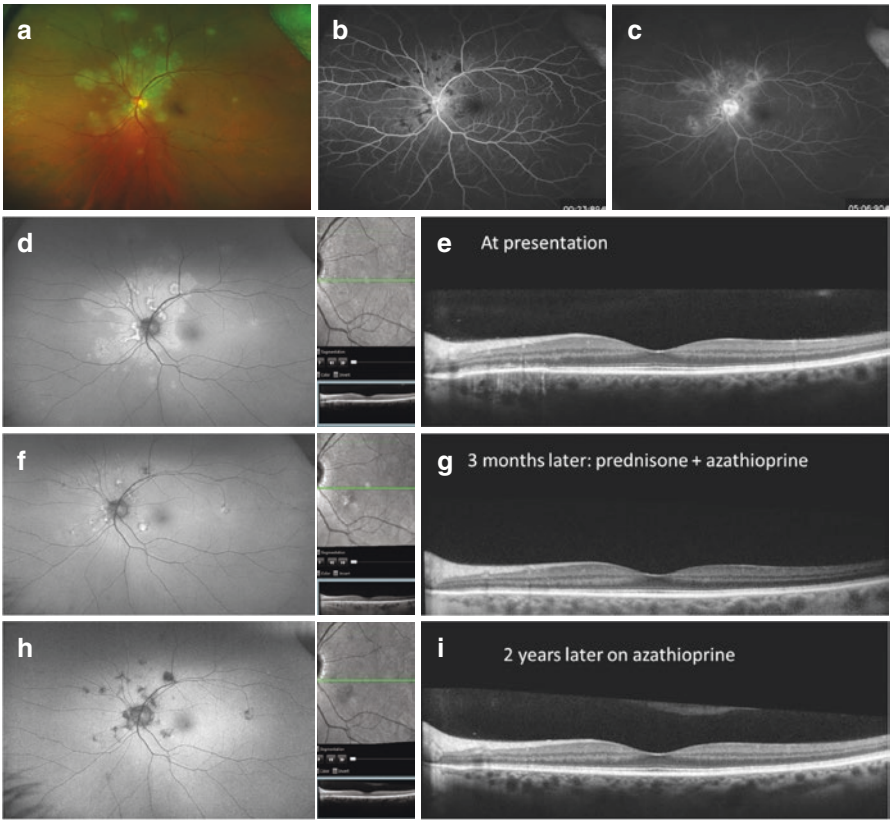

Fig. 6.3 Multimodal imaging in serpiginous choroidopathy. A 60-year-old Caucasian woman who was syphilis serology nonreactive and quantiferon negative presented with serpentine outer retinal yellowish grayish lesions emanating from the optic nerve prominently demonstrated on ultra-widefield multispectral imaging (**a**). (**b**, **c**) Lesions are hypofluorescent in the early phase ultra-widefield FA, and variably hyperfluorescent in later phases of the FA, particularly at the borders of the lesions. (**d**) On ultra-widefield fundus autofluorescence, most striking are the diffuse larger areas of hyperautofluorescence that correspond to hyperreflective disruption of the ellipsoid zone (EZ) and outer nuclear layer on OCT (**e**). Well-delineated lesions appear in jigsaw puzzle shapes that have a distinct hypoautofluorescent border with hyperfluorescent centers (**d**). Three months after initiating immunosuppression, the diffuse hyperautofluorescent areas have improved towards normal fundus autofluorescence, and some jigsaw lesions appear smaller. Improvement of hyperautofluorescence towards normal corresponds to improvement in outer retinal laminations on OCT with less hyperreflectivity of the outer nuclear layer (**f**, **g**). Two years after initiation of therapy, all lesions are uniformly hypoautofluorescent and surrounding retina has normal autofluorescence (**h**). On OCT, the EZ line appears relatively normal (**i**)

disruption or atrophy); to monitor choroidal involvement (choroidal lesions, choroidal thickening), particularly with enhanced depth imaging; to distinguish inflammatory lesions from complications such as choroidal neovascular membranes (CNVM), particularly with OCT-angiography; and to monitor complications of uveitis such as vitreomacular traction, macular holes, or epiretinal membranes.

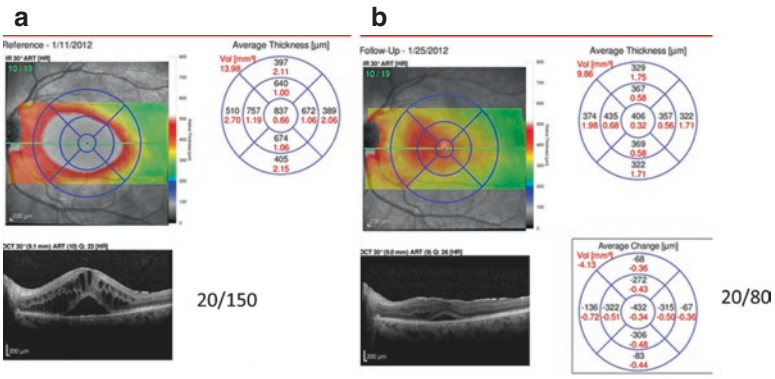

Fig. 6.4 Central subfield thickness is associated with visual acuity in uveitic CME. (**a**) This is a 55-year-old Caucasian woman with a history of retinal vasculitis and CME before treatment (**a**) and after intravitreal triamcinolone treatment (**b**). Visual acuity was 20/150 and improved to 20/80 despite stability of an ERM

For identification and monitoring treatment response in uveitic CME, OCT has now surpassed FA due to its noninvasive format, sensitivity, and reliability of quantification (Fig. 6.4) [12]. Chronic CME can result in disruption of the neural network between the photoreceptors and other retinal cells, eventually leading to gliosis, atrophy, and loss of vision. Tortorella and colleagues have shown that central subfield thickness (CFT) is correlated with poor vision in uveitic CME, as is ellipsoid zone (EZ) disruption and interdigitation zone disruption on SD-OCT. [22] Another study subsequently confirmed that in uveitic CME, CFT is correlated with visual acuity in a multiple regression analysis, as well as external limiting membrane (ELM) disruption, and intraretinal cyst area [23]. Perhaps another main feature of the latter study was that the extent of disorganization of the retinal inner layers (DRIL) was strongly associated with visual acuity, and that eyes with DRIL had worse VA than those without DRIL. While this finding was not significant after multiple regression analysis, this was because of a strong association with intraretinal cysts, which are independently associated with visual acuity. It has thus been proposed that DRIL can be used as an OCT biomarker in uveitic CME, to improve our ability to counsel our patients in terms of visual prognosis and risk stratification as well as to screen subjects for clinical trials [23].

In addition to its use for uveitic CME and other retinal structural abnormalities associated with inflammation as mentioned above, SD-OCT is useful to monitor regression or progression of outer retinal, inner retinal, and/or full-thickness retinal lesions. For instance, in ocular sarcoidosis, posterior polar outer retinal/inner choroidal lesion height appears to regress after steroid treatment. In other posterior pole-involving entities such as PIC or MFC, OCT can be used similarly [24]. We have found that in birdshot chorioretinopathy, about 35% of patients have macular outer retinal lesions seen on OCT, that these lesions correspond to logMAR visual acuity, and that they can respond to treatment with immunosuppression or steroids

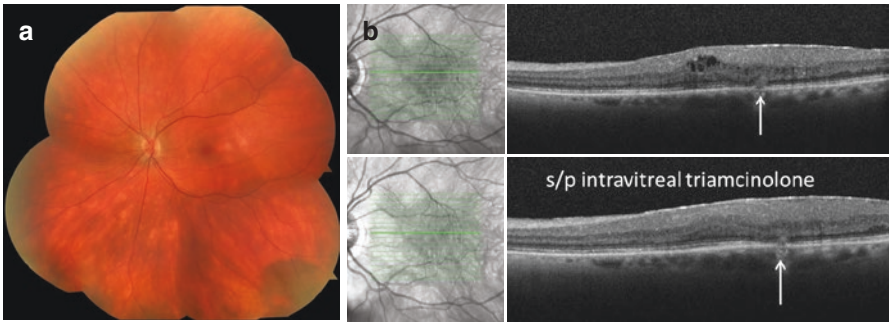

Fig. 6.5 Outer retinal lesions on OCT in birdshot chorioretinopathy. The patient is a 44-year-old Caucasian woman who had creamy choroidal lesions in the periphery and is HLA-A29+ (**a**). In addition to CME, the patient had outer retinal/inner choroidal lesions in the macula as seen on SD-OCT (**b**, upper panel) that consolidated in height upon treatment with intravitreal triamcinolone (**b**, lower panel)

(regression in height of lesions) (Fig. 6.5). Treatment responses to antivirals can also be monitored by SD-OCT in posterior-involving viral retinitis (Fig. 6.6). In terms of retinal lesion monitoring, SD-OCT is currently limited to the field of view that is able to be captured by OCT, which has increased in recent years with wide-field OCT.

With enhanced-depth imaging OCT, during which images are acquired with the OCT lens pushed closer to the eye thus placing the outer choroid in closer proximity to the zero delay line, choroidal lesions can be much more accurately identified [25], and choroidal thickness can be measured and monitored with reliability [26, 27]. In conditions such as birdshot chorioretinopathy, sarcoidosis, tuberculosis, VKH, sympathetic ophthalmia, and likely other uveitic conditions, choroidal thickening has been purported to be a surrogate for clinical inflammatory disease activity. In VKH, it has been shown by several groups that in the acute phase, the choroid is dramatically thickened, similar to what is seen histopathologically, and choroidal thickness can be monitored in a quantitative fashion into convalescence [28, 29]. Interestingly, in the long term, choroidal thickness in VKH is actually lower than age-matched controls without VKH [30]. In addition, Dastiridou and colleagues have shown, in a large 220 patient series of birdshot chorioretinopathy scanned with swept source OCT, that birdshot patients have decreased choroidal thickness overall, but in active disease the choroid is thicker than in inactive disease [31]. In our clinic, if either CME or chorioretinal disease is suspected, OCT is obtained, taking care to acquire images throughout the macula and macular peripapillary retina from arcade to arcade (Spectralis 30 × 25, 61 scan, ART 9 settings, as well as high-resolution vertical and horizontal scans through the fovea, all with EDI). If lesions extend outside the macula in the posterior pole, we acquire wide-field OCT images or directed extramacular scans.

In addition to the above uses for OCT, novel processing and acquisition methods can potentially be used to monitor disease activity in uveitis patients. For instance, custom software has been created that provides a measurement of vitreous signal intensity relative to RPE signal intensity on OCT, and that has correlation with

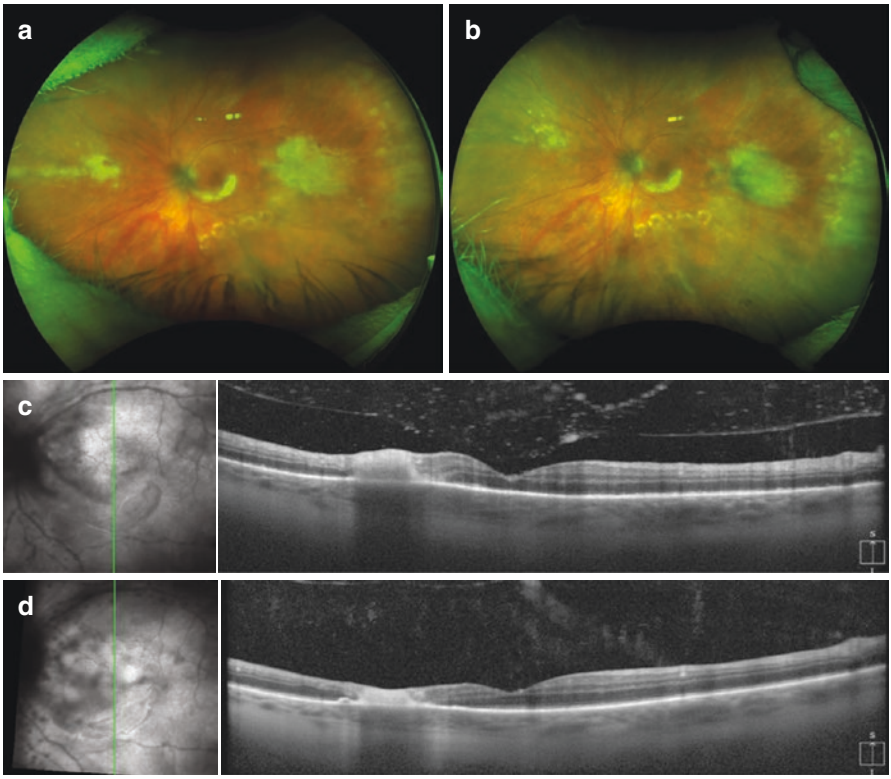

Fig. 6.6 Use of OCT in management of acute retinal necrosis (ARN). A fundus image of a 70-year-old Caucasian male with ARN from HSV2, at presentation (**a**) and at 1 month (**b**). At presentation, OCT shows full thickness retinal necrosis in the macula in addition to significant posterior vitreous cell (**c**). After 1 month of treatment with valacyclovir 2 g PO TID and biweekly intravitreal foscarnet injections, the lesion consolidated in size and the posterior vitreous cell has improved (**d**). Visual acuity improved from counting fingers OS to 20/150 + 1 OS

clinical vitreous haze scores using the NIH scale. If this software is further validated and is made available for wide clinical use, it can potentially provide a clinically useful outcome measure in some uveitis patients [32]. On the other hand, several groups have investigated the use of anterior segment OCT to grade anterior chamber cells in uveitis, which appears to correlate well with clinical grading [33, 34]. In another study, AS-OCT was used to distinguish AC cell type, and might potentially be useful to determine etiology of uveitis [35].

Ultrasound

B-can ultrasonography is quite useful in uveitis patients for several purposes including, but not limited to, assessment of CME when there is too much media opacity to utilize OCT or FA; assessment of choroidal thickening, masses, or posterior subtenon's fluid (T-sign) in posterior scleritis; assessment of progression of

retinoschisis (a complication of pars planitis, Fig. 6.7a,b); and assessment of extent and location of complications of uveitis such as serous, tractional or rhegmatogenous retinal detachment (Fig. 6.7d) particularly if there is too much media opacity to document by examination. Ultrasound biomicroscopy (UBM) is useful to assess for ciliary body, iris, or pars plana masses or abnormalities, ciliary body membranes and atrophy, nontraditional causes of uveitis such as uveitis-glaucoma-hyphema syndrome from a tilted or dislocated intraocular lens implant, and to document clock hours of snowbanking (Fig. 6.7c). In pars planitis patients, it is beneficial to document clock hours of snowbanking if considering treatment with cryopexy vs. laser or if needing to consider placement of vitrectomy ports when vitrectomy is necessary. Typically, not more than 3 clock hours of pars plana snowbanks are treated with cryopexy so as not to exacerbate intraocular

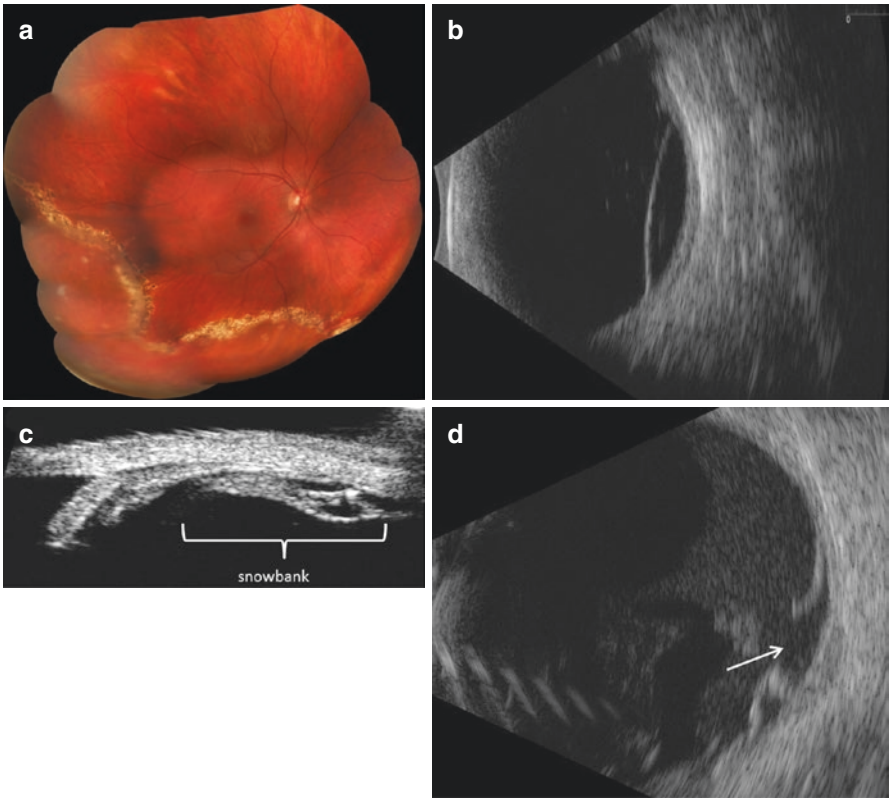

Fig. 6.7 Use of ultrasonography in uveitis. (**a**, **b**) A 7-year-old boy presented with pars planitis and retinoschisis documented by fundus photography (**a**) and B-scan ultrasonography (**b**). Retinoschisis was progressive despite resolution of vitreous haze with systemic immunosuppression. (**c**) Ultrasound biomicroscopy was used to document clock hours of snowbanking in the same pars planitis patient to plan for cryopexy treatment of presumed exudative retinoschisis. (**d**) A 33-year-old gentleman with a history of pars planitis presented with diffuse vitreous hemorrhage due to a macula-sparing rhegmatogenous retinal detachment with large horseshoe tear (arrow) documented by B-scan

inflammation. While rare, end-stage chronic uveitis with hypotony can be assessed to guide discussions on ocular prognosis by using UBM to identify ciliary body atrophy and/or ciliary body membranes.

Emerging Trends in Ophthalmic Imaging for Uveitis

Adaptive Optics

Adaptive optics (AO) imaging utilizes the technology developed for use in astronomical telescopes to improve visualization of cellular structures in the retina by reducing the effect of wavefront distortions introduced by optical media aberrations such as those located in the cornea and lens, using a deformable mirror. AO has been used in ophthalmology more commonly to study photoreceptor mosaics in inherited retinal disorders. In uveitis, several groups have begun to use AO in uveitis, either in posterior uveitis or in uveitis associated with retinal vasculitis. Biggee and colleagues showed that a commercially available AO-flood illuminated camera was able to document alterations in parafoveal cones in posterior uveitis patients, including subclinical changes not seen using other ophthalmic imaging modalities reviewed above. In some cases, there was reversibility of certain AO abnormalities with either time or treatment (Fig. 6.8), and in other cases, AO abnormalities were persistent, particularly if OCT abnormalities persisted [36]. Agarwal and colleagues showed that AO imaging was able to quantitate photoreceptor density reductions in white dot syndrome patients [37]. In patients with retinal vasculitis, two groups have shown that AO can detect perivascular infiltrates, which can reverse with treatment [38, 39].

Optical Coherence Tomography Angiography

OCTA is a method by which repeated high-resolution OCT scans obtained at the same location can identify small and large blood vessels due to decorrelation of static tissue vs. moving blood cells within blood vessels, without the use of intravenous dye. Currently, several groups have argued for its utility in distinguishing CNVM from inflammatory lesions in various choroid and retina-involving uveitic entities such as PIC and MFC (Fig. 6.9) [40–42].Pichi and colleagues have also shown that OCTA can be used to quantify iris vessels in anterior uveitis, and found that flow quantitation using iris OCTA could potentially be correlated to clinical grading of AC cell, although correlation analyses were not yet done. In birdshot chorioretinopathy, retinal and choroidal OCTA studies have shown capillary loops, telangiectatic vessels, and increased capillary spaces, as well as decreased choroidal blood flow in areas where there was RPE atrophy or disruption [43, 44]. It will require large longitudinal studies to determine the clinical significance of these OCTA imaging findings, and to develop OCTA to inform clinical management or endpoints in clinical trials.

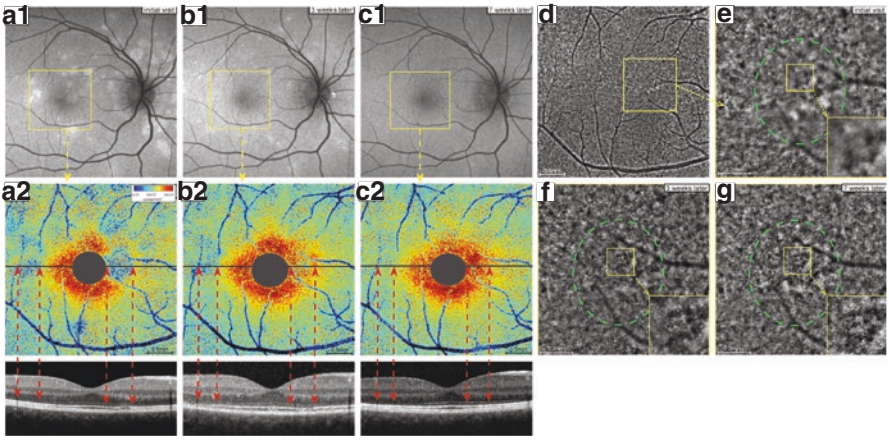

Fig. 6.8 Utility of adaptive optics in uveitis. (**a**) A 17-year-old Caucasian emmetropic woman presented with photopsias and small scotomas in the right eye. Examination, history, and standard ophthalmic imaging were consistent with MEWDS. Adaptive optics revealed multifocal areas of decreased cone density (middle panels show cone density maps) that improved to normal over time (**b**, **c**); Panels **d**–**g** show the cone mosaic transitioning from poor wave-guidance of cones within the lesions (**e**) to normal (**g**) over time. Adapted from Am J Ophthalmol Case Rep. 2016 Mar 11;1:16–22

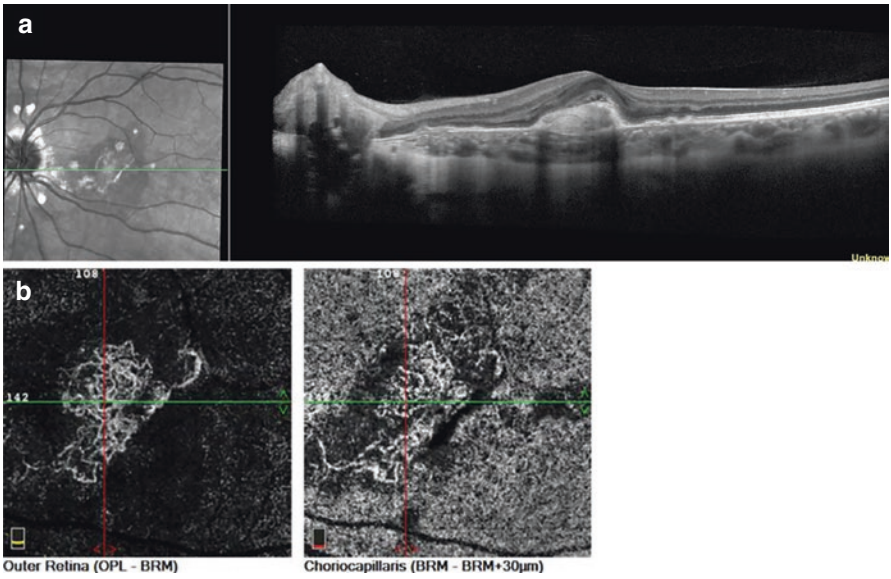

Fig. 6.9 OCTA in PIC patient with demonstrated choroidal neovascular membrane. (**a**) Infrared image and b-scan OCT of lesion as well as (**b**) choroidal neovascular membrane seen on OCTA

Summary

Given the variability in which our uveitis patients present, ophthalmic imaging can be extremely useful in aiding the development of a differential diagnosis, and allowing for improved ease of monitoring inflammatory activity and/or treatment response. For many uveitic conditions, and as described throughout this chapter, utilizing more than one imaging modality together, such as the combination of OCT with FAF and FA or ICGA, or ophthalmic ultrasonography, known as multimodal imaging, along with significant historical and examination details, may be crucial in the management of our uveitis patients for maximizing their long-term outcome. When ordering and utilizing ophthalmic imaging, as with laboratory testing, it is important to select imaging modalities based on knowledge of how the information might guide treatment augmentation or prognosis, rather than ordering a menu of studies indiscriminately. In this regard, scarce longitudinal data on the impact of imaging findings are available, but various case series and a few larger studies suggest potential utility of certain imaging modalities for specific groups of uveitic disease (i.e., OCT in uveitic CME). Advancements in imaging such as software applications to quantitate clinical parameters such as vitreous haze, aqueous cell, and FA retinal vascular leakage, may prove to be useful clinically as well as provide novel outcome measures for clinical trials. Furthermore, newer imaging modalities such as OCTA or adaptive optics, should they be validated in larger longitudinal studies, can potentially demonstrate new information regarding disease pathogenesis and/or clinical course.

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Surgery in Uveitis

7

Christopher D. Conrady, Lynn Hassman, and Akbar Shakoor

Introduction

Multiple complications occur in the setting of uveitis and require surgical management, including cataract formation, glaucoma, vitreous hemorrhage, and epiretinal membrane formation. Cataract and glaucoma are frequent complications of both the inflammatory disease and the steroids used to treat inflammation. Additionally, surgical techniques such as vitrectomy are utilized for diagnostic purposes.

While there are many things to consider in a uveitis patient, well-constructed plans prior to surgical intervention are important to minimize the intra- and postoperative complications related to uncontrolled inflammation and infection encountered in these patients. Surgery inherently induces inflammation in normal eyes and exacerbates underlying inflammation in uveitis eyes. Therefore, attaining inflammatory quiescence in uveitis is of paramount importance to ensure optimal visual outcomes and to prevent devastating complications such as hypotony and phthisis. In this chapter, we discuss the surgical management of uveitis cases with a special focus on cataract, glaucoma, and retinal surgeries.

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Perioperative Management

Without a doubt, the most important aspect of ocular surgery for uveitis patients is adequate inflammatory control. At least 3 months of preoperative quiescence is nearly universally agreed upon as a preoperative requirement, although this particular time frame is somewhat arbitrary and special considerations may require or permit earlier surgical intervention.

In eyes that were quiet before undergoing cataract surgery, up to 90% achieved a postoperative visual acuity of 20/40 or better, whereas only 23% of eyes with active inflammation achieved the same [1]. Even among patients with intermediate, posterior, and panuveitis undergoing cataract surgery in the MUST trial, 62% achieved postoperative visual acuity of 20/40 or better [2].

In addition to preoperative quiescence, extra perioperative control is required to offset the inflammatory insult of the surgery itself. Varied regimens are used and sometimes tailored to the severity of inflammation inherent to specific disease entities, individual patients and the surgical procedure. At minimum, frequent topical steroids, either prednisolone or difluprednate, are used preoperatively. Most commonly, an oral prednisone burst is started preoperatively and sometimes augmented with intraoperative local steroid treatments including posterior subtenon kenalog, intravitreal dexamethasone (Ozurdex), or even fluocinolone implant (Retisert). Intraoperative intravenous solumedrol is also often used.

While tailoring the level of steroid pretreatment to the individual patient based on historical severity of inflammation or history of side effects to steroids makes intuitive sense, comparable results have been reported with a variety of treatment regimens. There were similar visual outcomes between patients treated only with topical steroids and patients treated with oral dexamethasone for 7 days in addition to topical therapy before cataract surgery, although there was better postoperative inflammatory control with the addition of oral steroids [3]. There were no significant differences in visual acuity outcomes or postoperative inflammation in one study that compared perioperative PSTK with a 6-week 60 mg oral prednisone taper, [4] nor in another study comparing intraoperative Ozurdex with an 8-week 1 mg/kg prednisone taper [5]. Better control of postoperative cystoid macular edema occurred with administration of Ozurdex less than 4 weeks before cataract surgery compared to longer than 4 weeks preoperatively [6]. Additionally, there were no significant differences in outcomes between patients whose inflammation was controlled with fluocinolone implants (Retisert) or systemic immune suppression in the MUST trial [2].

We recommend a basic oral prednisone burst for all patients who are able to tolerate oral steroids, consisting of 60 mg daily of prednisone starting 3 days before surgery and continuing 2 days postoperatively for a total of 5 days, followed by 40 mg daily for 5 days, 20 mg daily for 5 days, and finally, 10 mg daily for 5 days (Fig. 7.1). This regimen should be in addition to topical postoperative steroids consisting, at a minimum, of prednisolone acetate four times daily, and can be augmented with more frequent or stronger topical drops, or with intraoperative subtenon

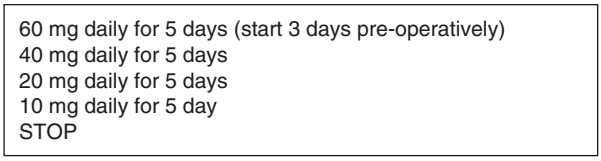

Fig. 7.1 Recommended perioperative oral prednisone regimen

kenalog, Ozurdex or Retisert, tailored to the individual patient. A slightly more prolonged course of oral steroids may sometimes be required in cases of known historical severe chronic inflammation.

Cataract Surgery in Uveitis

Cataract formation occurs earlier and more frequently in uveitis patients compared to the general population. Approximately 57% of intermediate uveitis, 70% of pediatric chronic anterior uveitis, and 78% of Fuchs heterochromatic iridocyclitis patients require cataract surgery [7, 8]. Additionally, medical and surgical therapies used to treat these patients can hasten the formation of cataracts.

The earlier occurrence of cataracts in the young uveitis population can have a significant impact on productivity and income, given that these patients are within working age, and can have even more significant an effect in the amblyopia-susceptible childhood years. Uveitic cataracts are associated with worse visual acuity, more frequent concomitant ocular comorbidities such as glaucoma, more previous ocular procedures including intravitreal injections and trabeculectomies, and shorter axial lengths, [9] all of which can complicate the surgical procedure and affect the final visual outcomes for these patients. Therefore, careful consideration should be given to preoperative counseling, disease management, and surgical planning for uveitic cataracts.

Preoperative Considerations

A careful discussion of the risks, benefits, and reasonable visual expectations is particularly important for the uveitis patient. Preexisting damage to the cornea, optic nerve, or retina may preclude a 20/20 visual outcome in these patients. For example, worse outcomes have been reported for patients with Behcet's disease, likely due to underlying chorioretinopathy and glaucomatous optic neuropathy (Table 7.1) [10]. Indeed, preoperative visual acuity is one of the most important predictors of postoperative visual recovery.

Despite poorer preoperative vision and more frequent surgical complexity, many patients with uveitis still gain a 4-line improvement in visual acuity comparable to nonuveitic patients (Table 7.1) [9]. When careful surgical technique is employed, significant worsening of vision is not necessarily more frequent in uveitis patients [9].

Table 7.1 Frequency (%) of 20/40 or better postoperative vision after cataract surgery, according to underlying diagnosis and disease activity

Disease	Percentage attaining ≥20/40 vision	
	Quiet	Active
Fuchs	92	78
Juvenile idiopathic arthritis	71	22
Intermediate	69–71	
Behcet's	36	
Posterior	46	
MUST noninfectious intermediate, posterior, and panuveitis[a]	62[a]	
Normal age-related cataracts[b]	96[b]	

Results compiled from Mehta et al., Sen et al.,[a] and Powe et al.[b] [1, 2, 11]

Table 7.2 Frequency (%) of 20/40 or better postoperative vision after cataract surgery, by IOL status

IOL Status	Percentage attaining ≥20/40 vision	
	Quiet	Active
With IOL	70	
Without IOL	54	23

Results compiled from Mehta et al. [1]

Additionally, similar outcomes are seen between phacoemulsification and small incision cataract surgery [8].

Finally, uveitis patients are often younger than typical cataract patients and may be unaccustomed to wearing glasses. Patient should be educated on the impending loss of accommodation and need for spectacle correction. Mini-monovision (~1 diopter difference between the two eyes) can be considered for patients without significant concomitant corneal or macular pathology.

Preoperative IOL Planning

While it was previously thought that intraocular lenses (IOL) should not be implanted in some eyes with uveitis, more recent data show that IOLs can be safely implanted with superior visual outcomes when meticulous surgical technique and inflammatory control are applied (Table 7.2).

Despite these encouraging data, there are several contraindications for IOL insertion, the foremost being active uveitis despite maximum medication. Additionally, rubeosis, hypotony, indeterminate cause of inflammation, previous IOL-related complications in the fellow eyes and surgery in children under 4 years of age have all been associated with poorer postoperative outcomes [12].

Challenges in biometric measurements may be encountered in patients with uveitic complications making IOL calculations difficult. These include band keratopathy, which can alter keratometry readings, posterior synechiae, hypotony, cystoid macular edema, and epiretinal membranes, which can each alter anterior chamber depth and axial lengths.

Table 7.3 Frequency (%) of 20/40 or better postoperative vision and posterior capsule opacification (PCO) by IOL type in quiet eyes

IOL type	Percentage attaining ≥20/40 vision	Percentage with PCO[a]
Acrylic	69	24
Heparin-coated PMMA	72	45
PMMA	69	53
Silicone	30	

Results compiled from Mehta et al. and Suresh et al.[a] [1, 14]

Table 7.4 Overview of special considerations in uveitic cataract cases

Perioperative inflammation control
3 or more months of quiescence
Adjunctive steroid use pre- and postoperatively
Lens choice
Acrylic vs. PMMA
Aphakia for very young, uncontrolled inflammation
Preparation for complex surgery
Pupillary membrane dissection
Synechiolysis
Pupillary expansion devices
Peripheral iridotomy
Capsular tension rings
Combination with other surgeries
Glaucoma procedures
Therapeutic vitrectomy for intermediate uveitis

Surgical Technique and Considerations in Uveitic Cataracts

IOL Choice

There has been much debate over the best IOL material to implant in uveitic eyes. During and after surgery, inflammatory cytokine release results in breakdown of the blood–aqueous barrier with release of cells and protein into the eye. Polymethylmethacrylate (PMMA) induces complement formation; however, heparin modification creates a more hydrophilic surface that reduces the adhesion of inflammatory debris and cells [12]. Silicone lenses are associated with more severe anterior capsular contraction [13]. Acrylic or PMMA appears to yield superior visual results overall, assuming that perioperative inflammation is well controlled (Table 7.3). It goes almost without saying that multifocal IOLs should not be placed in patients with concurrent retinal pathology or progressive glaucoma.

Other Surgical Considerations

The uveitic eye may present the surgeon with numerous challenges due to structural abnormalities inherent to both disease processes and treatment history (Table 7.4). Posterior synechiae require synechiolysis, which can be accomplished by stretching the pupil with a tool such a Malyugin manipulator (MicroSurgical Technology) or a

viscoelastic cannula or bimanually [15]. Additionally, an iris expansion device such as Malyugin Ring (MicroSurgical Technology) or iris hooks may be required. Merely expanding the pupil may release a mild pupillary membrane. To remove a thick pupillary membrane, a 25-guage retina forceps, such as the MAXGRIP (Alcon) can be used with or without an intraocular scissors such as the 23-gauge curved scissors (Grieshaber, Alcon). Care should be taken during these steps, as iris ischemia from chronic inflammation can predispose intraoperative floppy iris and hemorrhage causing hyphema.

Many uveitic eyes are young and present more plastic capsules than are normally encountered in senescent cataract surgery. This can make creating a capsulorrhexis more challenging. Trypan blue can be used to decrease the plasticity of the anterior capsule, in addition to increasing visualization in cases with PSC or vitreous debris. Pediatric anterior capsules tend to stretch and therefore initially undersizing the capsulorrhexis is sometimes advisable. Occasionally, the anterior capsule in chronic uveitis is thickened and friable, for which a pair of curved scissors are very useful. Preparing for the requirement for these extra instruments ahead of time will make for a more efficient, less complicated surgery in uveitis patients.

Thorough removal of nuclear and cortical material is important for minimizing postoperative inflammation. The posterior capsule can be polished with the irrigation/aspiration handpiece. An anterior capsule polisher, such as the Singer sweep (Epsilon) or curette style instrument, can be used to remove both cortical remnants and lens epithelial cells, reducing postoperative phimosis.

Surgeons should be aware of the potential for zonular instability, which can be iatrogenic due to prior surgeries or intraocular injections or the result of chronic inflammation and inflammatory cyclitic membranes. Surgeons should be prepared for a more difficult capsulorrhexis and have a low threshold for using a capsular tension ring in young eyes with zonular instability where the lifetime risk of IOL dislocation is increased. Additionally, because zonular instability may lead to future IOL decentration, multifocal IOLs may be ill advised. Despite these challenges, and the high rate of additional procedures (19–67%), the rate of serious intraoperative complications in the hands of experienced surgeons is not significantly elevated compared to more straightforward cases [9]. Lastly, in cases where the patient has had prior episodes of angle closure from anterior synechiae or iris bombé from posterior synechiae, one should have a low threshold to concomitantly create a large surgical iridotomy at the time of cataract surgery due to an already compromised angle [16].

Postoperative Complications

Persistent or recurrent inflammation can occur postoperatively in up to 53% of uveitis patients, and cystoid macular edema in up to 56% of uveitis patients [17], although these numbers can be reduced with appropriate perioperative management (Table 7.5). In one prospective study, 38% of uveitic eyes with activity in the 3 months before surgery had CME at 1 month post-op, compared to only 6% of eyes

Table 7.5 Frequency (%) of postoperative inflammatory complications in JIA patients

Postoperative complication	Frequency (%)
PCO	24–96[a]
Band keratopathy	32
Posterior synechiae	28
Ocular hypertension	15, 17.6[a]
CME	<5, 13.5–25[a]
Hypotony	9
Epiretinal membrane	5
Optic nerve edema	5

Compiled from Woreta et al. and Zhang et al.[a] [10, 22]

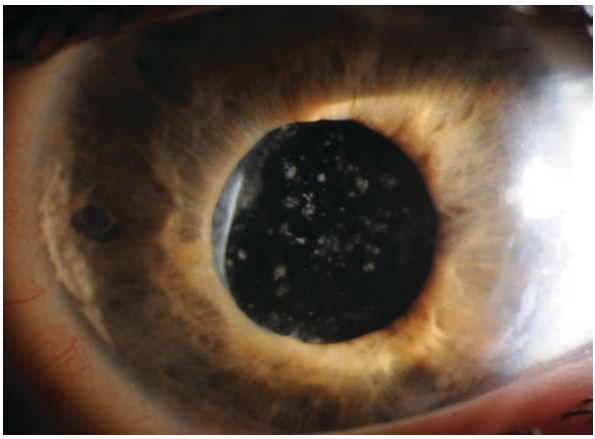

Fig. 7.2 Chronic anterior and posterior IOL deposits. This patient underwent combined pars plana vitrectomy and cataract surgery in the left eye for an amblyogenic posterior subcapsular cataract and intermediate uveitis at age 8. Her perioperative management consisted of prednisolone acetate and nevanac beginning 1 week prior to surgery as well as an oral prednisone burst of 35 mg daily starting 2 days preoperatively and continuing for 5 days postoperatively. The prednisone was tapered as follows: 5 days each of 25, 15, 5 mg. Postoperatively, her posterior capsule opacification and IOL deposits were treated 5 times with Nd:YAG laser over the subsequent 3 years. She also subsequently required two posterior synechiolysis procedures, as well as a surgical iridotomy and goniotomy for bombe iris and steroid-response glaucoma. Her right eye has remained quiet under adalimumab therapy and 7.5 mg weekly methotrexate

quiet for more than 3 months and 4% of nonuveitic controls [18]. In this study, a history of CME conferred a 3.6-fold risk for postoperative CME and active inflammation in the 3 months preceding surgery conferred a 6.2-fold risk [18]. Epiretinal membrane formation is also fairly common and can potentiate or even cause CME (Table 7.5).

Posterior capsule opacification occurs more frequently in uveitic eyes, at a rate of up to 58% in adults and up to 71–96% of children [8]. Inflammatory deposits also occur on the IOL in about 20% of eyes (Fig. 7.2) [14]. Late decentration of IOL due to capsular contraction has been reported in 2–40% of patients [7, 19]. While elevated intraocular pressure resolves in most patients, it can remain persistently elevated in up to 23% of adults and 50% of pediatric patients [8].

Band keratopathy can occur or progress in the setting of prolonged inflammation. More rarely, hypotony due to cyclitic membranes or ciliary body damage or inflammation can occur resulting in very poor postoperative vision or even phthisis.

Pediatric Postoperative Complications

Outcomes data from the 1990s revealed that pediatric eyes demonstrated postoperative inflammatory sequelae even more commonly than adults, and worse outcomes were initially found in patients with implanted IOLs [12]. These studies, however, occurred before the widespread use of immunomodulatory therapy.

Since that time, additional studies revealed that adequate immunosuppression resulting in disease quiescence of at least 3 months, coupled with perioperative steroid treatment, results in improved control of postoperative inflammation and good visual outcomes in most children [20, 21]. In fact, delayed IOL placement, which often necessitates sulcus placement of the IOL, may actually result in poorer visual acuity outcomes and more inflammation as a result of iris–haptic contact.

Despite the improvement in outcomes, it has been recommended that cataract surgery be delayed until after age 11 if possible, and avoided in eyes with shallow anterior chambers, hypotony, and for children less than 4 years of age [20]. Intraoperative posterior capsulorrhexis may be advisable in young patients who may have trouble sitting still for laser capsulotomy.

Glaucoma Management in Uveitis Patients

The development of ocular hypertension and subsequent glaucoma is more frequent in uveitis patients and results from both inflammation (i.e., uveitic glaucoma) and steroid therapy (i.e., steroid response glaucoma). The estimated incidence of glaucoma due to uveitis is 10–20% with rates as high as 46% in cases of severe, chronic uveitis [23]. Medical management of ocular hypertension in uveitis patients is similar to that of other forms of glaucoma with a few important caveats. In the uveitis population, especially during active inflammation, miotics are generally avoided due to their propensity to further induce breakdown of the blood–aqueous barrier, worsening inflammation, and inducing posterior synechiae [23]. Second, prostaglandins may worsen inflammation and cystoid macular edema in uveitis patients due to breakdown of the blood–aqueous barrier; however, there is little data to support this notion and many uveitis specialists will use them as first-line therapy due to their efficacy and ease of administration [24]. Caution should be used with α-adrenergic agonists, as they may be proinflammatory [25]. Despite these important differences, most patients can be effectively managed with medical therapy alone.

When medical therapy is insufficient, laser procedures or surgical interventions can be employed. While preformed routinely, unfortunately, there are no

randomized, controlled trials to specifically guide glaucoma treatment in uveitis patients. Consequently, therapy has been guided by nonuveitic randomized, controlled trials, retrospective studies, case reports, and clinical experience. The use of various glaucoma laser treatments is controversial in uveitis patients due to their propensity to incite inflammation. In uveitis patients, there are several laser treatment options worth mentioning. Selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT) are comparable 360° trabecular meshwork laser treatments used to lower intraocular pressure by 4–8 mmHg in open angle glaucoma [26]. The two procedures vary by the type of laser applied to the trabecular meshwork. However, these procedures have significant concerns for being inflammatory as there is significantly more cell following SLT than ALT and isolated case reports have reported severe bilateral anterior uveitis or unilateral severe iritis and choroidal effusions following SLT treatment [27–29]. As such, anterior uveitis has been considered a relative contraindication for SLT and ALT. A larger, more recent uncontrolled, retrospective study with long-term follow-up has not supported this paradigm and showed that SLT can effectively lower IOP in steroid-responsive and inflammation-controlled uveitis patients [30]. Unfortunately, this was not a randomized, controlled trial making it difficult to extrapolate the findings beyond the study. Thus, ALT and SLT should be pursued with caution as an adjuvant glaucoma therapy even in eyes that are without active inflammation and 180° or less treatment such as that used in pseudoexfoliation glaucoma should be considered to minimize inducing inflammation and IOP spikes. Perioperative steroids (topical, local injection, or oral) should be highly considered if ALT or SLT needs to be performed.

In patients who develop angle closure or are considered high risk for developing angle closure, a laser peripheral iridotomy (LPI) is indicated in which a full thickness peripheral hole is burned through the iris as an additional pathway for aqueous flow. Unfortunately, LPIs have a significantly higher rate of early failure in uveitis patients compared to nonuveitic patients and postprocedure iritis is not uncommon [31]. Multiple attempts, including surgical iridotomies, larger LPIs, and/or multiple LPIs, may be required due to the high propensity of the iridotomy to close in uveitis patients. LPIs also have the potential to induce focal zonular dehiscence, making an already potentially complex uveitic cataract surgery much more difficult when eventually indicated [32]. Consequently, the procedure is an effective means to alleviate angle closure/pupillary seclusion, but should be done with caution, especially in a uveitic eye, as close follow-up postprocedure to monitor the patency of the LPI and inflammation is required. One should highly consider a surgical PI in place of a laser PI, especially if the patient requires cataract surgery anyway.

Cyclodestructive procedures such as transscleral (TSCPC) and endoscopic (ECP) cyclophotocoagulation should be used with extreme caution in uveitis patients. The procedure is usually performed in refractory cases of glaucoma to effectively reduce aqueous production and lower IOP. However, uveitis patients are more prone to developing atrophic ciliary epithelium from ciliary membranes and intraocular inflammation and thus more prone to progress to hypotony. Despite these concerns, TSCPC has been shown to be an effective method to lower IOP in uveitis patients in retrospective studies except in juvenile idiopathic arthritis where

it has high failure rates as the primary interventional method [33, 34]. Micropulse TSCPC (mTSCPC) delivery may be a better option than more traditional applications due to lower rates of prolonged anterior chamber inflammation and phthisis bulbi [35]. mTSCPC is also much better tolerated than traditional TSCPC. However, more research is required, specifically in uveitis patients, to advocate the use of mTSCPC or TSCPC.

ECP is another cyclodesctructive procedure that can be performed through either an anterior limbal or *pars plana* approach and can be performed in phakic, pseudophakic, or aphakic eyes. Best visualization is obtained through a *pars plana* approach; however, this technique requires an anterior vitrectomy at the time of surgery. In the limbal approach, the anterior chamber is stabilized with viscoelastic, ciliary sulcus deepened with a cohesive viscoelastic, and the endoscopic probe is introduced to whiten and shrink the ciliary processes under direct visualization. The procedure can easily be combined with other intraocular surgeries such as cataract surgery or PPV. While the procedure requires intraocular surgery, the technique applies more targeted laser treatment than transscleral approach, resulting in less collateral damage, and anecdotally, lower rates of hypotony [36]. ECP lowers IOP in pediatric patients with uveitic glaucoma and is an especially intriguing option in cases where tubes or trabeculectomies are high risk to fail or have failed [37]. In cases of refractory glaucoma, ECP has been shown to be as efficacious as Ahmed tubes, but with lower complication rates [38]. Due to the lack of randomized control trials to support its use and conflicting data, it is difficult to suggest using cyclodestructive procedures as primary interventions to control IOP in uveitis patients due to concern of treatment failure, worsening inflammation, and causing hypotony. ECP may be the best salvage approach in refractory glaucoma in uveitis patients, as it is least likely to cause complications and is titratable based on direct visualization, but unfortunately requires intraocular surgery.

In those patients where medical/laser management with topical therapy and/or alteration/cessation of the offending medication fails to alleviate the elevated intraocular pressure, surgical intervention is required to prevent permanent optic nerve damage. Ideally, the operative eye should be devoid of inflammation at time of surgery, but this situation is not always possible with ongoing, uncontrolled IOP despite maximal medical therapy and active inflammation. To compound matters, patients with active uveitis are considered high risk for failure of common glaucoma procedures such as tube implants and trabeculectomies compared to their peers due to excessive scarring related to ongoing inflammation.

Surgical Techniques and Considerations

Angle surgeries are the standard of care for congenital glaucoma. In these procedures, maldeveloped tissue is excised from the angle to open a functionally closed angle. In pediatric-related uveitic glaucoma, these procedures have been abandoned by many due to the presumably different underlying mechanism of congenital and uveitic glaucoma. However, two small retrospective studies have shown the efficacy

of goniotomy as a first-line treatment of refractory glaucoma due to chronic uveitis with success rates approaching 70% [39–41]. Unfortunately, older age, aphakia, duration of glaucoma prior to intervention, and angle changes associated with chronic anterior uveitis were associated with worse outcomes [41]. Thus, angle surgeries such as goniotomies have favorable outcomes and should be considered as first-line treatment early in the disease process in children.

In the adult population, surgical management of glaucoma has expanded with the introduction of minimally invasive glaucoma surgery (MIGS) implants. For simplicity, MIGS, tubes, and trabeculectomies are the types of surgical treatment employed for adult glaucoma. Simply put, MIGS can be thought of as creating a bypass for aqueous flow out of the eye effectively lowering IOP. A full review on MIGS techniques and devices can been seen in *Richter and Coleman, 2016* [42]. Unfortunately, MIGS have not been studied in uveitis patients and there is little more than anecdotal evidence on their use in this population. As such, it is difficult to advocate for their use in an inflamed eye. However, they may have some role in uveitis patients who have been quiescent for some time, especially in combination with cataract surgery.

Drainage device placement is another option to significantly lower IOP in glaucoma patients. There are two major types of these devices: valved or nonvalved. Nonvalved devices include the Molteno, Baerveldt, Shocket, and Eagle Vision implant. The major valved device is the Ahmed valve in which fluid is restricted to a unidirectional flow from the anterior chamber to subconjunctival space. The technique can be modified into a *pars plana* approach and nonvalved implants can be ligated with suture to reduce risk of immediate postoperative hypotony. This surgery is very effective in lowering intraocular pressure in uveitic glaucoma by reducing IOP by over 20 mmHg in one study [43, 44]. Combination surgery with Ahmed valves and the surgically implanted fluocinolone acetonide implant (Retisert) resulted in longer duration of surgical success of the Ahmed valve than without the steroid implant in uveitis patients [45].

Trabeculectomies have been a tried and true method for lowering IOP for decades in situations where there is enough mobile conjunctiva. Unfortunately, uveitic glaucoma is a well-known risk factor for trabeculectomy failure due to the propensity of excessive scarring of the bleb from inflammation resulting in surgical failure. This has led many to suggest using an Ahmed or Baerveldt valve in uveitis patients, or at the very least, MMC treatment for first-time trabeculectomies. A retrospective study has shown that trabeculectomy with MMC is a viable first option in Vogt-Koyanagi-Harada disease, but 25% of patients needed an additional procedure to control IOP [46]. Another small study showed that in eyes where inflammation has been controlled, a trabeculectomy with MMC had similar success rates in uveitic and primary open-angle glaucoma patients [47]. In a retrospective comparison in uveitis patients, Ahmed valves had a higher cumulative success rate at 1 year and longer mean time to failure than trabeculectomies with MMC [48]. Thus, a tube or trabeculectomy is a reasonable option in eyes where inflammation is and has been controlled for some time. However, there may be higher success rates with drainage devices like the Ahmed tube in situations where there is active anterior chamber

inflammation, but the need for emergent lowering of IOP. A trabeculectomy with MMC for uncontrolled IOP for a posterior uveitis with proper postoperative inflammation control is not unreasonable. Similarly, trabeculectomies may be utilized in known steroid responders with posterior uveitis at the time of Retisert implantation. No randomized, controlled trial, however, has been performed to guide treatment or suggest superiority of either technique.

Vitreoretinal Surgery in Uveitis

Indications for Surgery

The therapeutic role of *pars plana* vitrectomy (PPV) in uveitis patients was first described in 1978 as part of the surgical management of uveitic cataracts [49]. Since its initial use with a *pars plana* lensectomy, vitrectomies have expanded to include both therapeutic and diagnostic roles in uveitis, especially in diagnostic dilemmas [50]. There are several clear indications for vitreoretinal surgery in uveitis. They include the following: treatment and diagnosis of endophthalmitis, vitreous biopsies for chronic inflammation with unclear diagnosis, implementation of sustained intravitreal drug delivery systems, repairing structural complications of uveitis (i.e., epiretinal membranes, retinal detachments, unresponsive cystoid macular edema, and cyclitic membranes resulting in chronic hypotony), and clearing media opacities precluding visualization of the posterior segment and/or causing significant vision loss (Table 7.6).

There is emerging evidence to suggest that PPVs may also serve some therapeutic benefit in intermediate uveitis by inducing remission in some patients and reducing long-term consequences in pediatric cases [51, 52]. As such, vitreoretinal (VR) surgery is a key surgical component of the treatment plan of most uveitis cases. Ideally, preoperative quiescence is obtained prior to surgery to reduce the risk of the procedure and postoperative complications. Occasionally, it is impossible to wait for disease quiescence before proceeding with surgery. For

Table 7.6 Indications for pars plana vitrectomy in vveitis patients

Media opacities
Cataract
Vitreous opacification
Structural complications
Cystoid macular Edema
Retinal detachment
Epiretinal membrane
Cyclitic membranes
Chronic hypotony
Lens induced uveitis
Endophthalmitis
Sustained intravitreal drug delivery
Diagnostic
Medically uncontrolled inflammation

example, surgical intervention in endophthalmitis and suspected infectious uveitis may be required at the time of diagnosis, making an ideal surgical situation unlikely.

Combined Surgical Approach

PPVs can also be combined with cataract surgery in uveitis patients to reduce long-term postoperative complications in both pediatric and adult patients as seen in two small studies [52, 53]. This approach may be particularly useful for patients with intermediate uveitis in whom simple core vitrectomy serves a therapeutic role. An IOL should not be implanted at the time of primary vitrectomy and lensectomy in an eye with active inflammation.

There are some relative contraindications to VR surgery in uveitis patients. They include exudative retinal detachments and inflammatory choroidal effusions. In the following section, we will discuss the basic surgical technique and important considerations of vitreoretinal surgery specifically in uveitis patients.

Surgical Technique and Considerations

VR surgery is performed using a standard three port PPV with 20-, 23-, 25- or 27-gauge instruments to gain access to the vitreous cavity (Fig. 7.3). The technique is similar in uveitis to other posterior segment cases with a few important considerations. Longer infusion tips may sometimes be required in uveitis cases due fibrovascular membranes with retinal traction and choroidal and scleral thickening, respectively. This is especially important to consider in cases of pars planitis in which thick inflammatory exudates/fibrosis/tractional membranes may overly port entry site and misplacement of the infusion cannula may result in suprachoroidal or subretinal infusion of fluid. In cases where the *pars plana* and peripheral retina cannot be visualized prior to surgery to guide the perioperative plan due to a dense cataract, vitreous opacities, or poor patient cooperation, ultrasound biomicroscopy should be considered to help facilitate safe port placement and surgery. Placement of the infusion port in a different quadrant, or an anterior chamber infusion could also be considered in this situation.

Standard VR instruments and techniques are then used to remove the lens, vitreous debris, and epiretinal membranes as indicated. In cases of complex pathology such as extensive proliferative vitreoretinopathy, utilizing a bimanual technique may be of some use to help identify dissection planes between retina and fibrovascular membranes not uncommonly encountered in uveitis patients. Tractional components causing refractory cystoid macular edema or epiretinal membranes should be relieved by a membrane peel under the aid of indocyanine green dye and/or triamcinolone acetonide (Kenalog). In these same patients, attempts should be made to release the posterior hyaloid if a posterior vitreous detachment (PVD) has not occurred. In children and young adults, inducing a PVD can be challenging due to the strong attachments of the

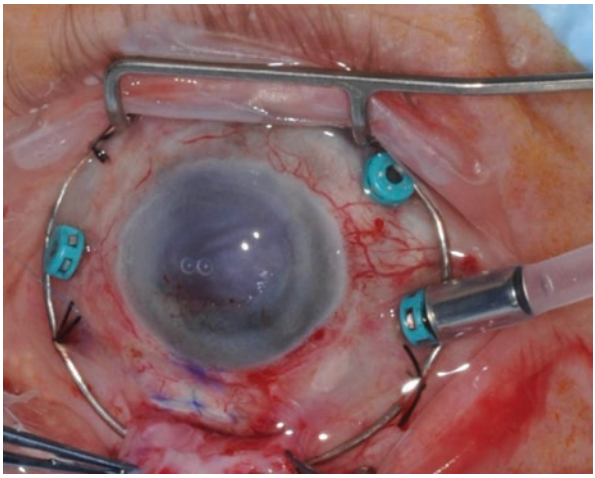

Fig. 7.3 Standard port placement in VR surgery. Ports are denoted by silver plugs with the infusion cannula the largest of the three (With permission from Glen Jenkins, Moran Eye Center ocular photographer)

hyaloid face to the retina. Iatrogenic retinal pathology is not uncommon in these cases, so extra care should be taken including the judicious use of triamcinolone acetonide (Kenalog) to delineate the vitreous. Once posterior pathology has been corrected, the peripheral retina should be thoroughly inspected and iatrogenic breaks should be demarcated with retinal laser or cryotherapy.

Retinal neovascularization is a frequent complication of intermediate uveitis. It may be a result of inflammatory mediators in the vitreous cavity or secondary to retinal nonperfusion due to inflammatory occlusive vasculopathy. To make this distinction, preoperative wide field fluorescein angiography may be employed prior to surgery to detect whether peripheral ischemia is present so that it may be treated with photocoagulation at the time of surgery [54]. In intermediate uveitis in which there is active neovascularization, cryotherapy and/or endolaser ablation to the snowbank should be considered, and in those without active neovascularization, two rows of endolaser may be applied to the pars plana to reduce inflammation and improve long-term visual acuity outcomes [55, 56].

Adjunctive inflammatory control with perioperative intravitreal or subconjunctival injection of steroids should be considered to reduce postoperative inflammation unless otherwise contraindicated in cases of noninfectious uveitis. Sustained therapy with Retisert implantation is also an option in patients where inflammation has required consistent systemic and/or local steroid therapy, where systemic medication results in only a partial response, or systemic therapy fails altogether. Proper informed consent is especially important, as 90% of patients develop cataracts and over 40% require glaucoma surgery due to persistently elevated intraocular pressures (IOP) following Retisert placement [57]. One group has suggested combining cataract surgery, a PPV, Retisert, and Ahmed tube placement in a single surgery in

patients with noninfectious posterior uveitis, as it resulted in good outcomes in their small retrospective study [58].

In cases where an infectious etiology has not been ruled out, proper antimicrobial therapy should be administered, especially if steroids are considered. In these specific cases, vitreous or anterior chamber samples should be sent for evaluation to accurately identify the offending organism. Multiplex PCR analysis is gaining momentum over traditional microbial techniques due to its increased sensitivity and should be used when possible [50]. In cases where lymphoma cannot be ruled out, the specimen should be sent for flow cytometry, cytology, and potentially cytokine analysis (refer to Chap. 5).

Lastly, hypotony is not uncommon in uveitis patients resulting in poor visual outcomes with rates as high as 10% in the Multicenter Uveitis Steroid Treatment trial [59]. Hypotony develops from chronic inflammatory damage to the ciliary body and/or ciliary body detachments from contraction of cyclitic membranes. While difficult to manage, PPV with silicone oil tamponade and removal of cyclitic membranes has been suggested in cases that do not respond to medical management. In two small studies, patients with chronic hypotony had a mean improvement in IOP and better visual acuities following dissection of cyclitic membranes with or without silicone oil tamponade [60, 61]. In two other small studies, PPV with silicone oil tamponade was sufficient to resolve hypotony [62, 63]. Some uveitis specialists have suggested implanting a Retisert at the time of surgery to help with hypotony due to its anti-inflammatory and IOP-raising effects. Unfortunately, a small retrospective study presented at Association for Research in Vision and Ophthalmology (ARVO) in 2009 evaluating the role of Retisert in hypotony did not support this hypothesis, as the patients with chronic hypotony did not improve with the implant [64]. Consequently, randomized, controlled trials are warranted to help us better understand the role of a PPV with silicone oil tamponade and Retisert placement in the management of hypotony in uveitis patients.

Concluding Thoughts

Medical and surgical management of complications related to uveitis are similar in many ways to nonuveitic cases; however, there are some important aspects to consider before pursuing treatment in uveitis patients. Most importantly, if quiescence can be achieved prior to surgery, better outcomes are more likely than when operating on inflamed eyes. Second, it is critical to limit inflammation by judiciously utilizing combined surgeries, the application of perioperative topical, local, and systemic steroids, and avoiding highly inflammatory procedures with high risk of failure. In complex cases requiring multiple subspecialists, patient care may best directed by a fellowship-trained uveitis specialist who has experience with appropriate surgical techniques and managing the various complications of the disease. Referral to a uveitis specialist may also be indicated in cases of uncontrolled inflammation and/or unclear diagnosis.

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Diagnostic Biopsy in Uveitis

8

Jaya B. Kumar and Sumit Sharma

Introduction

Elucidating the cause of uveitis is critical to evaluate for systemic disease and to determine treatment and prognosis. The diagnosis of various forms of uveitis is typically determined by a multitude of factors including patient history, clinical manifestations, course of uveitis, imaging, laboratory testing, and response to treatment [1, 2]. Unfortunately, most patients do not present with classic clinical findings and the underlying etiology is a diagnostic dilemma [2]. While serologic diagnosis is limited to a few entities (such as *syphilis*), the diagnostic yield of systemic diagnostic testing for many infectious and malignant processes can be quite low. Obtaining a sample of aqueous, vitreous, or chorioretinal tissue can help make the diagnosis and guide therapy when there is suspicion for malignancy, infection, or inflammation that fails to respond to medical therapy [2–4].

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Anterior Chamber Paracentesis

Anterior chamber (AC) paracentesis can play an important role in the diagnosis of anterior, intermediate, and posterior uveitis [5]. Harper et al. [6] demonstrated polymerase chain reaction (PCR) analysis of aqueous fluid as a useful adjunct in the diagnosis of posterior infectious uveitis with high sensitivity of 82% and specificity 100%, which was comparable to vitreous biopsy, 78% sensitivity, 93% specificity. Eyes with earlier sample collection (within 1 week of presentation), vascular or optic nerve inflammation, extensive retinitis, or immunocompromised status were more likely to have positive PCR results for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and or *Toxoplasma gondii*. However, the diagnostic yield of PCR for *Toxoplasmosis gondii* is higher in vitreous samples compared to aqueous humor [7–9].

Compared to vitreous biopsy, the diagnostic yield of AC paracentesis for bacterial endophthalmitis is lower [10]. Sjoholm-Gomez de Liano and colleagues performed both anterior chamber paracenteses and vitreous taps on 190 patients who presented with acute infectious endophthalmitis after cataract or glaucoma surgery, corneal ulcers, intravitreal injections, posttrauma, or an endogenous source. They found that compared to vitreous tap, anterior chamber tap had lower sensitivity and specificity in all types of endophthalmitis except in postsurgical endophthalmitis. Therefore, in the case of infectious endophthalmitis, AC paracentesis should be performed only in the absence of an adequate vitreous sample [10].

AC paracentesis has been deemed a relatively safe procedure that can be performed at the slit lamp [11, 12]. AC paracentesis is technically a simpler procedure to perform than a vitreous tap or biopsy, can be performed in the outpatient setting, and results may be faster to retrieve [5]. The primary disadvantage is the low sample volume acquired, usually between 100 and 200 μL, which limits molecular examination [13]. The main complications to note are hyphema which usually resolves without additional intervention and rarely traumatic cataract [11]. With proper technique, these complications can be minimized.

Technique

The eye should be anesthetized and prepped per local protocol. We typically use one drop of a topical anesthetic followed by a drop of 5% betadine. Next, a 30-gauge needle on a TB syringe (with the plunger in place) is inserted at the limbus pointing toward 6 o'clock, with careful attention to avoid touching the lens. Approximately 0.1–0.2 mL of fluid should be aspirated with the plunger by an assistant.

Vitreous Tap

Whereas AC paracentesis may be technically less challenging, vitreous sampling (either in the clinical setting with a vitreous tap or surgical vitreous biopsy) has the advantages of providing larger sample size and better diagnostic yield for infection

and malignancy. Manku and McCluskey [14] evaluated 59 patients with panuveitis or posterior uveitis undergoing vitreous tap or biopsy and found that vitreous sampling is not only a safe and useful method to diagnose or exclude malignancy and infection, but also changed management in many cases. For example, biopsy results revealed toxoplasmosis thought to be viral retinitis, malignant melanoma thought to be fungal endophthalmitis, chronic inflammation after retinal detachment initially diagnosed as neoplasm, three patients with infective endophthalmitis thought to have idiopathic uveitis, and one eye as lymphoma which was initially diagnosed as a metastasis [14].

Vitreous tap is an acceptable procedure for endophthalmitis and viral retinitis. Compared to vitreous biopsy, vitreous tap is a more cost-effective and convenient procedure that can be performed during a busy clinic or at the bedside in a hospital setting. The Endophthalmitis Vitrectomy Study (EVS) revealed no difference in microbial yield, complications, or visual outcome in vitreous samples obtained from vitreous biopsy (in the operating room) compared to a vitreous tap [15]. Vitreous tap is considered a safe procedure, with low complications rates. The rare complications that are seen include hypotony and retinal detachment [14]. There are a few challenges to consider when performing a vitreous tap. One, the increased viscosity of the vitreous may preclude adequate sample for analysis [10]. Second, patients with infectious endophthalmitis typically present with severe pain and inflammation which may decrease patient cooperation, and therefore fluid collection.

Technique

The eye is anesthetized and prepped per institution's standard protocol. We tend to use either subconjunctival lidocaine, or if there is severe pain, peribulbar lidocaine. A 25-gauge or 27-gauge needle on a 1–3 mL TB syringe is inserted into vitreous cavity through the pars plana, being careful to avoid hitting the lens if the patient is phakic, and gentle aspiration is used to obtain a sample. The needle sometimes needs to be redirected to get a better sample. We have found higher yields of getting vitreous fluid using a 1-mL TB syringe versus larger syringes. The rationale for this is unclear, but it is a safer procedure using the smaller volume syringe, as you can titrate the amount of fluid removed much more carefully. An attempt should be made to aspirate at least 0.2–0.3 mL of fluid.

Diagnostic Vitrectomy/Vitreous Biopsy

Diagnostic vitrectomy or vitreous biopsy is indicated in an inflamed eye with rapidly progressing disease and inconclusive workup, with high clinical suspicion for an infectious or malignant etiology. Specific indications for diagnostic vitrectomy when an infectious etiology is suspected include acute or chronic endophthalmitis (bacterial, fungal, parasitic, or viral) after surgery or intravitreal injection, trauma involving a foreign body, endogenous source, or vitritis, chorioretinitis, and

vasculitis [1, 3, 4, 15]. The most important noninfectious indications for diagnostic vitrectomy include primary vitreoretinal lymphoma (PVRL) and metastatic lesions (Fig. 8.1) [16].

PVRL, the great masquerader, is often misdiagnosed as intraocular inflammation and treated with steroids or as viral retinitis and treated with antivirals [17]. It is not until inflammation fails to improve that PVRL is typically suspected. It is crucial to diagnose PVRL as soon as possible, as most cases eventually involve the brain, which carries a poor survival prognosis [18]. If PVRL is suspected, lumbar puncture to evaluate cerebrospinal fluid and brain magnetic resonance imaging scan to

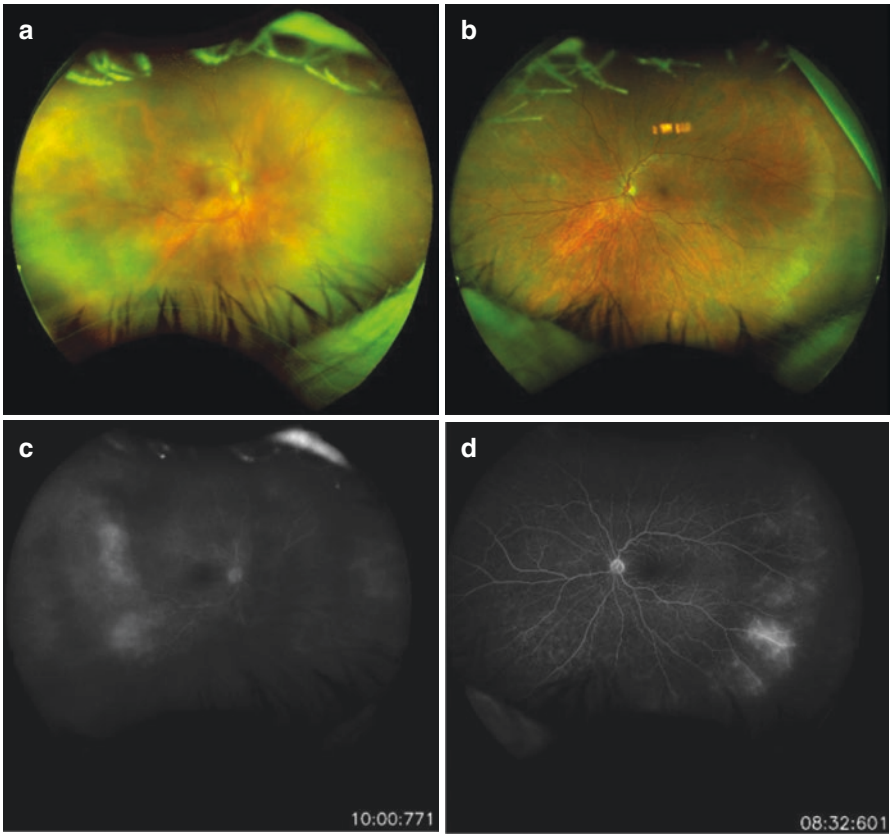

Fig. 8.1 A 66-year-old Caucasian woman who presented with floaters for several months, initially treated with topical, subtenon, and oral steroids with no improvement. Laboratory evaluation and MRI of the brain and orbits were unremarkable. Visual acuity was 20/25 in each eye. Widefield fundus photos revealed diffuse vitreous cell and haze in the right eye (**a**), mild tortuosity of retinal vessels, and no chorioretinal lesions or disc elevation (**a**, **b**). Late frames of widefield fluorescein angiogram revealed peripheral vascular leakage in both eyes (**c**, **d**). Given high suspicion for PVRL, diagnostic vitrectomy was performed in the right eye. Flow cytometry and cytology were positive for a diffuse large B-cell lymphoma

evaluate for intracranial lesions should be performed first. If neuroimaging and testing are unremarkable, diagnostic vitrectomy should be performed [17].

In addition to helping to provide a diagnosis, vitrectomy can also be therapeutic by reducing the inflammatory debris and media opacities, debulking infectious material in the eye, relieving traction, and removing the scaffold for potential membrane formation [2, 19, 20]. Furthermore, vitrectomy may have an adjunctive role to chemotherapy in PVRL. Bever and colleagues reported one case of a vitrectomized eye that had less lymphoma disease burden over the course of 3.5 years compared to the contralateral non-operated eye, while still on systemic chemotherapy [21].

Diagnostic vitrectomy is not without risk. The procedure can be surgically challenging from a visualization standpoint in cases with hazy media including keratic precipitates, posterior synechiae, and lens opacities [22]. Moreover, because these eyes are actively inflamed, disturbing the blood–retina barrier can lead to ciliary body dysfunction and subsequent hypotony [20]. Other risks include those of performing a pars plana vitrectomy including retinal tears, retinal detachment, cataract formation, proliferative vitreoretinopathy, and postoperative endophthalmitis [1]. Diagnostic vitrectomy is contraindicated in the presence of hemorrhagic choroidal detachment [22] and when retinoblastoma or uveal melanoma is suspected, due to risk of extrascleral extension [23, 24].

Three critical factors to optimize biopsy results include the surgeon's expertise in obtaining the sample, careful handling of the specimen, and an experienced pathology team to analyze the cells. Diagnosis of intraocular lymphoma is based on cytopathologic examination of lymphoma cells, defined as large round or oval nuclei surrounded by scant basophilic cytoplasm [18]. However, identification of these cells from vitreous samples is challenging, as these cells can be surrounded by an increased number of reactive inflammatory cells [17, 25]. Flow cytometry has been recognized as an important technique in characterizing vitreous cells and contrasting intraocular lymphoma from immune-mediated uveitis [26, 27]. Cytokine measurement has also shown to be an important adjunctive test when PVRL is suspected. IL-10, an immunosuppressive cytokine, is secreted by B-cell lymphomas [28], whereas IL-6, a proinflammatory cytokine, is seen in uveitic conditions [29]. A ratio of IL-10:IL-6 greater than 1 suggests PVRL; however, this should be evaluated in the context of the cytologic and flow cytometry results and cannot be used by itself to diagnose PVRL [30, 31]. A specific mutation L265P of the MyD-88 protein, associated with the innate immune system, previously shown in diffuse large B-cell lymphoma and Waldenstrom's macroglobulinemia, has been identified in PVRL [32]. This mutation may play an important role in the future of PVRL diagnosis. Moreover, there are specific inhibitors to this mutation that are being studied [33]. Therefore, obtaining an adequate vitreous sample for all of these analyses is critical. It is important to discuss the preferred media for analysis with your local lab prior to performing the diagnostic vitrectomy, as each lab is certified for analysis with different fixative/preservative medium.

Surgical Technique

Our standard approach to diagnostic vitrectomy includes a three-port system with either 23 or 25 gauge, both which have shown to provide adequate cellular yield [34, 35]. After all three sclerotomies are created in standard fashion, the infusion line is secured, checked to be in the vitreous cavity, but left unopened. A 10-mL syringe is connected to suction tubing and an undiluted sample of vitreous is manually aspirated (usually 2–3 mL) until the eye begins to collapse or choroidals form (Fig. 8.2). This undiluted vitreous should be aliquoted to different samples depending on the suspected diagnosis. If the diagnosis is unclear, we transfer 1–2 mL of the undiluted vitreous to 15 mL tissue culture media (our facility uses Roswell Park Memorial Institute 1640 medium (RPMI), Gibco Life Technology, Montgomery County, MD) to preserve cytologic details of cells for flow cytometry evaluation [25, 36, 37]. We then split the remainder of the sample into liquid cytology fixative (our facility uses CytoLyt, Hologic Inc., Malborough, MA) or send it for microbiologic and/or PCR analysis. Next, the infusion line is opened, core vitreous is cut, and manually aspirated into another 10-mL syringe. This sample is sent for bacterial and fungal culture and/or PCR analysis for HSV, VZV, CMV, and/or toxoplasmosis depending on the suspected diagnosis. A third 10-mL syringe is then used to manually aspirate additional vitreous which is split between tissue culture media and liquid cytology fixative. The diluted specimen can also be stored for universal PCR analysis and only sent off if all of the other testing is negative, as this is an expensive test, which is often not covered by insurance. The order of the samples should reflect the suspected diagnosis and if infectious etiologies have a higher suspicion, part of the undiluted specimen can also be sent for microbiologic analysis. The suction tubing should then be connected to the vitrectomy machine and the vitrectomy is completed. Fluid from the machine cassette can be submitted for additional flow cytometry or microbiological analysis. Samples should be taken immediately to flow cytometry,

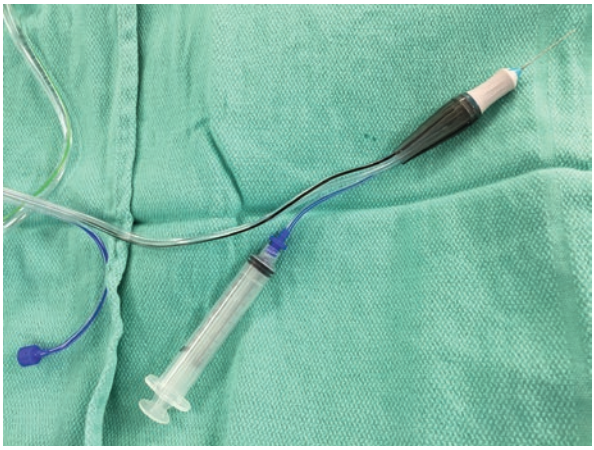

Fig. 8.2 Surgical setup for diagnostic vitrectomy showing a 10-mL syringe directly connected to suction tubing for manual aspiration

cytology, and microbiology, respectively, to improve viability [26]. If lymphoma is a suspected diagnosis, it is important to make sure that the pathologist is aware of the possibility and the laboratory is prepared to process the sample immediately, as lysis of cells can happen if the sample is allowed to sit unprocessed. It is also important that patients are not on systemic and/or corticosteroid treatment, as these have been shown to increase lysis of cells, decreasing the diagnostic yield [38, 39].

Other techniques have also been used to avoid the need for a skilled assistant while obtaining the vitreous sample. These include the use of a biopsy chamber fixed in line with the vitreous cutter as a "vitreous trap" to obtain the sample [40, 41]. Given that we send our samples in both tissue culture media and tissue fixative media and there is risk of losing some of the sample when obtained with these techniques, we prefer to aspirate the sample directly into a syringe with the use of an assistant. Others have advocated for infusion of perfluorocarbon liquid or air to avoid collapse of the eye while obtaining a much larger undiluted vitreous sample [42]. We have not found this to be necessary in obtaining adequate sample for diagnosis.

Chorioretinal Biopsy

Cells recovered from vitrectomy may be inflammatory and a diagnosis may not be possible. Direct sampling via chorioretinal biopsy can be useful in progressive lesions of unknown etiology, particularly if prior vitreous biopsy is inconclusive [43–47]. Compared to vitreous biopsy, chorioretinal biopsy offers the advantages of preserving the anatomical relationship between the retina and the choroid for histological evaluation and providing more tissue for immunohistochemistry [1, 47]. Mastropasqua et al. investigated the diagnostic value of chorioretinal biopsy in 29 patients with severe uveitis suspected to have PVRL. They reported that chorioretinal biopsy provided histologic diagnosis in 59% (18 of 29) of cases and helped exclude lymphoma in 31% cases [46]. Increased vitritis on presentation was an important marker that predicted a more definitive biopsy result. Furthermore, histological diagnosis was only possible in 16% of these cases from the vitreous sample alone in these 18 cases.

Although there are several techniques that have been described to obtain chorioretinal tissue including transscleral fine-needle aspiration or transscleral external biopsy, the most common approach is the internal transvitreal approach to obtain more tissue and maximize diagnostic yield [46, 48]. Compared to other procedures described for diagnostic biopsy, chorioretinal biopsy is technically the most challenging and confers the greatest iatrogenic risks including subretinal hemorrhage, vitreous hemorrhage, choroidal hemorrhage, and retinal detachment in addition to complications listed in the previous section for diagnostic vitrectomy [35]. Furthermore, most institutions perform this procedure infrequently, highlighting the importance of careful case selection process [47].

Surgical Technique

Transvitreal Biopsy

Initially described by Cole and colleagues, the internal transvitreal approach utilized 20-gauge instrumentation and vertical cutting scissors to remove chorioretinal tissue [48]. Our modified technique involves 23-gauge instrumentation. A standard three-port pars plana diagnostic vitrectomy is performed with samples obtained as described above. Next, the anatomical location for biopsy is identified and the margins are marked with confluent diathermy. With vertical cutting intraocular scissors, full-thickness chorioretinal tissue is incised. The infusion pressure should be elevated to prevent intraocular hemorrhage. Prior to fully excising the tissue sample, one of the sclerotomy sites should be enlarged to allow for removal of the sample and intraocular forceps should be used to grasp the tissue prior to cutting and explanting it from the eye [2, 49]. The tissue can then be either split into half with one half placed in tissue preservative media and the other half placed on a filter paper and then placed in liquid cytology fixative. The enlarged sclerotomy is then closed. Endolaser should be applied around the margins of the biopsy, air fluid exchange performed, followed by intraocular gas or silicon oil to provide retinal tamponade. Intraoperative optical coherence tomography (OCT) can help identify the optimal biopsy site, surgical margins, and evaluate the thickness of the chorioretinal lesion [49] (Fig. 8.3). If intraoperative OCT is not available, preoperative OCT (in office) of the anticipated biopsy site may assist with surgical planning.

Transscleral Biopsy

Martin and colleagues described the external chorioretinal biopsy technique starting with conjunctival peritomy, isolation of rectus muscles, and then 3-port pars plana vitrectomy [47]. Laser photocoagulation or cryotherapy is recommended 1–3 days prior to surgery if the view allows. If not, endolaser is recommended during vitrectomy around the biopsy site. On the external sclera, the biopsy site is marked and a 6-mm by 6-mm flap is outlined around the biopsy site. A full-thickness scleral flap is dissected and retracted posteriorly. Diathermy should then be applied through choroid and retina along the inner choroidal bed. With the infusion turned off, a 75 blade is used to create 2 incisions parallel to the limbus, 4 mm apart through the choroid and the retina. A 0.12 forcep is used to grasp the edge of the full-thickness choroid and retina, and Vannas scissors are used to cut perpendicular to the limbus to free the chorioretinal block. Scleral flap should then be closed with 9-0 nylon, followed by fluid-air exchange and intraocular gas to provide retinal tamponade.

Conclusion

The etiology of intraocular inflammation may be unclear, despite thorough clinical and laboratory evaluation. If the inflammation is rapidly progressing, fails to respond to treatment, or there is high suspicion for infection or malignancy, diagnostic

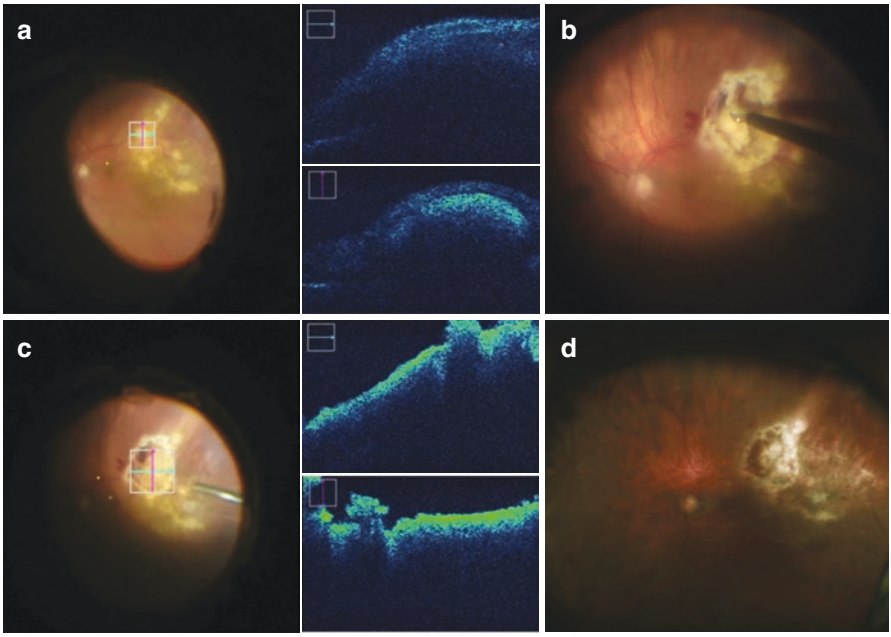

Fig. 8.3 Surgeon's view of chorioretinal lesion using intraoperative optical coherence tomography (OCT) highlighting areas of elevation prebiopsy (**a**), using vertical scissors to excise the lesion after performing diathermy (**b**), and postbiopsy with intraoperative OCT overlay (**c**). Intraoperative OCT was used to confirm that the lesion was excised down to bare sclera, the edges are flat, and there is minimal residual lesion left behind. Postoperative view (rotated to surgeon's view) of inferotemporal biopsied area with surrounding laser demarcation (**d**)

biopsy is warranted. Less invasive techniques are preferred, when appropriate. Surgical advancements and improved histopathologic testing have improved the diagnostic yield from vitreous and chorioretinal biopsies. Obtaining a tissue biopsy can play a critical role in the diagnosis of vision-threatening and potentially life-threatening diseases.

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Pediatric Uveitis

9

Eric Crowell and Ashvini Reddy

Epidemiology and Classification

As with all types of uveitis, the incidence and prevalence of uveitis in the pediatric age range vary between various studies in different geographic areas, but account for roughly 2–14% of all uveitis cases [1]. A recent claims-based study puts the prevalence of uveitis in the pediatric age group at 31 per 100,000 patients with boys more frequently diagnosed than girls (55%; 34 vs. 29 cases per 100,000 person-years) [1]. Of these, the clear majority are of noninfectious causes (94.5%). Of noninfectious causes, 15–47% of cases are related to juvenile idiopathic arthritis (JIA) [2].

As with adults, uveitis should be classified according to anatomic location, pathology, and course. This allows the physician to generate a meaningful differential diagnosis and further workup. Anterior uveitis accounts for 30–71% of cases; intermediate uveitis, 1.5–28%; posterior uveitis, 5–30%; and panuveitis, 13–21% [3].

Evaluation

Unlike adults, children often do not report symptoms of inflammation. This makes a detailed history and proper slit lamp examination tantamount to diagnosis and treatment of their disease. Laboratory and imaging testing should be based on the suspected diagnosis based on the anatomical location of the inflammation.

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Table 9.1 Differential diagnosis of uveitis by anatomical classification

Anterior
Juvenile idiopathic arthritis
Sarcoidosis
Tuberculosis
Syphilis
Lyme disease
Herpes simplex or varicella zoster virus
Fuchs heterochromic iridocyclitis (rubella virus)
Tubulointerstitial nephritis and uveitis syndrome
Kawasaki disease
Behçet disease
Granulomatosis with polyangiitis (rarely)
Orbital inflammatory syndrome (rarely)
Trauma
Idiopathic
Intermediate
Sarcoidosis
Tuberculosis
Syphilis
Lyme disease
Multiple sclerosis
Idiopathic (pars planitis)
Posterior
Sarcoidosis
Tuberculosis
Syphilis
Lyme disease
Bartonella henselae
Diffuse unilateral subacute neuroretinitis
Idiopathic
Panuveitis
Sarcoidosis
Tuberculosis
Syphilis
Herpes simplex or varicella zoster virus
Vogt-Koyanagi-Harada syndrome
Sympathetic ophthalmia
Behçet disease
Idiopathic

For a complete listing of differential diagnoses and associated workup, please see Table 9.1.

Anterior

Juvenile Idiopathic Arthritis (JIA)

JIA is defined broadly as arthritis of 6-week duration without an identifiable cause in children younger than 16 years of age. There are multiple subtypes of JIA which have prognostic factors to ocular involvement and need for screening. The subtypes

Table 9.2 Ocular screening frequency in JIA patients

JIA classification	Age of diagnosis, years	Disease duration, years	ANA positivity	Screening frequency, months
Oligoarticular or polyarticular	≤6	≤4	+	3
	≤6	≤4	–	6
	≤6	>4	+	6
	>6	≤4	+	6
	≤6	>4	–	12
	≤6	>7	+	12
	>6	>4	–	12
	>6	NA	–	12
Systemic arthritis (Still's)	NA	NA	NA	12
Psoriatic arthritis	NA	NA	NA	12
Enthesitic arthritis	NA	NA	NA	12 [48]

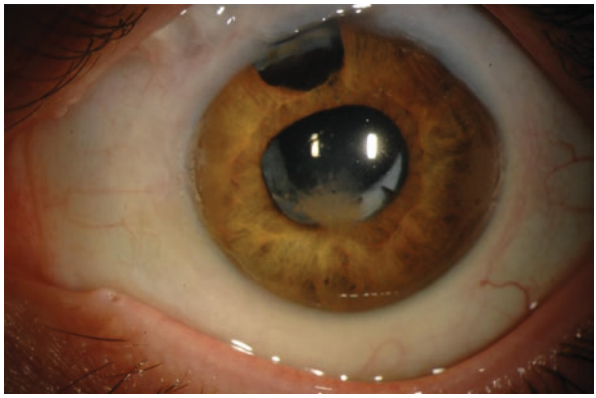

Fig. 9.1 JIA patient with band keratopathy and glaucoma surgery with trabeculectomy

and screening regimen can be seen in Table 9.2. The subtypes most frequently associated with uveitis are oligoarthritis (<5 joints), rheumatoid factor (RF)-negative polyarthritis (>5 joints involved), and psoriatic arthritis. Oligoarthritis is defined as four or fewer joints affected during the first 6 months of disease. It is predominant in young girls with positive antinuclear antibodies (ANA) testing and is most commonly associated with an anterior uveitis in roughly 10–30% of children. RF-negative polyarthritis involves five or more joints in the first 6 months of the disease. It is also more common in girls with a later age of onset than oligoarthritis with only about 10% of children developing ocular involvement.

Roughly 90% of ocular involvement occurs within the first 7 years of arthritis onset. The ocular involvement is typically bilateral and nongranulomatous [4]. Chronic inflammation can lead to band keratopathy, posterior synechiae, hypotony, glaucoma, cataract, and possibly phthisis (Fig. 9.1) [5–7].

The American Academy of Pediatrics has screening guidelines based on the category and age of onset of arthritis, presence of ANA positivity, and duration of the disease. These are included in Table 9.2. In the setting of dermatitis, arthritis, and

severe panuveitis with an autosomal dominant family history, one might consider Blau syndrome, otherwise known as familial juvenile systemic granulomatosis, which is often misdiagnosed as JIA-associated uveitis [8].

Tubulointerstitial Nephritis and Uveitis Syndrome (TINU)

TINU should be suspected in chronic or recurrent anterior uveitis in teenagers or young adults. The mean age of onset is 15 years and there is a strong association with HLA-DRB1∗0102 [9]. For a clinical diagnosis, the following criteria must be met [10]:

- Abnormal serum creatinine or decreased creatinine clearance
- Abnormal urinalysis including increased urinary beta2-microglobulin, proteinuria, eosinophilia, pyuria or hematuria, white cell casts, normoglycemic glucosuria
- Systemic illness including fever, weight loss, fatigue, arthralgias, myalgias

A recent study showed that in the setting of bilateral anterior uveitis, an elevated serum creatinine (>0.74 mg/dL ≤15 years of age, and >1.17 in >15 years) with an elevated urinary beta-2 microglobulin (>0.2 mg/L) has a positive predictive value of 100%, and a negative predictive value of 97% for TINU (refer to Chap. 5) [11]. The prognosis of TINU is good with treatment; yet, long-term follow-up is required due to possible recurrences of the inflammation [12]. While clinical presentation of TINU is typically with bilateral anterior uveitis, a retinal vasculitis and/or pinpoint chorioretinal lesions have also been seen in TINU.

Kawasaki Disease

Kawasaki disease is an IgA-mediated vasculitis affecting children younger than 5. The most common ocular findings are conjunctivitis and anterior uveitis along with more rare findings of keratitis, disc edema, and optic neuritis. Systemic manifestations include fever, cervical lymphadenopathy, desquamating rash that includes the palms and soles, and other mucous membrane changes such as the classic "strawberry tongue." Diagnostic criteria include a 5-day fever plus 4 of 5 of the following:

1. Erythema of lips or oral cavity or cracking of lips
2. Rash on trunk
3. Swelling or erythema of hands or feet
4. Conjunctival injection
5. Cervical lymphadenopathy of at least 15 mm [13]

Treatment of Kawasaki disease includes intravenous IgG and high-dose aspirin to reduce the incidence of coronary artery aneurysm and to prevent hypercoagulability. While topical steroids to help control the anterior chamber inflammation are warranted, systemic corticosteroids may increase the incidence of coronary artery aneurysm [14].

Intermediate Uveitis (IU)

IU in the pediatric population may be caused by a variety of conditions which should be investigated including sarcoidosis, syphilis, Lyme disease, multiple sclerosis (MS), and tuberculosis. Most often, a cause is not found and the idiopathic designation, pars planitis, is diagnosed.

Pars Planitis

Pars planitis, characterized by an intermediate uveitis with snowballs and snowbanks, typically found in young adults and children, accounts for 85–90% of cases of IU in children with a yearly incidence of 1.4–2 cases per 100,000 people. The pathogenesis of pars planitis is thought to be due to aberrant T cells that are autoreactive against a vitreoretinal antigen, although the specific autoantigens have yet to be proven. Associations have been made with specific HLA types including HLA-DR15. On histopathology, snowbanks and snowballs consist of mononuclear leukocytes, fibrocytes, vitreous collagen, Mueller cells, and fibrous astrocytes.

There is a spectrum of presentation for pars planitis, with about one-third following a benign course and the remaining following a chronic, smoldering course, as well as rare individuals who develop a severe course and/or who develop complications of pars planitis. Pars planitis patients who require treatment can be effectively treated with oral or local steroids, steroid-sparing anti-metabolite agents, or TNF-alpha inhibitors.

Pars plana vitrectomy with or without laser photocoagulation or cryopexy is also sometimes utilized for the treatment of pars planitis. Complications of pars planitis include cystoid macular edema, cataracts, amblyogenic vitreous opacities, retinoschisis, tractional retinal detachment, and occasional optic disc edema which can all lead to amblyopia and permanent vision loss if not recognized in a timely manner [15].

Prior to starting tumor necrosis factor-alpha (TNF-α) inhibitors, it is important to verify that the patient does not have multiple scerlosis-associated uveitis or neurological symptoms suggesting MS, since TNF-α inhibitors can cause worsening or unmasking of demyelinating disease. If neurological symptoms are present, there should be a low threshold to obtain an MRI of the brain prior to initiating TNF-alpha inhibitors, although MS in children is rare.

Posterior Uveitis

Toxoplasmosis [16]

Toxoplasmosis is the most common cause of posterior uveitis in both children and adults in the United States and in many other countries. *Toxoplasma gondii* causes the infection and is an obligate intracellular parasite for which cats are the definitive host. The full lifecycle can be seen in Fig. 9.2. Infection occurs when the oocysts are ingested from contaminated drinking water, undercooked infected meat, or through contact with infected cat feces. It can also be acquired as a congenital infection. The cyst form has a predilection for muscle and neural tissue, including the retina, and can remain dormant indefinitely. If the cyst ruptures, it releases tachyzoites which lead to inflammation. Classically, the active area of chorioretinal inflammation is along the border of an old atrophic scar and is thickened and cream-colored with overlying vitritis as seen in Fig. 9.3. In immunocompromised patients, the inflammation could be at a new site away from a previous scar and more diffuse. Congenital lesions are typically within the macula while newly acquired lesions are in the periphery [17]. The diagnosis is clinical, although ELISA for antibody testing from the serum can be undertaken [18]. Peripheral lesions often do not require treatment while those threatening the macula or optic nerve are typically treated with systemic antibiotics and corticosteroids. Classically, treatment is with pyrimethamine and sulfadiazine, although most clinicians now prefer sulfamethoxazole-trimethoprim due to its availability and safety profile with no need for blood monitoring. Intravitreal injection with

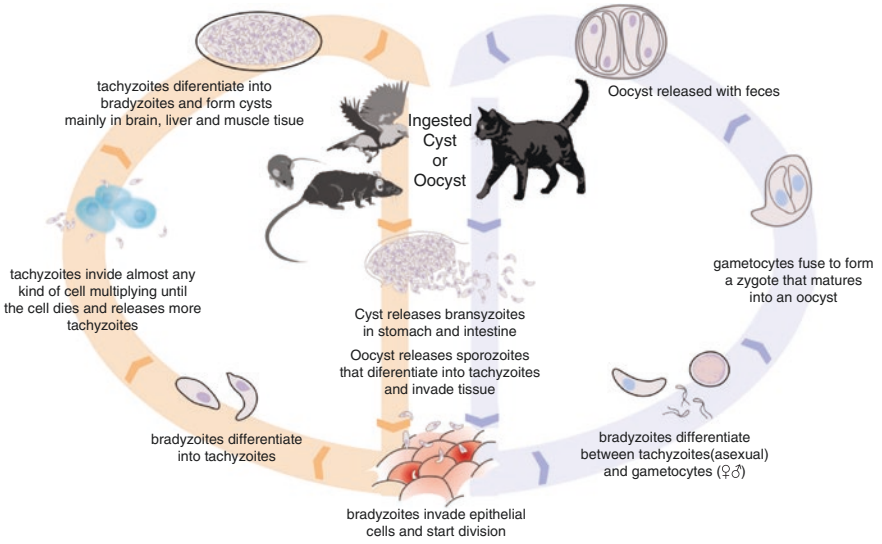

Fig. 9.2 Life cycle of *toxoplasma gondii* [49]

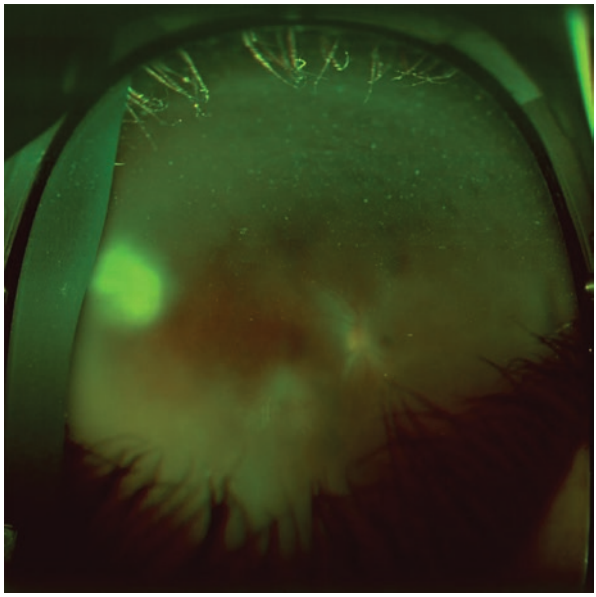

Fig. 9.3 New toxoplasmosis lesion seen superotemporally with overlying vitritis. Photo courtesy of Meghan Berkenstock

clindamycin and dexamethasone can also be performed. For those patients with recurrent infections, there is evidence that sulfamethoxazole-trimethoprim dosed three times weekly can prevent recurrence [19, 20].

Toxocara [21]

Ocular toxocariasis is a disease that affects children most commonly and is caused by the nematode larvae of intestinal parasites of dogs, *Toxocara canis*, or cats, *Toxacara cati*. It is contracted through the ingestion of eggs in contaminated soil with dog or cat feces.

The disease is usually unilateral and not associated with a systemic illness or eosinophilia and can present at any age [22]. There are three retinal forms of disease which include a macular granuloma, peripheral granuloma with macular traction, and endophthalmitis. Most often, these children present with decreased vision, leukocoria, or strabismus with very little inflammation. Serum titers for Toxocara can be tested to aid in diagnosis [23].

Treatment varies based on location of the lesion and amount of inflammation which can be so severe as to mimic endophthalmitis [24]. Peripheral lesions can often be observed while steroids, periocular or systemic, may be helpful to control related inflammation. Surgical intervention may be needed if there is significant retinal traction, cataract, or glaucoma. The inciting organism causing the inflammation is typically already dead and systemic anti-helminthics are not usually helpful in treatment of the disease.

Panuveitis

Sarcoidosis [25, 26]

Sarcoidosis can present differently in children compared to adults. This is especially true for younger patients who often develop a triad of uveitis, arthritis, and a rash, while older children (>8) have more classic adult-like presentation with pulmonary and lymph node involvement. The inflammation in sarcoidosis is most commonly anterior, but can cause inflammation throughout the entire eye. It is notable as a granulomatous type of inflammation with mutton fat keratic precipitates and iris nodules. Sarcoidosis may have optic nerve infiltration and a multifocal choroiditis which help to distinguish it from JIA.

Onset of sarcoidosis in young children with the mentioned triad and a family history is termed familial juvenile systemic granulomatosis, or Blau syndrome. Those with familial juvenile systemic granulomatosis are found to have a mutation in the NOD2 (CARD15) gene which is inherited in an autosomal dominant fashion.

Masquerades

Lymphomas/Leukemias [27]

Lymphomas and leukemias can also masquerade as intraocular inflammation. Lymphomas often present in children older than 15 and can involve vitreous cells or exudates, retinal hemorrhage or exudates, and choroidal granulomas. Leukemias, however, occur in children less than 15 years and may cause anterior chamber reaction with hypopyon, hyphema, or heterochromia. Hypopyons in these patients are atypical and commonly resistant to treatment with topical steroids and can appear rubbery, bloodstained, or have a reddish hue [28, 29].

Syphilis [30]

Syphilis, the great mimicker, can cause any type of inflammation. Whenever a patient presents with inflammation, syphilis should be checked. The CDC recommends testing for an automated treponemal test with a positive test reflexing to a nontreponemal test. Any positive treponemal test without history of treatment should be considered an active infection and treated as neurosyphilis.

Tuberculosis (TB)

Tuberculosis can also masquerade as any type of ocular inflammation and should be considered in any child with risk factors associated with the contraction of tuberculosis.

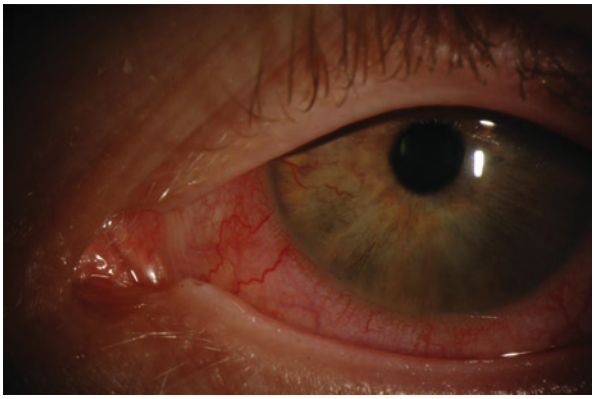

Fig. 9.4 Diffuse iris infiltrate with neovascularization in JXG. Photo courtesy of Bryn Burkholder

JXG [31]

Juvenile xanthogranuloma, a benign non-Langerhans cell histiocytosis, can also cause a reaction of the anterior chamber with hyphema and iris granulomas and invasion (Fig. 9.4). It has a male predominance with the median presentation age of 3.3 years (range from 6 months to 22 years) [32]. It most often involves skin granulomas and a full evaluation should be done along with a biopsy to rule out malignancy. Pathology shows foamy histiocytes arranged in multinucleated giant cells that show a particular staining pattern: CD68 positive, S100 negative, and CD1a negative. Often, cutaneous lesions resolve on their own; however, ocular involvement often needs treatment with topical or intralesional steroids to prevent complications such as glaucoma and hyphema.

Endophthalmitis

Endophthalmitis most commonly presents in children after trauma and any child with trauma should be closely monitored for its development. Additionally, intraocular foreign bodies after trauma may cause intraocular inflammation. Teenagers with endophthalmitis should be questioned about any illegal drug use, especially injectables, which may be leading to an endogenous endophthalmitis with an underlying systemic infection.

Congenital Infections

Any neonate with ocular inflammation should be evaluated for intrauterine or perinatal infections. The most common of these are toxoplasmosis, rubella, cytomegalovirus, herpesviruses, and syphilis, remembered through the acronym TORCHeS.

Treatment

The goal in pediatric uveitis, as in adult uveitis, is to eliminate inflammation before it causes any complications. Additional concerns such as amblyopia and side effects specifically affecting the pediatric population should be given special consideration. Uveitis from infectious or malignant causes should be treated according to the cause. Noninfectious causes of uveitis will thus be covered here. It is important to be aware of the ocular and systemic side effects of all treatments relevant to the pediatric population.

Medical

Most anterior uveitides should be treated with topical steroids such as prednisolone acetate 1% or difluprednate. Difluprednate is generally considered to be twice as potent as prednisolone acetate and tends to penetrate well into the vitreous, but it also has the unfortunate side effect of causing a higher prevalence of elevated IOP [33–35]. For severe anterior involvement or posterior segment involvement, one might consider sub-Tenon triamcinolone, intravitreal triamcinolone, or dexamethasone implants, although the main consideration in children for periocular steroids is the requirement for general anesthesia or sedation to perform these procedures as well as larger consequences with cataract formation in children than in adults. Systemic corticosteroids can also be considered. The most common side effects from steroids include IOP elevation and cataract formation [36–38]. Multiple studies have shown that a reasonable frequency of prednisolone acetate that does not contribute as much to cataract formation is less than BID dosing [39]. Systemic corticosteroids have additional risks in children, in that it can lead to growth retardation in addition to the traditional side effects in adults as peptic ulcers, hyperglycemia, hypertension, altered mental status, intracranial hypertension, and increased infection risk.

In the case that steroids cannot be tapered to a safe level or there are systemic manifestations of the underlying inflammation, systemic immunomodulatory therapy (IMT) should be considered. IMT often can eliminate the need for steroid therapy. All IMT has side effects and should only be administered by those who are familiar with monitoring these adverse effects. Co-management with a pediatric rheumatologist is strongly advised. It is also important to ensure that the parents and child understand the risks associated with inflammation and its treatment and are compliant with any prescribed treatment.

Methotrexate is possibly the most commonly used and most well-known drug employed to control inflammation in children. It has long been utilized for JIA-associated inflammation and is shown to be well tolerated. Methotrexate is an antimetabolite which inhibits nucleic acid synthesis. The exact mechanism by which it inhibits inflammation is not entirely understood, but it is thought to be due to its inhibition of purine metabolism. Side effects of methotrexate include

gastrointestinal disturbance most commonly and this can often be reduced by switching to the subcutaneous form of the medication. Folic acid supplementation can also help with some of the side effects. Other rare side effects of methotrexate include hepatic toxicity, interstitial pneumonitis, and cytopenia. Due to possible hepatotoxicity, it is advised not to prescribe this for patients with heavy alcohol intake. This is rarely an issue in the pediatric population, but should be a consideration in teenagers. Other antimetabolites that can be used include mycophenolate mofetil and azathioprine.

In addition to antimetabolites, biologic medications are being used with increased frequency to help with immunosuppression. These medications are antibodies with targets specific to the inflammatory cascade. Two of the most common biologics, infliximab and adalimumab, are monoclonal IgG antibodies which inhibit tumor necrosis factor alpha (TNF-α) [40, 41]. Other medications include abatacept, which prevents T-cell activation through antibodies targeting CD80 and CD86 signal molecules, and rituximab, which is an antibody to the CD20 protein found on B cells triggering cell death [42, 43].

There is some concern with IMT and long-term cancer risk. In most studies, extrapolating from transplant and rheumatologic studies with uveitis patients enrolled, there seems to be little increase in risk of long-term malignancy with antimetabolite and TNF inhibitors [44].

Surgical

Ocular complications from chronic inflammation include band keratopathy and cataract. Long-term treatment with corticosteroids can also lead to cataract and glaucoma. These complications can also lead to amblyopia and permanent blindness if not appropriately monitored and treated.

Treatment for band keratopathy involves chelation with ethylenediaminetetraacetic acid (EDTA). The corneal epithelium is removed, EDTA is applied to the surface, and then rinsed away. In some cases, treatment must be repeated.

Any intraocular surgery should be avoided if at all possible until the inflammation is controlled for at least 3 months before surgery. Uveitic cataract surgery can be complicated by hypotony, glaucoma, synechiae, membrane formation, cystoid macular edema, and retinal detachment. Intraocular lens implantation can be considered in children with a long history of quiescence, but is often avoided in younger children [45]. For children needing glaucoma surgery for increased intraocular pressure, there is no consensus technique. There are variable success rates with multiple different techniques which can vary from goniotomy/trabeculotomy to glaucoma drainage devices [46, 47]. Trabeculectomy has a high rate of failure from scarring in children and more so in children with uveitis. Small-gauge pars plana vitrectomy can be considered for amblyogenic vitreous haze in pediatric uveitis patients who have pars planitis or other cause of intermediate uveitis if in the amblyogenic age rage.

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