CHAPTER 12

Infectious Uveitis: Nonbacterial Causes

This chapter includes a related video. Go to www.aao.org/bcscvideo_section09 or scan the QR code in the text to access this content.

Highlights

- Viruses, fungi, protozoa, helminths, and bacteria can cause infectious uveitis, and any part of the uveal tract can be involved. This chapter on nonbacterial pathogens is organized according to the causative organism and subcategorized by the anatomical location of inflammation.
- Herpes simplex, varicella-zoster, and cytomegalovirus may cause an isolated anterior uveitis or retinitis. In all patients with suspected viral infection, the eyes should be dilated to look for possible posterior segment disease.
- The viral retinopathies include acute retinal necrosis, progressive outer retinal necrosis, cytomegalovirus retinitis, and nonnecrotizing herpetic retinopathy. Diagnosis is principally clinical, although polymerase chain reaction testing can be utilized to identify the causative pathogen.
- In humans, *Toxoplasma gondii* infection is either acquired or congenital. Recently acquired disease may present as a focal retinochoroiditis in the absence of a retinochoroidal scar.
- Ophthalmic presentations of ocular toxocariasis include a chronic endophthalmitis (25% of cases), a posterior pole granuloma (25% of cases), or a peripheral granuloma (50% of cases).

Viral Uveitis

Herpesviridae Family

The herpesviruses, which include some of the most common human viruses, are double-stranded DNA microorganisms. Members of the family Herpesviridae discussed in this chapter are herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus. For a discussion of Herpesviridae member *Human*

herpesvirus 8, which is associated with Kaposi sarcoma, see Chapter 13. For additional information, see BCSC Section 1, *Update on General Medicine*.

The uveitic entities associated with herpesvirus infection include isolated anterior uveitis and posterior uveitis or panuveitis. The following section is organized by anatomical involvement.

Herpes simplex virus, varicella-zoster virus, and cytomegalovirus

Anterior uveitis In immunocompetent patients, HSV, VZV, or CMV may cause an isolated acute or chronic anterior uveitis with or without keratitis. Dermatitis, rash, conjunctivitis, episcleritis, and scleritis may accompany HSV- and VZV-associated anterior uveitis but typically not anterior uveitis associated with CMV. Although bilateral cases of herpetic anterior uveitis have been reported, the disorder is classically unilateral.

FEATURES AND DIAGNOSIS Primary infection with VZV causes varicella (chickenpox), characterized by a full-body vesicular rash. Up to 40% of patients with primary VZV infection develop a *bilateral acute nongranulomatous anterior uveitis* that is asymptomatic, mild, and self-limiting. Reactivation of VZV within V_1 (ophthalmic division of cranial nerve V) causes herpes zoster ophthalmicus (HZO), a painful vesicular rash in the associated dermatome. Cutaneous vesicles at the tip of the nose (ie, Hutchinson sign) indicate nasociliary nerve involvement and an increased likelihood of ocular involvement (Fig 12-1). In patients with HZO, care should be taken to identify other ophthalmic manifestations of the disease, such as keratitis, anterior uveitis, conjunctivitis, episcleritis, scleritis, acute retinal necrosis, nonnecrotizing retinitis, and cranial nerve palsy.

Infection with VZV may be considered in the differential diagnosis of chronic unilateral anterior uveitis, even when the cutaneous component of the infection occurred in the past or was minimal when present. However, patients may also develop VZV-associated anterior uveitis without ever experiencing a cutaneous component (ie, varicella-zoster

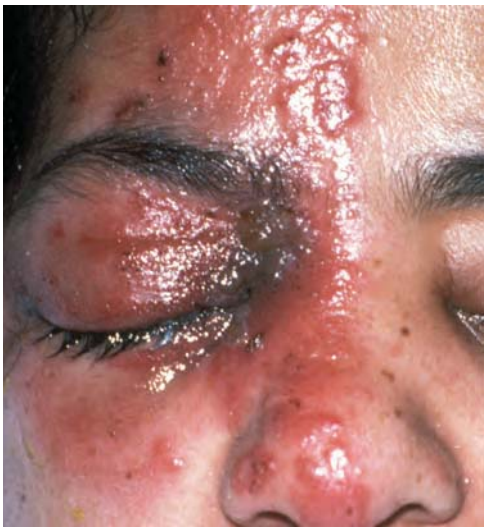

Figure 12-1 Herpes zoster ophthalmicus. Painful, dermatomal vesicular rash. *(Courtesy of Debra A. Goldstein, MD.)*

sine herpete). Primary infection or reactivation of *HSV-associated* anterior uveitis may also occur with or without blepharoconjunctivitis and periocular vesicles. See BCSC Section 8, *External Disease and Cornea,* for additional information about HSV, VZV, and CMV infections of the anterior segment.

Acute anterior chamber inflammation with ocular hypertension can be a helpful diagnostic hallmark of herpetic anterior uveitis. Although most inflammatory syndromes are associated with *decreased* intraocular pressure (IOP) as a result of ciliary body inflammation-related hyposecretion, herpetic anterior uveitis may cause trabeculitis that results in *very high IOP* (ie, 50–60 mm Hg). Elevated IOP can also be caused by inflammatory cells obstructing the trabecular meshwork. Of note, CMV has been associated with glaucomatocyclitic crisis and Fuchs uveitis syndrome, entities that may present with elevated IOP (see Chapter 8 for discussion of Fuchs uveitis syndrome).

Keratic precipitates (KPs) caused by HSV and VZV may be granulomatous or nongranulomatous and sometimes occur with associated pigmentation, especially in chronic uveitis. Diffuse, stellate KPs can occur with all three types of herpetic anterior uveitis, while ring-shaped clusters or scant, small, white-domed KPs are pathognomonic for CMV. Anterior uveitis may be accompanied by corneal endotheliitis and edema with all three viruses, but only HSV and VZV are associated with dendritiform epithelial involvement, reduced corneal sensation, and neurotrophic keratitis. Stromal keratitis is more typical of HSV and VZV than of CMV. Similarly, hyphema, hypopyon, and posterior synechia may be seen with HSV and VZV, but they do not routinely occur with CMV-associated anterior uveitis. Iris atrophy is a later characteristic of herpetic inflammation that is not typically present in the first few days to weeks of the initial episode of uveitis. The atrophy may be patchy or sectorial (Fig 12-2A) and is visualized as transillumination defects upon retroillumination at the slit lamp (Figs 12-2B, 12-3).

Distinguishing between HSV, VZV, and CMV can have implications for treatment and prognosis of anterior uveitis. When diagnostic uncertainty could change treatment, anterior chamber paracentesis may be performed to distinguish HSV and VZV from CMV (see the following section). In addition, all patients with suspected viral anterior uveitis should have a careful dilated examination of both eyes to assess for posterior segment disease, as a missed or delayed diagnosis could lead to blindness.

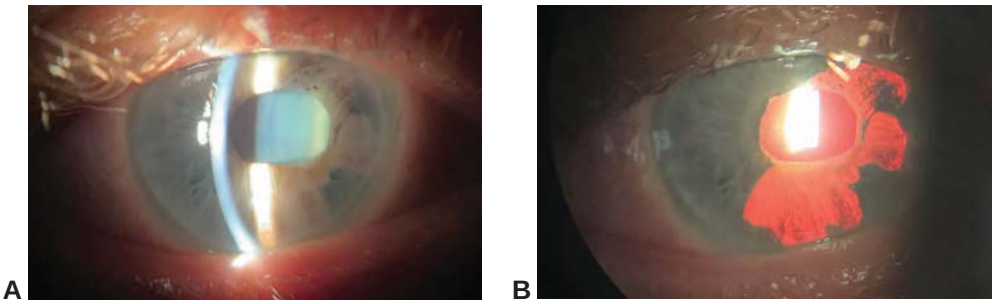

Figure 12-2 Iris stromal atrophy in a patient with herpes simplex virus anterior uveitis. **A,** Anterior segment photograph. **B,** Visualized as transillumination defects with retroillumination at the slit lamp. *(Courtesy of Sam S. Dahr, MD, MS.)*

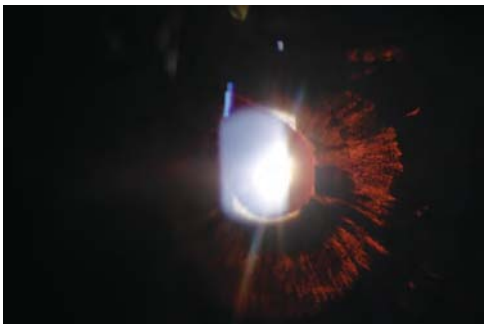

Figure 12-3 Iris transillumination defects in herpetic anterior uveitis. *(Courtesy of Bryn M. Burkholder, MD.)*

Chan NS, Chee SP. Demystifying viral anterior uveitis: A review. *Clin Exp Ophthalmol.* 2019;47(3):320–333.

Cohen EJ, Jeng BH. Herpes zoster: a brief definitive review. *Cornea.* 2021;40(8):943–949.

Terada Y, Kaburaki T, Takase H, et al. Distinguishing features of anterior uveitis caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus. *Am J Ophthalmol.* 2021;227:191–200.

Tran KD, Falcone MM, Choi DS, et al. Epidemiology of herpes zoster ophthalmicus: recurrence and chronicity. *Ophthalmology.* 2016;123(7):1469–1475.

TREATMENT Treatment for herpetic anterior uveitis includes antiviral therapy as well as topical corticosteroids and cycloplegic agents. Adjunctive IOP-lowering agents are often required throughout the disease course but can sometimes be tapered as the inflammation is better controlled. Recalcitrant cases may require surgical intervention to control IOP elevations.

Initiation of oral antiviral therapy at the onset of HSV-associated and VZV-associated anterior uveitis is typically necessary to control the inflammation. Systemic antiviral drugs such as acyclovir (400–800 mg, 5 times/day), famciclovir (250–500 mg, 3 times/day), and valacyclovir (500 mg to 1 g, 3 times/day) may help treat HSV- or VZV-related intraocular inflammation. The higher doses are usually needed for VZV. Prolonged topical corticosteroid therapy with very gradual tapering may also be required. In addition, systemic corticosteroids are sometimes necessary but should be used only with concurrent systemic antiviral therapy. Long-term, suppressive, low-dose antiviral therapy may be indicated in patients with HSV- and VZV-associated anterior uveitis, but randomized, controlled studies of their efficacy are lacking. The oral prophylactic dosage for patients with herpetic disease is acyclovir, 400 mg 2 times/day (for HSV infection), 800 mg 2 times/day (for VZV infection), or valacyclovir, 1 g/day.

As mentioned previously, HSV- and VZV-associated anterior uveitis should be distinguished from CMV-related disease when antiviral therapy is being considered. CMV-associated anterior uveitis will not respond to the antiviral therapy used for HSV and VZV, as the virus lacks the virally encoded thymidine kinase necessary for drug metabolism. If suspected herpetic anterior uveitis does not improve with empiric acyclovir or valacyclovir, diagnostic polymerase chain reaction (PCR) testing of aqueous fluid for CMV should be considered.

There is no standardized antiviral therapy for CMV-associated anterior uveitis. The infection was previously managed with topical corticosteroids and IOP-lowering agents alone. Additional treatment options include topical ganciclovir 0.15% gel, intravitreal foscarnet or

ganciclovir, high-dose oral valganciclovir (see the section "Cytomegalovirus retinitis"), and compounded 2% ganciclovir drops. Long-term systemic antiviral treatment may be limited by drug toxicity or drug resistance, and relapses of CMV-associated anterior uveitis are common after discontinuation of therapy.

La Distia Nora R, Putera I, Mayasari YD, et al. Clinical characteristics and treatment outcomes of cytomegalovirus anterior uveitis and endotheliitis: a systematic review and meta-analysis. *Surv Ophthalmol.* 2022;67(4):1014–1030.

Testi I, Aggarwal K, Jaiswal N, et al. Antiviral therapy for varicella zoster virus (VZV) and herpes simplex virus (HSV)-induced anterior uveitis: a systematic review and meta-analysis. *Front Med (Lausanne).* 2021;8:686427. doi:10.3389/fmed.2021.686427

CLINICAL PEARL

Characteristics of herpesvirus-associated anterior uveitis can include the following:

- unilateral presentation
- ocular hypertension with acute inflammation
- decreased corneal sensation and epithelial/stromal disease (more common with HSV and VZV)
- endotheliitis
- corneal stromal immune ring (more likely with CMV)

Iris atrophy and transillumination defects are a later finding (ie, not seen at initial presentation).

Posterior uveitis and panuveitis The herpetic retinopathies include acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), and CMV retinitis. Retinal lesions of presumed herpetic etiology that are not consistent with ARN, PORN, or CMV retinitis are grouped under the umbrella designation *nonnecrotizing herpetic retinopathy.* The risk for both types of viral retinitis is increased in immunocompromised patients. HZO can also be associated with vasculitis that can lead to anterior segment ischemia, retinal artery occlusion, and scleritis. Vasculitis in the orbit may cause cranial nerve palsies.

ACUTE RETINAL NECROSIS ARN may occur in healthy adults or children as well as in immunocompromised patients, including those with HIV infection. Acute, fulminant disease may arise without a systemic prodrome, often months or years after primary infection or following cutaneous or systemic herpetic infection such as varicella, herpes zoster, or herpetic encephalitis (HSV-1 or -2). Patients may have a history of recurrent cutaneous herpetic outbreaks. The prevalence of ARN is nearly equal between the sexes, with most cases clustering in patients in the fifth to seventh decades of life.

Patients with ARN usually present with acute unilateral vision loss, photophobia, floaters, and pain. The fellow eye is involved in approximately 36% of cases, usually within 6 weeks of disease onset, but sometimes months or years later. Panuveitis develops, beginning with substantial anterior segment inflammation, KPs, posterior synechiae, and elevated IOP, together with heavy vitreous cellular infiltration and haze. Within 2 weeks, the classic triad of occlusive retinal arteriolitis, vitritis, and a multifocal yellow-white peripheral retinitis evolves. Early on, the peripheral retinal lesions may be discontinuous with

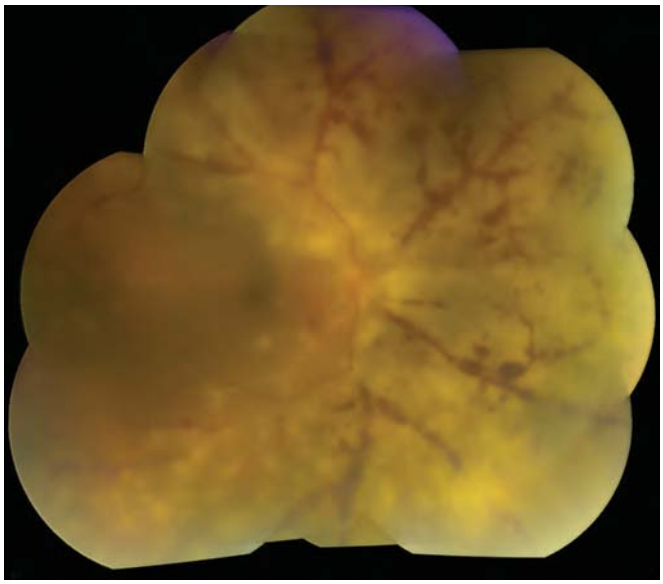

Figure 12-4 Acute retinal necrosis. Fundus photograph montage shows confluent peripheral retinitis with posterior extension. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

scalloped edges that appear to arise in the outer retina. Within days, the lesions coalesce to form a confluent 360° cream-colored peripheral retinitis that progresses in a posterior direction, leaving full-thickness retinal necrosis, arteriolitis, phlebitis, and occasional retinal hemorrhage in its wake (Fig 12-4). Widespread necrosis of the peripheral and midzonal retina, multiple posterior retinal breaks, and proliferative vitreoretinopathy may lead to combined tractional–rhegmatogenous retinal detachments in 75% of patients (Fig 12-5). Optic nerve swelling and a relative afferent pupillary defect may also develop.

The differential diagnosis of ARN includes CMV retinitis, atypical toxoplasmic retinochoroiditis, syphilis, lymphoma, leukemia, and autoimmune retinitis with retinal vasculitis (ie, Behçet disease). The American Uveitis Society has established criteria for the diagnosis of ARN solely on the basis of clinical findings and disease progression, independent of viral etiology or host immune status (Table 12-1).

Although the diagnosis of ARN is made clinically, PCR testing of aqueous or vitreous can be used to determine the etiology of ARN and has largely supplanted viral culture, intraocular antibody titers, and serology. For diagnosis of presumed ARN, aqueous (rather than vitreous) sampling is usually sufficient. Quantitative PCR may also add information regarding viral load, disease activity, and response to therapy. In rare cases in which PCR results are negative for necrotizing herpetic retinitis but clinical suspicion is high, endoretinal biopsy may be diagnostic.

Studies using PCR-based assays suggest that the most common cause of ARN is VZV, followed by HSV-1, HSV-2, and in rare cases, CMV. Patients with ARN caused by VZV or HSV-1 infection tend to be older (mean age, 40 years), whereas those with HSV-2 infection tend to be younger (<25 years). The risk of encephalitis and meningitis is higher among patients with ARN caused by HSV-1 than among those with VZV infection.

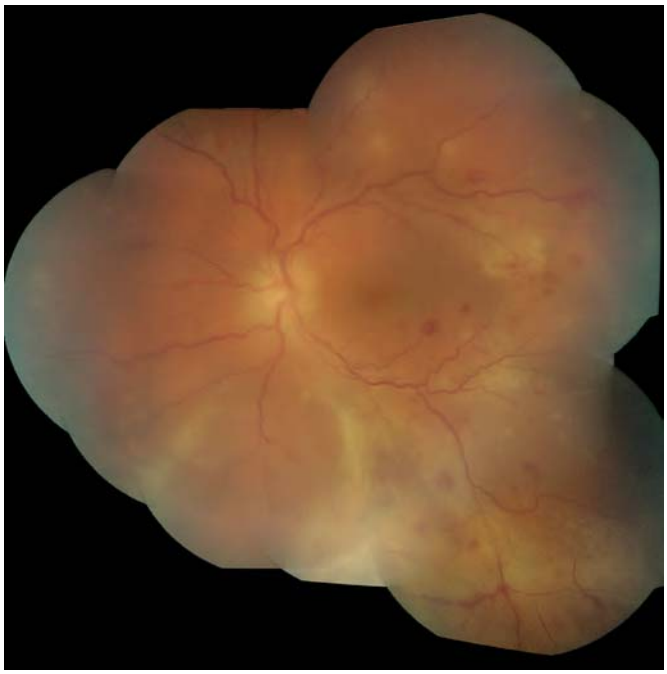

Figure 12-5 Acute retinal necrosis. Fundus photograph montage reveals vitritis, multifocal and confluent areas of retinitis, retinal vasculitis, retinal hemorrhage, optic nerve head edema, and retinal detachment. *(Reproduced from Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmic Technology Assessment.* Ophthalmology. *2017;124(3):382–392. © 2017 American Academy of Ophthalmology.)*

Table 12-1 American Uveitis Society Criteria for Diagnosis of Acute Retinal Necrosis

One or more foci of retinal necrosis with discrete borders, located in the peripheral retina[a]
Rapid progression in the absence of antiviral therapy
Circumferential spread
Occlusive vasculopathy with arteriolar involvement
Prominent vitritis, anterior chamber inflammation
Supportive, but not required: optic neuropathy/atrophy, scleritis, pain

[a] Macular lesions do not exclude diagnosis in the presence of peripheral retinitis.

Information from Holland GN; the Executive Committee of the American Uveitis Society. Standard diagnostic criteria for the acute retinal necrosis syndrome. *Am J Ophthalmol.* 1994;117(5):663–667.

Initiation of antiviral therapy for ARN should not be delayed while awaiting PCR results. Timely diagnosis and prompt treatment are essential, given the rapidity of disease progression, the frequency of retinal detachment, and the guarded visual prognosis. Intravenous acyclovir, 10 mg/kg every 8 hours for 10–14 days, is effective against HSV and VZV. However, reversible elevations in serum creatinine and liver enzyme levels may occur; in the presence of frank renal insufficiency, the dosage will need to be reduced. As induction therapy for HSV- and VZV-associated retinitis, oral valacyclovir at doses up to 2 g 3 times daily has been a successful alternative to intravenous acyclovir, with similar bioavailability.

After intravenous antiviral induction for VZV infection, treatment with acyclovir at 800 mg orally 5 times daily, valacyclovir (prodrug to acyclovir) at 1–2 g orally 3 times daily, or famciclovir at 500 mg orally 3 times daily should be continued for 3 months. For ARN associated with HSV-1 infection, the oral antiviral dose is one-half that for VZV. Extended antiviral therapy may reduce the incidence of contralateral disease or bilateral ARN by 80% over 1 year.

As first-line therapy for ARN or for disease that fails to respond to systemic treatment, intravitreal ganciclovir (2.0 mg/0.05 or 0.1 mL) and foscarnet (2.4 mg/0.1 mL) may be used with systemic antiviral therapy. An Ophthalmic Technology Assessment report by the American Academy of Ophthalmology suggests that the combination of high-dose oral and intravitreal antiviral therapies may decrease the risk of retinal detachment and severe vision loss, but no randomized clinical trials have investigated this regimen. Given the short intravitreal half-life of these drugs, injections may need to be repeated 2 or 3 times per week until the retinitis is stable, and then weekly if necessary (see Appendix B). Effective treatment should inhibit the development of new lesions and promote lesion regression over 4 days.

After 24–48 hours of antiviral therapy, systemic corticosteroids (prednisone, 1 mg/kg/day, up to 60–80 mg/day) can be introduced to treat intraocular inflammation and then tapered over several weeks. Aspirin and other anticoagulants have been used to treat an associated hypercoagulable state and prevent vascular occlusions, but the results are inconclusive.

Despite treatment, there is a high rate of retinal detachment, which may occur within weeks to months of ARN onset. The use of prophylactic barrier laser photocoagulation in areas of healthy retina at the posterior border of necrotic lesions to prevent retinal detachment is controversial, but it has been employed by some practitioners. When detachment occurs, vitrectomy techniques are preferred over standard scleral buckling. Nevertheless, optic nerve atrophy may be visually limiting even with a favorable retinal anatomical outcome.

Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmic Technology Assessment. *Ophthalmology.* 2017;124(3):382–392.

PROGRESSIVE OUTER RETINAL NECROSIS PORN is a morphologic variant of ARN that occurs in those who are profoundly immunosuppressed, most commonly owing to advanced AIDS (ie, $CD4^+$ T lymphocytes ≤50 cells/μL). The most common cause of PORN is VZV infection, although HSV has also been isolated. As with ARN, the retinitis begins as patchy areas of outer retinal whitening that coalesce rapidly. In contrast to ARN, the posterior pole may be involved early in the disease course, substantial vitreous cell and haze are typically absent, and the retinal vasculature is minimally involved, at least initially (Fig 12-6). Patients with PORN and HIV/AIDS frequently have a history of cutaneous zoster (67%) and eventually incur bilateral involvement (71%). Similar to ARN, there is a high rate (70%) of retinal detachment. The visual prognosis is poor; in the largest series reported to date, 67% of patients with PORN had a final visual acuity of no light perception. Although PORN is often resistant to treatment with intravenous acyclovir alone, management with combination systemic and intravitreal therapy using foscarnet and ganciclovir has been

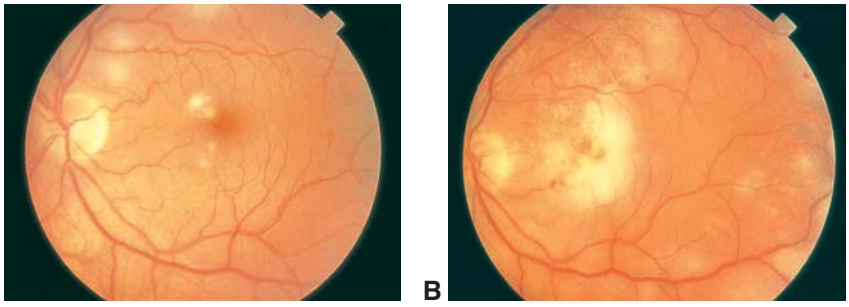

Figure 12-6 Progressive outer retinal necrosis. **A,** Fundus photograph showing multifocal areas of retinitis in the posterior pole. **B,** Fundus photograph taken 5 days later showing rapid disease progression and confluence of the areas of viral retinitis. *(Courtesy of E. Mitchel Opremcak, MD.)*

successful. Long-term suppressive antiviral therapy is required in patients with PORN and HIV/AIDS who are not able to achieve immune reconstitution through antiretroviral treatment. See also BCSC Section 12, *Retina and Vitreous,* for additional discussion of viral retinitis.

Engstrom RE Jr, Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome: a variant of necrotizing herpetic retinopathy in patients with AIDS. *Ophthalmology.* 1994;101(9):1488–1502.

Gore DM, Gore SK, Visser L. Progressive outer retinal necrosis: outcomes in the intravitreal era. *Arch Ophthalmol.* 2012;130(6):700–706.

NONNECROTIZING HERPETIC RETINOPATHY Nonnecrotizing herpetic retinopathy (nonnecrotizing posterior uveitis) may occur in patients with herpetic infections. Examples include acute retinochoroiditis with diffuse hemorrhages after acute VZV infection in children, and chronic choroiditis or retinal vasculitis in adults. In a study using PCR-based assays and local antibody analysis of aqueous fluid samples for herpesviruses in patients with "idiopathic posterior uveitis," 13% of cases had a confirmed viral etiology. Affected patients may be immunocompetent or immunocompromised. Inflammation is typically bilateral, and the disorder may present with uveitic macular edema, as a birdshot-like chorioretinopathy, or as an occlusive bilateral retinitis. The disease is initially resistant to conventional therapy with systemic corticosteroids and/or immunomodulatory therapy (IMT), but the response has been favorable when patients are switched to systemic antiviral medication.

Bodaghi B, Rozenberg F, Cassoux N, Fardeau C, LeHoang P. Nonnecrotizing herpetic retinopathies masquerading as severe posterior uveitis. *Ophthalmology.* 2003; 110(9):1737–1743.

Wensing B, de Groot-Mijnes JD, Rothova A. Necrotizing and nonnecrotizing variants of herpetic uveitis with posterior segment involvement. *Arch Ophthalmol.* 2011;129(4): 403–408.

Wu XN, Lightman S, Tomkins-Netzer O. Viral retinitis: diagnosis and management in the era of biologic immunosuppression: a review. *Clin Exp Ophthalmol.* 2019;47(3):381–395.

CYTOMEGALOVIRUS RETINITIS CMV causes symptomatic illness in immunocompromised children and adults (eg, those with leukemia, lymphoma, or HIV/AIDS), transplant recipients,

and other patients with conditions requiring systemic IMT. In addition, CMV retinitis is the most common ophthalmic manifestation of congenital CMV infection (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*) as well as of CMV opportunistic coinfection in patients with HIV/AIDS (see Chapter 13). Three distinct clinical variants have been associated with CMV:

- a classic or fulminant retinitis with large areas of retinal hemorrhage against a background of whitened, edematous, or necrotic retina; the retinitis typically appears in the posterior pole, near the vascular arcades, in the distribution of the nerve fiber layer, and associated with blood vessels (Fig 12-7)
- a granular or indolent form found most often in the retinal periphery, characterized by little or no hemorrhage, edema, or vascular sheathing; active retinitis may progress from the borders of the lesion (Fig 12-8)
- a perivascular form often described as a variant of "frosted-branch" angiitis, an undifferentiated retinal perivasculitis initially described in immunocompetent children but also seen in immunocompromised patients (Fig 12-9)

CMV reaches the eye hematogenously, with passage of the virus across the blood–ocular barrier, infection of retinal vascular endothelial cells, and cell-to-cell transmission of

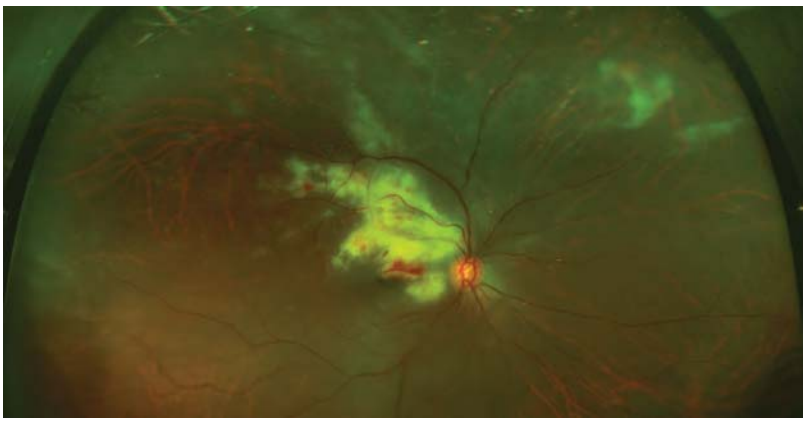

Figure 12-7 Cytomegalovirus retinitis. Wide-field fundus photograph shows fulminant retinitis without vitritis. *(Courtesy of Bryn M. Burkholder, MD.)*

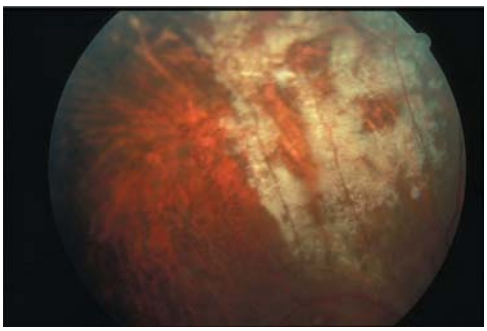

Figure 12-8 Cytomegalovirus retinitis. Fundus photograph shows the granular form. *(Courtesy of Careen Lowder, MD.)*

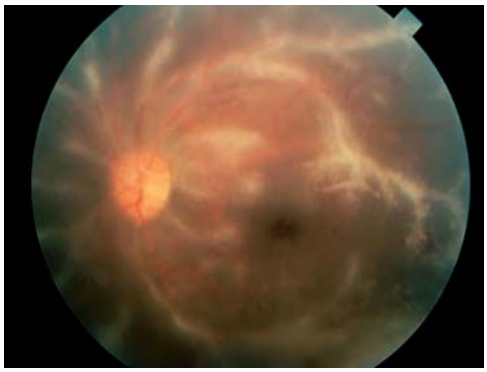

Figure 12-9 Cytomegalovirus retinitis. Fundus photograph shows "frosted-branch" perivasculitis. *(Courtesy of Albert T. Vitale, MD.)*

the virus within the retina. The histologic features of both congenital and acquired disease include a primary, full-thickness, coagulative, necrotizing retinitis and secondary diffuse choroiditis. Infected retinal cells show pathognomonic cytomegalic changes consisting of large eosinophilic intranuclear inclusions and small basophilic cytoplasmic inclusions. Viral inclusions may also be present in the retinal pigment epithelium (RPE) and vascular endothelium. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for examples of CMV histologic findings.

The prevalence of retinitis in children with congenital CMV infection is between 11% and 22%. Systemic manifestations of disseminated infection in this population include fever, thrombocytopenia, anemia, pneumonitis, and hepatosplenomegaly. Diagnosis is suggested by the clinical presentation; positive serum antibodies or PCR testing of urine, saliva, or intraocular fluids; and systemic findings. Serum antibody testing may be useful 5–24 months after the loss of maternal antibodies transferred after pregnancy.

CMV retinitis has also occurred later in life among children who initially had no discernible lesions ophthalmoscopically and with no evidence of systemic disease reactivation. This pattern suggests that even asymptomatic children with congenital CMV infection should be monitored at regular intervals for potential ocular involvement later in childhood. Resolution of the retinitis leaves both pigmented and atrophic lesions, with retinal detachment occurring in up to one-third of these children. Optic atrophy and cataract formation are common sequelae.

In patients who are immunosuppressed or immunocompromised for any reason, CMV retinitis is an opportunistic infection. See Chapter 13 for further discussion.

With the advent of antiretroviral therapy, the incidence of CMV retinitis has decreased by 80% in patients with AIDS who have access to adequate medical resources. CMV retinitis is now more commonly diagnosed in patients immunosuppressed by chemotherapy or those receiving IMT for systemic inflammatory diseases or after solid organ or hematopoietic stem cell transplants. In rare cases, CMV retinitis may develop after a local corticosteroid injection, including intravitreal administration. In patients without AIDS, CMV retinitis is more likely to present as the granular form with substantial anterior chamber and vitreous inflammation and occlusive vasculitis. In patients undergoing systemic immunosuppression or chemotherapy, anti-CMV treatment usually requires

close comanagement with other medical subspecialists. Although there are no specific screening guidelines for immunosuppressed patients with CMV viremia, indications for an ophthalmic examination can include ocular symptoms and active or recently active multiorgan CMV infection.

Management of CMV retinitis involves antiviral therapy and measures to restore natural immunity, if possible (ie, reducing or discontinuing systemic IMT). Options for treatment include intravenous ganciclovir or foscarnet, oral valganciclovir, and intravitreal ganciclovir or foscarnet. See Chapter 13 for further details about treatment of CMV retinitis.

Months or years after therapy, patients with immune recovery may develop uveitis (eg, immune recovery uveitis) despite the absence of CMV reactivation. Immune recovery uveitis occurs when the reconstituted immune system reacts to residual CMV antigens within the eye. Treatment may include topical, periocular, and oral corticosteroids. See Chapter 13 for further discussion of immune recovery uveitis.

Kempen JH, Min YI, Freeman WR, et al; Studies of Ocular Complications of AIDS Research Group. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology.* 2006;113(4);684–694.

Kim DY, Jo J, Joe SG, Kim JG, Yoon YH, Lee JY. Comparison of visual prognosis and clinical features of cytomegalovirus retinitis in HIV and non-HIV patients. *Retina.* 2017;37(2):376–381.

Schneider EW, Elner SG, van Kuijk FJ, et al. Chronic retinal necrosis: cytomegalovirus necrotizing retinitis associated with panretinal vasculopathy in non-HIV patients. *Retina.* 2013;33(9):1791–1799.

Shapira Y, Mimouni M, Vishnevskia-Dai V. Cytomegalovirus retinitis in HIV-negative patients—associated conditions, clinical presentation, diagnostic methods and treatment strategy. *Acta Ophthalmol.* 2018;96(7):e761–e767. doi:10.1111/aos.13553

Su YT, Chen YJ, Lin CP, et al. Clinical characteristics and prognostic factors affecting clinical outcomes in cytomegalovirus retinitis with or without HIV infection. *Retina.* 2023;43(1):57–63. doi:10.1097/IAE.0000000000003631

Epstein-Barr virus

Epstein-Barr virus (EBV) is a ubiquitous double-stranded DNA virus that is commonly associated with infectious mononucleosis (IM) and has been implicated in the pathogenesis of Burkitt lymphoma (especially among African children), nasopharyngeal carcinoma, Hodgkin disease, and Sjögren syndrome. EBV has a tropism for B lymphocytes, the only cells known to have surface receptors for the virus.

Congenital EBV infection may result in congenital cataract. Acquired EBV (eg, IM) is more likely to have ocular manifestations, most commonly a mild, self-limited follicular conjunctivitis. Less frequent anterior segment or external ocular manifestations of IM include epithelial or stromal keratitis; episcleritis; bilateral granulomatous anterior uveitis; dacryoadenitis; and in rare cases, cranial nerve palsies and Parinaud oculoglandular syndrome.

EBV is only rarely associated with posterior segment manifestations such as isolated optic disc edema and optic neuritis, macular edema, retinal hemorrhages, retinitis (including ARN), punctate outer retinitis, choroiditis, multifocal choroiditis with panuveitis (MFCPU), pars planitis and vitritis, progressive subretinal fibrosis, and secondary choroidal neovascularization (CNV). In the absence of systemic EBV-related disease or recently

acquired IM, the virus is unlikely to be the cause of these findings. Serum antibody testing against a variety of EBV-specific capsid antigens is rarely useful in proving causality because of the very high seroprevalence of EBV (90%) in the adult population. The presence of EBV DNA or anti-EBV antibodies in ocular fluids has been cited as evidence of the causal role of EBV in ocular inflammation, but an intraocular EBV-associated malignancy, especially when the patient has HIV infection, could masquerade as ocular inflammation.

Most EBV-associated ocular disease is self-limiting. The presence of anterior uveitis may necessitate topical corticosteroids and cycloplegia. Posterior segment inflammation can be treated with systemic corticosteroids. For the management of necrotizing retinitis/ARN in patients with EBV, systemic antiviral therapy with acyclovir or ganciclovir may be considered.

Alba-Linero C, Rocha-de-Lossada C, Rachwani-Anil R, et al. Anterior segment involvement in Epstein-Barr virus: a review. *Acta Ophthalmol.* 2022;100(5):e1052–e1060. doi:10.1111/aos.15061

Cunningham ET, Zierhut M. Epstein-Barr virus and the eye. *Ocul Immunol Inflamm.* 2020;28(4):533–537.

Schaal S, Kagan A, Wang Y, Chan CC, Kaplan HJ. Acute retinal necrosis associated with Epstein-Barr virus: immunohistopathologic confirmation. *JAMA Ophthalmol.* 2014;132(7):881–882.

Smit D, Meyer D, Maritz J, de Groot-Mijnes JDF. Polymerase chain reaction and Goldmann-Witmer coefficient to examine the role of Epstein-Barr virus in uveitis. *Ocul Immunol Inflamm.* 2019;27(1):108–113.

Rubella

The rubella virus is the prototypical teratogenic viral agent that can affect the retina through transplacental transmission (ie, congenital rubella syndrome [CRS]) or acquired infection (ie, German measles). Although rubella infection remains an important cause of blindness in resource-limited regions and nations, the epidemic pattern of the disease was interrupted in the United States in 1969 by introduction of the rubella vaccine. The peak age of incidence has shifted from 5–9 years in the pre-vaccine era to 15–19 years and more recently to 20–24 years. Approximately 5%–25% of women of childbearing age are susceptible to primary infection.

Congenital rubella syndrome

The classic features of CRS are cardiac malformations (eg, patent ductus arteriosus, interventricular septal defects, and pulmonic stenosis), ocular findings (eg, chorioretinitis, pigmentary retinopathy, cataract, corneal clouding, microphthalmia, strabismus, and glaucoma), and deafness (Fig 12-10). Hearing loss is the most common systemic finding. In addition, individuals with CRS are at increased risk for diabetes and diabetic retinopathy later in life. Although the mechanism of rubella embryopathy is not known at the cellular level, the virus is thought to inhibit cellular division and establish a chronic, persistent infection during organogenesis. The persistence of viral replication after birth, with ongoing tissue damage, is central to the pathogenesis of CRS and may explain the appearance of hearing and neurologic and/or ocular deficits long after birth.

Figure 12-10 Congenital rubella syndrome. External photograph shows a patient who had cataract, esotropia, cognitive impairment, congenital heart disease, and deafness. *(Courtesy of John D. Sheppard Jr, MD.)*

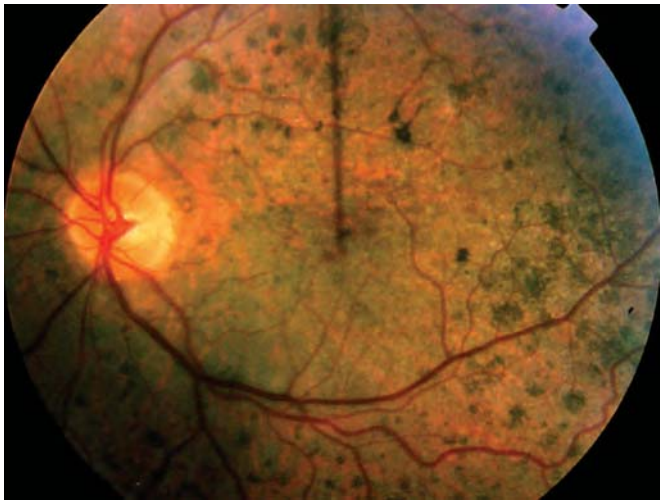

Figure 12-11 Congenital rubella syndrome. Fundus photograph demonstrates a salt and pepper fundus with diffuse retinal pigment epithelial mottling and pigment clumping. *(Courtesy of Albert T. Vitale, MD.)*

The most common ocular manifestation of CRS is a unilateral or bilateral pigmentary retinopathy (25%–50% of cases), followed by cataract (15%) and glaucoma (10%). The pigmentary disturbance, often described as salt and pepper fundus, shows considerable variation, ranging from finely stippled, bone spicule–like, small, black, irregular masses to gross pigmentary irregularities with coarse, blotchy mottling (Fig 12-11). This mottling can be stationary or progressive. Despite loss of the foveal light reflex and prominent pigmentary changes, neither vision nor electroretinogram results are typically affected, and retinal vessels appear normal. The optic nerves are also normal in appearance unless compromised by glaucoma. The most frequent cause of poor visual acuity in CRS is microphthalmia and congenital (nuclear) cataracts. Histologic studies of the lens reveal retained cell nuclei in the embryonic nucleus as well as anterior and posterior cortical degeneration. Although rare, CNV is another cause of vision loss in patients with CRS.

These pigmentary retinal changes and associated systemic findings, together with a history of maternal exposure to rubella, suggest the diagnosis of CRS. Serologic criteria for rubella infection include a fourfold increase in rubella-specific immunoglobulin (Ig) G in paired sera 1–2 weeks apart or the new appearance of rubella-specific IgM. Because the fetus is capable of mounting an immune response to the rubella virus, specific IgM or IgA antibodies to rubella in the cord blood confirm the diagnosis.

The differential diagnosis of congenital rubella retinitis includes the other entities associated with the TORCH syndrome (eg, *t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, and *h*erpesviruses). Other viral illnesses, such as mumps, roseola subitum, and postvaccination encephalitis, should also be considered and ruled out by appropriate serologic tests. There is no specific antiviral therapy for congenital rubella, and treatment is supportive.

Arnold JJ, McIntosh ED, Martin FJ, Menser MA. A fifty-year follow-up of ocular defects in congenital rubella: late ocular manifestations. *Aust N Z J Ophthalmol.* 1994;22(1):1–6.

Mets MB, Chhabra MS. Eye manifestations of intrauterine infections and their impact on childhood blindness. *Surv Ophthalmol.* 2008;53(2):95–111.

Acquired rubella

Acquired infection presents with a prodrome of malaise and fever in adolescents and adults before onset of the rubella exanthem. An erythematous, maculopapular rash appears first on the face, spreads toward the hands and feet, involves the entire body within 24 hours, and disappears by the third day. Although the rash is not always prominent and the occurrence of fever is variable, lymphadenopathy is invariably present.

The most frequent ocular complication of postnatally acquired rubella is conjunctivitis (70% of cases), followed by rare occurrences of epithelial keratitis and retinitis. Acquired rubella retinitis has been described in adults presenting with acute-onset decreased vision and multifocal chorioretinitis. Reported findings include large areas of bullous retinal detachment, underlying pigment epithelial detachment involving the entire posterior pole, anterior chamber and preretinal vitreous cells, and dark gray atrophic lesions of the RPE. The retinal vessels and optic nerve typically appear normal, and there are no retinal hemorrhages. The retinal detachments resolve spontaneously, and visual acuity returns to normal. Chronic rubella virus infection has been implicated in the pathogenesis of Fuchs uveitis syndrome (see Chapter 8), as evidenced by the presence of rubella-specific intraocular antibody production and the intraocular persistence of the virus.

Uncomplicated acquired rubella does not require specific therapy; however, rubella retinitis and postvaccination optic neuritis may respond well to systemic corticosteroids.

Matalia J, Vinekar A, Anegondi N, et al. A prospective OCT study of rubella retinopathy. *Ophthalmol Retina.* 2018;2(12):1235–1240.

Lymphocytic Choriomeningitis Virus

Lymphocytic choriomeningitis virus (LCMV) is an under-recognized fetal teratogen that should probably be included among the "other agents" in the TORCH group of congenital infections. The microbe is a single-stranded RNA virus and a member of the family Arenaviridae.

Systemic findings include macrocephaly, hydrocephalus, and intracranial calcifications. Neurologic abnormalities, seizures, and mild cognitive impairment may also occur. Ocular findings include macular and peripheral chorioretinal scars, similar in morphology and distribution to those in congenital toxoplasmosis. Serologic testing of the mother and the infant helps distinguish LCMV from toxoplasmosis. Other findings include optic atrophy, strabismus, and nystagmus.

Mumps

The *Mumps virus* is a member of the family Paramyxoviridae (other members include measles, parainfluenza, and respiratory syncytial virus). A single-stranded RNA virus, mumps is acquired by respiratory droplets and may cause parotitis, aseptic meningitis, and orchitis. In rare cases, mumps may cause inflammation involving the cornea, optic nerve, or retina.

Measles (Rubeola)

Congenital and acquired measles infections are caused by a single-stranded RNA virus of the genus *Morbillivirus* of the family Paramyxoviridae. The virus is highly contagious and is transmitted either directly or via aerosolization of nasopharyngeal secretions to the mucous membranes of the conjunctiva or respiratory tract of susceptible individuals or transplacentally from a pregnant woman to her fetus.

Despite the existence of an effective vaccine, measles remains a leading cause of mortality among children worldwide. Measles is rare in the United States, although there was an outbreak in 2018.

Congenital measles infection may cause cataract, optic disc drusen, and a bilateral diffuse pigmentary retinopathy involving the posterior pole and retinal periphery. The retinopathy may be associated with normal or attenuated retinal vessels, retinal edema, and macular star formation. Electroretinographic results and visual acuity are usually normal.

The most common ocular manifestations of acquired measles are keratitis and a mild, papillary, nonpurulent conjunctivitis. In countries with prevalent malnutrition, corneal scarring may cause post-measles blindness, a significant problem worldwide.

Measles retinopathy is more common in acquired than in congenital disease, presenting with profound loss of vision 6–12 days after the appearance of the characteristic exanthem; it may be accompanied by encephalitis. Acquired measles retinopathy is characterized by attenuated arterioles, diffuse retinal edema, macular star formation, scattered retinal hemorrhages, blurred optic disc margins, and clear media. Optic disc pallor and a secondary pigmentary retinopathy with either a bone spicule or salt-and-pepper appearance may subsequently develop.

The differential diagnosis of congenital measles retinopathy includes the TORCH entities, atypical retinitis pigmentosa, and neuroretinitis. For acquired measles retinopathy, considerations include central serous chorioretinopathy, Vogt-Koyanagi-Harada syndrome (bullous detachments may resolve, leaving extensive RPE disruption), retinitis pigmentosa, syphilis, and other viral retinopathies.

The diagnosis of measles and its ocular sequelae is made clinically and through serologic testing. For patients with acute measles retinopathy, systemic corticosteroids may be considered.

Hübschen JM, Gouandjika-Vasilache I, Dina J. Measles. *Lancet.* 2022;399(10325):678–690.

Lee JH, Agarwal A, Mahendradas P, et al. Viral posterior uveitis. *Surv Ophthalmol*. 2017;62(4): 404–445.

Subacute sclerosing panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a rare, late complication of acquired measles infection. It most often affects unvaccinated children in late childhood or adolescence, 6–8 years after the primary infection. Visual impairment, behavioral disturbances, and memory impairment may insidiously develop, followed by myoclonus and progression to spastic paresis, dementia, and death within 1–3 years.

Ocular findings are reported in up to 50% of patients with SSPE and may precede the neurologic manifestations by several weeks to 2 years. The most consistent finding is a maculopathy consisting of focal retinitis and RPE changes, occurring in 36% of patients with SSPE (Fig 12-12). Retinitis may progress to involve the peripheral retina, but there is usually minimal or no vitritis. Other intraocular findings include optic disc inflammation and papilledema, optic atrophy, macular edema, macular pigment epithelial disturbances, small intraretinal hemorrhages, gliotic scar, white retinal infiltrates, serous macular detachment, drusen, preretinal membranes, and macular hole. Other associations are cortical blindness, hemianopia, horizontal nystagmus, and ptosis.

The diagnosis of SSPE is based on clinical examination, electroencephalographic abnormalities, raised IgG antibody titer against measles in the plasma and cerebrospinal fluid, and/or panencephalitis found on magnetic resonance imaging or brain biopsy.

The differential diagnosis of the ophthalmic findings includes viral retinitis caused by HSV, VZV, and CMV infection. Intermediate uveitis and retinal vasculitis associated with multiple sclerosis may also be considered. Definitive treatment of SSPE remains undetermined.

Yuksel D, Sonmez PA, Yilmaz D, Senbil N, Gurer Y. Ocular findings in subacute sclerosing panencephalitis. *Ocul Immunol Inflamm.* 2011;19(2):135–138.

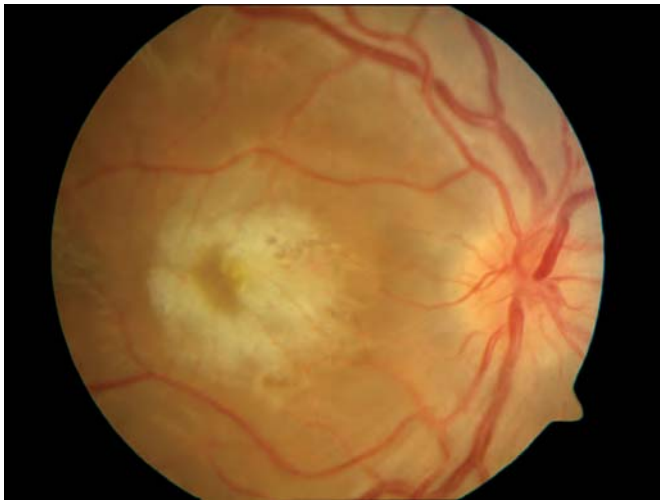

Figure 12-12 Subacute sclerosing panencephalitis in acquired measles infection. Fundus photograph of macular retinitis. *(Courtesy of Emad B. Abboud, MD.)*

West Nile Virus

West Nile virus (WNV) is a single-stranded RNA virus and member of the family Flaviviridae; it belongs to the Japanese encephalitis virus serocomplex and is endemic to Europe, Australia, Asia, and Africa. The virus is transmitted from birds (the natural host) to humans through the bite of an infected mosquito. The peak onset of the disease is late summer, but it can occur anytime between July and December. The incubation period ranges from 3 to 14 days. Eighty percent of WNV infections are subclinical. Twenty percent of infections present as a febrile illness, often accompanied by myalgia, arthralgia, headache, conjunctivitis, lymphadenopathy, and a maculopapular or roseolar rash. Severe neurologic disease (ie, meningitis or encephalitis) may occur, especially in association with diabetes and advanced age.

Presenting ocular symptoms include pain, photophobia, conjunctival hyperemia, and blurred vision. A characteristic multifocal chorioretinitis is present in most affected patients, together with nongranulomatous anterior uveitis and vitreous inflammatory cells. Chorioretinal lesions vary in size (200–1000 μm) and number and may affect the midzone and/or posterior pole, often in linear arrays following the course of retinal nerve fibers (classic appearance). Active lesions appear whitish to yellow, are flat and deep, and evolve with varying degrees of pigmentation and atrophy.

In patients with WNV infection, fluorescein angiography (FA) reveals central hypofluorescence with late staining of active lesions and early hyperfluorescence with late staining of inactive lesions. Inactive or partly active lesions may also have a targetlike appearance with central hypofluorescence caused by blockage from pigment and peripheral hyperfluorescence due to atrophy (Fig 12-13). Indocyanine green angiography reveals hypofluorescent spots, more numerous than those apparent on FA or ophthalmoscopy.

Other findings may include intraretinal hemorrhages, optic disc edema, optic atrophy, and less commonly, focal retinal vascular sheathing and occlusion, cranial nerve VI

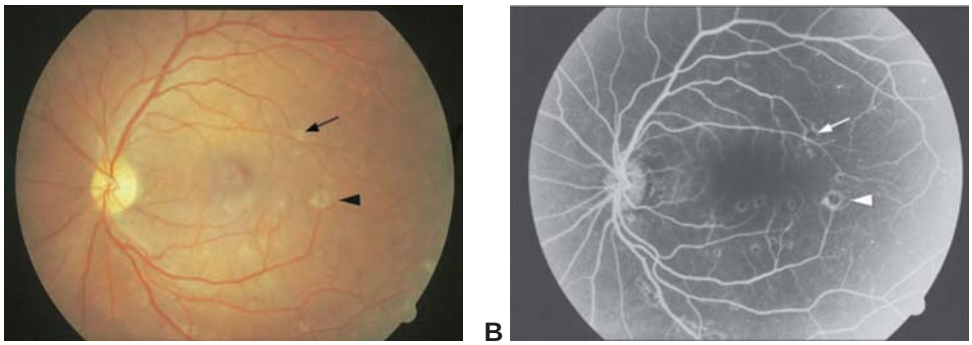

Figure 12-13 West Nile virus chorioretinitis. **A,** Fundus photograph showing multiple active *(arrow)* and partially active *(arrowhead)* discrete cream-colored chorioretinal spots (100–300 μm). **B,** The corresponding fluorescein angiogram shows early hypofluorescence *(arrow)* on the active chorioretinal spots (acute stage) and focal hypofluorescence with a surrounding hyperfluorescent ring *(arrowhead)* on the partially active lesions (subacute stage). On the late-phase angiogram (not shown), there was subsequent staining. *(Reproduced with permission from Chan CK, Limstrom SA, Tarasewicz DG, Ling SG. Ocular features of West Nile virus infection in North America: a study of 14 eyes.* Ophthalmology. *2006;113(9):1539–1546.)*

palsy, and nystagmus. Of note, congenital WNV infection has been reported in an infant who had chorioretinal scarring without intraocular inflammation.

In most patients, intraocular inflammation associated with WNV infection has a self-limiting course, with a return of visual acuity to baseline after several months. In others, loss of vision may occur because of CNV, foveal scar, ischemic maculopathy, vitreous hemorrhage, tractional retinal detachment, optic nerve pathology, and retrogeniculate damage. Diabetes has been implicated as a risk factor for WNV-related death and may increase the risk of WNV-associated ocular involvement.

Ocular findings in patients with systemic symptoms suggestive of WNV infection or with meningoencephalitis may prompt WNV serologic testing. The differential diagnosis includes syphilis, MFCPU, histoplasmosis, sarcoidosis, and tuberculosis.

Currently, there is no vaccine or specific antiviral treatment for WNV infection. Patients receive supportive therapy. Anterior uveitis may be treated with topical corticosteroids. The efficacy of systemic and periocular corticosteroids for chorioretinal manifestations is unknown. Public health strategies directed at prevention are the mainstays of WNV infection control.

Khairallah M, Ben Yahia S, Attia S, Zaouali S, Ladjimi A, Messaoud R. Linear pattern of West Nile virus–associated chorioretinitis is related to retinal nerve fibres organization. *Eye (Lond).* 2007;21(7):952–955.

Khairallah M, Ben Yahia S, Letaief M, et al. A prospective evaluation of factors associated with chorioretinitis in patients with West Nile virus infection. *Ocul Immunol Inflamm.* 2007;15(6):435–439.

Rousseau A, Haigh O, Ksiaa I, Khairallah M, Labetoulle M. Ocular manifestations of West Nile virus. *Vaccines (Basel).* 2020;8(4):641. doi:10.3390/vaccines8040641

Rift Valley Fever

Rift Valley fever is a febrile illness caused by *Rift Valley fever virus,* a member of the family Bunyaviridae. One of 3 clinical syndromes may develop: (1) an uncomplicated, febrile, influenza-like illness; (2) hemorrhagic fever; or (3) encephalitis. Ophthalmic findings may include anterior uveitis, vitritis, a macular or paramacular retinitis (classic finding) (Fig 12-14), retinal hemorrhage, retinal vasculitis, and optic nerve edema. Anterior uveitis

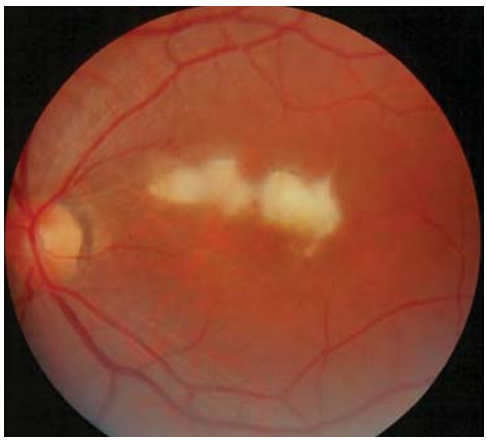

Figure 12-14 Rift Valley fever. Fundus photograph from a 44-year-old male farmer from Saudi Arabia who presented with decreased vision and macular retinitis sparing the fovea. He had a history of fever and contact with animal abortus. *(Courtesy of Albert T. Vitale, MD.)*

occurs in 31% of patients with Rift Valley fever. Patients may also develop macular scarring, vascular attenuation, retinal ischemia, and/or optic atrophy.

The differential diagnosis includes viral entities such as measles, rubella, influenza, dengue fever, and WNV infection as well as bacterial illnesses such as brucellosis, Lyme disease, toxoplasmosis, cat-scratch disease, and rickettsial diseases. The diagnosis of Rift Valley fever is made clinically and serologically.

Al-Hazmi A, Al-Rajhi AA, Abboud EB, et al. Ocular complications of Rift Valley fever outbreak in Saudi Arabia. *Ophthalmology.* 2005;112(2):313–318.

Human T-cell Lymphotropic Virus Type 1

Human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus that is endemic in Japan, the Caribbean islands, and parts of Central and South America. It accounts for approximately 1% of uveitis cases in Japan. The diagnosis is made by serologic testing. The major target cell of HTLV-1 is the $CD4^+$ T cell. HTLV-1 infection is the established cause of HTLV-1 uveitis (HU), adult T-cell leukemia/lymphoma (ATL), and HTLV-1–associated myelopathy/tropical spastic paralysis (HAM/TSP).

Most cases of HU (75%) are classified as an intermediate uveitis. Patients present with blurred vision and floaters caused by a mild granulomatous anterior uveitis (20% of HU cases), unilateral vitritis (60%), membranous vitreous opacities, and/or snowballs. Retinal vasculitis (60%), exudative retinal lesions (25%), optic disc abnormalities (20%), and uveitic macular edema (3%) may also be found.

Additional ocular manifestations of HTLV-1 infection include retinal infiltrates caused by secondary ATL (Fig 12-15A). Patients with HAM/TSP may have retinal degeneration, optic neuropathy, and keratoconjunctivitis sicca. HTLV-1–associated keratopathy (previously referred to as *HTLV-1–related chronic interstitial keratitis*) has been described in Brazilian and Caribbean patients but has not been found among Japanese patients. These corneal lesions likely represent lymphoplasmacytic infiltrates and are asymptomatic (Fig 12-15B).

Although HU responds to topical, periocular, or systemic corticosteroids, one-half of patients may experience recurrent disease. For HU cases that progress despite therapy, the clinician should consider mimics of HU such as retinal infiltration caused by ATL (see Fig 12-15A) or retinal degeneration associated with HAM/TSP.

Goto H, Mochizuki M, Yamaki K, Kotake S, Usui M, Ohno S. Epidemiological survey of intraocular inflammation in Japan. *Jpn J Ophthalmol.* 2007;51(1):41–44.

Kamoi K, Watanabe T, Uchimaru K, et al. Updates on HTLV-1 uveitis. *Viruses.* 2022; 14(4):794. doi:10.3390/v14040794

Dengue Fever

Dengue fever, the most common mosquito-borne viral disease in humans, is caused by *Dengue virus,* a member of the family Flaviviridae. The virus is transmitted by the bite of an infected *Aedes aegypti* mosquito and is endemic within more than 100 countries in the tropical and subtropical regions of the globe.

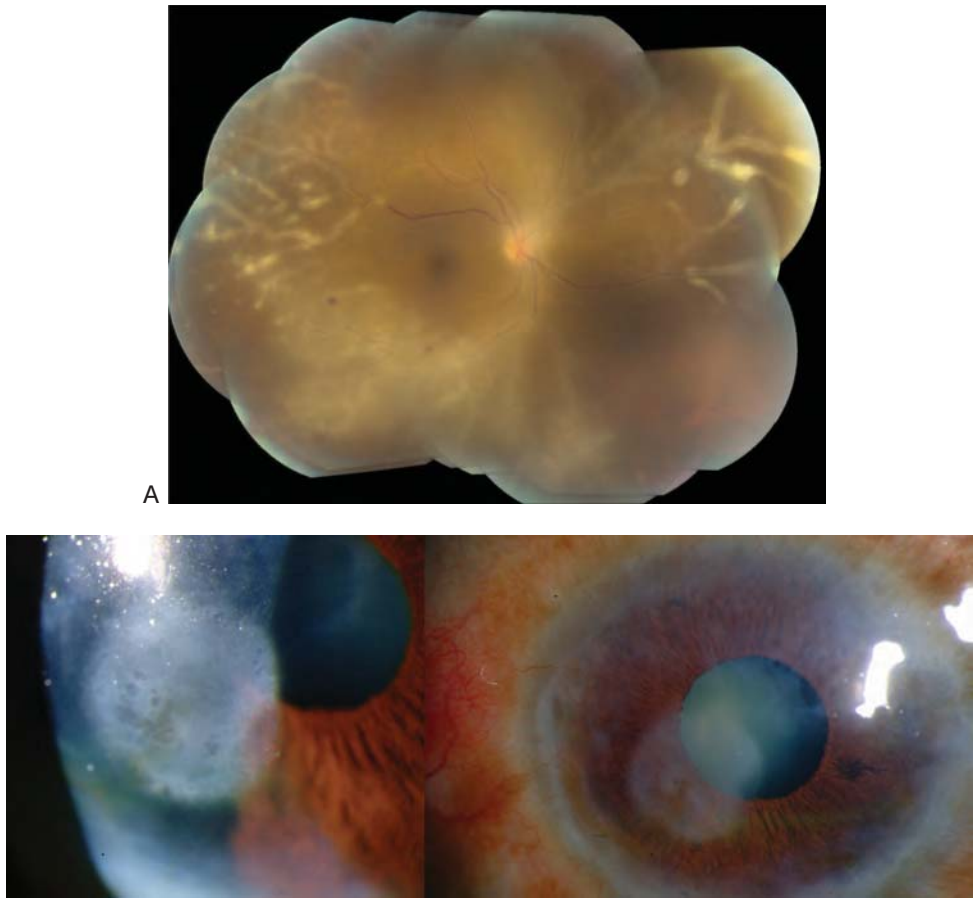

Figure 12-15 Human T-cell lymphotropic virus type 1–associated adult T-cell leukemia/lymphoma. **A,** Fundus photograph montage shows retinal and vascular infiltrates. **B,** Anterior segment photograph of keratopathy. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

Systemic signs and symptoms of dengue infection include fever, headache, myalgia, purpuric rash, and other bleeding manifestations secondary to thrombocytopenia. For many patients, this initial infection may be low grade, and they may not mention symptoms unless specifically asked during the history and review of systems. The most common ocular manifestation is petechial subconjunctival hemorrhage. Variable degrees of anterior chamber and vitreous cells may also occur.

One month after the onset of systemic disease, approximately 10% of patients develop maculopathy or "foveolitis" that causes a sudden decrease in vision and central scotoma, often without clinical lesions on examination. FA may show early focal arteriolar knobby hyperfluorescence in the macula with late leakage and/or staining; optical coherence tomography (OCT) angiography may show disruption of the foveal avascular zone (Fig 12-16). OCT may show macular edema, subretinal fluid, or disruption of the inner segment/outer segment junction.

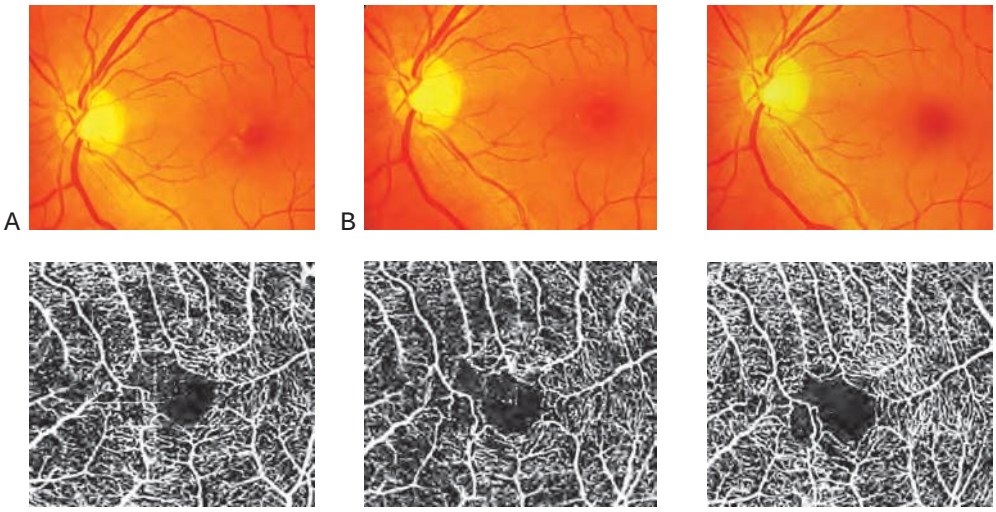

Figure 12-16 Dengue fever. A 46-year-old man presented with decreased vision 1 week after an episode of dengue fever. **A,** Small, white patches of retinal opacification with a few superficial hemorrhages. **B, C,** The lesions gradually resolved after a course of oral corticosteroids. **D–F,** Optical coherence tomography (OCT) angiogram shows enlargement of the foveal avascular zone and loss of retinal superficial capillary plexus, which remained unchanged on follow-up. *(Reproduced with permission from Bajgai P, Singh R, Kapil A. Progression of dengue maculopathy on OCT-angiography and fundus photography*. Ophthalmology. *2017;124(12):1816.)*

The diagnosis of dengue fever is based on clinical findings combined with positive serologic testing. Although the infection is not endemic to the United States, dengue virus–associated maculopathy should be considered in patients presenting with suggestive findings and a history of recent travel to an endemic area. There is no well-defined treatment algorithm for dengue affecting the posterior segment, but local and systemic corticosteroids may be used.

Ng CWK, Tai PY, Oli Mohamed S. Dengue maculopathy associated with choroidopathy and pseudohypopyon: a case series. *Ocul Immunol Inflamm.* 2018;26(5):666–670.

Somkijrungroj T, Kongwattananon W. Ocular manifestations of dengue. *Curr Opin Ophthalmol.* 2019;30(6):500–505.

Vijitha VS, Dave TV, Murthy SI, et al. Severe ocular and adnexal complications in dengue hemorrhagic fever: a report of 29 eyes. *Indian J Ophthalmol.* 2021;69(3):617–622.

Chikungunya Fever

Chikungunya fever is a potentially fatal illness resembling dengue fever that is caused by an arthropod-borne *Alphavirus.* Patients present with fever, headache, fatigue, nausea, vomiting, myalgia, arthralgia, and rash. Chikungunya translates to "that which bends up," a reference to the polyarthropathy, tenosynovitis, and stooped posture of some affected patients. The virus is typically transmitted to humans via mosquito bite. Maternal-fetal

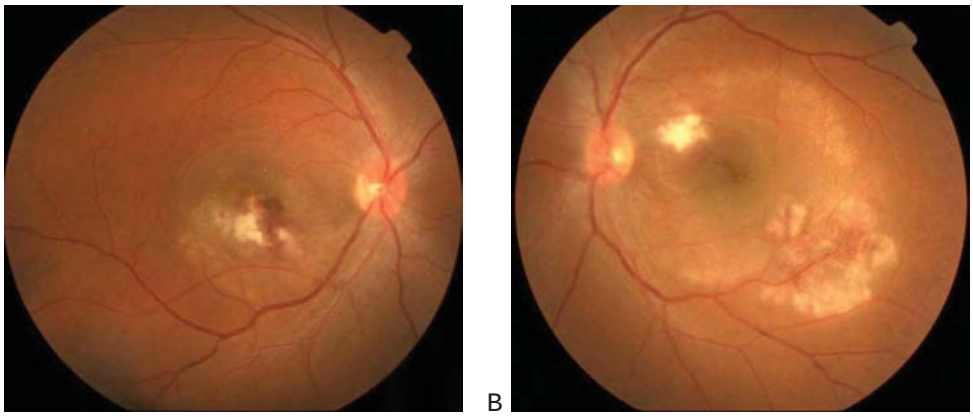

Figure 12-17 Chikungunya fever. Color fundus photographs. **A,** Retinitis with hemorrhages, right eye. **B,** Multifocal retinitis, left eye. *(Reproduced with permission from Mahendradas P, Ranganna SK, Shetty R, et al. Ocular manifestations associated with chikungunya.* Ophthalmology. *2008;115(2):287–291.)*

transmission has also been documented. Recent outbreaks have occurred in Africa, Asia, Europe, and the Americas.

In a 2006 epidemic of chikungunya fever in India, ocular manifestations included both anterior uveitis and retinitis, and less frequently, nodular episcleritis. Each had a typically benign course. Anterior uveitis may be granulomatous or nongranulomatous and is associated with ocular hypertension. Chikungunya retinitis may resemble herpetic retinitis. However, chikungunya retinitis features focal, multifocal, or confluent retinochoroiditis in the posterior pole with retinal hemorrhage and minimal vitritis (Fig 12-17), whereas herpetic retinitis involves the peripheral retina with higher-grade vitritis.

Diagnosis may be confirmed serologically by IgM antibodies, virus isolation, or PCR. Although retinitis has been treated with systemic acyclovir and corticosteroids, no evidence suggests that this therapy improves visual outcome.

Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. *J Ophthalmic Inflamm Infect.* 2013;3(1):35. doi:10.1186/1869-5760-3-35

Zika Virus

Zika virus (ZIKV), an arbovirus and member of the family Flaviviridae, is named after a forest in Uganda. Similar to dengue and chikungunya viruses, ZIKV is transmitted to humans by mosquito (often *Aedes aegypti*) bite. Coinfection with any of these 3 distinct viral diseases may occur in endemic areas. A large proportion of patients infected with ZIKV have no symptoms or minimal symptoms (ie, fever, headache, rash, arthralgia, myalgia, conjunctivitis) that typically resolve within a week.

Acute ZIKV infection in adults has caused individual cases of conjunctivitis, anterior uveitis, posterior uveitis with numerous chorioretinal lesions, and unilateral acute maculopathy. There is no defined treatment, but topical, systemic, or local corticosteroids may be considered.

Brazil experienced an epidemic of ZIKV that began in April 2015. A 20-fold spike in newborns with microcephaly was noted in the ensuing months, suggesting congenital ZIKV infection. The US Centers for Disease Control and Prevention (CDC) has defined *congenital Zika syndrome* as having 5 features:

- microcephaly
- structural brain abnormalities
- ocular findings
- congenital contractures such as clubfoot
- hypertonia restricting body movement soon after birth

No reports of uveitis have been associated with congenital ZIKV infection. Instead, observed ocular abnormalities have included microphthalmia, cataract, glaucoma, iris coloboma, retinal pigment mottling, chorioretinal atrophy, and optic nerve hypoplasia or atrophy (Fig 12-18). No vaccine exists to prevent Zika infection at this time. In the United States, where mosquito-borne transmission of ZIKV has been reported, current prevention efforts focus on education and mosquito control. See also BCSC Section 1, *Update on General Medicine*.

De Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. *JAMA Ophthalmol.* 2016;134(5):529–535.

De Paula Freitas B, Ventura CV, Maia M, Belfort R Jr. Zika virus and the eye. *Curr Opin Ophthalmol.* 2017;28(6):595–599.

Furtado JM, Espósito DL, Klein TM, Teixeira-Pinto T, da Fonseca BA. Uveitis associated with Zika virus infection. *N Engl J Med.* 2016;375(4):394–396.

Kodati S, Palmore TN, Spellman FA, Cunningham D, Weistrop B, Sen HN. Bilateral posterior uveitis associated with Zika virus infection. *Lancet.* 2017;389(10064):125–126.

Parke DW III, Almeida DR, Albini TA, Ventura CV, Berrocal AM, Mittra RA. Serologically confirmed Zika-related unilateral acute maculopathy in an adult. *Ophthalmology.* 2016; 123(11):2432–2433.

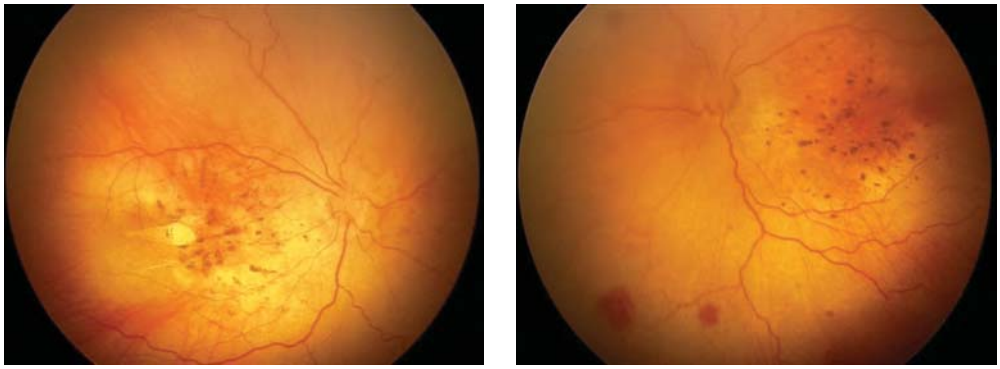

Figure 12-18 Congenital Zika syndrome. Fundus photographs show bilateral pigmentary clumping within the macula. *(Reproduced with permission from Miranda HA II, Costa MC, Frazão MAM, Simão N, Franchischini S, Moshfeghi DM. Expanded spectrum of congenital ocular findings in microcephaly with presumed Zika infection.* Ophthalmology. *2016;123(8):1788–1794.)*

Ebola Virus

Ebola virus disease (EVD) was first discovered in 1976 near the Ebola River in the Democratic Republic of the Congo. The virus is transmitted through direct contact with infected blood and/or body fluids. Sexual transmission has also occurred in survivor populations. EVD is characterized as a hemorrhagic fever; other acute symptoms are easy bruising, headache, weakness and fatigue, nausea and vomiting, and diarrhea. Patients with acute EVD may also experience conjunctivitis, subconjunctival hemorrhage, and acute vision loss of unclear etiology. Symptoms may appear 2–21 days after initial exposure.

Survivors of EVD may experience "post–Ebola virus disease syndrome," which can include arthralgias, myalgias, fatigue, weight loss, headache, neurocognitive deficits, psychosocial issues, and eye disease. One of the most common ophthalmic manifestations affecting Ebola survivors is uveitis. Patients may also have episcleritis, interstitial keratitis, anterior uveitis, chorioretinal lesions, or optic neuropathy. In one patient, a unilateral acute hypertensive anterior uveitis appeared 9 weeks after systemic viremia had resolved, and Ebola virus was isolated from the aqueous humor. This patient also developed iris heterochromia and uveal edema that eventually resolved (Fig 12-19). RPE cells also may be a potential reservoir for the virus. In a prospective longitudinal cohort, recurrent uveitis occurred more frequently in Ebola survivors when compared with a control population.

PREVAIL III Study Group, Sneller MC, Reilly C, Badio M, et al. A longitudinal study of Ebola sequelae in Liberia. *N Engl J Med.* 2019;380(10):924–934.

Varkey JB, Shantha JG, Crozier I, et al. Persistence of Ebola Virus in ocular fluid during convalescence. *N Engl J Med.* 2015;372(25):2423–2427. Published correction appears in *N Engl J Med.* 2015;372(25):2469.

SARS-CoV-2 and COVID-19

To date, millions of cases of COVID-19 and subsequent deaths have been reported worldwide. Systemic infection ranges from asymptomatic to severe respiratory distress and failure of multiple organ systems. In various studies, SARS-CoV-2 has been found in tears from 0%–57% of patients with the disease. The implications of viral transmission via the ocular surface have yet to be elucidated. Ophthalmic manifestations of COVID-19 are relatively rare and range from mild conjunctivitis and subconjunctival hemorrhage to retinopathy and vascular occlusions. The pathogenesis of the retinal vascular disease may be related to widespread systemic inflammation and derangements in coagulation parameters as well as direct viral infection.

COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Accessed December 7, 2022. https://coronavirus.jhu.edu/map.html

D'Alessandro E, Kawasaki A, Eandi CM. Pathogenesis of vascular retinal manifestations in COVID-19 patients: a review. *Biomedicines.* 2022;10(11):2710. doi:10.3390/biomedicines10112710

Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(180):1708–1720.

Xia J, Tong J, Liu M, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol.* 2020;92(6):589–594.

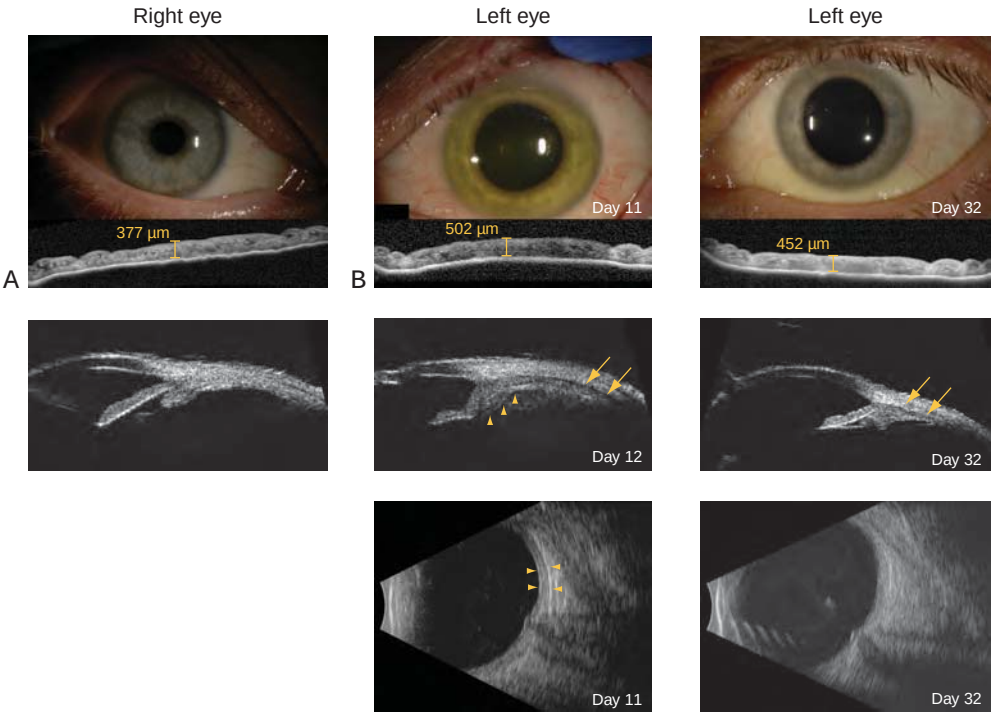

Figure 12-19 Late-onset panuveitis and iris heterochromia in an Ebola survivor. **A,** Slit-lamp photograph of right eye with corresponding anterior segment OCT at baseline. **B,** At day 11, the iris of the left eye had turned green and showed edema. **C,** By day 32, the iris had reverted to its original blue color, and the iris edema had improved. **D,** Ultrasound biomicroscopy (UBM) image shows normal ciliary body anatomy of the right eye. **E,** At day 12, UBM of the left eye shows ciliary body swelling *(arrowheads)* and supraciliary/choroidal effusion *(arrows)* consistent with progressive panuveitis, choroiditis, and evolving hypotony. **F,** Subsequent UBM shows decreased ciliary body swelling and resolution of supraciliary/choroidal effusion *(arrows)* by day 32. **G,** B-scan ultrasonography shows choroidal thickening at day 11 *(arrowheads)*. **H,** At day 32, the choroidal thickening had resolved. *(Reproduced with permission from Shantha JG, Crozier I, Varkey JB, et al. Long-term management of panuveitis and iris heterochromia in an Ebola survivor.* Ophthalmology. *2016;123(12):2626–2628.e2.)*

Other Viral Diseases

Acute anterior uveitis may also occur with other viral infections. The uveitis observed with influenza, adenovirus infection, and infectious mononucleosis is mild and transient. Synechiae and ocular damage seldom occur. Uveitis associated with adenovirus infection is usually secondary to corneal disease (see BCSC Section 8, *External Disease and Cornea).*

Fungal Uveitis

Candidiasis and aspergillosis are covered in Chapter 14. For a discussion of cryptococcosis, see Chapter 13.

Ocular Histoplasmosis Syndrome

Ocular histoplasmosis syndrome (OHS) is a multifocal chorioretinitis presumed to be caused by *Histoplasma capsulatum*. Primary infection occurs after inhalation of the fungal spores, and ocular disease likely arises from hematogenous dissemination to the choroid. OHS is usually found in *Histoplasma* endemic areas such as the Ohio and Mississippi River valleys, but it may occur in nonendemic areas as well. Most affected patients are of northern European descent, and men and women are equally at risk.

Initial choroidal infection is usually asymptomatic and subsides, leaving multiple small atrophic scars and depigmentation of the RPE *(histo spots)*. The choroiditis may disrupt Bruch membrane, choriocapillaris, and RPE, allowing proliferation of subretinal vessels and development of CNV years later. The diagnosis of OHS is suggested by the clinical triad of histo spots without vitreous cells, peripapillary pigment changes, and macular CNV. Histo spots may appear in the macula or periphery, are discrete and punched out, and are usually asymptomatic (Fig 12-20). Approximately 1.5% of patients from endemic areas exhibit typical peripheral histo spots, often first appearing during adolescence. Linear equatorial streaks are present in 5% of patients (Fig 12-21).

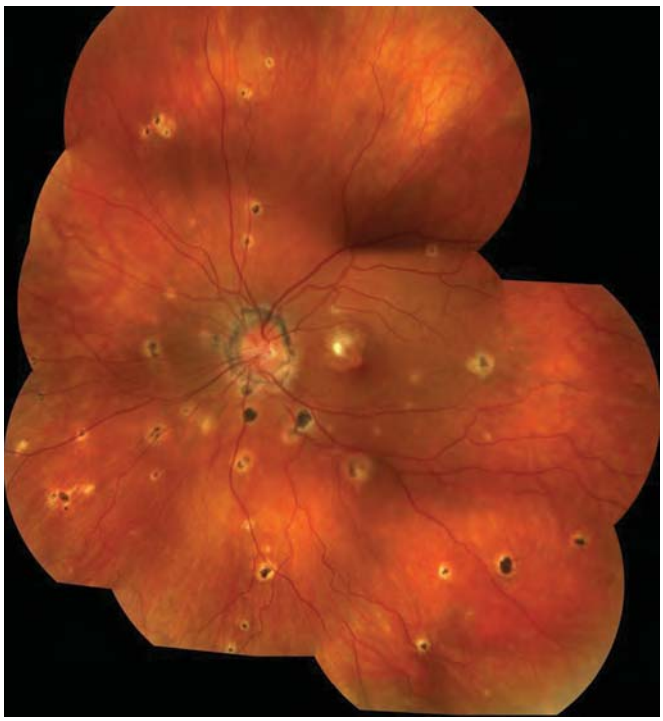

Figure 12-20 Ocular histoplasmosis syndrome. Fundus photograph montage shows peripapillary pigmentary scarring; midperipheral chorioretinal scars, or histo spots (some pigmented and fibrotic); and spontaneously regressed, nasal, juxtafoveal choroidal neovascular membrane in the absence of vitreous cells. Visual acuity was 20/25. *(Courtesy of Ramana S. Moorthy, MD.)*

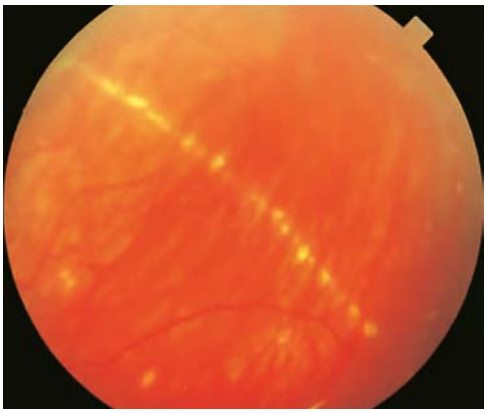

Figure 12-21 Ocular histoplasmosis syndrome. Fundus photograph shows linear equatorial streaks. *(Courtesy of E. Mitchel Opremcak, MD.)*

The early, acute granulomatous lesions of OHS are rarely seen but may be treated with oral or regional (periocular) corticosteroids. The foci of active choroiditis hypofluoresce on early FA and then hyperfluoresce in a staining pattern late in the imaging study. In contrast, areas of active CNV hyperfluoresce early and then exhibit hyperfluorescent leakage pattern in later FA.

Over time, new choroidal scars develop in more than 20% of patients; however, only 3.8% of these cases progress to CNV. When histo spots appear in the macular area, the patient has a 15% chance of developing CNV within 5 years; if no spots are observed, the probability falls to 5%.

Macular CNV is heralded by metamorphopsia and a profound reduction in central vision, which typically brings the patient to the attention of the ophthalmologist. The mean age of patients presenting with maculopathy is 41 years. Ophthalmoscopy of active neovascular lesions reveals a yellow-green subretinal membrane typically surrounded by a pigment ring. There may be associated intraretinal or subretinal fluid and subretinal hemorrhage. Massive subretinal exudation, hemorrhage, and retinal detachment can lead to subretinal fibrosis. Intravitreal vascular endothelial growth factor (VEGF) inhibitors are the primary treatment for OHS-associated macular CNV. See BCSC Section 12, *Retina and Vitreous*, for further details about VEGF inhibitors and alternative treatments for CNV, including thermal laser photocoagulation, photodynamic therapy, intravitreal corticosteroids, and submacular surgery.

The differential diagnosis for OHS includes disorders associated with CNV, such as age-related macular degeneration, myopic degeneration, angioid streaks, choroidal rupture, undifferentiated CNV, MFCPU, and punctate inner choroidopathy. Granulomatous fundus lesions (eg, toxoplasmosis, tuberculosis, coccidioidomycosis, syphilis, sarcoidosis, and toxocariasis) may mimic the scarring of OHS.

Cionni DA, Lewis SA, Petersen MR, et al. Analysis of outcomes for intravitreal bevacizumab in the treatment of choroidal neovascularization secondary to ocular histoplasmosis. *Ophthalmology*. 2012;119(2):327–332.

Diaz RI, Sigler EJ, Rafieetary MR, Calzada JI. Ocular histoplasmosis syndrome. *Surv Ophthalmol*. 2015;60(4):279–295.

Spencer WH, Chan CC, Shen DF, Rao NA. Detection of *Histoplasma capsulatum* DNA in lesions of chronic ocular histoplasmosis syndrome. *Arch Ophthalmol.* 2003;121(11): 1551–1555.

Toussaint BW, Kitchens JW, Marcus DM, et al. Intravitreal aflibercept injection for choroidal neovascularization due to presumed ocular histoplasmosis syndrome: The HANDLE Study. *Retina.* 2018;38(4):755–763.

Xu TT, Reynolds MM, Hodge DO, Smith WM. Epidemiology and clinical characteristics of presumed ocular histoplasmosis in Olmsted County, Minnesota. *Ocul Immunol Inflamm.* 2022;30(5):1039–1043.

Coccidioidomycosis

Coccidioidomycosis is a disease produced by the dimorphic soil fungus *Coccidioides immitis,* which is endemic to the San Joaquin Valley of central California, parts of the southwestern United States, and portions of Central and South America. Infection follows inhalation of dust-borne arthrospores, most commonly resulting in pulmonary infection and secondary dissemination to the central nervous system, skin, skeleton, and eyes. Approximately 40% of infected patients become symptomatic, with most presenting with a mild upper respiratory tract infection or pneumonitis approximately 3 weeks after exposure to the organism. Erythema nodosum or multiforme may appear days to weeks after the onset of symptoms. Disseminated infection is rare, occurring in fewer than 1% of patients with pulmonary coccidioidomycosis.

Ocular coccidioidomycosis is likewise uncommon, even with disseminated disease. Ocular manifestations include blepharitis, keratoconjunctivitis, phlyctenular and granulomatous conjunctivitis, episcleritis and scleritis, and cranial nerve palsies and orbital infection. Uveal involvement is rarer still. Intraocular manifestations include unilateral or bilateral granulomatous anterior uveitis, iris granulomas, and a multifocal chorioretinitis characterized by multiple discrete, yellow-white lesions usually less than 1 disc diameter located in the postequatorial fundus. These choroidal granulomas may resolve, leaving punched-out chorioretinal scars. Vitreous cellular infiltration, vascular sheathing, retinal hemorrhage, serous retinal detachment, and involvement of the optic nerve have also been reported (Fig 12-22).

In the correct clinical context, the diagnosis of coccidioidomycosis is established by seropositive results for anti-coccidioidal antibodies in the serum, cerebrospinal fluid, vitreous, and aqueous, as well as by skin testing for exposure to coccidioidin.

The Infectious Diseases Society of America recommends initiating treatment for coccidioidomycosis with an oral azole antifungal drug such as fluconazole or itraconazole. Surgical debulking of anterior chamber granulomas, pars plana vitrectomy, and intraocular injections of amphotericin and voriconazole may be required. With systemic disease, much higher doses and a longer duration of intravenous amphotericin therapy or oral voriconazole therapy may be needed. Despite aggressive treatment, visual outcomes are often poor, and enucleation may be necessary for pain and blindness.

Shields RA, Tang PH, Bodnar ZM, Smith SJ, Silva AR. Optical coherence tomography angiography highlights chorioretinal lesions in ocular coccidioidomycosis. *Ophthalmic Surg Lasers Imaging Retina.* 2019;50(3):e71–e73. doi:10.3928/23258160-20190301-14

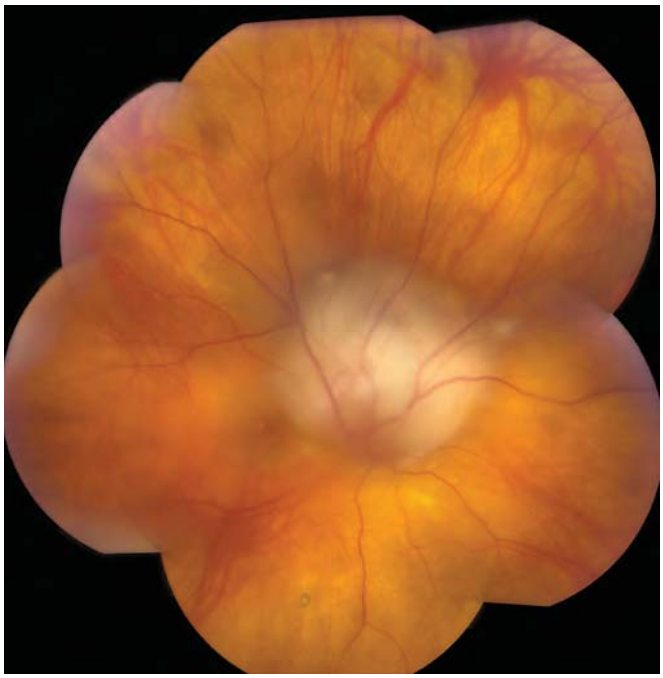

Figure 12-22 Ocular coccidioidomycosis. Fundus photograph montage shows a subretinal lesion involving the optic nerve and peripapillary retina. Associated subretinal fluid extended into the subfoveal region. *(Courtesy of Henry Wiley, MD, and Jared E. Knickelbein, MD, PhD.)*

Toomey CB, Gross A, Lee J, Spencer DB. A case of unilateral coccidioidal chorioretinitis in a patient with HIV-associated meningoencephalitis. *Case Rep Ophthalmol Med.* 2019 Oct 7;2019:1475628. doi:10.1155/2019/1475628

Vasconcelos-Santos DV, Lim JI, Rao NA. Chronic coccidioidomycosis endophthalmitis without concomitant systemic involvement: A clinicopathological case report. *Ophthalmology*. 2010;117(9):1839–1842.

Protozoal Uveitis

Toxoplasmosis

Ocular toxoplasmosis is the most common form of infectious posterior uveitis in adults and children. It is caused by the parasite *Toxoplasma gondii,* a single-cell, obligate, intracellular, apicomplexan parasite with a worldwide distribution. Felines are the definitive hosts of *T gondii;* humans and a variety of other animals serve as intermediate hosts. *T gondii* has a complex life cycle and exists in 3 major forms:

- the oocyst, or soil form (10–12 μm), which contains sporozoites
- the tachyzoite, or infectious form (4–8 μm)
- the tissue cyst, or latent form (10–200 μm), which contains as many as 3000 bradyzoites (Fig 12-23)

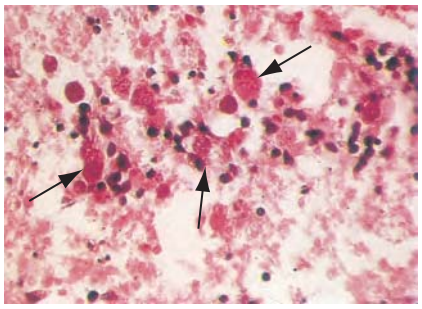

Figure 12-23 Ocular toxoplasmosis. Histologic examination of *Toxoplasma gondii* infection of the retina. Note the cysts *(arrows)* in the necrotic retina.

Transmission of *T gondii* to humans and other animals may occur with all 3 forms of the parasite through a variety of vectors. Tachyzoites, the proliferative form of the parasite, are found in the circulatory system and may invade nearly all host tissues. In an immunocompetent host, tachyzoite proliferation eventually stops. However, some microorganisms may persist as dormant bradyzoites within intercellular tissue cysts (see Fig 12-23).

The reported seropositivity rates of toxoplasmosis among healthy adults vary considerably worldwide. The CDC estimates that 11% of the US population aged 6 years and older is infected with *T gondii.* Of that group, 2% may develop ocular toxoplasmosis. In contrast, an estimated 80% of the population in southern Brazil is infected with *T gondii,* and up to 18% of these individuals may develop eye disease. Some studies show a greater genotypic heterogeneity of parasites in Brazil than in North America. Such differences may contribute to variance in disease severity and ocular involvement in different regions of the world.

Human infection by *T gondii* may be either congenital or acquired. The principal modes of transmission include

- ingestion of undercooked infected meat containing tissue cysts
- ingestion of contaminated water, fruit, or vegetables with oocysts
- contact with cat feces, cat litter, or soil containing oocysts
- primary infection during pregnancy resulting in transplacental transmission
- blood transfusion or organ transplantation

Data collected from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) showed an age-adjusted seroprevalence of *T gondii* of 9.1% among women of childbearing age (15–44 years) in the United States. Thus, most women of childbearing age in the United States are at risk for primary *T gondii* infection. The American Academy of Pediatrics estimates that the incidence of primary infection during pregnancy in the United States is approximately 0.2–1.1 per 1000 pregnant women, translating to 800–4400 women with acute *T gondi* infection among the 4 million annual pregnancies in the country.

Overall, 40% of primary maternal infections result in congenital infection, with transplacental transmission highest during the third trimester. The risk of severe disease developing in the fetus is inversely proportional to gestational age. Disease acquired early in pregnancy may result in spontaneous abortion, stillbirth, or severe congenital disease,

whereas disease acquired later in gestation may produce latent infection in an asymptomatic, healthy-appearing infant. Chronic or recurrent maternal infection during pregnancy probably does not confer a major risk of congenital toxoplasmosis because maternal immunity protects against fetal transmission; however, congenital toxoplasmosis may occur in an immune pregnant mother reinfected with a new, more virulent strain.

Centers for Disease Control and Prevention, Division of Parasitic Diseases and Malaria. Toxoplasmosis. Accessed September 8, 2022. https://www.cdc.gov/dpdx/toxoplasmosis/

Furtado JM, Winthrop KL, Butler NJ, Smith JR. Ocular toxoplasmosis I: parasitology, epidemiology and public health. *Clin Exp Ophthalmol.* 2013;41(1):82–94.

Presentation

The classic presentation of congenital toxoplasmosis, which includes retinochoroiditis, hydrocephalus or microcephaly, intracranial calcifications, and cognitive impairment (Sabin's tetrad), occurs in fewer than 10% of infected children. The most common abnormality in patients with congenital toxoplasmosis is retinochoroidal lesions, found in up to 80% of cases. Lesions are bilateral in approximately 85% of affected individuals and tend to occur in the posterior pole and macula (Fig 12-24). Posterior segment involvement may be subclinical and chronic. As many as 85% of infected children develop retinochoroiditis after a mean of 3.7 years, and 25% of these become blind in one or both eyes. For newborns with congenital toxoplasmosis during the first year of life, most experts recommend antiparasitic therapy to reduce disease burden, regardless of the presence of ocular and/or systemic signs.

Although toxoplasmosis after infancy was previously considered reactivation of congenital disease, it is now recognized that ocular toxoplasmosis in children and adults may represent newly acquired infection in a substantial proportion of cases. In one study, acquired postnatal infection accounted for up to two-thirds of cases of ocular toxoplasmosis.

Depending on the location of the retinochoroidal lesion, presenting symptoms of acquired toxoplasmosis frequently include unilateral blurred or hazy vision and floaters. A mild to moderate granulomatous anterior uveitis is often observed, and up to 20% of patients have acutely elevated IOP at presentation. Classically, ocular toxoplasmosis

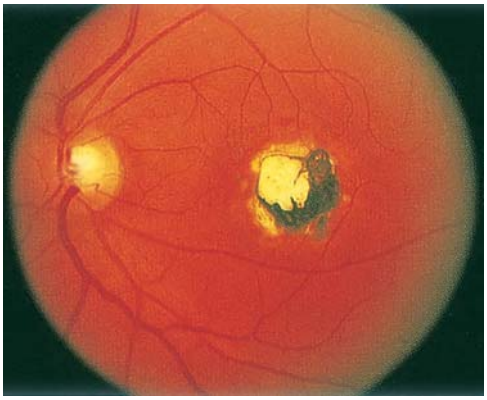

Figure 12-24 Congenital toxoplasmosis. Fundus photograph of quiescent, partially pigmented congenital toxoplasmic macular scar. This patient has 20/400 visual acuity. *(Courtesy of John D. Sheppard Jr, MD.)*

appears as a focal, white retinochoroiditis often adjacent to a pigmented retinochoroidal scar (Fig 12-25), with moderate overlying vitreous inflammation ("headlight in the fog") (Fig 12-26). In the absence of a retinochoroidal scar, recently acquired disease often presents as a focal retinochoroiditis (Fig 12-27). Retinochoroiditis lesions occur more commonly in the posterior pole, but they are occasionally found immediately adjacent to or directly involving the optic nerve, where they may be mistaken for optic neuritis. Retinal vessels in the vicinity of an active lesion may show perivasculitis with diffuse venous sheathing and segmental arterial plaques (previously known as Kyrieleis arteriolitis). Vascular occlusions may also be present. Additional ocular complications include cataract, persistent vitreous opacities, macular edema, retinal detachment, epiretinal membranes, optic atrophy, and CNV.

In immunocompromised and older patients, retinochoroiditis may present with atypical findings, including large, multiple, and/or bilateral lesions with or without associated retinochoroidal scars. This more severe clinical picture can also occur in patients who receive corticosteroids without concomitant antiparasitic therapy (Fig 12-28). Ocular

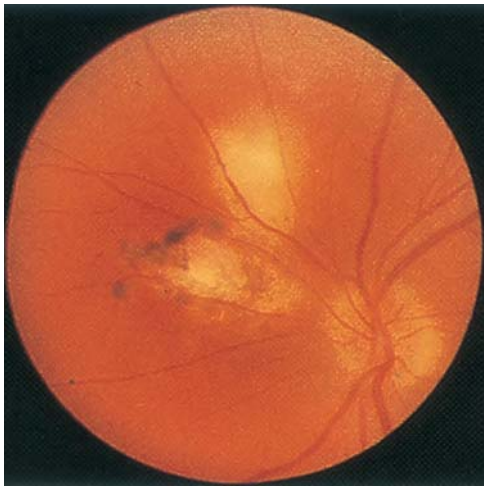

Figure 12-25 Ocular toxoplasmosis. Fundus photograph shows active retinochoroiditis adjacent to a partially pigmented retinochoroidal scar.

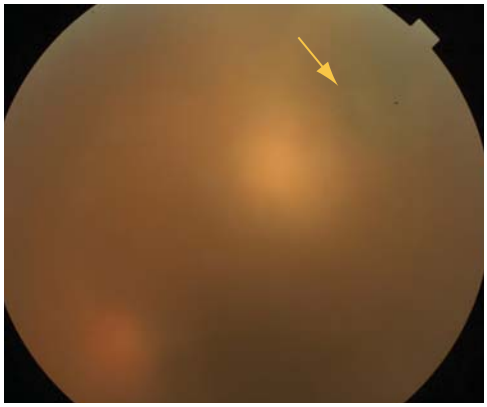

Figure 12-26 Ocular toxoplasmosis. Fundus photograph shows focal retinitis adjacent to a pigmented scar *(arrow)* with dense overlying vitritis, producing a "headlight in the fog" appearance. *(Courtesy of Emillio M. Dodds, MD.)*

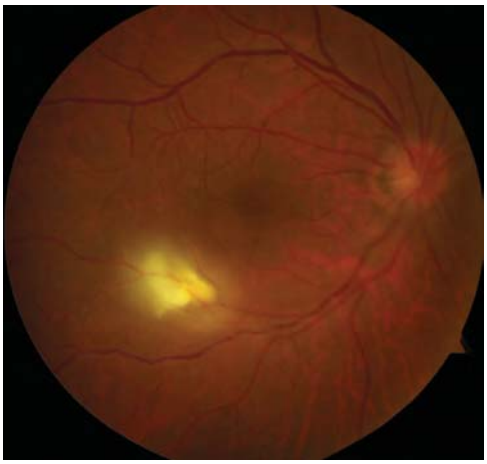

Figure 12-27 Ocular toxoplasmosis. Fundus photograph shows toxoplasmic retinochoroiditis in the absence of a previous retinochoroidal scar. *(Originally published in the Retina Image Bank website. Gregg T. Kokame, MD, and James C. Lai, MD, Retina Consultants of Hawaii. Photograph by Jaclyn Pisano, Retina Consultants of Hawaii. Retina Image Bank; 2012. Image number 1346. © American Society of Retina Specialists.)*

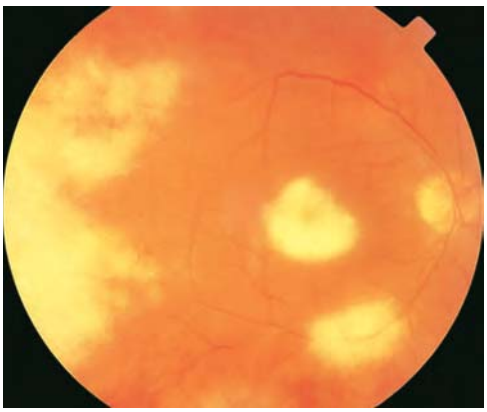

Figure 12-28 Ocular toxoplasmosis. Fundus photograph shows widespread retinal necrosis and multiple patches of retinochoroiditis after periocular corticosteroid injection. *(Courtesy of E. Mitchel Opremcak, MD.)*

toxoplasmosis may simulate herpetic ARN. Other atypical presentations include neuroretinitis, unilateral pigmentary retinopathy simulating retinitis pigmentosa, and other forms of intraocular inflammation in the absence of retinochoroiditis, as well as punctate outer retinal toxoplasmosis (PORT). Characteristics of PORT include small, multifocal lesions at the level of the outer retina, with exudation to the subretinal space and scant overlying vitreal inflammation (Fig 12-29).

Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. *Clin Exp Ophthalmol.* 2013;41(1):95–108.

Goh EJH, Putera I, La Distia Nora R, et al. Ocular toxoplasmosis. *Ocul Immunol Inflamm.* 2022 Sep 12:1–20. Epub ahead of print. doi:10.1080/09273948.2022.2117705

Jones JL, Bonetti V, Holland GN, et al. Ocular toxoplasmosis in the United States: recent and remote infections. *Clin Infect Dis.* 2015;60(2):271–273.

Diagnosis

In most cases, toxoplasmic retinochoroiditis is clinically diagnosed on the basis of the characteristic fundus lesion. Positive serologic testing for anti–*T gondii* IgG or IgM confirms

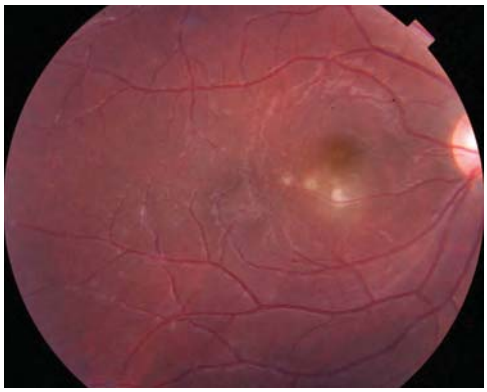

Figure 12-29 Punctate outer retinal toxoplasmosis. Fundus photograph shows deep retinal lesions. *(Courtesy of Emilio M. Dodds, MD.)*

exposure to the parasite. IgG antibodies appear after the first 2 weeks of infection, typically remain detectable for life at variable levels, and cross the placenta. In contrast, IgM antibodies increase in number early during the acute phase of the infection, typically remain detectable for less than 1 year, and do not cross the placenta. In the appropriate clinical context, the presence of anti–*T gondii* IgG antibodies supports the diagnosis of toxoplasmic retinochoroiditis. The presence of IgM confirms congenital infection in newborns but indicates newly acquired disease in adults. In cases of diagnostic uncertainty, PCR testing of aqueous humor and vitreous fluid may be performed.

Greigert V, Di Foggia E, Filisetti D, et al. When biology supports clinical diagnosis: review of techniques to diagnose ocular toxoplasmosis. *Br J Ophthalmol.* 2019;103(7):1008–1012.

Maldonado YA, Read JS; AAP Committee on Infectious Diseases. Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. *Pediatrics*. 2017;139(2): e20163860. doi:10.1542/peds.2016-3860

Treatment

Ocular toxoplasmosis is a progressive and recurrent disease. New lesions may occur at the margins of old scars as well as elsewhere in the fundus, and toxoplasmic cysts may be present in a normal-appearing retina. In the immunocompetent patient, the disease may have a self-limiting course. Without treatment, the borders of the lesions become sharper and less edematous over a 6- to 8-week period, and RPE hyperplasia occurs gradually over a period of months. In the immunocompromised patient, the disease is often more severe and progressive.

Although numerous medications may be used to treat toxoplasmosis, there is no consensus regarding the most efficacious regimen. Most antibiotics have efficacy against the active tachyzoite only, not the tissue-encysted bradyzoite. In immunocompetent patients, firm evidence showing that antimicrobial therapy alters the natural history of toxoplasmic retinochoroiditis is limited. Thus, in this population, some clinicians may elect to observe small lesions in the retinal periphery that are not associated with a notable decrease in vision or vitritis.

Other clinicians treat virtually all patients in an effort to reduce the number of subsequent recurrences and minimize structural complications associated with intraocular

inflammation. Treatment may also shorten the duration of parasitic replication, accelerating cicatrization and ultimately reducing retinochoroidal scars.

In addition, treatment is indicated for the following populations: immunocompromised patients (ie, those with HIV/AIDS, with neoplastic disease, or receiving IMT), patients with congenital toxoplasmosis, and pregnant women with recently acquired disease.

Other relative treatment indications include

- lesions threatening the optic nerve, fovea, or major vasculature
- decreased vision
- lesions associated with moderate to severe vitreous inflammation
- lesions greater than 1 disc diameter
- persistence of disease for more than 1 month
- presence of multiple active lesions

Table 12-2 summarizes treatment options for toxoplasmosis. Many ophthalmologists use trimethoprim-sulfamethoxazole (160 mg/800 mg, 2 times/day) because of its accessibility, simplicity of administration, and cost. Intravitreal clindamycin (1 mg/0.1 mL) with or without periocular dexamethasone 400 mg/0.1 mL may also be injected as an off-label use, either in combination with systemic therapy or as monotherapy in patients who do not tolerate systemic therapy (see Appendix B).

In immunocompetent patients, systemic corticosteroids (approximately 0.25–0.75 mg/kg, typically not more than 60 mg/day) may be considered after 48 hours of antimicrobial therapy. The use of systemic corticosteroids without appropriate antimicrobial coverage or the use of long-acting periocular and intravitreal corticosteroid formulations such as triamcinolone acetonide is contraindicated because of the risk of potentiating a severe retinitis (see Fig 12-28) that may progress to panophthalmitis, blindness, or even loss of the eye. However, topical corticosteroids can be used liberally in the presence of prominent anterior segment inflammation. Systemic corticosteroid treatment may be used for 3–5 weeks or until inflammation begins to subside and the retinal lesion shows signs of early cicatrization. Antimicrobial coverage should be continued for the entire period of systemic corticosteroid use.

In cases of newly acquired toxoplasmosis during pregnancy, treatment is given to prevent infection of the fetus or limit fetal damage if infection has already occurred, as well as to limit the destructive sequelae of intraocular disease in the mother. Spiramycin (treatment dose, 400 mg 3 times/day) reduces the rate of tachyzoite transmission to the fetus and may be used safely without major risk of teratogenicity. This drug has limited availability in the United States, but it can be directly obtained from the US Food and Drug Administration. Substitutions for spiramycin include azithromycin, clindamycin, and atovaquone. Sulfonamides may be used safely in the first 2 trimesters of pregnancy. Alternatively, intravitreal clindamycin and short-acting periocular corticosteroids (eg, dexamethasone) may be used in women who are pregnant to reduce adverse effects of systemic treatment (see preceding paragraphs and Appendix B).

Patients with HIV/AIDS and toxoplasmosis require extended systemic treatment given the frequent association of ocular disease with cerebral involvement (56% of cases)

Table 12-2 Systemic Treatment of Toxoplasmosis

Medication	Dosing	Indication	Adverse Effects
Pyrimethamine, sulfadiazine, and folinic acid	Pyrimethamine: loading dose, 50–100 mg; treatment dose, 25–50 mg/day for 4–8 weeks; sulfadiazine: treatment dose, 1 g, 4 times/day; and folinic acid: 5–10 mg/day	Classic triple therapy	Pyrimethamine: myelosuppression, leukopenia, thrombocytopenia Sulfa compounds: rash, gastrointestinal intolerance, crystalluria, kidney stones, and Stevens-Johnson syndrome Monitor with complete blood count every 2 weeks
Clindamycin	300 mg, 4 times/day	Used alone or as a substitution for sulfa medication in triple therapy	Pseudomembranous colitis
Azithromycin	500 mg daily or 500 mg ×1 day, then 250 mg daily	Used alone or in place of other medications	
Atovaquone	750 mg, 2–4 times/day	Used alone or in place of other medications	
Trimethoprim-sulfamethoxazole	160 mg/800 mg, 2 times/day	Used alone	Stevens-Johnson syndrome
Pyrimethamine, sulfadiazine, and folinic acid	Pyrimethamine: 2 mg/kg for 1 day, then 1 mg/kg daily; sulfadiazine: 50 mg/kg 2 times/day; and folinic acid, 7.5 mg/day	Congenital toxoplasmosis	See classic triple therapy
Spiramycin	400 mg 3 times/day	Used in pregnancy	

and the frequency of recurrent ocular disease when anti-*Toxoplasma* medication is discontinued. The best regimen for secondary prophylaxis is undetermined; however, atovaquone acts synergistically with pyrimethamine and sulfadiazine and thus may be useful for reducing the dose and toxicity of these drugs in the treatment of patients with AIDS and toxoplasmosis. The management of ocular toxoplasmosis in association with HIV/AIDS is also covered in Chapter 13.

Among patients with recurrent toxoplasmic retinochoroiditis, long-term intermittent trimethoprim-sulfamethoxazole treatment (160 mg/800 mg 3 times per week) was shown to decrease the risk of reactivation over a 20-month period. Similarly, the utility of prophylactic antimicrobial treatment shortly before and after intraocular surgery in patients with

inactive *Toxoplasma* scars—particularly scars close to the optic disc or fovea—was raised by a report describing an association between cataract surgery and increased risk of reactivation of otherwise inactive toxoplasmic retinochoroiditis. However, there is no consensus regarding this treatment approach or the optimal antibiotic regimen in this clinical situation.

Feliciano-Alfonso JE, Muñoz-Ortiz J, Marín-Noriega MA, et al. Safety and efficacy of different antibiotic regimens in patients with ocular toxoplasmosis: systematic review and meta-analysis. *Syst Rev.* 2021;10(1):206. doi:10.1186/s13643-021-01758-7

Fernandes Felix JP, Cavalcanti Lira RP, Grupenmacher AT, et al. Long-term results of trimethoprim-sulfamethoxazole versus placebo to reduce the risk of recurrent *Toxoplasma gondii* retinochoroiditis. *Am J Ophthalmol.* 2020;213:195–202.

Kim SJ, Scott IU, Brown GC, et al. Interventions for toxoplasma retinochoroiditis: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2013;120(2):371–378.

Soheilian M, Ramezani A, Azimzadeh A, et al. Randomized trial of intravitreal clindamycin and dexamethasone versus pyrimethamine, sulfadiazine, and prednisolone in treatment of ocular toxoplasmosis. *Ophthalmology*. 2011;118(1):134–141.

Helminthic Uveitis

Helminths (derived from the Greek word for *worms*) are multicellular organisms that can be free living or parasitic. Approximately 280 species are recognized.

Toxocariasis

Ocular toxocariasis (OT) is a zoonotic infection caused by *Toxocara canis* and *Toxocara cati.* Dogs and cats, the definitive hosts of the roundworms, pass eggs via their feces into the environment (often into the soil). According to the CDC, 30% of dogs younger than 6 months are infected with *T canis,* and 25% of cats are infected with *T cati.* Transmission to humans occurs through ingestion of viable *T canis* eggs in soil or food or via the fecal–oral route. Risk factors include exposure to playgrounds, sandboxes, kittens, and puppies, as well as the pica eating disorder. In rare cases, humans may acquire the infection from undercooked meat.

NHANES data from 2011–2014 suggested an overall *Toxocara* seroprevalence of 5.1% in the United States. In children, the rate of antibody positivity has been associated with lack of health insurance. In a large population treated for uveitis at tertiary care centers in northern California, the prevalence of OT was recently estimated to be 1%.

In humans, *Toxocara* organisms grow in the small intestine, enter the portal circulation, and disseminate hematogenously to various parts of the body, including the liver, heart, lungs, brains, or muscles (known as *visceral toxocariasis,* or *VT*) as well as the eyes. The larvae do not undergo further development in the human but rather cause a local inflammatory reaction. Ova are not shed in the gastrointestinal tract, so stool analysis for larvae is not helpful for diagnosis.

VT usually affects children younger than 3 years. Symptoms may include fever, coughing, enlarged liver, pneumonia, and meningoencephalitis. Peripheral eosinophilia may also be present. OT is found in older children, typically without substantial eosinophilia. OT and VT rarely present simultaneously.

Ophthalmic presentations include a chronic endophthalmitis (25% of OT cases), a posterior pole granuloma (25%; Fig 12-30), or a peripheral granuloma (50%), sometimes with fibrous bands in the vitreous that may extend posteriorly (Fig 12-31). Any of these presentations may produce leukocoria. Uncommon variants include unilateral pars planitis with diffuse peripheral inflammatory exudates, granulomas involving the optic nerve, and diffuse unilateral subacute neuroretinitis. Table 12-3 summarizes the patterns of manifestation of ocular toxocariasis.

OT is principally a clinical diagnosis. Serologic testing may suggest prior exposure, although patients with OT may also have negative serology results. Antibody testing of ocular fluids may be positive despite negative serology results. PCR testing is not readily available for OT; however, vitrectomy specimens have yielded larvae (Fig 12-32). In cases with media opacity, B-scan ultrasonography and/or computed tomography (CT) may show vitreous membranes and/or tractional detachment and may confirm the absence of calcium, a potential finding in retinoblastoma.

The differential diagnosis of OT includes retinoblastoma, infectious endophthalmitis, Coats disease, familial exudative vitreoretinopathy, persistent fetal vasculature, toxoplasmosis, undifferentiated intermediate uveitis/pars planitis, retinopathy of prematurity, combined hamartoma of the retina and RPE, and diffuse unilateral subacute neuroretinitis.

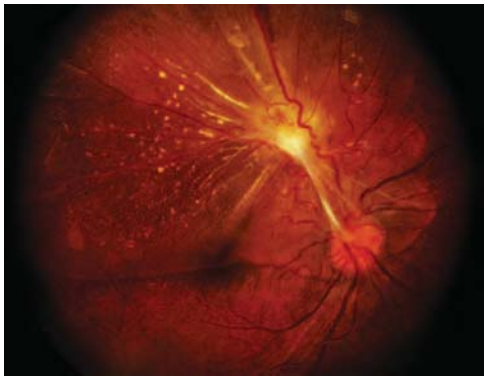

Figure 12-30 Ocular toxocariasis. Fundus photograph shows *Toxocara* posterior pole granuloma causing macular pucker. *(Originally published in the Retina Image Bank website. Photograph by H. Michael Lambert, MD. Retina Image Bank; 2015. Image number 23430. © American Society of Retina Specialists.)*

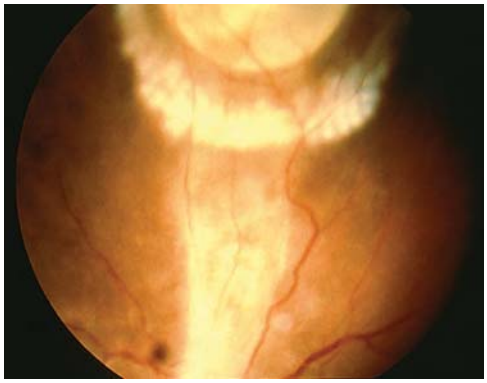

Figure 12-31 Ocular toxocariasis. Fundus photograph shows *Toxocara* peripheral granuloma. *(Originally published in the Retina Image Bank website. Thomas M. Aaberg, MD, and Thomas M. Aaberg Jr; image number 3508. © American Society of Retina Specialists.)*

Table 12-3 Patterns of Manifestation of Ocular Toxocariasis

Syndrome	Age at Onset, y	Characteristic Lesion
Chronic endophthalmitis	2–9	Chronic unilateral uveitis, cloudy vitreous, cyclitic membrane
Localized granuloma	6–14	Occurs in the macula and peripapillary region Solitary, white, retinal elevation; minimal reaction; 1–2 disc diameter
Peripheral granuloma	6–40	Peripheral hemispheric masses with dense connective tissue strands in the vitreous cavity that may connect to the disc Rarely bilateral

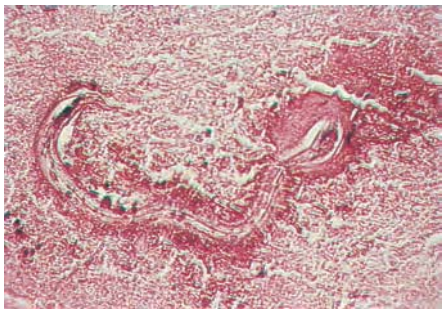

Figure 12-32 Ocular toxocariasis. Histologic examination of an eosinophilic vitreous abscess. The organism is in the center of the abscess.

The migrating larvae of other helminths such as *Baylisascaris procyonis* may also simulate OT. In contrast to children with OT, children with retinoblastoma are typically younger, lack substantial inflammation, and show lesion growth.

Patients with VT are usually treated with oral albendazole. For OT, the use of anthelminthic therapy is not established but may be considered if the larvae appear active. Typically, local and systemic corticosteroids are used to reduce inflammation and minimize structural complications, which may later be amenable to vitreoretinal surgical techniques.

Ahn SJ, Woo SJ, Jin Y, et al. Clinical features and course of ocular toxocariasis in adults. *PLoS Negl Trop Dis.* 2014;8(6):e2938. doi:10.1371/journal.pntd.0002938

Arevalo JF, Espinoza JV, Arevalo FA. Ocular toxocariasis. *J Pediatr Ophthalmol Strabismus.* 2013;50(2):76–86.

Centers for Disease Control and Prevention. Ocular toxocariasis—United States, 2009–2010. *MMWR.* 2011;60(22):734–736.

Farmer A, Beltran T, Choi YS. Prevalence of *Toxocara* species infection in the U.S.: results from the National Health and Nutrition Examination Survey, 2011–2014. *PLoS Negl Trop Dis.* 2017;11(7):e0005818. doi:10.1371/journal.pntd.0005818

Li S, Sun L, Liu C, et al. Clinical features of ocular toxocariasis: a comparison between ultra-wide-field and conventional camera imaging. *Eye (Lond).* 2021;35(10):2855–2863.

Ma G, Holland CV, Wang T, et al. Human toxocariasis. *Lancet Infect Dis.* 2018;18(1):e14–e24. doi:10.1016/S1473-3099(17)30331-6

Woodhall D, Starr MC, Montgomery SP, et al. Ocular toxocariasis: epidemiologic, anatomic, and therapeutic variations based on a survey of ophthalmic subspecialists. *Ophthalmology.* 2012;119(6):1211–1217.

Cysticercosis

Cysticercosis is the most common ocular tapeworm infection. Human infection is caused by *Cysticercus cellulosae,* the larval stage of the cestode *Taenia solium,* which is endemic to Mexico, Africa, Southeast Asia, eastern Europe, Central and South America, and India. Humans acquire the disease via fecal–oral transmission or by consuming undercooked infected pork. The eggs mature into larvae, penetrate the intestinal mucosa, and spread hematogenously to the eye via the posterior ciliary arteries.

Ocular cysticercosis usually affects individuals between the ages of 10 and 30 years, without sex predilection. Cysticercosis may affect any structure of the eye, orbit, or adnexa, but it most frequently involves the subretinal space (Fig 12-33). Larvae may perforate the retina, gaining access to the vitreous cavity (Fig 12-34). Other presentations include a subconjunctival or eyelid nodule.

Figure 12-33 Ocular cysticercosis. Fundus photograph shows a subretinal lesion. *(Courtesy of Preema Abraham, MD, and the Retina Image Bank. © American Society of Retina Specialists.)*

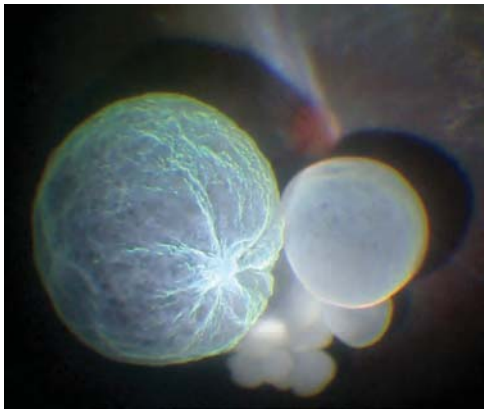

Figure 12-34 Ocular cysticercosis. Fundus photograph of multiple intravitreal cysts. *(Courtesy of Vishal Agrawal, MD, and the Retina Image Bank. © American Society of Retina Specialists.)*

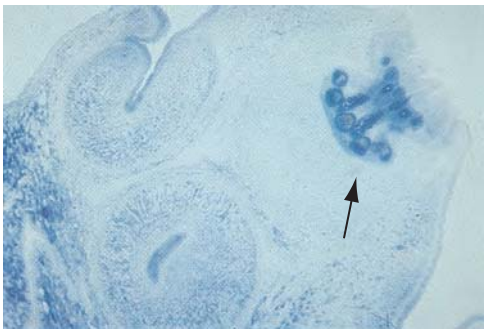

Figure 12-35 Cysticercosis. Histologic examination shows the protoscolex, or head, of the larva *(arrow).*

Patients may be asymptomatic with relatively good vision or may report floaters, mobile foreign body sensations, ocular pain, photophobia, redness, and decreased vision. Larvae are observed in the vitreous or subretinal space in up to 46% of infected patients. A globular translucent cyst is seen, with an invaginated or evaginated head, or scolex, that undulates in response to the examining light (Fig 12-35; see also Fig 12-34). Exudative, rhegmatogenous, or tractional retinal detachment may occur. In patients with neural cysticercosis, CT may reveal intracerebral calcification or hydrocephalus.

The differential diagnosis for cysticercosis includes conditions associated with leukocoria (retinoblastoma, Coats disease, retinopathy of prematurity, persistent fetal vasculature, toxocariasis, and retinal detachment) and diffuse unilateral subacute neuroretinitis.

Larvae death provokes panuveitis. Laser photocoagulation alone may also provoke severe inflammation. Hence, early removal of intraocular larvae, often via vitreoretinal surgical techniques with perioperative systemic corticosteroids, is advocated. Anthelminthic drugs plus systemic corticosteroids may be used for extraocular disease.

Pujari A, Bhaskaran K, Modaboyina S, et al. Cysticercosis in ophthalmology. *Surv Ophthalmol.* 2022;67(2):544–569.

Sheemar A, Gaur N, Thakur PS, et al. Optical coherence tomography features of ocular cysticercosis: a review of literature with observer variation. *Ophthalmic Surg Lasers Imaging Retina.* 2022;53(8):446–454.

Diffuse Unilateral Subacute Neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) is an uncommon but important disease likely caused by infection with a nematode that migrates through the subretinal space. The mean age of affected patients is 14 years (range, 11–65 years). Evidence to date suggests that DUSN can be caused by 2 types of nematodes that differ in size and geographic region. The smaller worm, measuring 400–1000 μm in length, has been proposed to be either *Ancylostoma caninum* (the dog hookworm) or *T canis,* although there are no reports of the latter being isolated from an eye with DUSN. The larger worm is believed to be *Baylisascaris procyonis* (the raccoon roundworm), which measures 1500–2000 μm in length and has been found in the northern midwestern United States and Canada. The disease has also been reported outside North America.

The clinical course of DUSN is characterized by the insidious unilateral loss of vision from recurrent episodes of focal, multifocal, or diffuse inflammation of the retina, RPE, and optic nerve. The early stages of the disease are marked by moderate to severe vitritis; optic disc edema; and multiple, focal, gray-white lesions in the postequatorial fundus that range from 1200 μm to 1500 μm in size (Fig 12-36A). These lesions are transient and may be associated with overlying exudative retinal detachment. The worm may be visualized in the subretinal space, especially in the early stages (Fig 12-36B). Diffuse outer retinal disruption may be observed on OCT (Fig 12-36C). Differential diagnosis at this phase of the disease includes sarcoidosis-associated uveitis, MFCPU, acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent white dot syndrome, serpiginous choroiditis, Behçet disease, toxocariasis, OHS, nonspecific optic neuritis, and papillitis. Later disease stages are typified by retinal arteriolar narrowing, optic atrophy, diffuse pigment epithelial degeneration, and abnormal electroretinographic results (Fig 12-37). These findings may be confused with those of posttraumatic chorioretinopathy, occlusive vascular disease, toxic retinopathy, and retinitis pigmentosa. Rare bilateral cases have been reported, and cases of DUSN have also been associated with neurologic disease (neural larva migrans).

The diagnosis is based on clinical findings and is most strongly supported by the observation of a worm in the subretinal space (Video 12-1). Results of systemic and laboratory evaluations are typically negative for patients with DUSN.

VIDEO 12-1 How to find a live worm in diffuse unilateral subacute neuroretinitis.
Courtesy of Carlos A. A. Garcia, MD.

In patients with DUSN, medical therapy with corticosteroids alone may only transiently control inflammation. Direct laser photocoagulation of the worm in the early phases of the disease does not appear to be inflammatory and may be highly effective in halting progression of the disease (Fig 12-38). Successful treatment and immobilization of the subretinal worm have been reported with oral thiabendazole (22 mg/kg twice daily for 2–4 days with a maximum dose of 3 g) or albendazole (200 mg twice daily for 30 days), which may be a better-tolerated alternative. If the worm cannot be visualized, patients may undergo a course of anthelminthic therapy to increase the chance of identifying and treating the nematode. If inflammation does not improve after laser therapy alone, anthelminthic therapy may be used to treat a presumed second undetected nematode.

de Amorim Garcia Filho CA, Bezerra Gomes AH, de A Garcia Soares AC, de Amorim Garcia CA. Clinical features of 121 patients with diffuse unilateral subacute neuroretinitis. *Am J Ophthalmol.* 2012;153(4):743–749.

Mazzeo TJMM, Dos Santos Motta MM, Curi ALL. Diffuse unilateral subacute neuroretinitis: review article. *J Ophthalmic Inflamm Infect.* 2019;9(1):23. doi:10.1186/s12348-019-0191-x

Souza EC, Casella AM, Nakashima Y, Monteiro ML. Clinical features and outcomes of patients with diffuse unilateral subacute neuroretinitis treated with oral albendazole. *Am J Ophthalmol.* 2005;140(3):437–445. Published correction appears in *Am J Ophthalmol.* 2006;141(4):795–796.

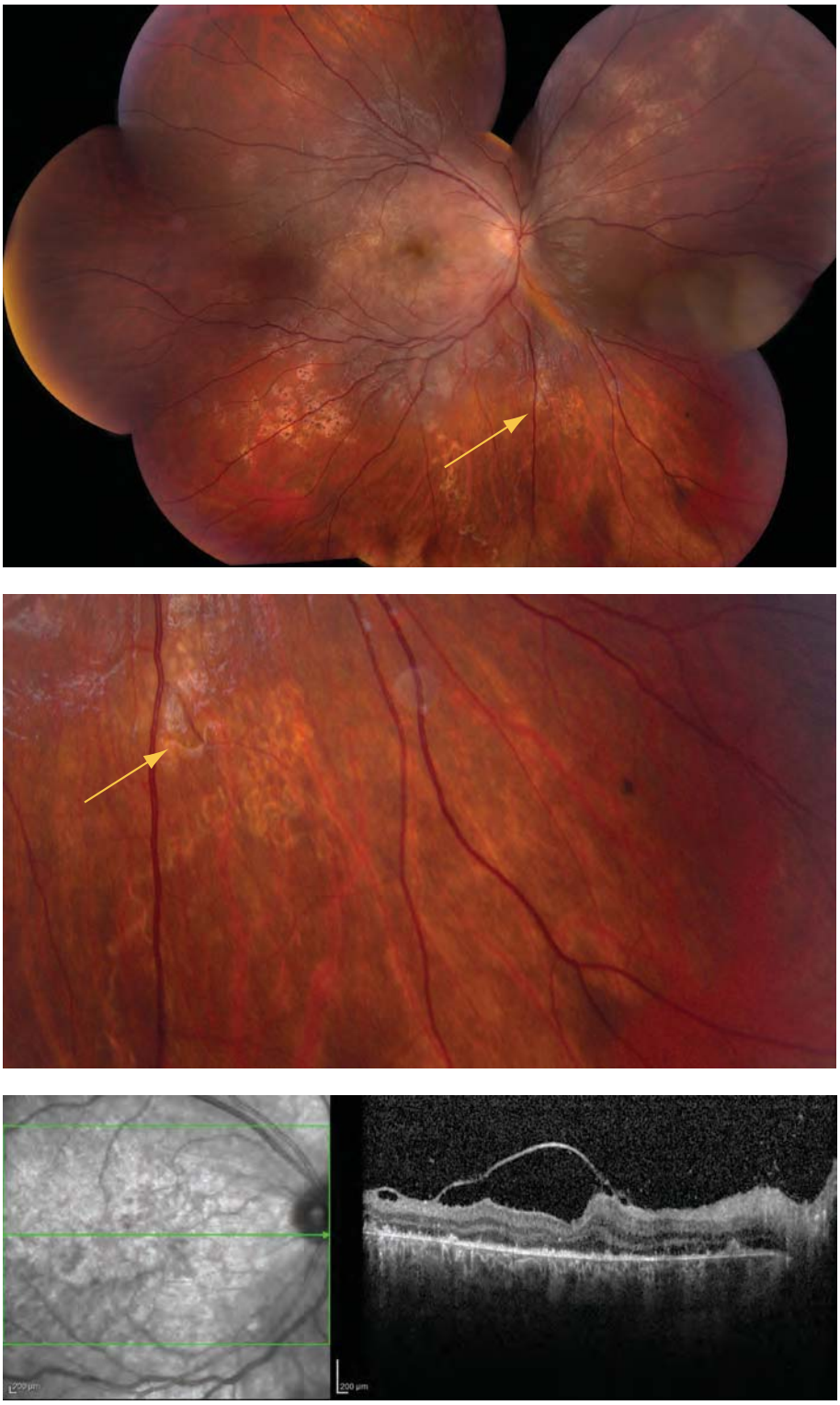

Figure 12-36 Diffuse unilateral subacute neuroretinitis. **A,** Fundus photograph montage shows diffuse whitening in the macula with discrete whiplike deep tracks in the periphery *(arrow)*. **B,** The nematode is moving in the subretinal space *(arrow)*. **C,** OCT through the fovea shows traction from preretinal membranes and irregular disruption of outer retinal structures. *(Courtesy of Wendy M. Smith, MD.)*

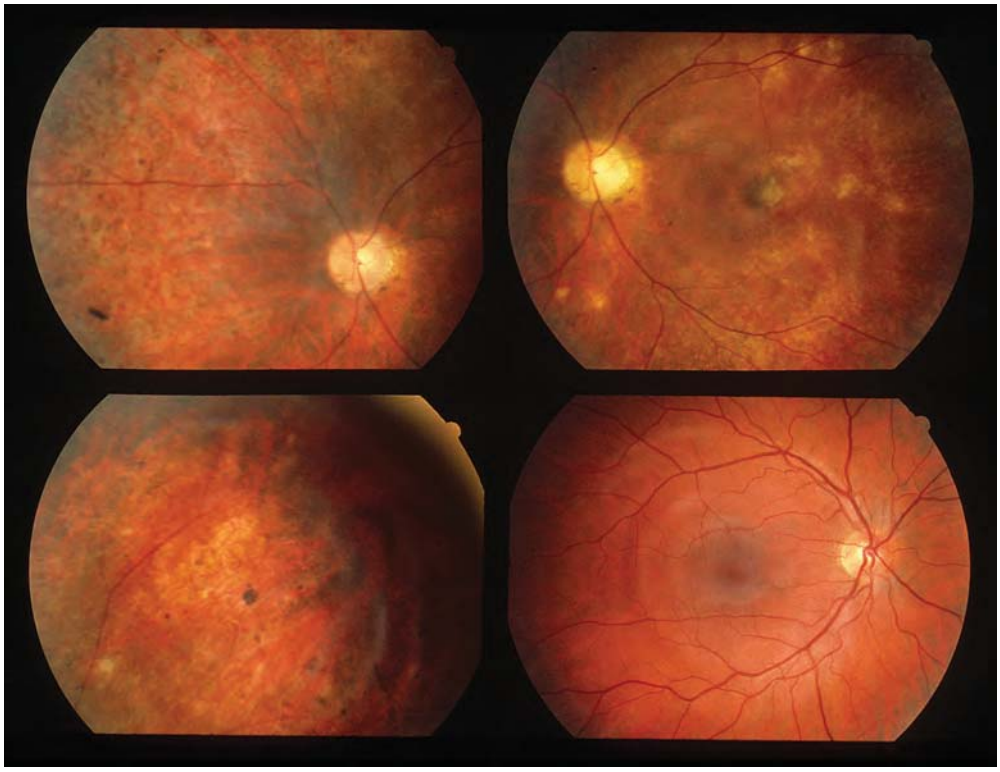

Figure 12-37 Diffuse unilateral subacute neuroretinitis. Fundus photographs from a 23-year-old man. *(Originally published in the Retina Image Bank website. Howard Schatz, MD. Retina Image Bank; 2013. Image number 6039. © American Society of Retina Specialists.)*

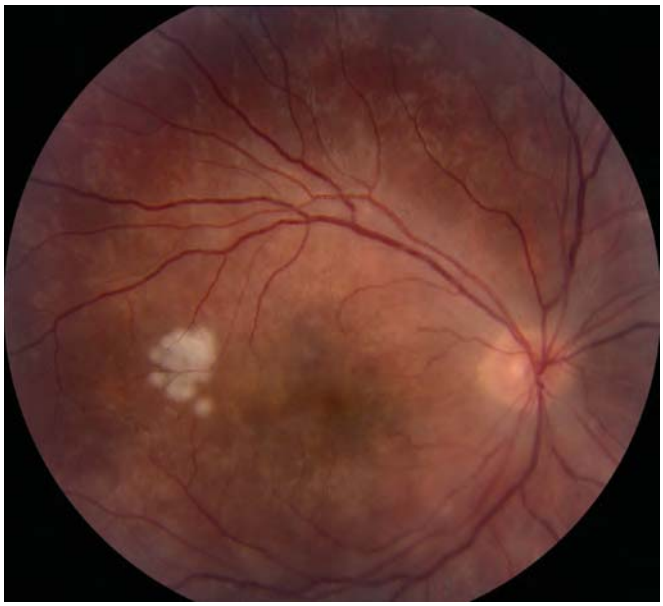

Figure 12-38 Diffuse unilateral subacute neuroretinitis. Fundus photograph from the same patient shown in Figure 12-36 after the nematode was visualized and treated with laser photocoagulation. *(Courtesy of Wendy M. Smith, MD.)*

Onchocerciasis

Onchocerciasis, commonly known as *River Blindness,* is endemic in many areas of sub-Saharan Africa and in isolated foci in Central and South America. Worldwide, at least 25 million people are infected, including almost 300,000 who are blind and 800,000 who are visually impaired. Humans are the only host for the *Onchocerca volvulus* parasite. As the vector, female black flies that breed near rivers bite an infected human and ingest microfilariae. The infective larvae are then transmitted to another human with a subsequent black fly bite. Microfilariae probably reach the eye by various routes:

- direct invasion of the cornea from the conjunctiva
- penetration of the sclera, both directly and through the vascular bundles
- hematogenous spread (possibly)

Microfilariae can be observed swimming freely in the anterior chamber. They may also be seen in the cornea, where dead microfilariae can cause stromal punctate keratitis. Anterior uveitis may lead to synechiae, secondary glaucoma, and cataract. In the posterior segment, RPE disruption and focal atrophy may occur. Advanced disease often manifests as severe chorioretinal and optic atrophy (Fig 12-39).

A diagnosis of onchocerciasis is suspected on the basis of the clinical appearance and a history of pathogen exposure in an endemic area. It is confirmed by detecting microfilariae in small skin biopsies or in the eye. Ivermectin, the treatment of choice, is given every 3–6 months as long as there is evidence of skin or eye infection. Topical corticosteroids can be used to control associated anterior uveitis.

Ivermectin effectively kills the microfilariae, but it does not have a permanent effect on the adult worms. Concomitant doxycycline therapy helps kill the adult worms by eradicating the symbiotic partner—*Wolbachia* bacteria. Lastly, patients coinfected with *O volvulus* and *Loa loa* are at risk of a fatal encephalitic reaction to ivermectin,

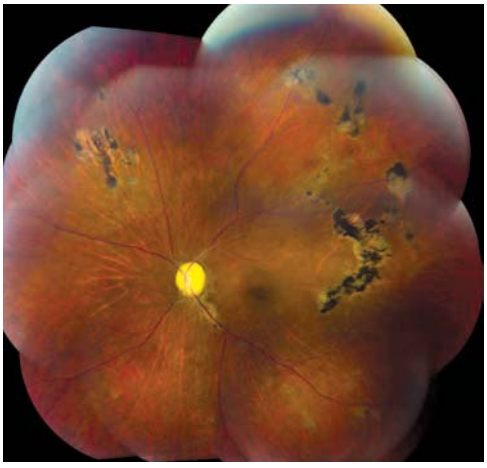

Figure 12-39 Onchocerciasis. Fundus photograph montage shows optic nerve pallor and extensive chorioretinal scars involving both the periphery and the posterior pole. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

so consultation with a specialist in infectious diseases should be obtained for these individuals.

Brattig NW, Cheke RA, Garms R. Onchocerciasis (river blindness) - more than a century of research and control. *Acta Trop.* 2021 Jun;218:105677. doi:10.1016/j.actatropica.2020.105677

Ejere HO, Schwartz E, Wormald R, Evans JR. Ivermectin for onchocercal eye disease (river blindness). *Cochrane Database Syst Rev.* 2012;8:CD002219.