CHAPTER 11

Focal and Diffuse Retinal and Choroidal Inflammation

Highlights

- The most important step in managing chorioretinal inflammation is distinguishing between noninfectious and infectious etiologies.
- Noninfectious forms of chorioretinal inflammation, particularly the white dot syndromes, have characteristic features that can be useful in identifying these entities, for which the workup, treatments, and prognoses vary substantially.
- A good history and high index of suspicion are necessary to obtain the appropriate laboratory tests for patients with infectious forms of chorioretinal inflammation.
- Primary vitreoretinal lymphoma can masquerade as uveitis.

Overview

A variety of inflammatory diseases are associated with yellow-white lesions of the retina and choroid. This chapter highlights various focal and diffuse retinal and choroidal inflammatory diseases that can cause such lesions. When the term *standard treatment* is used to describe therapy, options for inflammatory eye disease include corticosteroids in the acute phase and immunosuppressive agents for longer-term therapy. Choice of immunosuppressive therapy can vary widely. Other therapies or disease-specific treatment options are also outlined as appropriate. See BCSC Section 9, *Uveitis and Ocular Inflammation,* for more in-depth information on these diseases, further detail on treatment approaches, and additional illustrations.

Agarwal A. *Gass' Atlas of Macular Diseases.* 2 vols. 5th ed. Saunders; 2012:805–1064.

Albert DM, Miller JW, Azar DT, Young LH. Intermediate and Posterior Uveitis section. *Albert and Jakobiec's Principles and Practice of Ophthalmology*. 4th ed. Springer; 2022:4025–4363.

Foster CS, Vitale AT, Jakobiec FA. *Diagnosis and Treatment of Uveitis.* 2nd ed. Jaypee Brothers Medical Publishers; 2013.

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Noninfectious Retinal and Choroidal Inflammation

White Dot Syndromes

The term *white dot syndromes* has been used to refer to the following conditions (Table 11-1):

- acute posterior multifocal placoid pigment epitheliopathy
- serpiginous choroiditis
- multiple evanescent white dot syndrome
- birdshot chorioretinopathy
- multifocal choroiditis (MFC)
- multifocal choroiditis and panuveitis syndrome
- punctate inner choroiditis or choroidopathy (PIC)

Many authorities now believe that MFC and PIC are part of a spectrum of the same condition. Acute zonal occult outer retinopathy, acute macular neuroretinopathy, and acute idiopathic maculopathy are often included in discussions of the more classic white dot syndromes listed previously because of their presumed inflammatory etiology and the frequently shared symptoms of decreased vision, scotomata, and photopsias; thus, in this chapter, they are discussed under White Dot Syndromes.

Acute posterior multifocal placoid pigment epitheliopathy

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE; also known as *AMPPPE* or *AMPPE*) is an uncommon, bilateral inflammatory disease characterized by the acute onset of blurred vision, scotomata, and in some patients, photopsias. Approximately one-third of patients describe an antecedent flulike illness. Men and women are affected equally; onset usually occurs in early adulthood to middle age. Mild anterior chamber and vitreous inflammation may be present. The lesions, which are typically multiple, yellow-white, placoid, and variable in size, occur at the level of the outer retina (retinal pigment epithelium, RPE) and inner choroid (choriocapillaris) (Fig 11-1). Recurrences are uncommon. The etiology is unknown, although the condition is characterized by hypoperfusion of the choriocapillaris that results in injury to the overlying RPE. Systemic involvement—especially cerebral vasculitis—may occur in rare cases, and neurologic symptoms should prompt urgent neuroimaging. APMPPE-like lesions may be present in patients with sarcoidosis, syphilis, and tuberculosis; therefore, testing to exclude these conditions should be considered.

In the acute stage, fluorescein angiography (FA) of active lesions shows early blockage followed by progressive late leakage and staining. Indocyanine green angiography (ICGA) shows early and late (persistent) hypofluorescence, corresponding to and often extending beyond those lesions identified clinically and on FA. Optical coherence tomography (OCT) through active lesions reveals outer retinal lesions associated with disruption of the outer retinal hyperreflective bands. Autofluorescence in and around active lesions varies over time and may be either increased or decreased at presentation; it tends to decrease as disease activity subsides. With time, hypoautofluorescence develops in areas of RPE disruption. The fundus appearance and visual symptoms typically improve within weeks.

There is no definitive evidence that treatment with corticosteroids is beneficial in altering the outcome for APMPPE, but systemic corticosteroids are required in cases with

Table 11-1 White Dot Syndromes: Comparative Findings, Course, and Treatment

Disease	Laterality	Age	Sex	Notable Findings	Course	Treatment
APMPPE	Bilateral	Early adulthood to middle age	M = F	Early blockage (hypofluorescence) and late staining (hyperfluorescence) on fluorescein angiogram Cerebral vasculitis in rare cases No vitritis	Spontaneous resolution with good visual prognosis; recurrences rare	No proven treatment Evaluate for cerebral vasculitis if indicated; when it is present, systemic corticosteroids required
Serpiginous choroiditis	Bilateral	Young to middle age	M = F	Angiogram findings similar to those in acute APMPPE; presence of vitritis should raise suspicion for tubercular serpiginous-like choroiditis	Central vision loss due to scarring; chronic, progressive	Standard autoimmune disease treatment
MEWDS	Unilateral	Young to middle age	F > M	Central foveal granularity on clinical examination with surrounding hyperfluorescent lesions in wreathlike pattern on FA; usually no vitritis	Spontaneous resolution with good visual prognosis; recurrences rare	No proven treatment
Birdshot chorioretinopathy	Bilateral	Late middle age	F > M	Strong association with HLA-A29 Vitritis Possible nyctalopia, diminished contrast sensitivity, and decreased color vision	Vision loss due to CME, CNV, epiretinal membrane formation, and/or outer retinal atrophy; chronic, progressive	Standard autoimmune disease treatment
MFC	Bilateral	Young	F > M	Chorioretinal lesions evolve to burnt-out or punched-out scars; usually minimal or no vitritis, but some cases can have moderate vitritis	Central vision loss due to direct central macular involvement or CNV; chronic, progressive	Standard autoimmune disease treatment
PIC	Bilateral	Young	F > M	Subtype of MFC distinguished by lack of vitritis and smaller (100–300 μm), round, yellow lesions that are usually confined to the posterior pole	Central vision loss due to CNV; self-limited or chronic, progressive	Standard autoimmune disease treatment

APMPPE = acute posterior multifocal placoid pigment epitheliopathy; CME = cystoid macular edema; CNV = choroidal neovascularization; HLA = human leukocyte antigen; MEWDS = multiple evanescent white dot syndrome; MFC = multifocal choroiditis; PIC = punctate inner choroiditis/choroidopathy.

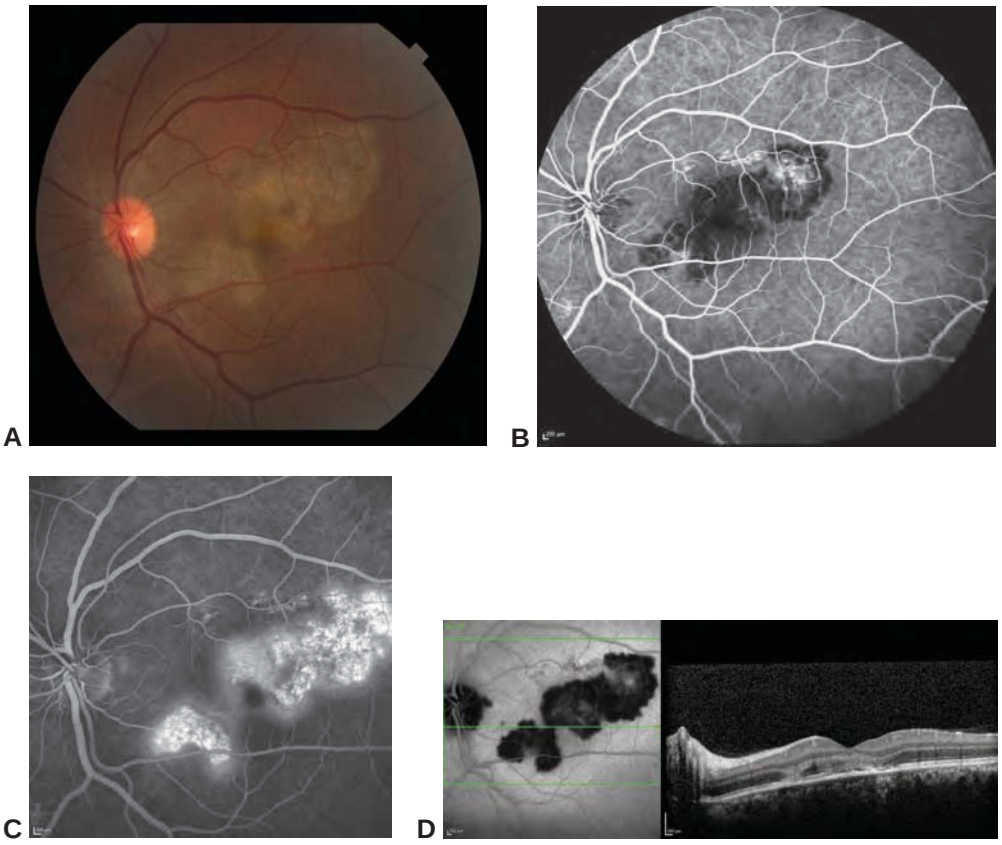

Figure 11-1 Acute posterior multifocal placoid pigment epitheliopathy (APMPPE). **A,** Color fundus photograph of the left eye of a 23-year-old male patient shows confluent yellowish placoid lesions in the posterior pole. The right eye (not pictured) was also involved. Early **(B)** and late-phase **(C)** fluorescein angiography (FA) demonstrates hypofluorescence (due to decreased choriocapillaris perfusion and/or thickening of the retinal pigment epithelium [RPE]), and hyperfluorescence, respectively. **D,** Indocyanine green angiography (ICGA; *left*) shows hypofluorescence of the lesions, and the optical coherence tomography (OCT) scan *(right)* demonstrates outer retinal involvement in the areas of lesions. *(Courtesy of Lucia Sobrin, MD.)*

cerebral vasculitis. Severe APMPPE may be difficult to distinguish from serpiginous choroiditis (discussed in the following section); this difficulty led to the introduction of the term *ampiginous* to characterize the APMPPE–serpiginous choroiditis disease continuum. Other entities in this placoid disorder continuum include *persistent placoid maculopathy,* which is characterized by central macular involvement, a longer healing time, and a high risk of choroidal neovascularization (CNV); and *relentless placoid chorioretinitis,* which is characterized by the frequent occurrence of smaller, geographically distributed lesions that typically require immunosuppressive treatment.

Marchese A, Agarwal AK, Erba S, et al. Placoid lesions of the retina: progress in multimodal imaging and clinical perspective. *Br J Ophthalmol.* 2022;106(1):14–25.

Serpiginous choroiditis

Serpiginous choroiditis, also known as *geographic choroiditis* or *helicoid peripapillary choroidopathy,* is an uncommon, often vision-threatening, recurring inflammatory disease involving the outer retina, RPE, and choroid. Serpiginous choroiditis tends to affect men and women equally; onset typically occurs in middle age. Persistent scotomata and decreased central vision are common symptoms. Classically, lesions first appear at or near the optic nerve head and extend centrifugally in a serpentine pattern. With numerous recurrences, a serpiginous (pseudopodial) or geographic (maplike) pattern of chorioretinal scarring develops (Fig 11-2). Findings on clinical examination and through multimodal imaging of active serpiginous lesions resemble those of severe APMPPE. Lesions tend to occur near or adjacent to inactive scars from prior episodes of inflammation. Recent, active inflammation can be detected noninvasively as hyperautofluorescence on fundus autofluorescence (FAF) (see Fig 11-2). CNV can occur at the edge of the chorioretinal scars.

In endemic areas, such as India, tuberculosis is recognized as producing serpiginous-like lesions, leading some clinicians to describe such lesions as tubercular serpiginous-like choroiditis. In patients with serpiginous-like lesions, evaluation for tuberculosis, sarcoidosis, and syphilis should be considered.

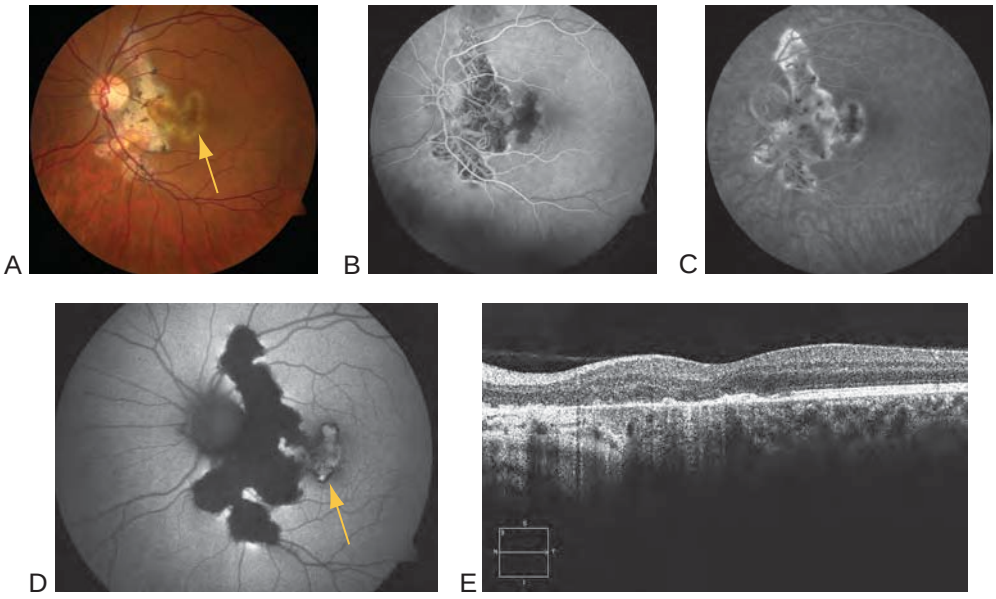

Figure 11-2 Serpiginous choroiditis. **A,** Color fundus photograph shows an old peripapillary chorioretinal scar with an active serpentine lesion *(arrow)* extending centrifugally into the fovea. **B,** Early-phase FA demonstrates classic hypofluorescence, with hyperfluorescence of the edge of the older peripapillary chorioretinal scar. **C,** Late-phase angiogram demonstrates hyperfluorescence of involved areas. **D,** Fundus autofluorescence (FAF) image demonstrates a complete absence of autofluorescence in the area of older chorioretinal scarring; in contrast, there is hyperautofluorescence in the area of active extension *(arrow).* **E,** OCT image demonstrates disorganization of outer retinal layers and choroid nasal to and underneath the fovea, which corresponds to the involved areas. *(Courtesy of Stephen J. Kim, MD.)*

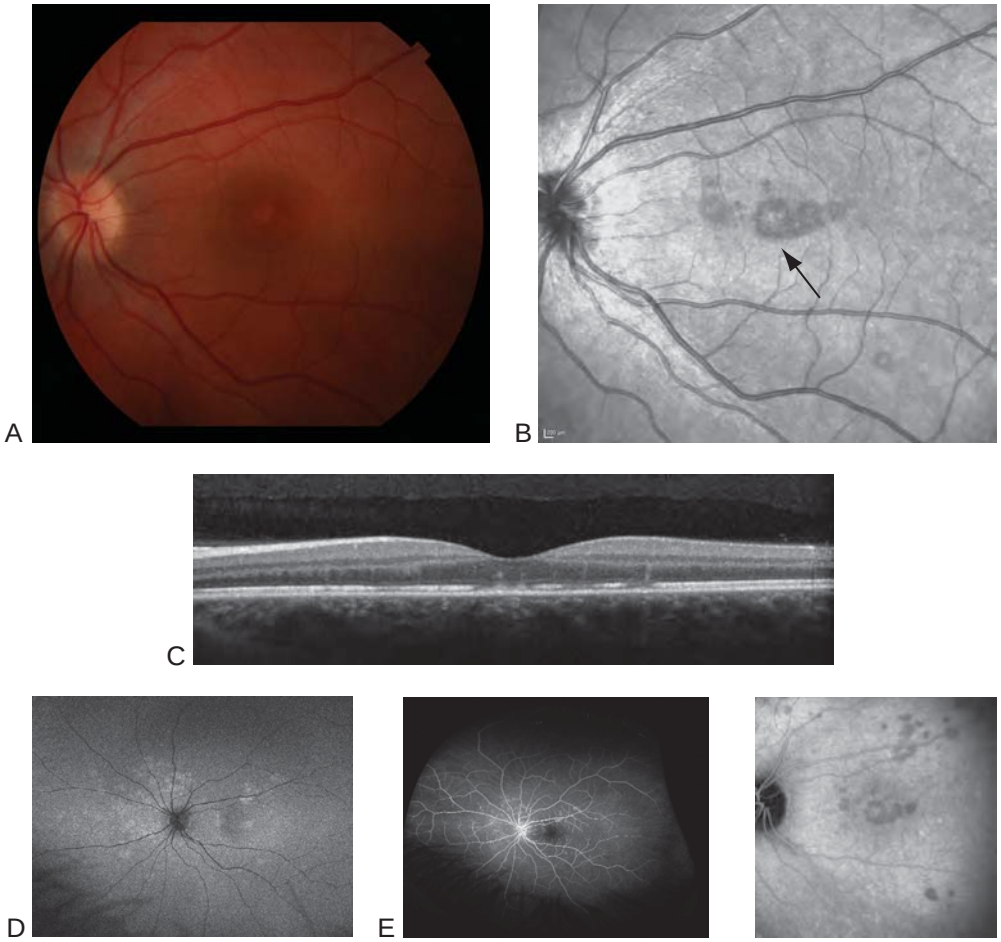

Figure 11-3 Multiple evanescent white dot syndrome (MEWDS). **A,** Color fundus photograph demonstrates foveal granularity. **B,** In the red-free image, the lesions *(arrow)* are more readily apparent than they are on the fundus photograph. **C,** OCT image demonstrates disruption of the outer retinal hyperreflective bands and RPE. **D,** FAF image shows hyperautofluorescence of the lesions. **E,** FA demonstrates hyperfluorescent lesions. **F,** ICGA shows hypofluorescence of the lesions. *(Courtesy of Lucia Sobrin, MD.)*

Multiple evanescent white dot syndrome

Multiple evanescent white dot syndrome (MEWDS) is an acute-onset syndrome characterized by multiple small gray, white, or yellow-white dots at the level of the outer retina in and around the posterior pole (Fig 11-3). Affected individuals are typically young to middle aged; women are affected more often than men. The etiology of MEWDS is unknown, although one-third of patients describe a flulike prodrome. Symptoms tend to be unilateral and include decreased vision, scotomata, and sometimes photopsias. In some patients, an unusual foveal granularity consisting of tiny yellow-orange flecks at the level of the RPE also develops and may persist long after resolution of the other lesions of MEWDS. Abnormalities on ICGA suggest RPE abnormalities. Mild anterior chamber cell reaction or vitritis may be

present but is more commonly absent. Temporal visual field abnormalities and an enlarged blind spot are common, and an afferent pupillary defect is often present.

FA reveals multiple punctate, hyperfluorescent lesions associated with the dots observed clinically, typically in a wreathlike configuration. Mild, late leakage and staining of the optic nerve head are often observed. ICGA shows hypofluorescence around the optic nerve head as well as multiple hypofluorescent dots, which are typically more numerous than those observed either clinically or on FA. OCT taken through active lesions reveals dome-shaped outer retinal lesions associated with disruption of the outer retinal hyperreflective bands. FAF imaging often shows focal hyperautofluorescence in the area of the white dots. On electroretinographic (ERG) testing, some patients show delayed light-adapted (LA) (photopic flicker) responses and decreased bright-flash, dark-adapted a-wave amplitudes. In most patients, the symptoms and fundus findings start to improve in 2–6 weeks without treatment.

Birdshot chorioretinopathy

Birdshot chorioretinopathy, previously called *vitiliginous chorioretinitis,* is bilateral and affects women more often than men, typically in late middle age. Most patients with birdshot chorioretinopathy are White, and in more than 90% of patients, test results are positive for human leukocyte antigen (HLA)–A29; birdshot chorioretinopathy has the strongest association documented between a disease and HLA class I. Early symptoms include floaters and blurred or decreased vision. Later in the course of disease, nyctalopia, diminished contrast sensitivity, and decreased color vision may occur as photoreceptors degenerate from ongoing inflammation. Examination reveals vitreous inflammation, which is typically mild and is associated with multiple yellow-white choroiditis spots that are often most prominent nasal to the optic nerve head (Fig 11-4). FA often shows leakage from the retinal vessels and optic nerve head, frequently producing cystoid macular edema (CME). Variable amounts of outer retinal atrophy can also be present, resulting in window defects. Choroidal lesions are best visualized using ICGA. OCT and FAF can be used to assess the extent of outer retinal atrophy.

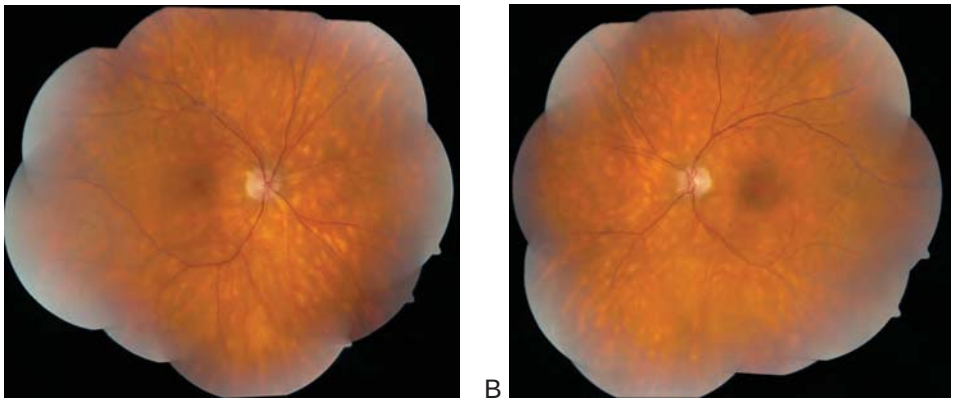

Figure 11-4 Color fundus photograph montage of the right **(A)** and left **(B)** eyes of a patient with birdshot chorioretinopathy demonstrates multiple creamy, yellow-white choroiditis lesions scattered around the posterior pole and midperiphery. The images are slightly hazy due to vitritis. *(Courtesy of Stephen J. Kim, MD.)*

The disease is chronic, progressive, and prone to recurrent episodes of inflammation. Vision loss may be caused by CNV, CME, epiretinal membrane formation, and/or outer retinal atrophy, which can be extensive and is associated with optic atrophy in advanced cases. Disease activity and progression may be assessed in the office using multimodal imaging (FA, ICGA, spectral-domain OCT, enhanced depth OCT, and FAF) and through periodic electrophysiologic (ERG), color vision, retinal nerve fiber layer OCT, and visual field testing—each of which may show a degree of dysfunction far greater than that suggested by Snellen visual acuity assessments. Common ERG abnormalities include prolonged LA implicit times and decreased b-wave amplitudes.

Multifocal choroiditis, including punctate inner choroiditis

Use of the terms *idiopathic multifocal choroiditis, multifocal choroiditis and panuveitis (MFCPU), recurrent multifocal choroiditis (RMC), punctate inner choroiditis* or *choroidopathy (PIC), pseudo-presumed ocular histoplasmosis syndrome (pseudo-POHS),* and *subretinal fibrosis and uveitis syndrome,* among others, is both inconsistent and confusing in the literature. Current recommendations suggest that only the term *multifocal choroiditis (MFC)* should be used to refer to the occurrence of discrete chorioretinitis lesions in the absence of an identifiable underlying infection (such as tuberculosis or histoplasmosis) or systemic inflammation (such as sarcoidosis). In MFC, lesions are commonly clustered in the macula and around the optic nerve head, although they can also occur in the mid- and far periphery and are frequently aligned in a curvilinear manner—configurations sometimes referred to as *Schlaegel lines* (Fig 11-5). Blurred or decreased vision and scotomata are the most common symptoms. Affected individuals are typically young, myopic, and female. Clinical examination usually reveals little or no anterior chamber or vitreous inflammation, although patients may have mild to moderate vitreous inflammation—a presentation some clinicians mean when using the term *MFCPU.* Decreased central vision

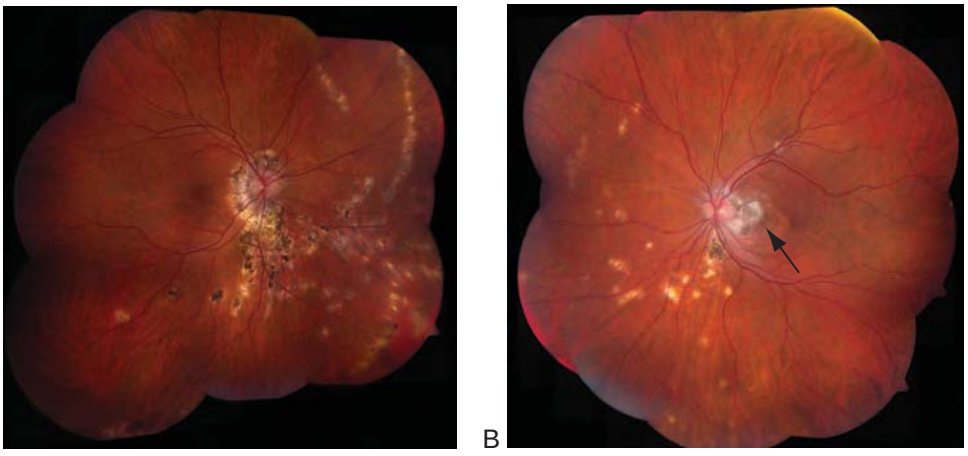

Figure 11-5 Multifocal choroiditis. Color fundus photograph montage of the right **(A)** and left **(B)** eyes showing multifocal chorioretinal scars, some with a punched-out appearance clustered in the macula and around the optic nerve. Note the curvilinear pattern of lesions nasally (more evident in the right), referred to as *Schlaegel lines.* The patient was a young female with myopia and 20/200 vision in the left eye due to previous choroidal neovascularization (CNV; *arrow*). *(Courtesy of Stephen J. Kim, MD.)*

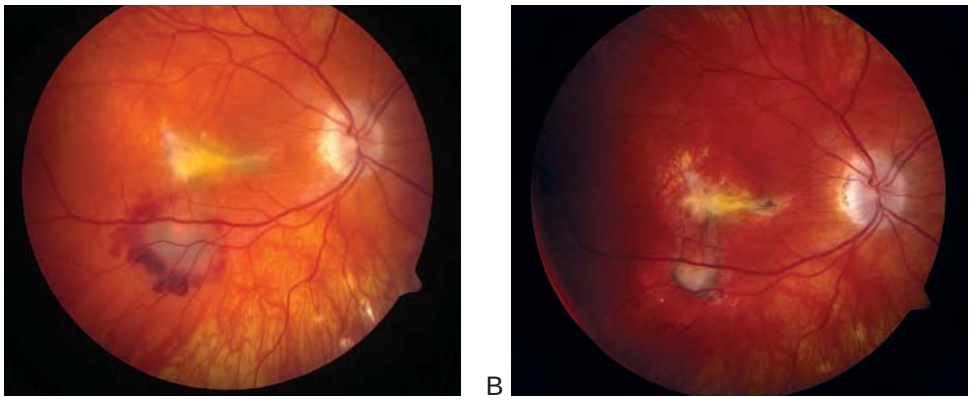

Figure 11-6 Choroidal neovascularization (CNV). **A,** Fundus photograph from a patient with multifocal choroiditis with central subfoveal fibrosis and CNV with adjacent subretinal hemorrhage inferiorly. **B,** After CNV resolves, subretinal fibrosis occurs at the site of previous CNV inferiorly. *(Courtesy of Stephen J. Kim, MD.)*

results most frequently from direct central macular involvement or from CNV, which occurs in one-third of patients (Fig 11-6). Subretinal fibrosis may occur in and around lesions and, when the central macula is involved, can also limit vision.

Acute zonal occult outer retinopathy

Acute zonal occult outer retinopathy (AZOOR), a presumed inflammatory disease, damages broad zones of the outer retina in 1 or both eyes. AZOOR typically occurs in young women with myopia, and onset is acute and unilateral. Three-fourths of cases progress to bilateral involvement. Initial symptoms include photopsia, nasal visual field loss, and sometimes an enlarged blind spot; visual acuity is affected in rare instances. On initial presentation, the fundus may appear normal or show evidence of mild vitritis. Nearly 25% of patients have an afferent pupillary defect. Angiographic findings may include retinal and optic nerve head capillary leakage, especially in patients with evidence of vitritis. On ERG, a delayed LA response is common; multifocal ERG shows decreased responses in areas of the visual field defect. Visual field testing may show scotomata, which can enlarge over weeks or months.

Some patients recover from AZOOR, whereas others have persistent, large visual field defects, which tend to stabilize over 6 months. Permanent visual field loss is often associated with late development of fundus changes. Depigmentation of large zones of RPE usually corresponds to scotomata (Fig 11-7); narrowed retinal vessels may be visible within these areas. In some patients, the late fundus appearance may resemble cancer-associated retinopathy or retinitis pigmentosa.

Mrejen S, Khan S, Gallego-Pinazo R, Jampol LM, Yannuzzi LA. Acute zonal occult outer retinopathy: a classification based on multimodal imaging. *JAMA Ophthalmol.* 2014;132(9):1089–1098.

Acute macular neuroretinopathy

Acute macular neuroretinopathy (AMN) is a rare condition characterized by the acute onset of paracentral scotomata in 1 or both eyes in young, otherwise healthy patients. The pathogenesis of AMN is unclear. Women outnumber men nearly 6 to 1 in this condition.

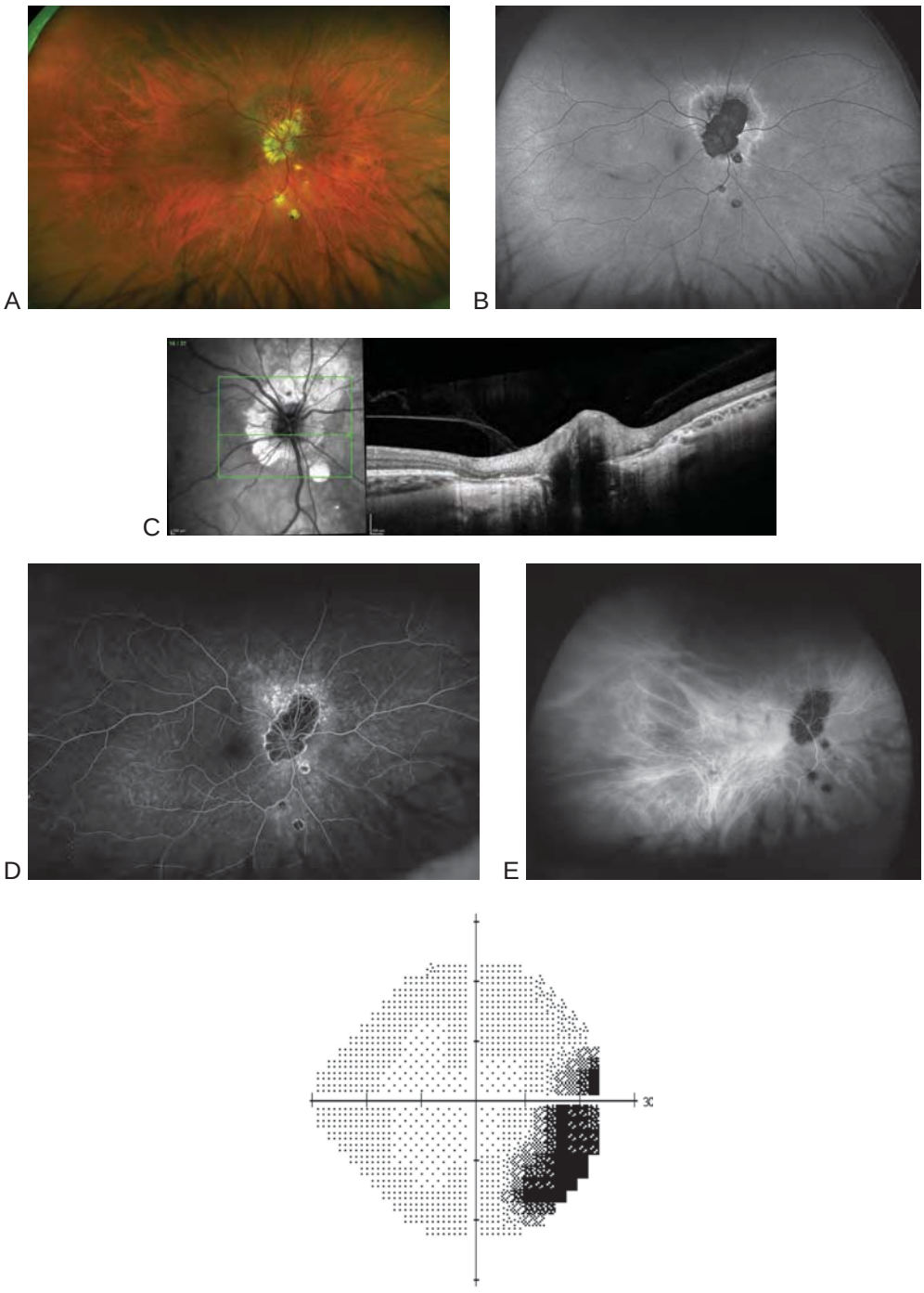

Figure 11-7 Acute zonal occult outer retinopathy (AZOOR). **A,** Annular depigmentation of the RPE can be seen around the optic nerve. **B,** FAF demonstrates a trizonal pattern of changes extending from the optic nerve: hypoautofluorescence adjacent to the nerve, an intermediate area of hyperautofluorescence, and normal autofluorescence. **C,** OCT image demonstrates outer retinal atrophy in the involved area. **D,** FA shows hypofluorescence in the area of peripapillary atrophy surrounded by staining. **E,** ICGA shows hypofluorescence of the peripapillary lesion. **F,** Humphrey 24-2 visual field shows enlargement of the blind spot. *(Courtesy of Lucia Sobrin, MD.)*

Clinically, reddish-brown teardrop or wedge-shaped lesions are observed around the fovea. The tips of these lesions point centrally; the lesions correspond in size and location to the subjective paracentral scotomata. The lesions can be difficult to see on fundus examination or with traditional color photography but are apparent on near-infrared imaging and multicolor images. The retinal vessels and optic nerve are unaffected, and there is no vitreous inflammation. High-resolution OCT is particularly helpful for visualizing the lesions, which characteristically involve the outer retina—including both the outer nuclear layer and the hyperreflective bands associated with the photoreceptors of the ellipsoid zone (Fig 11-8). These OCT changes are believed to result from ischemia of the deep capillary plexus of the central retina. AMN lesions can be distinguished from paracentral acute middle maculopathy (PAMM) lesions, which present with hyperreflectivity of the inner plexiform layer and inner nuclear layer (INL) and progress to INL thinning without outer retinal involvement (see Chapter 6).

Fawzi AA, Pappuru RR, Sarraf D, et al. Acute macular neuroretinopathy: long-term insights revealed by multimodal imaging. *Retina.* 2012;32(8):1500–1513.

Acute idiopathic maculopathy

Acute idiopathic maculopathy (AIM) is a rare disorder that presents with sudden, severe central or paracentral vision loss, typically in younger individuals following a flulike illness.

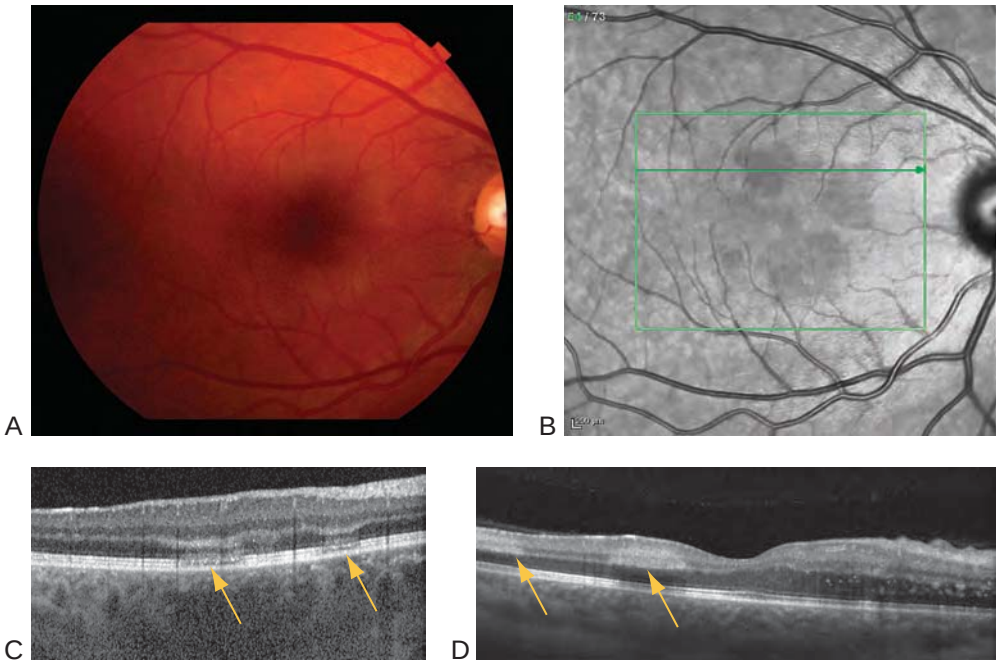

Figure 11-8 Acute macular neuroretinopathy (AMN). Reddish-brown lesions in the macula are difficult to see in a color fundus photograph **(A),** but they are apparent in a near-infrared image **(B). C,** OCT image demonstrates involvement of the outer nuclear layer, external limiting membrane, and ellipsoid zone *(arrows).* **D,** OCT image from a patient with ischemic retinal vasculitis shows involvement of the inner nuclear layer *(arrows),* which distinguishes paracentral acute middle maculopathy (PAMM) from AMN. *(Courtesy of Lucia Sobrin, MD.)*

Men and women are affected equally. The cause is unknown, although isolated cases have been associated with coxsackievirus infection. Initially, only central unilateral lesions were described, but both bilateral and eccentric macular lesions have since been added to the disease spectrum. The main clinical finding is an exudative neurosensory macular detachment with little or no vitreous inflammation and variable discoloration of the underlying RPE (Fig 11-9). Mild optic nerve head swelling, retinal hemorrhages, vasculitis, and subretinal infiltrates occur infrequently. FA typically shows progressive irregular hyperfluorescence at the level of the RPE, followed in the late stages by pooling in the detachment space. High-resolution OCT imaging documents the size and extent of the detachment space and shows loss of the hyperreflective outer retinal bands associated with the photoreceptors and RPE. The lesions resolve spontaneously but leave a bull's-eye pattern of RPE alteration. Typically near-complete recovery of vision occurs over weeks to months.

Freund KB, Yannuzzi LA, Barile GR, Spaide RF, Milewski SA, Guyer DR. The expanding clinical spectrum of unilateral acute idiopathic maculopathy. *Arch Ophthalmol.* 1996;114(5):555–559.

Figure 11-9 Acute idiopathic maculopathy. **A,** Retinal hemorrhages and an exudative neurosensory macular detachment with underlying yellowish discoloration. **B,** OCT through the lesion shows subretinal fluid with hyperreflective debris and loss of the outer retinal bands. *(Courtesy of Lucia Sobrin, MD.)*

Chorioretinal Autoimmune Conditions

The following sections detail selected autoimmune diseases that affect the retina and choroid. These conditions are generally treated using standard autoimmune treatment options. Specific treatment considerations are mentioned when applicable.

Inflammatory vasculitis

See BCSC Section 9, *Uveitis and Ocular Inflammation,* Chapter 5 for a full list of causes of inflammatory vasculitis.

Behçet disease Behçet disease is a complex systemic disorder characterized by recurrent attacks of inflammation and vascular occlusion involving multiple organ systems. The disease tends to affect men more than women and is particularly common in regions along the Silk Road trading routes: Japan, Southeast Asia, the Middle East, and the Mediterranean. The etiology is unknown.

There are no specific tests to confirm a diagnosis of Behçet disease, but it is associated with the major histocompatibility complex HLA-B5 allele, and more specifically with HLA-B51 (the predominant split antigen). The diagnosis is based on clinical criteria (Table 11-2). Recurrent oral ulceration affects nearly all patients, and genital ulcers and cutaneous lesions such as erythema nodosum are common. Central nervous system involvement may develop in more than 50% of patients and should be suspected in any patient with neurologic signs. Other systemic manifestations include arthritis, epididymitis, and intestinal ulcers.

Uveitis is common in patients with this disorder and may be anterior, posterior, or diffuse (panuveitis). Posterior segment involvement may include vitritis, an occlusive retinal vasculitis, intraretinal hemorrhages, macular edema, focal areas of retinal necrosis, and ischemic optic neuropathy. Recurring episodes of retinal vasculitis may lead to severe ischemia and retinal neovascularization, which is often treated with panretinal photocoagulation. Despite treatment, the visual prognosis is often poor because of progressive retinal ischemia from recurring episodes of occlusive vasculitis. Treatment with azathioprine and cyclosporine has been shown to reduce ocular manifestations in prospective trials. Biologic agents, such as inhibitors of tumor necrosis factor α, as well as interferon, are also quite effective.

Tugal-Tutkun I, Ozdal PC, Oray M, Onal S. Review for diagnostics of the year: multimodal imaging in Behçet uveitis. *Ocul Immunol Inflamm.* 2017;25(1):7–19.

Table 11-2 International Clinical Criteria for Diagnosis of Behçet Disease

Recurrent oral ulceration (aphthous or herpetiform) at least 3 times in 1 year in addition to 2 of the following:

- recurring genital ulcerations
- ocular inflammation
- skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules)
- positive pathergy test

Adapted from the International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet.* 1990;335(8697):1078–1080.

Lupus vasculitis Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder that most commonly affects women of childbearing age. Black and Hispanic women are at higher risk than White women. As a multisystem disease, SLE can involve almost every ocular and periocular structure. Approximately 3%–10% of patients with SLE have retinal findings ranging from asymptomatic cotton-wool spots and intraretinal hemorrhages to macular infarction with severe central vision loss (Fig 11-10). Lupus choroidopathy is less common and presents as multifocal serous retinal detachments. The retinal and choroidal pathology is vascular and thought to be autoimmune in nature.

The presence of retinal vascular occlusion, including cotton-wool spots, is indicative of active systemic inflammation and should prompt treatment. Sarcoidosis can also cause retinal vasculitis and should be considered in the differential diagnosis (see BCSC Section 9, *Uveitis and Ocular Inflammation*).

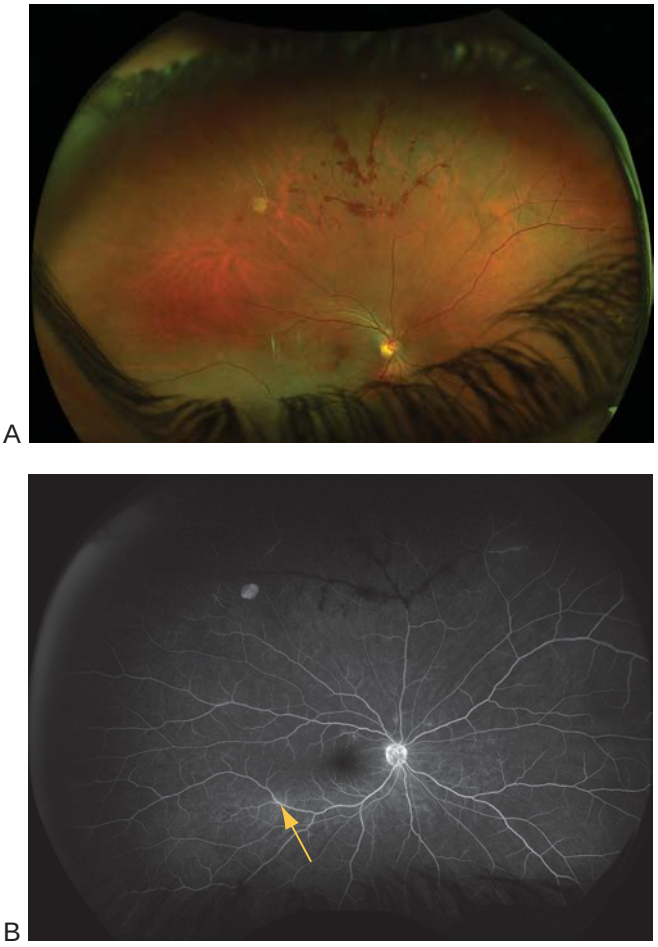

Figure 11-10 Vasculitis secondary to systemic lupus erythematosus. **A,** Fundus photograph shows perivascular exudate and perivascular hemorrhages superiorly. **B,** Late-phase FA image reveals retinal nonperfusion superiorly and mild perivascular leakage along the inferior arcade *(arrow)*. *(Courtesy of Lucia Sobrin, MD.)*

Vogt-Koyanagi-Harada disease

Vogt-Koyanagi-Harada (VKH) disease (or syndrome) is a systemic autoimmune disorder in which T lymphocytes are directed against melanocytes in the eye, auditory system, meninges, and skin. VKH disease most commonly affects people of Asian, American Indian, Asian Indian, Mediterranean, and Middle Eastern descent. Ocular findings are typically bilateral and include vitreous inflammation associated with serous retinal detachment. Optic nerve head hyperemia and edema are common. FA studies can be particularly helpful in monitoring disease activity and often show multiple RPE leaks in the areas of detachment, a finding referred to as the "starry sky" or "Milky Way" sign (Fig 11-11). Depigmentation of the choroid results in the classic orange-red fundus discoloration, or "sunset glow" fundus appearance, as the uveitis subsides.

A diagnosis of VKH disease should be made only in patients who have not had a penetrating ocular injury or ocular surgery in either eye, to help distinguish this disease from sympathetic ophthalmia. VKH disease is called *probable* when characteristic ocular inflammation occurs in the absence of skin or neurologic findings; it is called *incomplete* when either skin or neurologic findings but not both are present; and it is called *complete* when both skin and neurologic findings develop.

The clinical course of VKH disease can be divided into 3 phases:

1. *prodromal phase:* characterized by a flulike illness with symptoms that can include headache, meningismus, tinnitus, and dysacusis
2. *acute uveitic phase:* closely follows the prodromal phase; characterized by pain, photophobia, and vision loss accompanied by the onset of bilateral panuveitis with serous retinal detachments
3. *chronic (convalescent) phase:* the uveitis subsides, but depigmentation of the skin (vitiligo), eyelashes (poliosis), and uvea can occur; ocular depigmentation may develop at the limbus ("Sugiura" sign), the trabecular meshwork ("Ohno" sign), or the choroid ("sunset glow" fundus appearance)

Sympathetic Ophthalmia

Sympathetic ophthalmia, a rare condition that occurs after penetrating ocular injury or ocular surgery, is caused by exposure of the immune system to sequestered uveal antigens (see BCSC Section 9, *Uveitis and Ocular Inflammation*). The ocular findings in sympathetic ophthalmia are clinically and histologically indistinguishable from those in VKH disease. Inflammation of the exciting (injured or operated) and sympathizing (fellow) eye may occur days to decades after the initial insult. As in VKH disease, the inflammation is bilateral and is characterized by the presence of panuveitis, often associated with areas of serous retinal detachment and yellowish white midperipheral choroidal lesions (Dalen-Fuchs nodules). Nonocular complications, such as vitiligo or poliosis, can occur but are much less common than in VKH disease. Moreover, in the rare instances when sympathetic ophthalmia does follow either injury or surgery, standard treatments almost always control the inflammation. Therefore, enucleation or evisceration of an injured eye to minimize risk of sympathetic ophthalmia is rarely practiced.

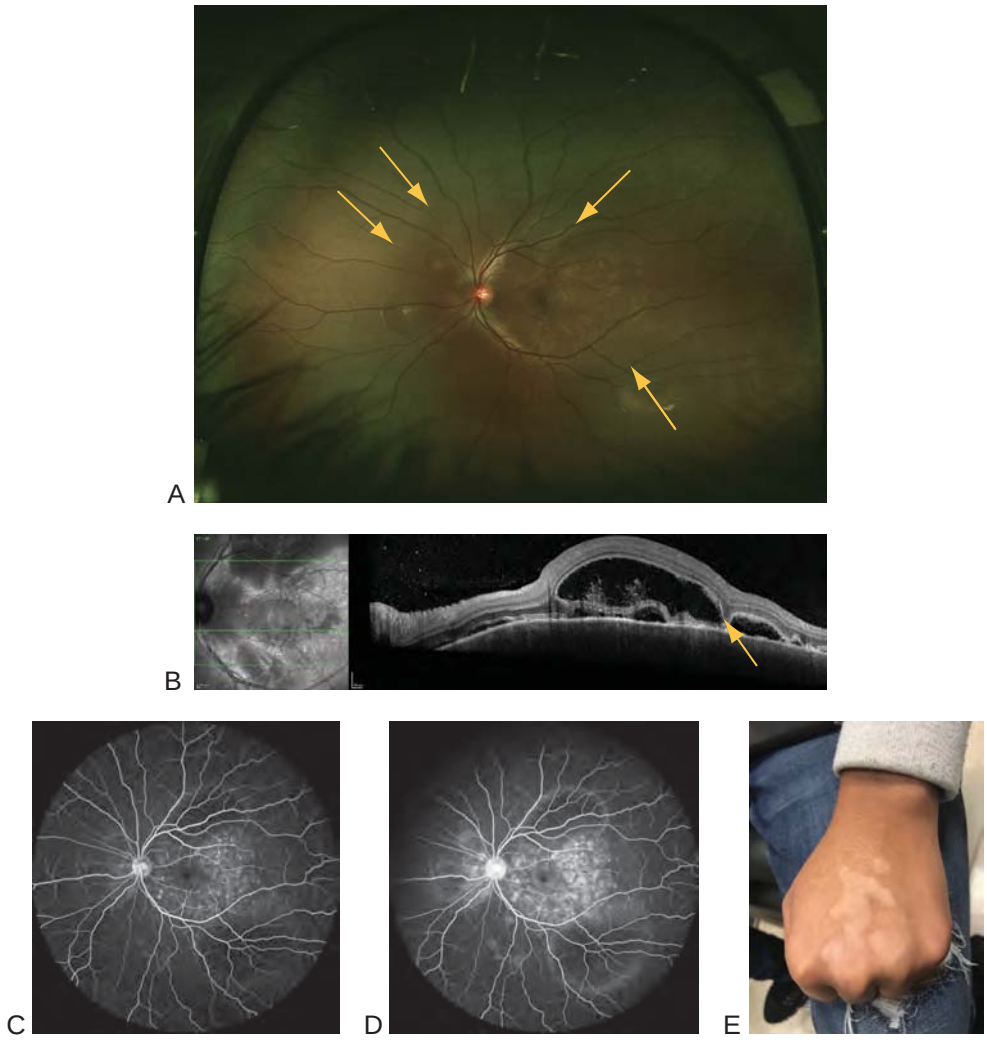

Figure 11-11 Vogt-Koyanagi-Harada (VKH) disease. **A,** Fundus photograph (left eye) taken during an acute uveitic phase in a patient with multiple serous detachments *(arrows).* **B,** OCT shows vitreous cells, subretinal fluid, and subretinal inflammatory debris, septae, and bacillary layer detachment *(arrow).* **C,** Early-phase FA shows multifocal pinpoint RPE leakage ("starry sky" appearance). **D,** Late-phase FA shows pooling of fluid in the subretinal space. **E,** Three months after presentation, vitiligo developed on the dorsum of the patient's hand. *(Courtesy of Lucia Sobrin, MD.)*

Uveitis Masquerade: Intraocular Lymphoma

Primary vitreoretinal lymphoma (*PVRL;* previously called *primary intraocular lymphoma PIOL*), is a non-Hodgkin diffuse large B-cell lymphoma and is considered the most aggressive of the ocular lymphomas. Half of all cases of PVRL occur in patients older than 60 years. In most patients with PVRL, central nervous system (CNS) involvement will develop. Conversely, of patients who present with CNS involvement, approximately 20% will have intraocular involvement. HIV infection is associated with an increased risk of

lymphoma that ranges from 50-fold (with potent antiretroviral therapy) to more than 500-fold (prior to—or without access to—potent antiretroviral therapy).

Diagnosis of PVRL may be challenging, as PVRL often masquerades as posterior uveitis. Clinical features suggestive of PVRL include

- incomplete or transient response to corticosteroid treatment
- presence of atypical large vitreous cells, which may be uncharacteristically white and/or align along a single vitreous fibril ("string of pearls" pattern; Fig 11-12) or appear as a sheet formed by multiple, aligned vitreous fibrils (aurora borealis effect)
- presence of subretinal and/or sub-RPE infiltrates, which may be transient and/or shift location over time (Fig 11-13)

Optic nerve head edema and serous retinal detachment may also occur.

Patients with suspected PVRL should undergo magnetic resonance imaging of the brain with contrast material as well as a lumbar puncture for cytologic studies to evaluate for CNS involvement. A confirmatory CNS or vitreoretinal biopsy is usually performed. Best results are obtained when the vitreoretinal biopsy specimen is obtained as part of a surgical vitrectomy (as opposed to a vitreous tap) and both undiluted and diluted samples are taken. It is notoriously difficult to arrive at a diagnosis on the basis of tests of a vitreous specimen because of the low cell concentrations and the propensity of lymphoma cells to undergo autolysis. Because corticosteroids will also reduce cell count, it is best to stop any corticosteroid treatments for a period of weeks before a planned biopsy. Best results are achieved with rapid test processing and analysis by cytopathology, immunoglobulin or T-cell receptor gene rearrangement studies, flow cytometry, cytokine analyses (IL-10:IL-6 ratio >1.0), and *MYD88* mutation detection. Current management practices involve both chemotherapy and radiation treatment. Intravitreal injection of methotrexate and rituximab can be effective at controlling intraocular disease, but the recurrence rate is high and the long-term prognosis guarded.

In contrast with PVRL, uveal lymphoma is usually more indolent and is associated with systemic lymphoma in up to one-third of cases. Characteristic clinical findings include uveal thickening, which often produces a birdshot uveitis–like fundus appearance,

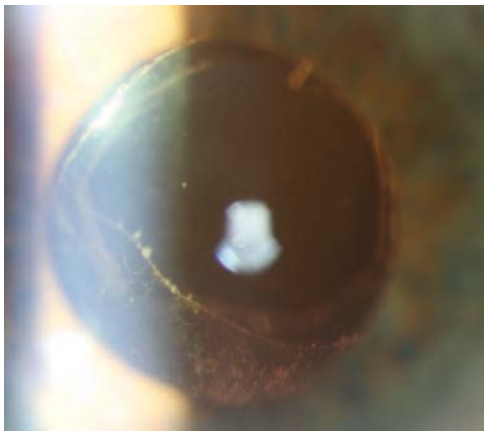

Figure 11-12 Classic "string of pearls" pattern, consisting of large lymphoma cells connected by vitreous fibrils, in an eye with primary vitreoretinal lymphoma (PVRL). Vitreous cells are larger and less abundant in PVRL than in typical vitritis and tend to aggregate. Note the distinct differences when compared to the string of pearls pattern seen in *Candida* endophthalmitis (see Fig 11-20). *(Courtesy of Anthony B. Daniels, MD, MSc.)*

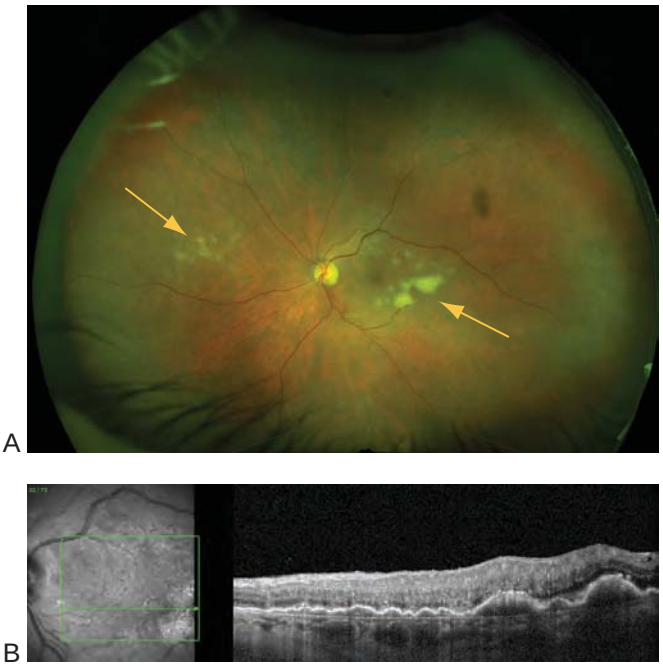

Figure 11-13 Primary vitreoretinal lymphoma. **A,** Fundus photograph shows sub-RPE infiltrates *(arrows)* in a patient with known central nervous system B-cell lymphoma. **B,** OCT shows diffuse sub-RPE hyperreflective material. *(Courtesy of Lucia Sobrin, MD.)*

with or without serous retinal detachment (Fig 11-14). Episcleral involvement may manifest anteriorly as salmon-colored conjunctival infiltration or posteriorly as a juxtascleral mass on ultrasonography. Biopsy of affected tissues can confirm the diagnosis. Evaluation

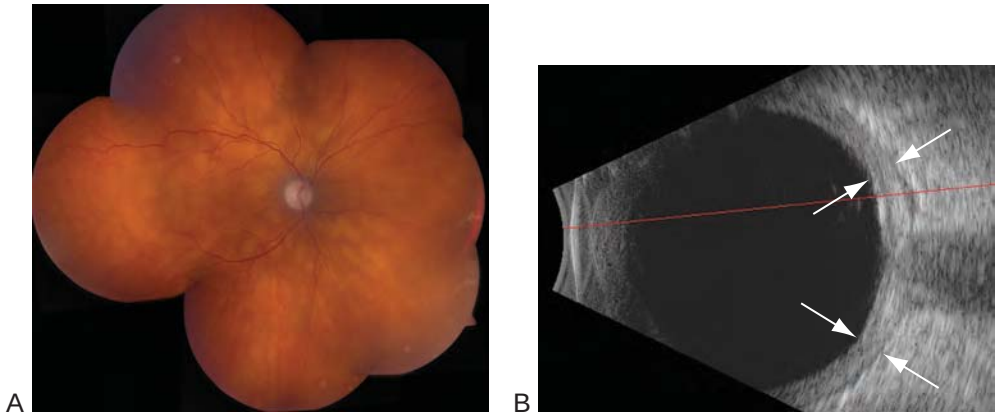

Figure 11-14 Uveal lymphoma. **A,** Fundus photograph demonstrates birdshot uveitis–like fundus appearance. **B,** B-scan ultrasonography reveals characteristic uveal thickening *(arrows)*. *(Courtesy of Stephen J. Kim, MD.)*

for systemic involvement includes use of computed tomography (CT) or combined CT and positron emission tomography (PET) imaging of the thorax, abdomen, and pelvis.

Chan CC, Sen HN. Current concepts in diagnosing and managing primary vitreoretinal (intraocular) lymphoma. *Discov Med.* 2013;15(81):93–100.

Infectious Retinal and Choroidal Inflammation

The following sections briefly describe selected infectious diseases that can cause retinal and choroidal inflammation.

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) causes the most common infectious congenital syndrome worldwide and can result in congenital CMV retinitis (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* Chapter 27 for additional discussion). CMV retinitis is also the most common ocular opportunistic infection in adult patients with advanced AIDS and usually occurs when $CD4^+$ T-cell counts are less than 50/μL. Patients with CMV retinitis typically present with floaters or decreased vision. Clinically, CMV retinitis has a characteristic appearance that consists of opacification of the necrotic retina, typically along retinal vessels and often with areas of hemorrhage (Fig 11-15). Periphlebitis and "frosted branch" angiitis—florid, dense, perivascular exudation that often obliterates visualization of the retinal vessels—may be prominent features. The degree of vitreous inflammation is highly variable but often minimal in immunocompromised patients. Early CMV retinitis may resemble the cotton-wool spots associated with HIV-related retinopathy. Although the diagnosis is often made clinically, polymerase chain reaction (PCR)–based analysis of ocular fluids may be diagnostic in unclear cases.

CMV retinitis can be treated with oral valganciclovir, or with ganciclovir or foscarnet, administered systemically or intravitreally. High-dose induction therapy is typically given for 2–3 weeks, after which maintenance therapy is continued until immune reconstitution

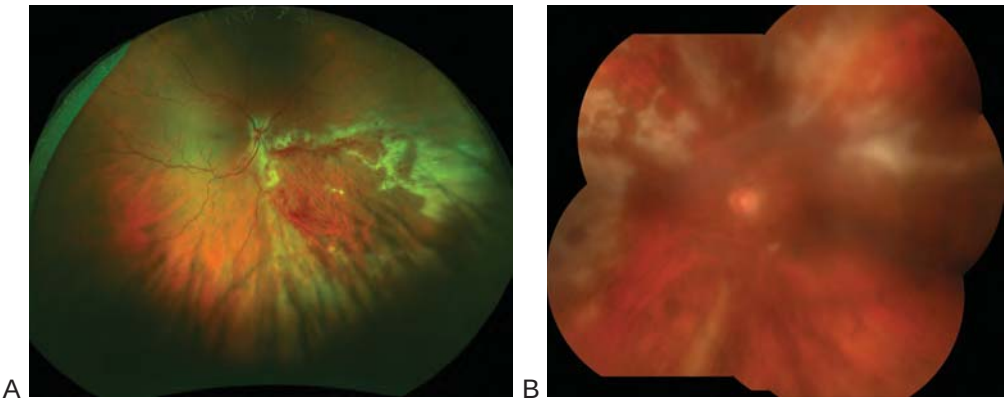

Figure 11-15 Cytomegalovirus retinitis. **A,** Retinitis with a hemorrhagic component in a patient with AIDS. **B,** Granular appearance of retinitis in a patient after renal transplant. *(Courtesy of Lucia Sobrin, MD.)*

results in restoration of anti-CMV T-cell immunity—usually at $CD4^+$ T-cell counts greater than 200/μL. Immune recovery uveitis and its complications, most notably CME and epiretinal membrane formation, occur in approximately 20% of HIV-seropositive patients following immune reconstitution. Up to 50% of eyes with CMV retinitis eventually develop a rhegmatogenous retinal detachment.

CMV retinitis can occur in the absence of HIV infection/AIDS. This scenario almost always is associated with relative immunosuppression, such as that which occurs in organ transplant recipients and in other patients with use of systemic corticosteroids, steroid-sparing immunosuppressive agents, or chemotherapeutics.

Non-CMV Necrotizing Herpetic Retinitis

Both varicella-zoster virus (VZV) and herpes simplex virus (HSV) infection can cause necrotizing retinitis in patients, whether or not they are immunocompromised. Unlike CMV infection, these infections can progress rapidly and therefore should be treated aggressively. Two distinct clinical syndromes have been described: *acute retinal necrosis (ARN)* and *progressive outer retinal necrosis (PORN)*.

Characteristic features of ARN include the presence of 1 or more foci of retinitis, which usually occur in the periphery and are associated with occlusive retinal vasculitis and moderate to severe anterior chamber and vitreous inflammation (Fig 11-16).

PORN occurs in patients who are severely immunocompromised and consists of rapidly progressive, multifocal necrotizing retinitis with little or no anterior chamber or vitreous inflammation. PORN is rare because it occurs only with more severe immunosuppression in which the immune system is unable to mount any significant response to infection. Compared with ARN, PORN is associated with more rapid progression (Fig 11-17).

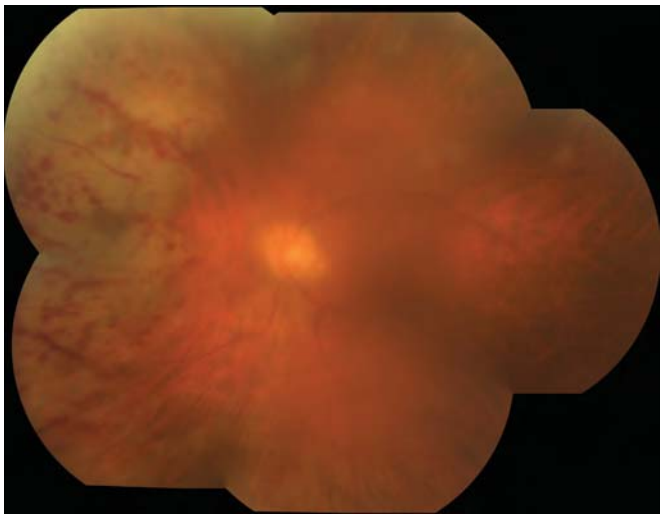

Figure 11-16 Peripheral necrotizing herpetic retinitis (acute retinal necrosis). Color fundus photograph montage shows intraretinal hemorrhage and full-thickness opacification of the retina. *(Courtesy of Lucia Sobrin, MD.)*

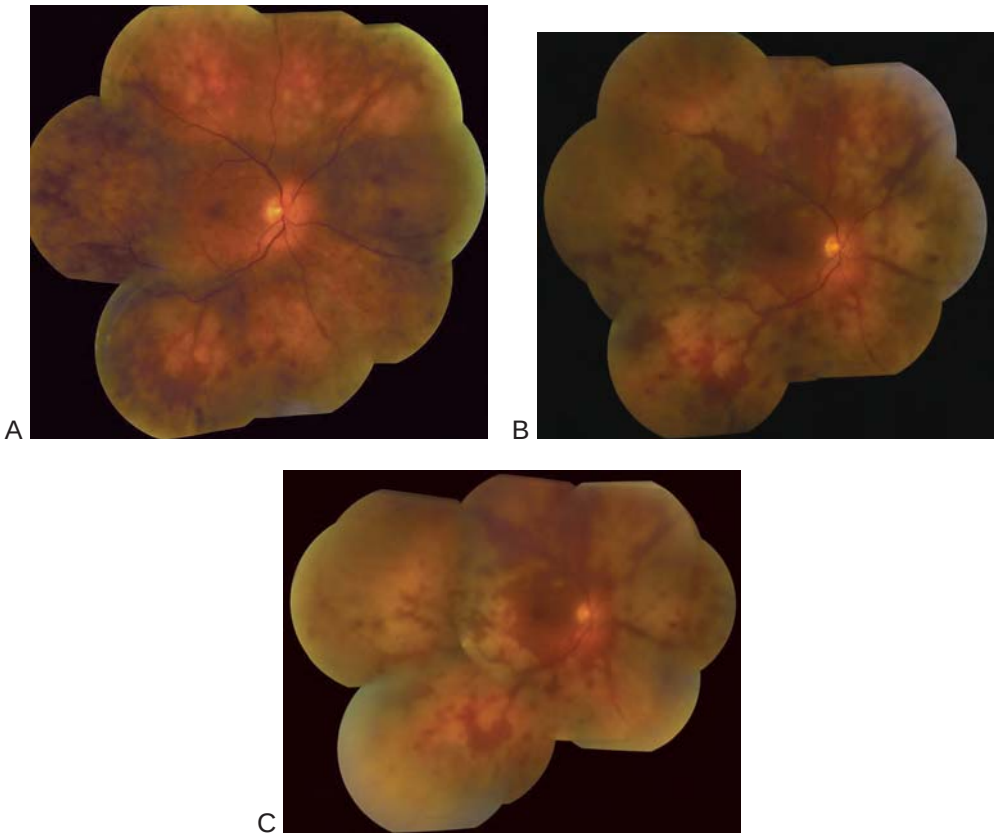

Figure 11-17 Progressive outer retinal necrosis (PORN) syndrome in a patient severely immunocompromised from high-dose chemotherapy for mantle cell lymphoma. The color fundus photograph montages show the rapid progression of retinitis and coalescence of lesions in the absence of vitreous inflammation from initial presentation **(A),** day 3 **(B),** and day 6 **(C).** An aqueous biopsy specimen was positive for varicella-zoster virus on polymerase chain reaction (PCR) testing. *(Courtesy of Daniel F. Martin, MD, and Stephen J. Kim, MD.)*

Evaluation should include serologic testing for syphilis as well as intraocular fluid aspiration for use in PCR analysis for VZV, HSV, CMV, and *Toxoplasma gondii.* VZV infection is the most commonly identified cause of both ARN and PORN. Because ARN and PORN progress rapidly, treatment should commence immediately upon suspicion of either (Table 11-3). Some specialists initiate therapy with intraocular injection of ganciclovir or foscarnet, particularly when the macula or optic nerve is threatened. High-dose antiviral therapy, using either intravenous acyclovir or oral valacyclovir (2 g, 3 times daily), should be administered initially. Thereafter, immunocompetent patients should be treated with oral suppressive therapy; treatment duration can vary from several months to long-term, even lifelong treatment. Patients with HIV infection/AIDS should be treated at least until the $CD4^+$ cell count exceeds 200/μL, or perhaps indefinitely. Once antiviral therapy is initiated, systemic corticosteroids may be added in nonimmunocompromised patients and then tapered over several weeks. Retinal detachment is a common complication of

Table 11-3 Treatment Options for Herpetic Retinitis Caused by Cytomegalovirus (CMV), Varicella-Zoster Virus (VZV), or Herpes Simplex Virus (HSV) Infection

Intraocular Treatment			
Causative Virus	**Drug**	**Dose**	**Maintenance/Suppression**
CMV, VZV, HSV	Ganciclovir	2 mg	
	Foscarnet	1.2–2.4 mg	
CMV only	Ganciclovir intraocular implant[a]	4.5 mg	The implant was designed to release the drug over a 5- to 8-month period.
Systemic Treatment			
Causative Virus	**Drug**	**Induction/High Dose**	**Maintenance/Suppression**
CMV			
	Valganciclovir	900 mg twice daily	900 mg once daily
	Ganciclovir[b]	5 mg/kg, intravenously, every 12 hours for 2 weeks	
	Foscarnet[b,c]	90 mg/kg, intravenously, every 12 hours for 2 weeks	
VZV/HSV			
	Acyclovir[b]	10 mg/kg, intravenously, every 8 hours	800 mg, orally, 5 times daily
	Valacyclovir[b]	2 g, orally, 3 times daily	1 g, orally, 3 times daily
	Prednisone (optional)	0.5 mg/kg/day for 3–6 weeks[d]	

[a] No longer clinically available.
[b] Standard adult dosages. Monitoring of kidney function is required, as kidney toxicity can occur. Note that ganciclovir-resistant CMV strains exist; thus, after initiation of ganciclovir, close monitoring for response is required.
[c] Monitoring of bone marrow function is required, as suppression can occur.
[d] After antiviral therapy is initiated.

necrotizing retinitis, occurring in up to 70%–75% of cases, and reattachment surgery often is complex and requires silicone oil placement.

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

Endogenous Bacterial Endophthalmitis

Endogenous bacterial endophthalmitis results from hematogenous seeding of the eye, typically during transient bacteremia. A wide range of bacteria can cause endogenous bacterial endophthalmitis. In North America, 40% of cases occur in patients with endocarditis, most typically caused by infection with either *Staphylococcus* or *Streptococcus* species. In contrast, 60% of endogenous endophthalmitis cases in Asia occur in patients with liver abscesses caused by *Klebsiella pneumoniae* infection. Nearly one-third of cases occur in patients who have urinary tract infections, most often caused by *Escherichia coli.* Other

cases can be associated with intravenous drug use or with procedures known to produce bacteremia, particularly placement of indwelling catheters.

Clinical presentation can vary and depends on both the size of the inoculum and the virulence of the organism; it ranges from a focal chorioretinitis (Fig 11-18) with little vitreous inflammation to a dense panophthalmitis that obscures the view of the posterior segment. Although decreased vision and eye pain are common symptoms, many patients do not have any constitutional symptoms. The patient should undergo systemic evaluation for the source of infection, and treatment with systemic antibiotics should be initiated. In addition, intravitreal injection of broad-spectrum antibiotics should be considered.

Fungal Endophthalmitis

Endophthalmitis caused by fungal infections may be either endogenous or exogenous. *Exogenous fungal endophthalmitis* is uncommon in North America and Europe. In contrast, in tropical regions such as India, fungi account for up to one-fifth of culture-positive cases following surgery or trauma. *Endogenous fungal endophthalmitis* is rare regardless of setting and typically occurs in either severely immunocompromised patients with persistent fungemia or otherwise healthy persons who inject drugs following transient fungemia.

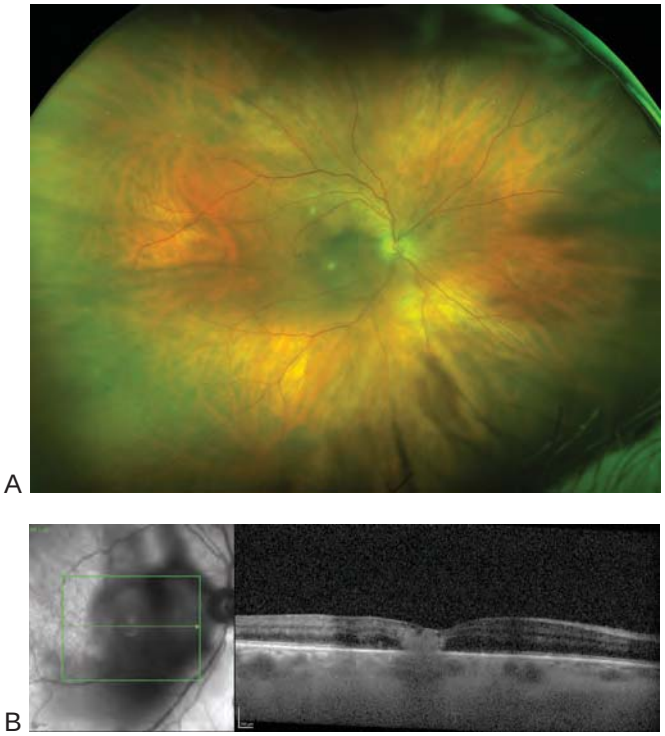

Figure 11-18 Endogenous bacterial endophthalmitis. **A,** Fundus photograph from a patient with *Streptococcus mitis* endocarditis shows 3 focal yellow chorioretinal infiltrates, as well as vitritis concentrated over the macula. **B,** OCT demonstrates the full-thickness hyperreflectivity of the macular chorioretinal lesion. *(Courtesy of Lucia Sobrin, MD.)*

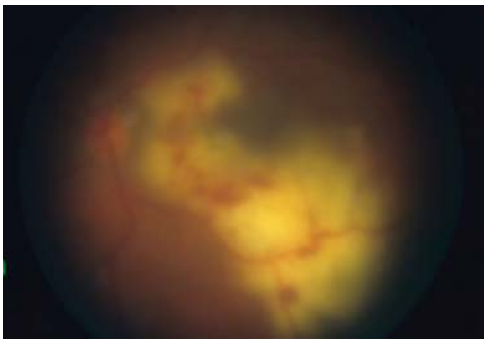

Figure 11-19 Fundus photograph of endophthalmitis caused by infection with *Aspergillus* species. Features present include vitritis, a diffuse macular chorioretinal lesion with subretinal infiltration, and intraretinal hemorrhage. *(Courtesy of Dean Eliott, MD.)*

The clinical presentation is often subacute, and the diagnosis is typically delayed for weeks. *Aspergillus* (Fig 11-19) and *Fusarium* are the most commonly identified pathogens. Fungal keratitis may also progress to endophthalmitis, most typically when caused by *Fusarium*. Treatment is frequently difficult and typically involves vitrectomy, intravitreal injection of amphotericin B (5 μg/0.1 mL) and/or voriconazole (0.1 mg/0.1 mL), and systemic antifungal therapy. Two-thirds of patients with fungal endophthalmitis lose useful vision.

Endogenous yeast endophthalmitis is most frequently caused by *Candida* species. Affected patients frequently have previously used illicit intravenous drugs or indwelling catheters or have undergone long-term antibiotic treatment or immunosuppressive therapy. Many also have a history of hyperalimentation, recent abdominal surgery, or diabetes mellitus. The initial intraocular inflammation is usually mild to moderate, and yellow-white choroidal or chorioretinal lesions may be single or multiple (Fig 11-20). Subretinal infiltrates may coalesce into a mushroom-shaped white nodule that projects through the retina into the vitreous. Exogenous *Candida* endophthalmitis is rare.

The diagnosis of *Candida* endophthalmitis is usually made according to the history, clinical setting, and presence of characteristic fundus features. Intraocular culture specimens are best obtained during pars plana vitrectomy.

If the macula is not involved, the visual prognosis after treatment is generally good. Chorioretinal lesions are often successfully treated with systemic medications alone, for example, intravenous fluconazole or voriconazole, which penetrates the eye well.

Durand ML. Bacterial and fungal endophthalmitis. *Clin Microbiol Rev.* 2017;30(3):597–613.

Ocular Tuberculosis

Even though one-third of the world's population has been exposed to *Mycobacterium tuberculosis,* active *M tuberculosis* uveitis is uncommon, even in endemic areas. Suggestive clinical findings include solitary (Fig 11-21) or MFC, serpiginous-like chorioretinitis, and Eales disease–like peripheral nonperfusion in association with uveitis. Patients suspected of having tuberculous uveitis should undergo testing for prior *M tuberculosis* exposure, including a chest x-ray and a blood-based interferon-gamma release assay.

Once the diagnosis of ocular tuberculosis is either confirmed or strongly suggested, the patient should be treated for extrapulmonary tuberculosis as recommended by either the US Centers for Disease Control and Prevention (CDC) or the World Health Organization.

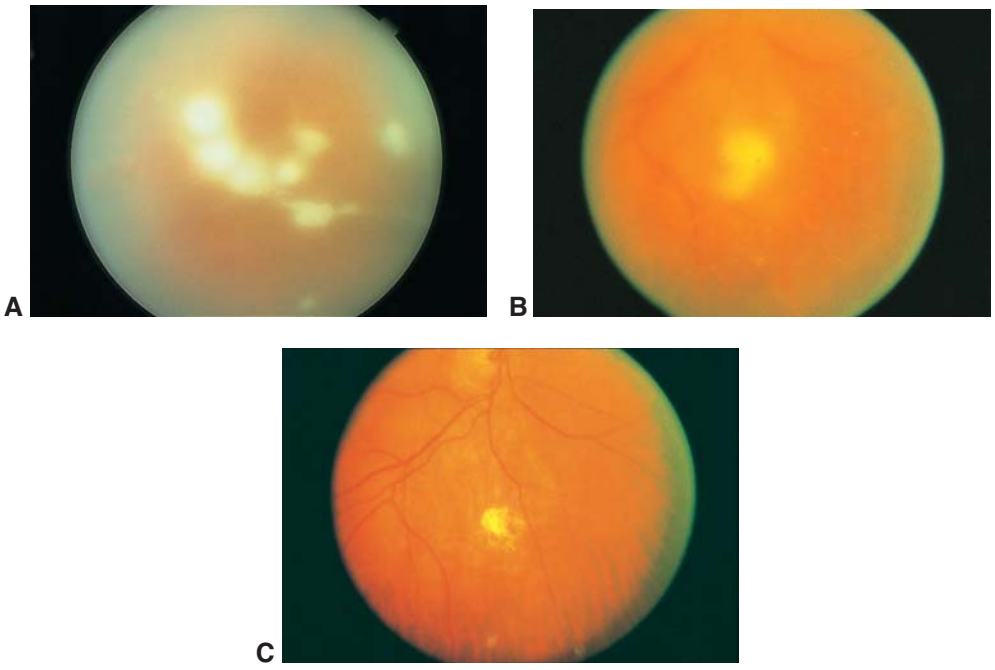

Figure 11-20 Fundus photographs of endogenous yeast *(Candida)* endophthalmitis. **A,** Note the vitreous infiltrates in a "string of pearls" configuration. **B,** Photograph from a patient with endogenous endophthalmitis before treatment. **C,** After treatment with vitrectomy and intravitreal amphotericin B, the endogenous endophthalmitis shown in **B** was resolved. *(Courtesy of Harry W. Flynn, Jr, MD.)*

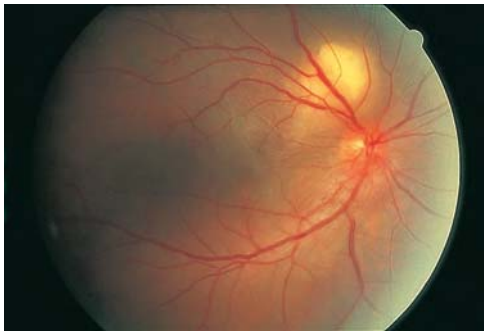

Figure 11-21 Ocular tuberculosis. Fundus photograph shows a choroidal granuloma superotemporal to the optic nerve head. The inflammation can be localized to the choroid as the overlying retina and retinal vessels are relatively spared. *(Courtesy of Janet L. Davis, MD.)*

Ethambutol hydrochloride, a medication commonly used in the treatment of tuberculosis, can cause optic neuropathy; patients taking ethambutol need close monitoring for this treatment complication.

Agrawal R, Testi I, Mahajan S, et al; Collaborative Ocular Tuberculosis Study Consensus Group. Collaborative Ocular Tuberculosis Study consensus guidelines on the management of tubercular uveitis—report 1: guidelines for initiating antitubercular therapy in tubercular choroiditis. *Ophthalmology.* 2021;128(2):266–276.

Syphilitic Retinochoroiditis

Uveitis is often the presenting sign of syphilis but can occur at any stage of the infection. Syphilitic uveitis is confirmed through serologic testing. The traditional screening algorithm for syphilis uses a nontreponemal assay (eg, the nonspecific but quantitative VDRL or rapid plasma reagin [RPR] test) for primary evaluation and if the test is reactive, a treponemal assay (eg, fluorescent treponemal antibody absorption [FTA-ABS] test, *Treponema pallidum* particle agglutination assay [TP-PA], microhemagglutination assay for *T pallidum* antibodies [MHA-TP]) for confirmation. More recently, laboratories have reversed the order in which treponemal and nontreponemal tests are performed, leading to the development of the reverse sequence syphilis screening (RSSS) algorithm. Although the CDC currently continues to recommend the traditional testing approach, it provides a recommended algorithm for the use of RSSS. Briefly, initial testing is done with a treponemal assay, followed by a quantitative nontreponemal test for confirmation. Discordant samples are resolved on the basis of a second treponemal assay.

For patients with uveitis whose serologic test results are positive for syphilis, cerebrospinal fluid (CSF-) VDRL titers should be assessed before and, if the CSF-VDRL results are positive, after completion of treatment in order to document a complete response.

Many patients with syphilitic uveitis present with a nondescript panuveitis, which supports the need for routine syphilis testing in all sexually active patients with uveitis. Specifically suggestive clinical findings include inflammatory ocular hypertensive syndrome, iris roseola, and retinochoroiditis. The retinochoroiditis is often diaphanous—appearing less opaque than either herpetic or toxoplasmic retinitis—and is accompanied by overlying inflammatory accumulations called *retinal precipitates.* A distinctive form of syphilitic outer retinitis termed *acute syphilitic posterior placoid chorioretinitis (ASPPC)* is characterized by the presence of a placoid, round or oval, yellow lesion that involves or is near the macula (Fig 11-22). Because coinfection is common, all patients with syphilis should be tested for HIV. Patients with syphilitic uveitis should be treated for neurosyphilis.

Begaj T, Sobrin L. Ophthalmic consequences of syphilis. *Int Ophthalmol Clinics.* 2022;62(2):251–268.

Ocular Bartonellosis

Cat-scratch disease, caused by *Bartonella,* is associated with 2 ocular syndromes: Parinaud oculoglandular syndrome, which consists of conjunctival inflammation with preauricular adenopathy; and Leber stellate neuroretinitis, which includes macular star formation and optic nerve head swelling, often associated with a peripapillary serous macular detachment (Fig 11-23). Cat-scratch disease is the most common cause of neuroretinitis with stellate maculopathy, but several other infectious diseases can have this presentation, including toxoplasmosis, ehrlichiosis, and syphilis. Small, focal areas of retinitis or chorioretinitis are frequently noted in patients with *Bartonella* neuroretinitis. In rare cases, an optic nerve head angiomatous lesion can develop. Treatment with antibiotics is necessary in immunocompromised adults or in patients with persistent infection.

Toxoplasmic Chorioretinitis

Toxoplasmosis is the most common cause of posterior segment infectious disease worldwide. The causative organism, *Toxoplasma gondii,* is an obligate intracellular parasite.

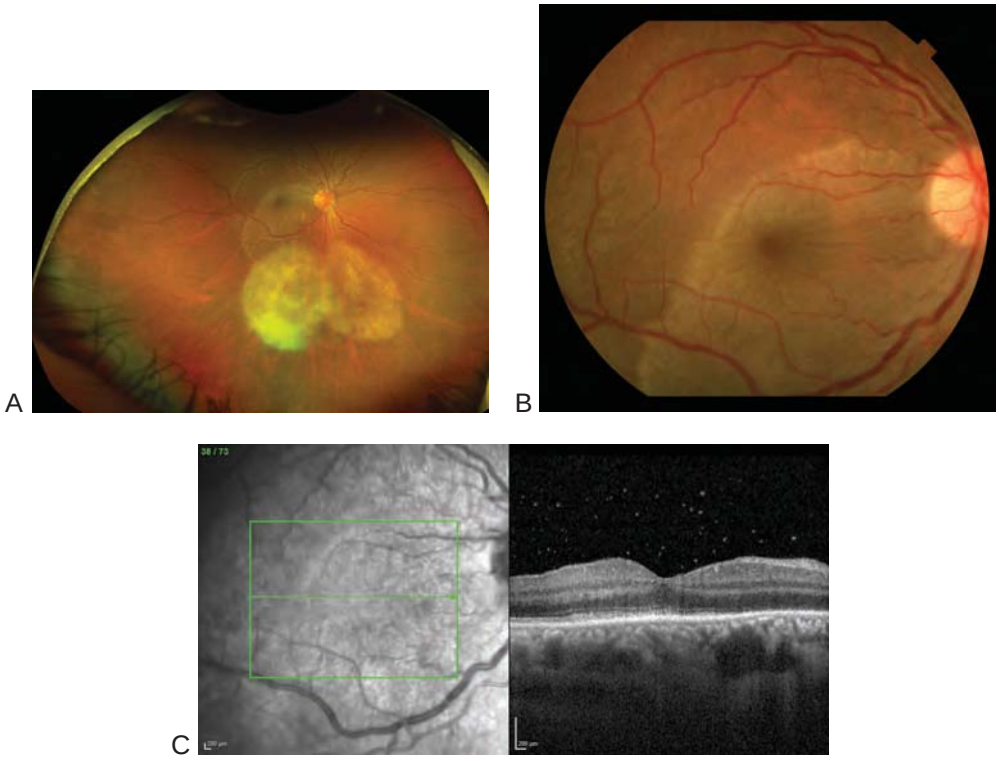

Figure 11-22 Syphilitic retinochoroiditis. **A,** Ultra-wide-field fundus photograph montage shows a right eye with a large placoid yellow lesion in the macula consistent with acute syphilitic posterior placoid chorioretinitis (ASPPC). In the inferior midperiphery are 2 other large areas of retinitis with overlying retinal precipitates. **B,** Fundus photograph shows a magnified view of ASPPC. **C,** OCT image demonstrates disruption of outer retinal layers with hyperreflective deposits in the area of ASPPC. *(Courtesy of Lucia Sobrin, MD.)*

Because seropositivity for *T gondii* is very common, seropositivity alone does not confirm that uveitis is related to toxoplasmosis. Congenital disease occurs via transplacental infection; a pregnant woman acquires the organism through exposure to tissue cysts or oocytes in uncooked meat or substances contaminated with cat feces (see also BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* Chapter 25). The typical ocular finding in congenital toxoplasmosis is a chorioretinal scar, usually in the macula and often bilateral.

Most cases of toxoplasmosis are currently assumed to be acquired postnatally, although proving this assumption can be difficult. A positive serologic test result for immunoglobulin (Ig) M anti–*T gondii* antibodies supports the diagnosis of acquired disease. PCR analysis of ocular fluids for *T gondii* DNA and determining the Goldmann-Witmer coefficient to compare the IgG level in ocular fluid with that in serum can also assist in confirming the diagnosis. Of note, PCR analysis of ocular fluid for *Toxoplasma* is not as sensitive or specific as PCR analysis of ocular fluid for herpes virus (see BCSC Section 9, *Uveitis and Ocular Inflammation,* Chapter 5).

Decreased vision and floaters are the most common presenting symptoms of toxoplasmic chorioretinitis. Clinically, the condition consists of a focal area of intense, necrotizing

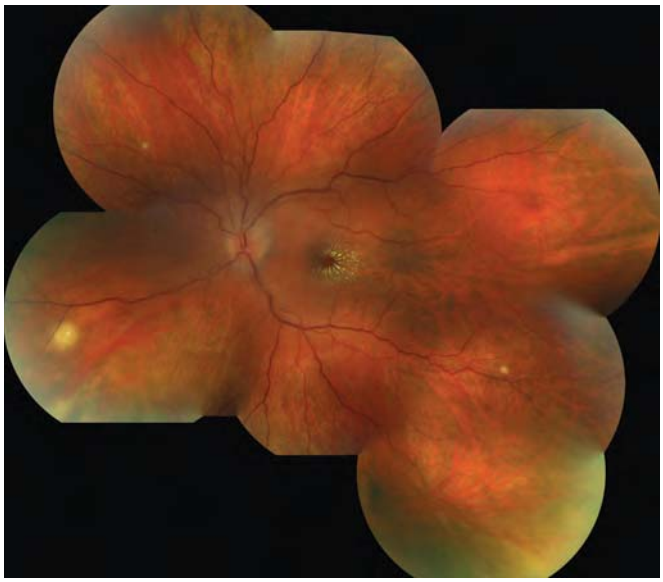

Figure 11-23 Color fundus photograph montage of neuroretinitis shows optic nerve head swelling and a macular star formation resulting from cat-scratch disease *(Bartonella henselae infection)*. In the inferonasal periphery, a small focal area of chorioretinitis is visible. Two smaller foci are visible in the inferotemporal and superonasal periphery. *(Courtesy of Lucia Sobrin, MD.)*

chorioretinitis, typically with moderate to severe overlying vitreous inflammation (Fig 11-24). Recurring disease is indicated by an adjacent or nearby chorioretinal scar. Multiple active lesions are rare and should prompt HIV testing and inquiry for other possible causes of immunosuppression. HIV-seropositive patients with ocular toxoplasmosis have a high risk of CNS involvement and thus should undergo magnetic resonance imaging with contrast material. Older adult patients may present with more aggressive disease because of their relative immunosuppression.

Active ocular toxoplasmosis is commonly treated with antibiotics, despite the lack of well-designed randomized controlled trials. The simplest approach is treatment with trimethoprim-sulfamethoxazole. Classic therapy uses sulfadiazine with pyrimethamine and prednisone (prescribed with folinic acid and accompanied by regular monitoring of blood cell counts); the addition of clindamycin results in so-called quadruple therapy. Atovaquone and azithromycin are also commonly used in clinical practice. None of these approaches has been shown to be superior to another for the final visual outcome, lesion size, or recurrence rate. Treatment typically lasts 4–6 weeks, and complete healing of active lesions occurs over 4–6 months. When used, systemic corticosteroids should be given under antibiotic cover. Use of long-acting, depot periocular or intraocular corticosteroid injections should be avoided. Long-term maintenance treatment with trimethoprim-sulfamethoxazole has been used to decrease the attack rate in patients experiencing frequent recurrences or in severely immunosuppressed patients. Intravitreal clindamycin with or without dexamethasone has been used to treat vision-threatening lesions or for patients who are intolerant of or who do not respond to systemic therapy.

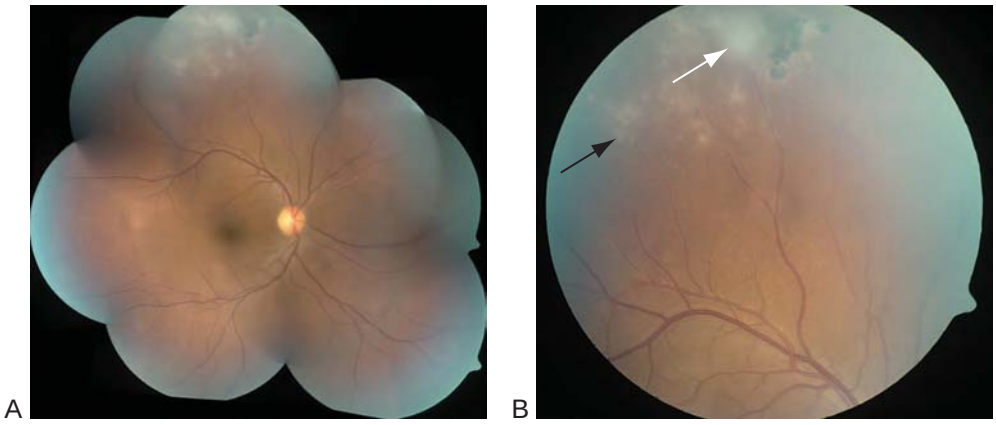

Figure 11-24 Toxoplasmic chorioretinitis. **A,** Color fundus photograph montage from a patient with recurring toxoplasmic chorioretinitis. **B,** Color fundus photograph shows white focal retinitis *(white arrow)* with overlying vitreous inflammation, which creates a "headlight in the fog" appearance, with an adjacent pigmented chorioretinal scar. Accompanying perivasculitis and nonspecific exudates are present, in addition to distinct lobular periarteriolar collections of cells *(black arrow)* called *Kyrieleis plaques*. *(Courtesy of Stephen J. Kim, MD.)*

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.

Toxocariasis

Toxocariasis is a parasitic infection caused by 1 of 2 roundworms, *Toxocara canis* or *Toxocara cati,* which are common intestinal parasites of dogs and cats, respectively. Humans are most commonly infected following ingestion of soil or vegetables contaminated by the *Toxocara* eggs. Although ocular toxocariasis is part of a systemic infestation by the nematode, systemic manifestations such as visceral larva migrans, fever, and eosinophilia are relatively uncommon. Children and young adults are affected disproportionately. Common ocular symptoms include decreased vision and floaters. The condition is unilateral in most cases and typically has 1 of 3 presentations:

- peripheral granuloma, which often produces a traction band that extends toward the macula (Fig 11-25) and occasionally mimics unilateral intermediate uveitis with snowbank formation
- posterior pole granuloma, which can decrease vision dramatically when the central macula is involved
- moderate to severe panuveitis that can mimic endogenous endophthalmitis

Enzyme-linked immunosorbent assay (ELISA) analysis of serum or intraocular fluids can help establish the diagnosis in these cases but is relatively insensitive. Vitreous inflammation, CME, and traction retinal detachment are the most common causes of vision

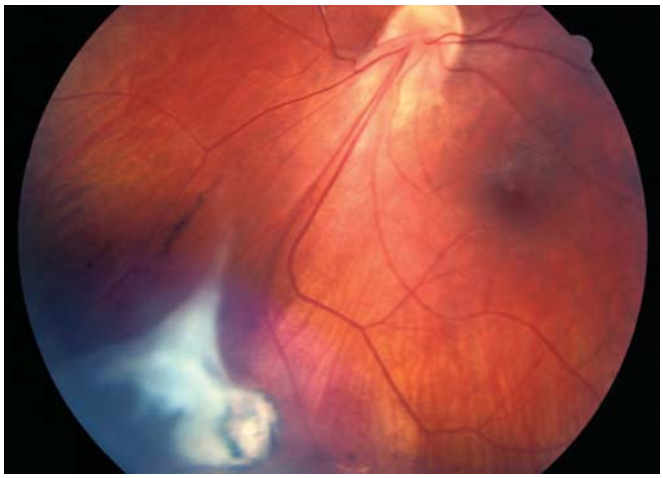

Figure 11-25 Fundus photograph from a 6-year-old boy with reduced and distorted vision. The image shows a peripheral toxocariasis cyst with associated fibrosis *(bottom left)*. The fibrosis results in considerable traction, and the macula is dragged inferiorly and distorted. *(Courtesy of Colin A. McCannel, MD.)*

loss. Most specialists assume that the uveitis of toxocariasis represents an immune response to antigens released from a dead or dying worm. Thus, treatment typically involves use of local or systemic corticosteroids, and anthelmintic therapy has little or no therapeutic role.

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.

Ocular Lyme Borreliosis

Lyme disease is caused by the spirochete *Borrelia burgdorferi,* which is transmitted to humans through the bite of infected ticks. Following the tick bite, the disease usually occurs in 3 stages. In stages 1 and 2, systemic manifestations consist of myalgias, arthralgias, fever, headache, malaise, and a characteristic skin lesion known as *erythema chronicum migrans* (bull's-eye rash), which consists of an annulus of erythema surrounding an area of central clearing. In stage 3, as neurologic or musculoskeletal findings manifest, ocular inflammation may develop but is uncommon. Lyme disease–related ocular findings include keratitis, scleritis, and uveitis, which may include anterior chamber or vitreous inflammation, retinal vasculitis, papillitis, or optic neuritis. Chronic uveitis in patients who reside in or have traveled to an endemic area or who have had a recent tick bite or an erythema migrans–like skin lesion should suggest the possibility of Lyme disease.

Initial serologic testing is performed using a sensitive ELISA. If an ELISA is positive or equivocal, separate IgM immunoblotting (if symptoms have been present for fewer than 30 days) and IgG immunoblotting should be performed on the same blood sample. A diagnosis of Lyme disease is supported only when results of both tests are positive. The 2 tests are designed to be used together; thus, the initial ELISA test should not be skipped.

Treatment for early disease consists of tetracycline, doxycycline, or penicillin. Advanced disease may require intravenous ceftriaxone or penicillin.

Raja H, Starr MR, Bakri SJ. Ocular manifestations of tick-borne diseases. *Surv Ophthalmol.* 2016;61(6):726–744.

Diffuse Unilateral Subacute Neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) is a rare condition that typically occurs in otherwise healthy, young patients and is caused by the presence of a mobile subretinal nematode. The causative nematodes in DUSN have yet to be definitively established, although *Toxocara* species, *Baylisascaris procyonis,* and *Ancylostoma caninum* have all been implicated. Prompt diagnosis and treatment of the condition can help prevent vision loss, which may be severe. The clinical findings in DUSN can be divided into acute and end-stage manifestations. In the acute phase, patients frequently have decreased visual acuity, vitritis, papillitis, and clusters of gray-white or yellow-white outer retinal and choroidal lesions. The clustering of the lesions is important because it often helps localize the mobile nematode. The degree of vision loss is often greater than might be expected from clinical examination findings. If DUSN is left untreated, late sequelae ultimately develop and include optic atrophy, retinal arterial narrowing, and diffuse RPE disruption with severe vision loss. The late findings may be misinterpreted as unilateral retinitis pigmentosa.

If the nematode can be visualized, it should be destroyed using laser photocoagulation (Fig 11-26).

de Amorim Garcia Filho CA, 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.

West Nile Virus Chorioretinitis

West Nile virus infection is transmitted to humans through the bite of an infected mosquito of the genus *Culex,* with birds serving as the primary reservoir. Human infection is most often subclinical, although a febrile illness occurs in approximately 20% of cases. Neurologic disease (meningitis or encephalitis) is common, frequently found in association with diabetes mellitus and advanced age. Ocular manifestations occur primarily in diabetic patients with encephalitis. The eye manifestation most commonly noted with West Nile virus infection is a multifocal chorioretinitis that is usually bilateral and includes lesions arranged in distinctive linear clusters that often follow the course of retinal nerve fibers (Fig 11-27). Vision typically remains good unless the lesions involve the central macula.

Zika Virus Chorioretinitis

Zika virus (ZIKV) is a member of the family Flaviviridae and is related to yellow fever virus, dengue virus, and West Nile virus. ZIKV is spread primarily by the female *Aedes aegypti* mosquito. Infection in adults is often asymptomatic or results in only mild symptoms. Infection during pregnancy, however, can result in severe microcephaly and other

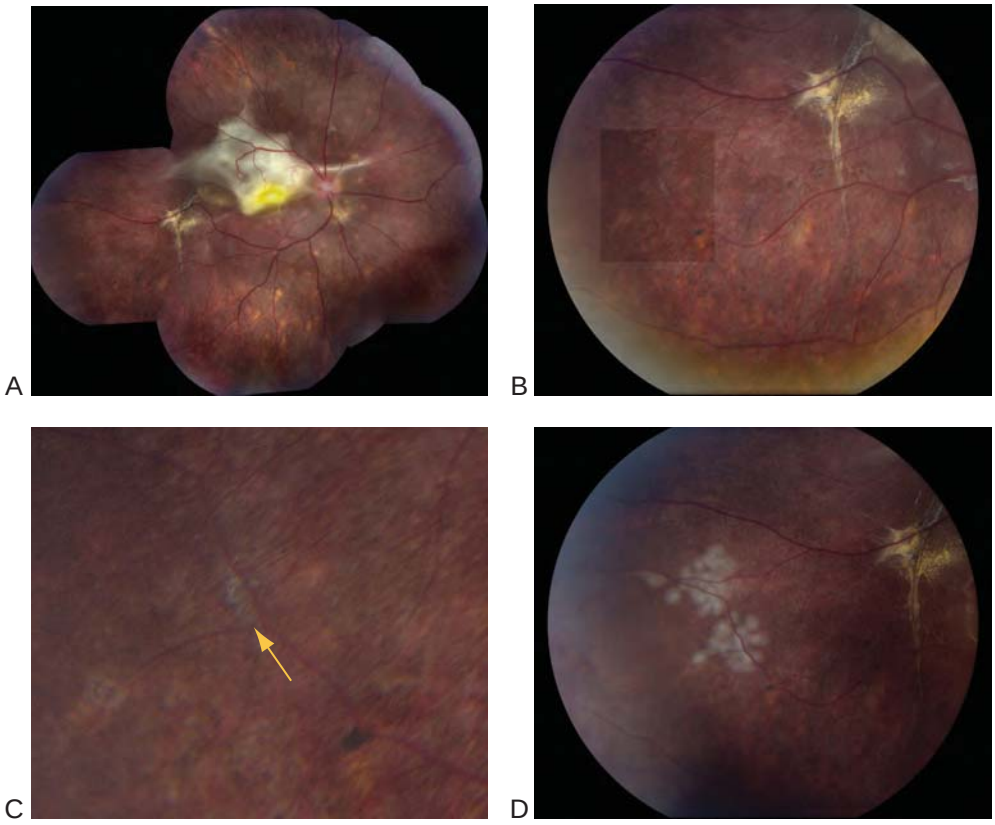

Figure 11-26 Diffuse unilateral subacute neuroretinitis. An 11-year-old boy presented with decreased vision in the right eye. Examination findings included moderate vitritis and a relative afferent pupillary defect in addition to multiple chorioretinal lesions and submacular fibrosis. A worm was not found, and the patient was treated with albendazole. **A,** Once vitreous inflammation had decreased, multifocal areas of chorioretinal scarring in the periphery as well as submacular fibrosis were visible. **B,** In the inferotemporal periphery, a worm was identified. **C,** With higher magnification, the small grayish worm *(arrow)* was visible. **D,** Laser spots were applied directly to the worm. The patient's vision subjectively improved, and no further lesions or inflammation was seen. *(Courtesy of Jaclyn Kovach, MD.)*

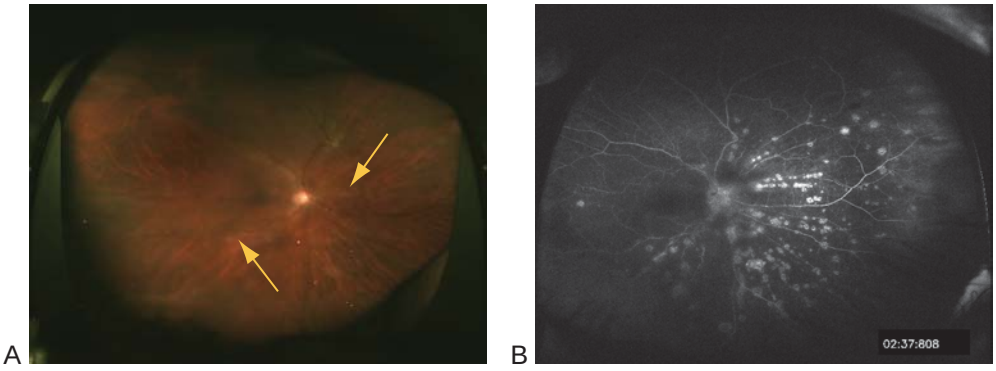

Figure 11-27 West Nile virus chorioretinitis. **A,** Fundus photograph shows chorioretinal lesions in a linear configuration *(arrows)*. **B,** FA image shows staining of lesions that are characteristically arranged in a linear configuration in some areas. *(Courtesy of Dean Eliott, MD.)*

brain malformations in some infants. Macular and optic nerve abnormalities as well as chorioretinal lesions have been reported in some patients with ZIKV infection.

Ebola Virus Panuveitis

Ebola virus causes a severe and fatal hemorrhagic fever in humans; the mortality rate is as high as 90%. The virus is transmitted by direct contact with infected blood or other body fluids. Among survivors, uveitis has been described. There has been 1 report of severe panuveitis that occurred after the patient experienced a complete systemic recovery but still had persistent viral replication in the aqueous humor.

Chikungunya Virus Retinitis

Chikungunya virus (CHIKV) is a species of the genus *Alphavirus*. Typically, the virus is transmitted to humans by a mosquito bite. The most common symptoms of CHIKV infection are fever and joint pain. Several ocular findings have been reported, including retinitis and optic neuritis, but anterior uveitis may be the most common presentation.