CHAPTER 9

Posterior Uveitis: The White Dot Syndromes

Highlights

- White dot syndromes are noninfectious inflammatory chorioretinopathies that usually have no associated systemic inflammatory disease.
- A patient with a suspected white dot syndrome should be evaluated for tuberculosis and syphilis.
- Diagnosis of a white dot syndrome is based primarily on clinical characteristics observed on ophthalmic examination and imaging; there are no confirmatory diagnostic tests.
- Many white dot syndromes require treatment with systemic immunomodulatory therapy.
- Diagnosis and management of autoimmune retinopathy can be challenging because the presence of most serum antiretinal antibodies has unclear significance and the disease may have a poor response to therapies used for other types of ocular inflammation.

Definitions

Posterior uveitis is defined as intraocular inflammation that involves mainly the retina and/or choroid. Although inflammatory cells may be observed in the vitreous, the main site of inflammation must be retinal or choroidal to be defined as posterior uveitis. Retinal vasculitis *with vascular occlusion* is also classified as posterior uveitis. Posterior segment findings such as macular edema, *peripheral* retinal vasculitis, and optic disc edema are not indicators of posterior or panuveitis unless retinal or choroidal inflammatory lesions are also present. For example, if an eye with human leukocyte antigen (HLA)-B27–associated anterior uveitis develops macular edema, the inflammation is not reclassified as posterior uveitis.

This chapter discusses the *white dot syndromes,* a group of posterior uveitic entities that usually have no associated systemic inflammatory disease:

- birdshot chorioretinopathy
- acute posterior multifocal placoid pigment epitheliopathy

- serpiginous choroiditis
- multifocal choroiditis and panuveitis
- punctate inner choroiditis
- subretinal fibrosis and uveitis syndrome
- multiple evanescent white dot syndrome
- acute retinal pigment epitheliitis
- acute zonal occult outer retinopathy
- acute idiopathic maculopathy

Although autoimmune retinopathy is not a white dot syndrome, it is also included in this chapter because it is a presumably immune-mediated retinal degeneration that shares symptoms (eg, decreased vision, scotomas, photopsias) with the white dot syndromes. Posterior uveitis and panuveitis with systemic manifestations are covered in Chapter 10.

Overview of the White Dot Syndromes

The white dot syndromes are a group of inflammatory chorioretinopathies characterized by multiple, discrete yellow-white lesions at the level of the retina, outer retina, retinal pigment epithelium (RPE), choriocapillaris, and/or choroid. The morphology of the lesions varies from syndrome to syndrome, although there is some overlap. Symptoms include photopsias, blurred vision, nyctalopia, floaters, an enlarged blind spot, and visual field loss. A viral prodrome may also be described. Although bilateral or asymmetric presentation is typical with these disorders, unilateral involvement also occurs. See Table 9-1 for a summary of patient demographics and clinical findings associated with white dot syndromes.

The etiology of the white dot syndromes is unknown. Some investigators have postulated an infectious cause; others have proposed an autoimmune/inflammatory origin. The increased prevalence of systemic autoimmune disease in patients and their family members suggests that immune dysregulation does play a role in the pathogenesis of these syndromes.

The differential diagnosis of the white dot syndromes includes both infectious (eg, syphilis, tuberculosis [TB], diffuse unilateral subacute neuroretinitis [DUSN], and ocular histoplasmosis syndrome [OHS]) and noninfectious diseases (ie, sarcoidosis, sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome, and intraocular lymphoma). Although the diagnosis of a white dot syndrome is based primarily on clinical characteristics observed on ophthalmic examination and imaging, a careful history and review of systems as well as targeted laboratory testing are indicated to investigate the differential diagnoses in the workup of patients with a suspected white dot syndrome. Of note, there are no confirmatory diagnostic tests for the majority of the white dot syndromes.

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Gass JD. Are acute zonal occult outer retinopathy and the white spot syndromes (AZOOR complex) specific autoimmune diseases? *Am J Ophthalmol.* 2003;135(3):380–381.

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Birdshot Chorioretinopathy

Birdshot chorioretinopathy (BCR; also known as *birdshot uveitis, birdshot retinochoroidopathy,* and *vitiliginous chorioretinitis*) is most common in women and in individuals of northern European descent. Age at onset of BCR was traditionally 50–60 years; however, owing to improvements in diagnostic testing, diagnosis is increasingly common in patients younger than 45 years. No systemic disease is consistently associated with BCR, although the disorder is highly correlated with the HLA-A29 allele, with a sensitivity of 96% and a specificity of 93%. However, given that the HLA-A29 haplotype is common (eg, occurring in approximately 7% of the US population) whereas BCR is relatively rare, identification of the allele alone does not confirm a diagnosis. Uveitis with clinical features consistent with BCR must also be present.

Manifestations

Presenting symptoms may be bilateral or asymmetric and include blurred vision, floaters, nyctalopia, and color vision disturbances. Patient-reported symptoms may be out of proportion to visual acuity measurements, reflecting diffuse retinal dysfunction. In addition, unusual visual phenomena such as pinwheels, sparkles, or flickering lights may be indicators of subtle disease activity. Anterior segment inflammation is typically minimal or absent. Although patients usually have some inflammatory cells in the vitreous, they often lack substantial vitreous haze.

Ophthalmoscopy reveals characteristic multifocal, hypopigmented, cream-colored ovoid lesions (50–1500 µm) at the level of the choroid and RPE in the posterior and midzones of the fundus. These lesions often (but not exclusively) have a nasal and radial distribution that emanates from the optic nerve and frequently follows the underlying choroidal vessels (Fig 9-1). At initial presentation, the lesions may be prominent, or they may be quite subtle. Retinal vasculitis (best seen angiographically), uveitic macular edema, and optic disc inflammation are prominent features of active disease. Late complications of BCR include optic atrophy, macular thinning, loss of peripheral visual field, and choroidal neovascularization (CNV).

Key metrics for monitoring BCR disease progression and response to therapy include fluorescein angiography (FA), indocyanine green angiography (ICGA) (as accessible), optical coherence tomography (OCT), and visual field evaluations. Serial full-field electroretinogram (ERG), with attention to the 30-Hz flicker implicit time and scotopic b-wave amplitudes, may also be used. On FA, findings vary and can be subtle or nonspecific. For example, early lesions may show initial hypofluorescence with subtle late staining, whereas retinal vasculitis of the large arcade vessels or diffuse small vessel leakage, macular edema, and optic disc leakage represent more obvious active disease (Fig 9-2). ICGA may disclose multiple hypocyanescent (hypofluorescent) spots, typically in greater numbers than observed on clinical examination or FA (Fig 9-3). Although fundus autofluorescence (FAF) imaging is less useful than other techniques in detecting active BCR, it may reveal *hypo*autofluorescent areas of RPE atrophy, suggestive of long-standing disease. Visual field evaluation, meanwhile, may show substantial field loss despite good vision and minimal or no macular edema (Fig 9-4).

OCT may show signs of disease activity such as cystoid or noncystoid macular thickening (ie, inflammatory thickening without frank intraretinal fluid). Changes in macular thickening are best appreciated on OCT change maps collected over sequential visits

Table 9-1 Selected White Dot Syndromes

	BCR	APMPPE	Serpiginous Choroiditis	MFCPU
Age, years	30–70	20–50	20–60	10–70
Sex	F > M	M = F	M = F	F > M (3:1 ratio)
Laterality	Bilateral, may be asymmetric	Bilateral, may be asymmetric	Usually bilateral, may be asymmetric	Usually bilateral, may be asymmetric
Systemic associations	80%–98% HLA-A29 allele	Viral prodrome, cerebrovasculitis, CSF abnormalities	Rule out TB-associated disease	None
Onset	Insidious	Acute	Variable	Insidious
Course	Chronic, progressive	Self-limited	Chronic, recurrent	Chronic, recurrent
Symptoms	Blurred vision, floaters, photopsias, disturbed night and color vision	Photopsias, central and/or peripheral vision loss	Blurred vision, scotomas	Blurred vision, floaters, photopsias, metamorphopsia, scotomas, blind-spot enlargement
Examination findings	Vitritis; ovoid, creamy, white-yellow, posterior and midzone lesions, 50–1500 µm; do not pigment	Multifocal, flat, yellow-white lesions, 1–2 disc areas; outer retina/RPE with evolving pigmentation	Geographic, gray-white or creamy yellow, peripapillary, macular chorioretinal lesions with centrifugal extension; activity at leading peripheral edge with RPE/choriocapillaris atrophy in its wake	Myopia, anterior uveitis (50%), vitritis (100%); active white-yellow chorioretinal lesions, 50–200 µm; evolving to punched-out scars
Structural complications	Retinal vasculitis, disc edema, ME, CNV (6%)	Disc edema, pigment alterations	CNV (25%), RPE mottling, scarring, loss of choriocapillaris	Optic disc edema, peripapillary pigment changes, ME (14%–44%), macular subretinal fibrosis, CNV
FA findings	Early hypofluorescence vs silence, subtle late stain; leakage from disc, vessels, ME; delayed retinal circulation time	Acute lesions: early blockage, late staining; late window defects	Early hypofluorescence; late staining/leakage of active border; leakage in presence of CNV	Early blockage, late staining of lesions; leakage from ME; CNV
ICGA findings	Corresponding hypocyanescent lesions more numerous than on examination, FA	Hypocyanescent spots corresponding to those seen on examination, FA	Early hypocyanescence; late staining more widespread than seen on examination, FA	Multiple hypocyanescent lesions, confluence around optic nerve more numerous than seen on examination, FA
FAF findings	HypoAF spots more numerous than clinically apparent lesions; macular hypoAF	HyperAF areas correspond to FA blockage; hypoAF areas correspond to areas of staining; FAF findings lag FA findings	HyperAF active lesions; hypoAF scarred lesions	Acute lesions variably hyper- to hypoAF; may be more numerous with FAF than clinically

PIC	SFU	MEWDS	AZOOR	AIM
20–40	20–40	10–50	15–65	20–40
F (90%)	F (>95%)	F > M (3:1 ratio)	F > M (3:1 ratio)	M = F
Usually bilateral, often asymmetric	Bilateral, asymmetric	Usually unilateral	Bilateral (76%)	Usually unilateral
None	None	Viral prodrome (50%)	Systemic autoimmune disease (28%)	Viral prodrome, coxsackievirus, and hand-foot-and-mouth disease
Acute	Insidious	Acute	Insidious	Acute
Self-limited	Chronic, recurrent	Self-limited	Chronic, recurrent (31%)	Self-limited
Paracentral scotomas, photopsias, metamorphopsia	Blurred vision	Blurred vision, paracentral scotomas, photopsias	Photopsias, scotomas	Blurred vision, central scotoma
Myopia, vitritis absent; yellow-white chorio-retinal lesions, 100–300 μm; may develop pigment	Mild to moderate vitritis; 50–500 μm white-yellow lesions posterior pole to midperiphery; RPE; hypertrophy; atrophy; large stellate zones of subretinal fibrosis	Myopia; mild anterior uveitis; vitritis; small white-orange, evanescent, perifoveal dots, 100–200 μm; outer retina/RPE; macular granularity	Initially normal to subtle RPE changes; late pigment migration; focal perivenous sheathing	Minimal to no cells; white/gray/yellow RPE discoloration and thickening; sparse intraretinal hemorrhages
CNV (17%–40%), serous detachment over confluent lesions	Neurosensory retinal detachment, ME, CNV	Disc edema, venous sheathing	RPE mottling, occasional ME	RPE granularity, rarely CNV
Early blockage or hyperfluorescence; variable late leakage/staining of acute lesions; leakage in presence of ME; CNV	Multiple areas of alternating hypo- and hyperfluorescence; late staining	Early punctate hyperfluorescence, wreathlike configuration; late staining of lesions, optic nerve	In acute stage: normal with increased retinal circulation time; in late stage: diffuse hyperfluorescence; RPE atrophy	Early hypo- or hyperfluorescence followed by late stippled hyperfluorescent staining of the RPE and pooling of dye
Multiple hypocyanescent, peripapillary, posterior pole lesions, corresponding to those seen on examination, FA	Hypocyanescent lesions	Multiple hypocyanescent spots, larger and more numerous than on examination, FA	Hypocyanescence in atrophic areas with late leakage in subacute areas	Hypocyanescence
Similar to MFCPU	No information	HyperAF spots corresponding to lesions on clinical examination	Lesions may have central hypoAF with peripheral hyperAF border	HypoAF

(Continued)

Table 9-1 *(continued)*

	BCR	APMPPE	Serpiginous Choroiditis	MFCPU
OCT findings	ME; loss of inner/outer segment line (ellipsoid zone); diffuse choroidal thickening; suprachoroidal fluid	Outer retinal hyperreflectivity with intra- and subretinal fluid	Outer retinal hyperreflectivity and thickening of underlying choroid in active lesions; retinal and RPE atrophy in scarred lesions	Sub-RPE deposits with overlying outer retinal disruption, thickening of underlying choroid (when active); CNV
Electrophysiology, VF findings	ERG: abnormal rod and cone responses; diminished b-wave; prolonged 30-Hz flicker implicit times VF: SITA 24-2 can show extensive loss even if central VA is preserved; MD may correlate with subjective vision changes	EOG: variably abnormal	ERG: normal	ERG: abnormal, extinguished responses
Visual prognosis	Guarded without treatment	Variable	Guarded	Guarded
Treatment	Systemic or local corticosteroids; IMT	Observation; systemic corticosteroids, especially with CNS involvement	Systemic and/or local corticosteroids; IMT; intravitreal anti-VEGF therapy for CNV	Systemic or local corticosteroids; IMT; intravitreal anti-VEGF therapy for inflammatory CNV

AIM = acute idiopathic maculopathy; APMPPE = acute posterior multifocal placoid pigment epitheliopathy; AZOOR = acute zonal occult outer retinopathy; BCR = birdshot chorioretinopathy; CNS = central nervous system; CNV = choroidal neovascularization; CSF = cerebrospinal fluid; EOG = electro-oculogram; ERG = electroretinogram; F = female; FA = fluorescein angiography; FAF = fundus autofluorescence; HLA = human leukocyte antigen; hyperAF = hyperautofluorescence/hyperautofluorescent; hypoAF = hypoautofluorescence/hypoautofluorescent; ICGA = indocyanine green

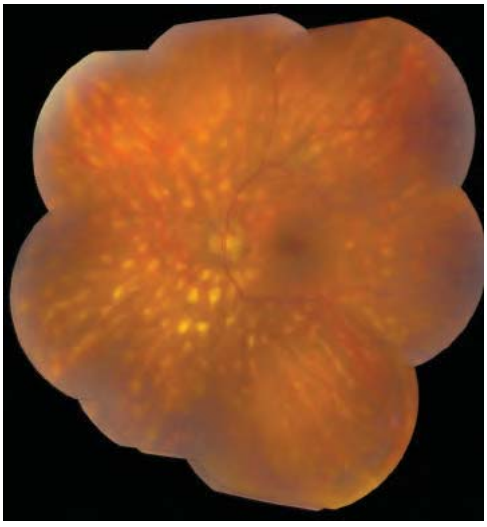

Figure 9-1 Birdshot chorioretinopathy. Fundus photograph showing multiple cream-colored ovoid lesions in the posterior pole and midzone. *(Courtesy of H. Nida Sen, MD/National Eye Institute.)*

PIC	SFU	MEWDS	AZOOR	AIM
Similar to MFCPU; inactive lesions may have posteriorly bowed RPE and outer retinal structures	Variable retinal edema; subretinal fluid and subretinal fibrosis	Abnormal hyperreflectivity and/or disruption of the inner/outer segment line	Loss of the inner/outer segment line (ellipsoid zone)	Subretinal fluid with hyperreflective debris in the subretinal space
ERG: normal	ERG and EOG: markedly attenuated	ERG: diminished a-wave, early receptor potentials (reversible)	ERG, mfERG: abnormal	ERG: normal mfERG: abnormal
VF: enlargement of blind spot (41%)		VF: enlarged blind spot, paracentral scotomas	VF: temporal, superior defects (corresponding to affected retina); enlarged blind spot	VF: central scotoma
Variable	Guarded	Good	Guarded	Variable
Observation; intravitreal anti-VEGF therapy for CNV; local or systemic corticosteroids; IMT	Systemic or local corticosteroids; IMT	Observation	Systemic or local corticosteroids; IMT	Observation; systemic corticosteroids if slow resolution

(continued) angiography; IMT = immunomodulatory therapy; M = male; MD = mean deviation; ME = macular edema; MEWDS = multiple evanescent white dot syndrome; MFCPU = multifocal choroiditis with panuveitis; mfERG = multifocal electroretinogram; OCT = optical coherence tomography; PIC = punctate inner choroiditis; RPE = retinal pigment epithelium; SFU = subretinal fibrosis and uveitis syndrome; SITA = Swedish Interactive Thresholding Algorithm; TB = tuberculosis; VEGF = vascular endothelial growth factor; VA = visual acuity; VF = visual field.

(see Fig 9-3A, C). Enhanced depth imaging OCT may be useful for evaluating choroidal thickening in early disease, and results correlate with hypocyanescent lesions observed on ICGA (see Fig 9-3B, D). In later stages of undertreated BCR, OCT may show macular thinning associated with patchy or diffuse loss of photoreceptors (ie, inner/outer segment line or ellipsoid zone) and chronic diffuse intraretinal cysts (Fig 9-5).

Böni C, Thorne JE, Spaide RF, et al. Choroidal findings in eyes with birdshot chorioretinitis using enhanced-depth optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2016;57(9):591–599.

Le Piffer AL, Boissonnot M, Gobert F, et al. Relevance of wide-field autofluorescence imaging in birdshot retinochoroidopathy: descriptive analysis of 76 eyes. *Acta Ophthalmol*. 2014;92(6):e463–e469.

Differential diagnosis

The differential diagnosis of BCR includes TB, syphilis, multifocal choroiditis with panuveitis (MFCPU), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multiple

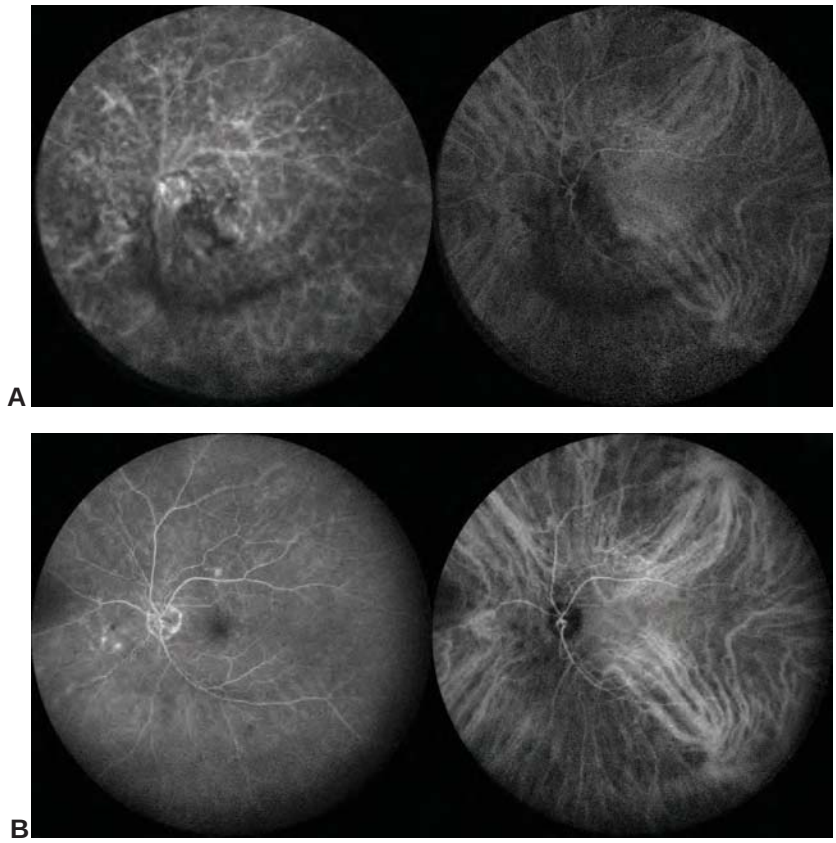

Figure 9-2 Birdshot chorioretinopathy. **A,** Fluorescein angiography (FA) *(left)* shows diffuse retinal vasculitis and shadowing from vitreous debris. Indocyanine green angiography (ICGA) *(right)* shows hypocyanescent lesions. **B,** After systemic immunomodulatory therapy, FA *(left)* shows resolution of the retinal vasculitis and vitreous debris with a few residual hyperfluorescent window defects. A few hypocyanescent lesions remain on ICGA *(right)*. *(Courtesy of Wendy M. Smith, MD.)*

evanescent white dot syndrome (MEWDS), OHS, autoimmune retinopathy, intraocular lymphoma, and especially sarcoidosis, which may present with chorioretinal lesions of similar morphology and distribution.

Disease course

Although a small subset of patients may have self-limited disease, the clinical course of BCR is characteristically chronic and progressive. Despite good visual acuity and minimal vitreous cells, patients with BCR may still experience progressive, diffuse, inflammatory retinal degeneration that manifests as visual field loss and dysfunction on full-field electroretinogram (ERG). If the clinician simply monitors visual acuity, disease progression will be missed. However, early and aggressive efforts to control inflammation may improve clinical outcomes.

Knickelbein JE, Jeffrey BG, Wei MM, et al. Reproducibility of full-field electroretinogram measurements in birdshot chorioretinopathy patients: an intra- and inter-visit analysis. *Ocul Immunol Inflamm.* 2021;29(5):848–853.

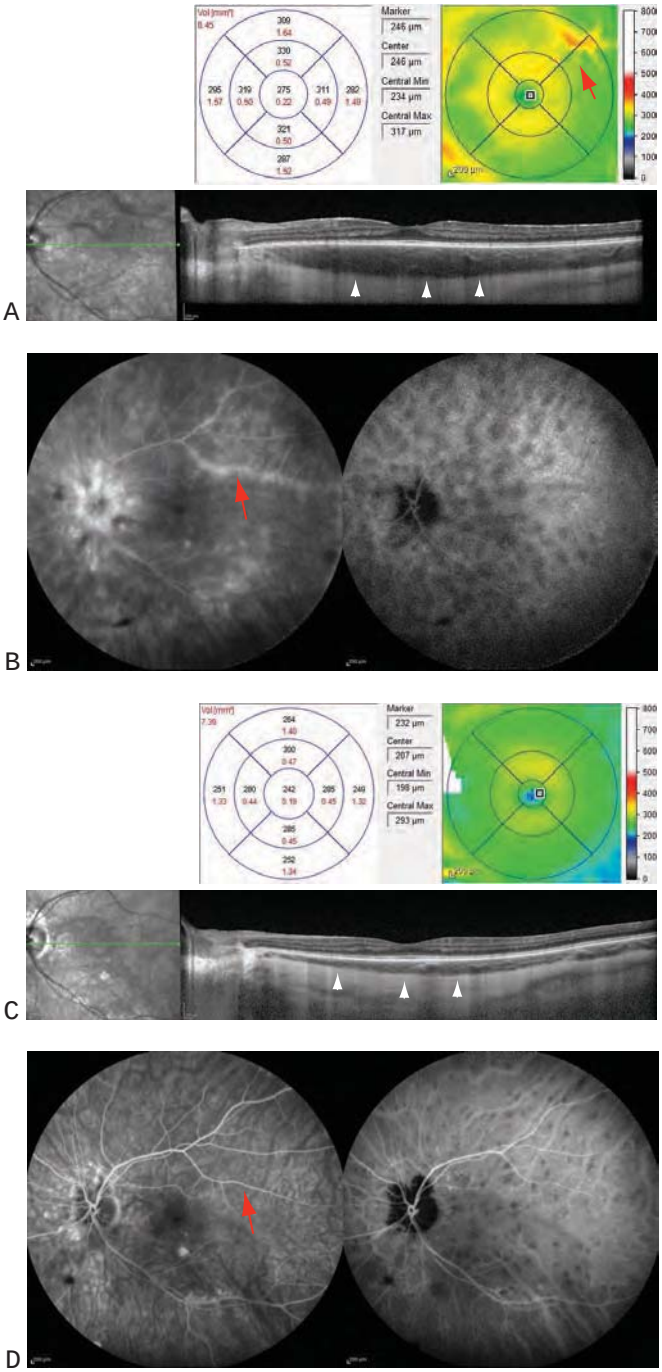

Figure 9-3 Birdshot chorioretinopathy. Multimodal imaging at presentation and after 5 years of systemic immunomodulatory therapy (IMT). **A,** Optical coherence tomography (OCT) heat map shows thickening along a vessel in the superior arcade *(arrow)*. Enhanced depth imaging (EDI) OCT scan shows diffuse choroidal thickening but no intraretinal fluid *(arrowheads)*. **B,** FA *(left)* shows venular arcade leakage *(arrow corresponds to thickening on OCT heat map)* and disc/peripapillary leakage. ICGA *(right)* shows confluent hypocyanescent spots emanating from the optic nerve, most with no correlate on FA. **C,** Five years later, OCT heat map shows mild thinning. EDI-OCT shows significant decrease in choroidal thickness *(arrowheads)*. **D,** FA *(left)* shows resolution of venular and disc leakage *(arrow)* with residual window defects. ICGA *(right)* shows near resolution of the hypocyanescent spots. *(Courtesy of Wendy M. Smith, MD.)*

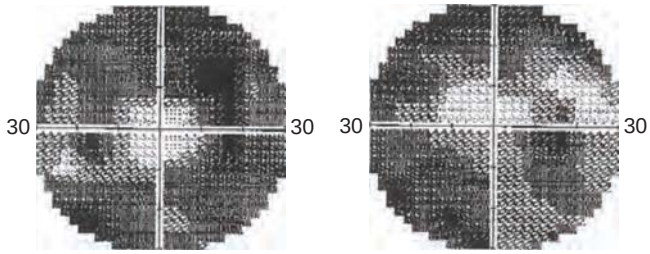

Figure 9-4 Birdshot chorioretinopathy. Visual fields from a 61-year-old woman with extensive visual field loss in both eyes despite 20/20 vision and absence of macular edema. *(Courtesy of Sam S. Dahr, MD, MS.)*

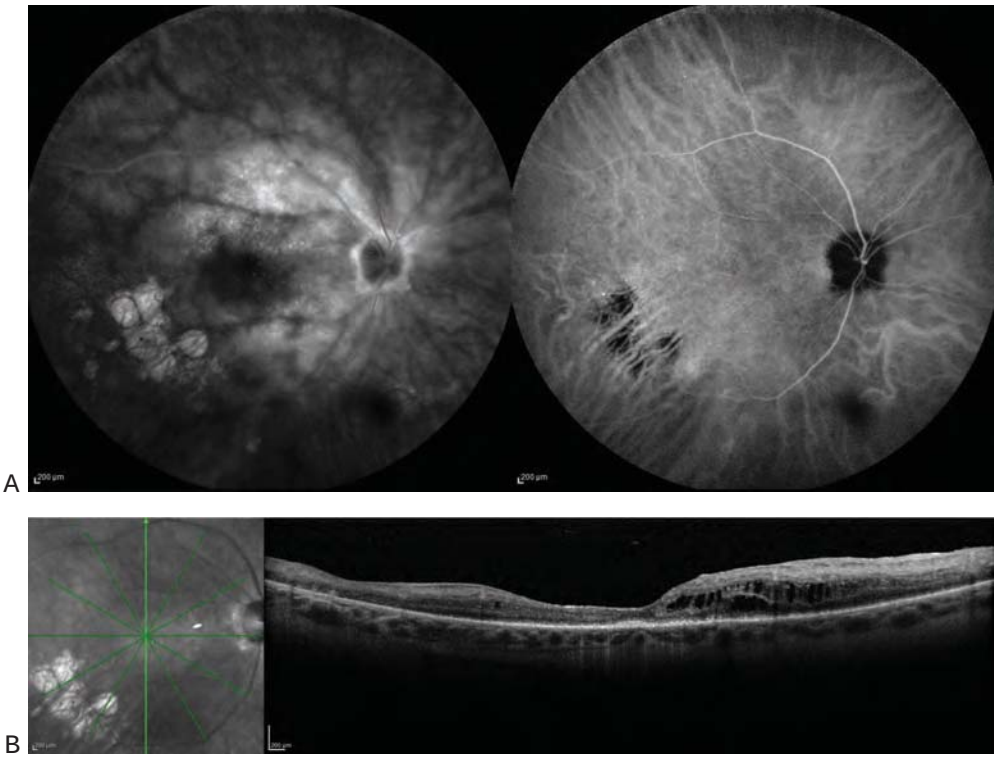

Figure 9-5 Birdshot chorioretinopathy in a patient whose diagnosis and treatment were considerably delayed. **A,** FA *(left)* shows vascular attenuation, diffuse posterior pole small-vessel leakage, and window defects in the inferotemporal macula from chorioretinal scars. The hypocyanescent lesions on ICGA *(right)* correspond to the chorioretinal scars. **B,** OCT shows chronic-appearing intraretinal fluid with loss of outer retinal structures and retinal pigment epithelium (RPE) damage. The choroid (partially visualized) appears thin. *(Courtesy of Wendy M. Smith, MD.)*

Minos E, Barry RJ, Southworth S, et al. Birdshot chorioretinopathy: current knowledge and new concepts in pathophysiology, diagnosis, monitoring and treatment. *Orphanet J Rare Dis.* 2016;11(1):61. doi.org/10.1186/s13023-016-0429-8

Papadia M, Pavésio C, Fardeau C, et al. HLA-A29 birdshot retinochoroiditis in its 5th decade: selected glimpses into the intellectual meanderings and progresses in the knowledge of a long-time misunderstood disease. *Diagnostics (Basel).* 2021;11(7):1291. doi:10.3390/diagnostics11071291

Treatment

Given the chronic nature of BCR, extended immunomodulatory therapy (IMT) is anticipated in most patients and may include methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, and/or tumor necrosis factor α (TNF-α) inhibitors. Systemic and/or local corticosteroid injections can be used as a bridge until IMT takes effect, typically 2–4 months for some therapeutic improvement and up to 6–12 months for full effect. Depending on individual response, refinement of the IMT regimen may take even longer, and some patients may need combination therapy, typically an antimetabolite and an anti-TNF agent. The long-acting intravitreal fluocinolone acetonide insert (0.18 mg) or implant (0.59 mg) may be used in patients who cannot tolerate systemic therapy (although they may be insufficient as monotherapy) or combined with systemic therapy for breakthrough inflammation. Patients with asymptomatic or minimally symptomatic BCR who lack objective findings such as macular edema, angiographic edema or vasculitis, or visual field/ERG dysfunction may be monitored closely, but the majority of patients with BCR will require corticosteroids and corticosteroid-sparing IMT.

Crowell EL, France R, Majmudar P, Jabs DA, Thorne JE. Treatment outcomes in birdshot chorioretinitis: corticosteroid sparing, corticosteroid discontinuation, remission, and relapse. *Ophthalmol Retina.* 2022;6(7):620–627.

Menezo V, Taylor SR. Birdshot uveitis: current and emerging treatment options. *Clin Ophthalmol.* 2014;8:73–81.

Tomkins-Netzer O, Taylor SRJ, Lightman S. Long-term clinical and anatomic outcome of birdshot chorioretinopathy. *JAMA Ophthalmol.* 2014;132(1):57–62.

Acute Posterior Multifocal Placoid Pigment Epitheliopathy

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an inflammatory disease that manifests as choriocapillaritis with secondary RPE involvement. The disorder presents equally in otherwise healthy men and women, typically before age 50 years.

The etiology of APMPPE is poorly understood, although patients may report a viral prodrome. Infectious associations include group A streptococcus, adenovirus type 5, TB, Lyme disease, and mumps virus. APMPPE has also been reported after vaccination for varicella, hepatitis B, swine flu, and meningococcus. Noninfectious disease associations include erythema nodosum, granulomatosis with polyangiitis, polyarteritis nodosa, scleritis and episcleritis, sarcoidosis, and ulcerative colitis. A rare but potentially life-threatening association also exists between APMPPE and cerebral vasculitis. Therefore, patients with APMPPE and central nervous system (CNS) symptoms such as headache should undergo urgent neurologic evaluation including neuro-imaging and cerebrospinal fluid studies. Although most patients with APMPPE do not experience major extraocular manifestations, the disease associations mentioned here highlight the need for a careful review of patient symptoms, with referral to an appropriate nonophthalmic specialist as required for further assessment.

Manifestations

Patients with APMPPE typically present with sudden-onset unilateral photopsias and vision loss. Involvement of the fellow eye may occur within days to weeks. Anterior segment inflammation is absent or minimal, and vitritis is typically mild. Fundus examination demonstrates large, flat, yellow-white, RPE-involving placoid lesions throughout the posterior pole

(Fig 9-6), with lesion size varying from 1 to 2 disc areas. New peripheral lesions may develop in a linear or radial array. Rapid lesion evolution is a disease hallmark. Papillitis may also occur, but macular edema is uncommon. Other atypical findings include retinal vasculitis, retinal vascular occlusive disease, retinal neovascularization, and exudative retinal detachment. The RPE lesions usually resolve over a period of 2–6 weeks, leaving variable areas of depigmentation and pigment clumping.

In the acute disease phase, FA shows early hypofluorescent lesions (see Fig 9-6C) and late hyperfluorescent staining (see Fig 9-6D). As lesions evolve toward RPE depigmentation and loss, early blockage transitions to transmission hyperfluorescence with late staining. With ICGA, choroidal hypocyanescence with hypervisualization of the underlying choroidal vessels is seen in both the acute and inactive disease stages, with the lesions shrinking in the inactive stages (see Fig 9-6B). On both FA and ICGA, perfusion abnormalities are more numerous than the overlying placoid lesions.

FAF findings lag behind the appearance of clinically evident lesions, and FAF lesions are fewer than the clinical lesions. They are initially hyperautofluorescent and may evolve into areas of hypoautofluorescence over time (Fig 9-7A). OCT of acute lesions shows hyperreflectivity of the outer retinal layers as well as subretinal or intraretinal fluid (Fig 9-7B). As the lesions resolve, outer retinal and photoreceptor loss may be observed.

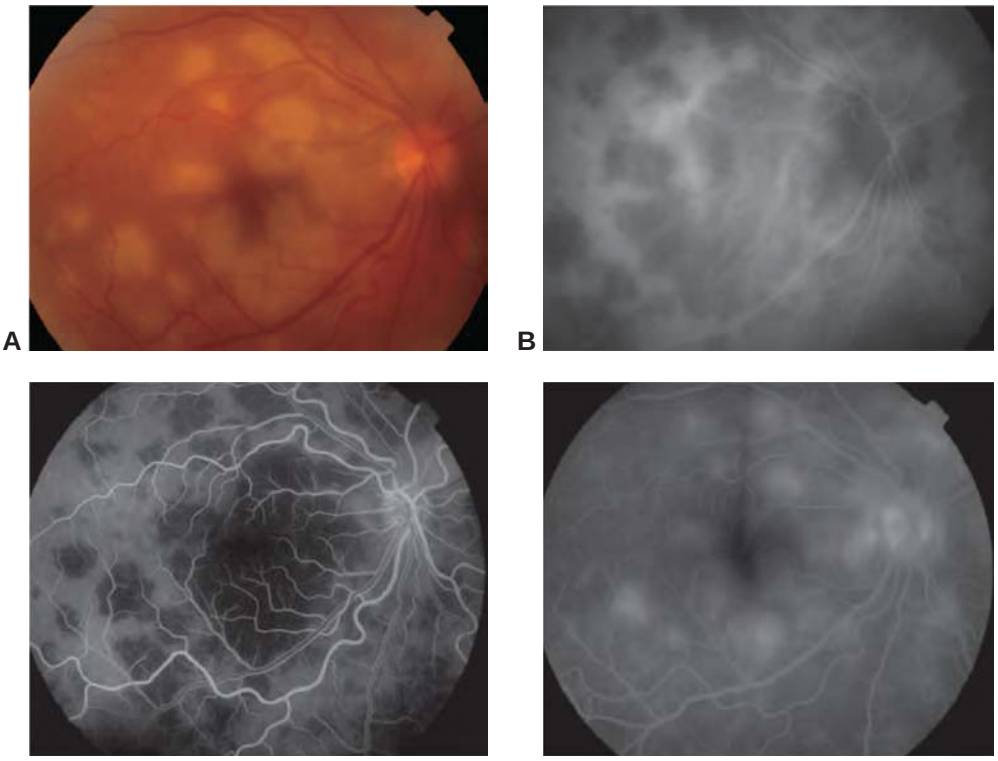

Figure 9-6 Acute posterior multifocal placoid pigment epitheliopathy. **A,** Fundus photograph shows multifocal placoid lesions in the macula. **B,** ICGA shows multiple mid-phase hypocyanescent lesions. **C,** FA shows early hypofluorescent lesions. **D,** FA shows late-phase staining. *(Courtesy of Albert T. Vitale, MD.)*

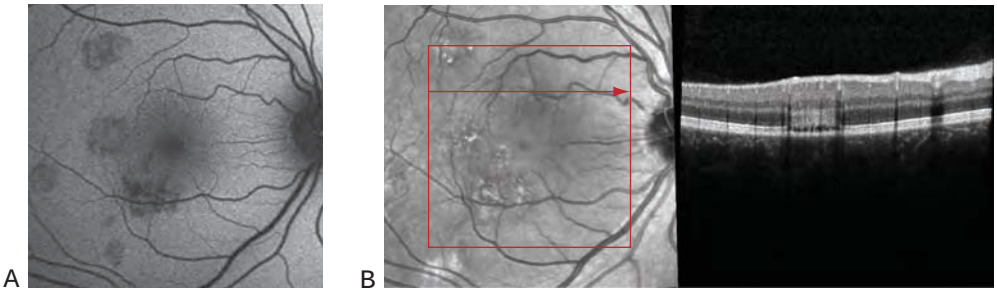

Figure 9-7 Acute posterior multifocal placoid pigment epitheliopathy. **A,** Fundus autofluorescence (FAF) image showing scattered, inactive, hypoautofluorescent lesions. **B,** OCT through an active lesion *(red horizontal arrow),* demonstrating hyperreflectivity of the outer retina and RPE, a sliver of subretinal fluid, and focal disruption of the photoreceptor layer. *(Courtesy of Bryn M. Burkholder, MD.)*

Differential diagnosis

APMPPE is a clinical diagnosis based on examination findings and ancillary studies such as FA, ICGA, FAF, and OCT. The differential diagnosis of active APMPPE includes syphilis, TB, pneumocystis choroiditis, endogenous fungal endophthalmitis, sarcoidosis, and choroidal metastasis or lymphoma. Although active lesions in APMPPE, ampiginous choroiditis, and serpiginous choroiditis may have similar appearances, APMPPE is usually an acute, nonrecurring disease, unlike ampiginous and serpiginous choroiditis, which are insidious and progressive. The OCT findings in active APMPPE can resemble the serous retinal detachments in Vogt-Koyanagi-Harada syndrome, but other clinical features should differentiate the two entities. (See Chapter 10 for further discussion of Vogt-Koyanagi-Harada syndrome.) While inactive APMPPE scars can look similar to the lesions in MFCPU and punctate inner choroiditis, these entities are usually not included in the differential diagnosis of active APMPPE.

Prognosis

Most patients with APMPPE have a good prognosis, with visual acuity returning to 20/40 or better within 6 months. However, 20% are left with residual visual dysfunction. Risk factors for vision loss include foveal involvement at presentation, older age at presentation, unilateral disease, a longer interval between initial and fellow eye involvement, and recurrence. Although patients with APMPPE are often simply observed, corticosteroid therapy may be considered to hasten lesion resolution, especially in those with extensive macular involvement. In patients with APMPPE and concurrent CNS vasculitis, prompt systemic corticosteroid treatment is indicated to reduce CNS morbidity and mortality.

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Testi I, Vermeirsch S, Pavesio C. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE). *J Ophthalmic Inflamm Infect.* 2021;11(1):31. doi:10.1186/s12348-021-00263-1

Serpiginous Choroiditis

Serpiginous choroiditis, also known as *geographic* or *helicoid choroidopathy,* is a rare, chronic, relentlessly progressive posterior uveitis that affects adult men and women equally. It is hypothesized to be an immune-mediated occlusive vasculitis. Although associations between serpiginous choroiditis and systemic diseases have been inconsistent, the disorder has been reported in patients with Crohn disease, sarcoidosis, and polyarteritis nodosa. TB can cause a serpiginous-like choroiditis; thus, all patients with suspected serpiginous choroiditis should be tested for TB exposure.

Manifestations

Patients with serpiginous choroiditis present with decreased vision, painless paracentral scotomas, a quiet anterior chamber, and minimal to no vitreous cells. The disease is usually bilateral but may be asymmetric. Active gray-white or creamy yellow RPE-level lesions originate in the peripapillary region and progress in a serpentine or pseudopodial manner (Fig 9-8A). However, one-third of patients may have macular serpiginous choroiditis, in which the serpentine lesions arise principally within the macula rather than the peripapillary region. Without treatment, serpiginous lesions evolve slowly into areas of atrophic retina, RPE, and choriocapillaris, often with fibrosis and/or hyperpigmentation. New activity usually occurs at the edge of a scarred lesion and may have associated shallow subretinal fluid. In up to 25% of patients, CNV develops at the border of an old serpiginous scar.

On FA, active serpiginous choroiditis lesions or lesion edges show early hypofluorescence of the entire active area, followed by late hyperfluorescent staining (Fig 9-8B, C). In contrast, scarred lesions show sharp margins and areas of hypofluorescence (secondary to loss of choriocapillaris and blocking by RPE hyperplasia) and transmission hyperfluorescence (due to atrophic RPE) on early FA. Later FA images of scarred lesions show staining of atrophic and hyperplastic RPE and fibrosis that has well-defined borders (versus the fuzzier borders of active staining/leaking lesions). ICGA of both acute and old lesions reveals hypocyanescence throughout all phases and may reveal more extensive involvement than seen on FA. In patients with active CNV, early hyperfluorescence with late leakage is seen on FA, whereas hypercyanescence is seen on ICGA. FAF is also very useful for monitoring serpiginous choroiditis, with inactive scarred lesions appearing hypoautofluorescent and newly active lesions appearing hyperautofluorescent (Fig 9-9A).

Findings on OCT also vary depending on disease stage. OCT of active lesions shows normal or slightly increased retinal thickness due to hyperreflective, blurred, and thickened outer retinal structures (Fig 9-9B). The underlying choroid is usually thickened, and there may be associated shallow subretinal fluid. In contrast, scarred lesions are characterized by retinal thinning with loss of outer retinal structures and a deeper, patchy hyperreflectivity of the choroid from enhanced light transmission through atrophic RPE.

Bansal R, Gupta A, Gupta V. Imaging in the diagnosis and management of serpiginous choroiditis. *Int Ophthalmol Clin*. 2012;52(4):229–236.

Treatment

The course of serpiginous choroiditis involves centrifugal extension, progressive chorioretinal scarring, and often a poor visual outcome. Initial treatment of serpiginous choroiditis usually requires systemic and/or local corticosteroids to quiet active lesions, particularly those

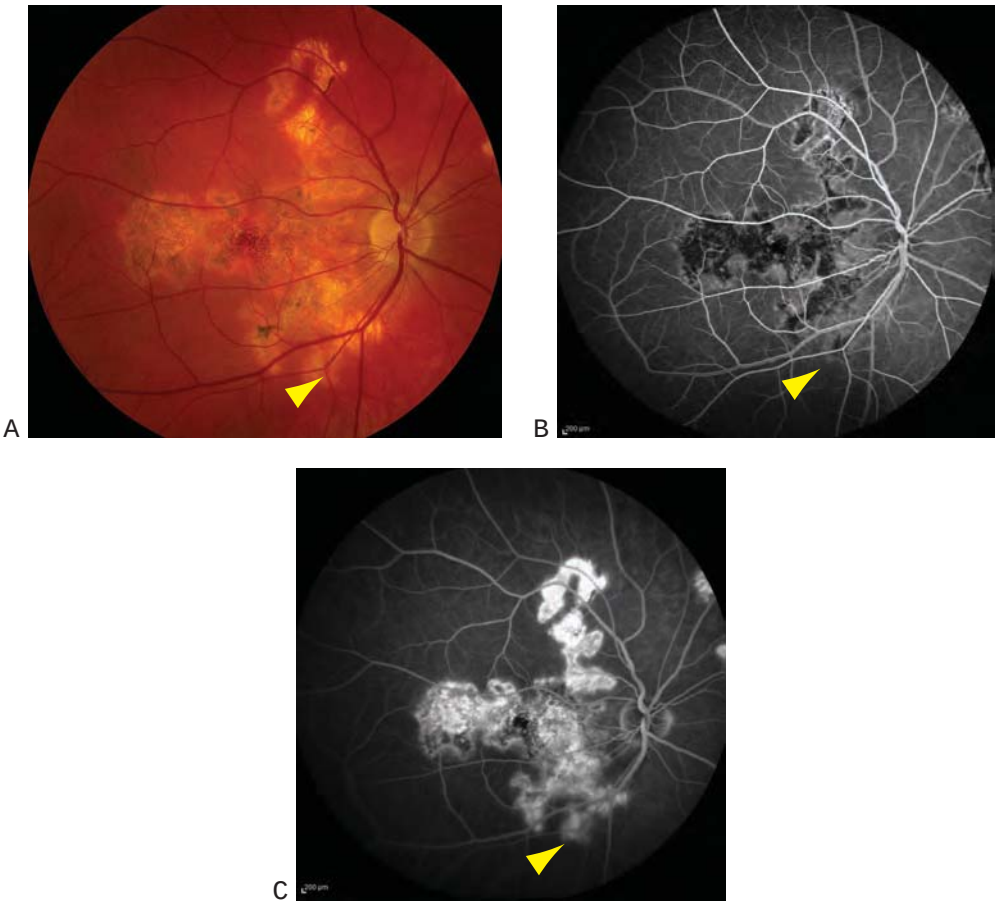

Figure 9-8 Serpiginous choroiditis. **A,** Color fundus photograph shows areas of active choroiditis at the inferior border of the macular lesion *(arrowhead)*. **B,** Early FA shows blocked fluorescence *(arrowhead)*. **C,** Late FA shows late staining and leakage at the active border of the lesion *(arrowhead)*. *(Courtesy of Wendy M. Smith, MD.)*

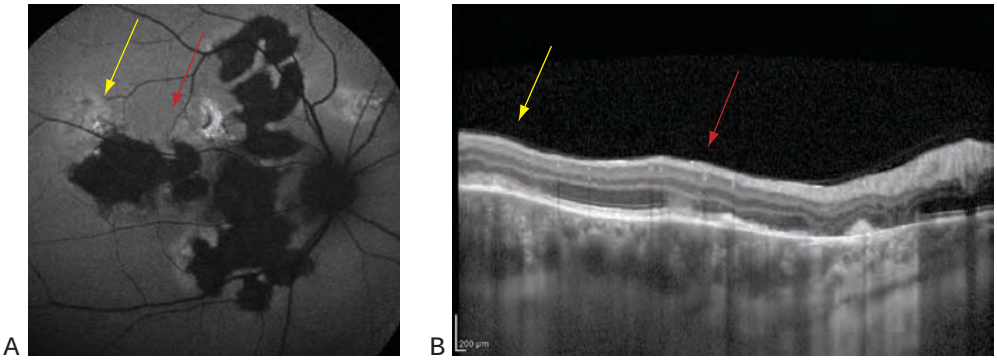

Figure 9-9 Serpiginous choroiditis. **A,** FAF shows areas of hyperautofluorescence *(yellow and red arrows)* signifying new or recent activity. **B,** OCT scan through active lesions demonstrates outer retinal blurring and hyperreflectivity *(yellow and red arrows)* and thickening of the underlying choroid. *(Courtesy of Wendy M. Smith, MD.)*

threatening the fovea. Early addition of systemic IMT improves the long-term prognosis of patients with serpiginous choroiditis by reducing progression and recurrence. Options for systemic IMT include the following medications:

- combination therapy with an antimetabolite and a T-cell inhibitor
- cytotoxic therapy with cyclophosphamide or chlorambucil. Although the associated adverse effects are more severe than those associated with other systemic IMT, this class of agents has been shown to induce long, drug-free remissions in serpiginous choroiditis.
- TNF inhibitors (may be considered as long as TB test results are negative and/or TB has been treated)

Adjunctive treatment for inflammatory CNV can involve anti-vascular endothelial growth factor (anti-VEGF) agents and/or intravitreal corticosteroids.

Presumed immune-mediated serpiginous choroiditis must be distinguished from infectious diseases that can simulate it. Rare mimics of serpiginous choroiditis include herpetic or syphilitic choroiditis as well as TB. As noted previously, tuberculous uveitis may also present as a *multifocal serpiginoid choroiditis* or *serpiginous-like choroiditis;* therefore, all patients with features of serpiginous uveitis should have TB screening tests (see Chapter 11). TB-associated serpiginous-like choroiditis requires treatment with quadruple drug therapy and may also require corticosteroids and IMT for post-infection inflammation.

Dutta Majumder P, Biswas J, Gupta A. Enigma of serpiginous choroiditis. *Indian J Ophthalmol.* 2019;67(3):325–333.

Ebrahimiadib N, Modjtahedi BS, Davoudi S, Foster CS. Treatment of serpiginous choroiditis with chlorambucil: a report of 17 patients. *Ocul Immunol Inflamm.* 2018;26(2):228–238.

Papasavvas I, Jeannin B, Herbort CP Jr. Tuberculosis-related serpiginous choroiditis: aggressive therapy with dual concomitant combination of multiple anti-tubercular and multiple immunosuppressive agents is needed to halt the progression of the disease. *J Ophthalmic Inflamm Infect.* 2022;12(1):7.

Ampiginous Choroiditis, or Relentless Placoid Chorioretinitis

Ampiginous choroiditis, also called *relentless placoid chorioretinitis,* is an uncommon entity that has features of both serpiginous choroiditis and APMPPE. Affected men and women, typically between 10 and 50 years of age, present with floaters, photopsias, paracentral scotomas, and decreased vision, as well as variable degrees of anterior segment inflammation and vitritis.

The creamy-white placoid lesions of acute ampiginous choroiditis are clinically and angiographically similar to the active lesions of serpiginous choroiditis and APMPPE. Similar to serpiginous choroiditis lesions, ampiginous choroiditis abnormalities may develop at the border of a scarred lesion as well as de novo. In addition, untreated lesions evolve into chorioretinal atrophy, and advanced disease may be clinically indistinguishable from that of serpiginous choroiditis, including the development of CNV. Moreover, active and scarred lesions in ampiginous choroiditis are essentially identical to those of serpiginous choroiditis on FA (Fig 9-10). However, the clinical courses of the two diseases differ. For example, the active

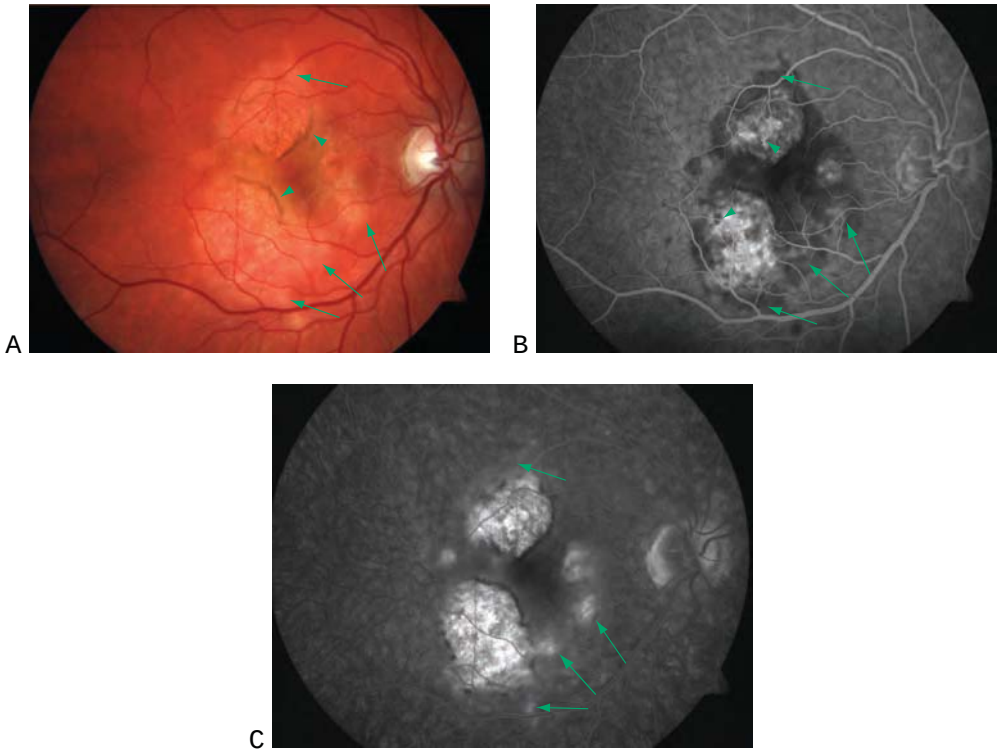

Figure 9-10 Ampiginous choroiditis, subacute lesion. **A,** Fundus photograph shows a white placoid lesion with active edges *(arrows)* and older pigmented edges *(arrowheads)*. **B,** Early-phase FA shows mixture of early blockage within newer parts of the lesion *(arrows)* and transmission within older parts of the lesion *(arrowheads)*. **C,** Late-phase FA shows staining throughout the lesion, although staining of the active edges is more subtle *(arrows)* than staining of the older central portion of the lesion. *(Courtesy of Sam S. Dahr, MD, MS.)*

lesions of ampiginous choroiditis are often multifocal and distinctly separate, unlike those of serpiginous choroiditis, which arise from a single location and are clustered. In addition, lesions of ampiginous choroiditis occur in the periphery and may predate those in the posterior pole, and macular lesions do not radiate from the peripapillary area as they do in serpiginous choroiditis.

In patients with ampiginous choroiditis, prolonged periods of chronic disease activity may be characterized by the appearance of more than 50 multifocal lesions, which appear throughout the fundus and progress over a 2-year period. Depending on disease severity and clinical course, treatment may include systemic and/or local corticosteroids, systemic IMT, and/or anti-VEGF therapy. As with all diseases characterized by chorioretinal lesions, TB-associated serpiginous-like choroiditis should be ruled out in patients with suspected ampiginous choroiditis.

Jones BE, Jampol LM, Yannuzzi LA, et al. Relentless placoid chorioretinitis: a new entity or an unusual variant of serpiginous chorioretinitis? *Arch Ophthalmol.* 2000;118(7):931–938.

Jyotirmay B, Jafferji SS, Sudharshan S, Kalpana B. Clinical profile, treatment, and visual outcome of ampiginous choroiditis. *Ocul Immunol Inflamm.* 2010;18(1):46–51.

Multifocal Choroiditis With Panuveitis, Punctate Inner Choroiditis, and Subretinal Fibrosis and Uveitis Syndrome

Multifocal choroiditis with panuveitis (MFCPU), punctate inner choroiditis (PIC), and subretinal fibrosis and uveitis syndrome (SFU) are a subset of white dot syndromes with similar features. Some authorities have traditionally defined them as discrete disorders; however, others consider them to be a single disease (often called *multifocal choroiditis*) that falls along a continuum, with the presence of fibrosis or panuveitis described separately. For this discussion, MFCPU, PIC, and SFU are considered discrete disorders.

Essex RW, Wong J, Jampol LM, Dowler J, Bird AC. Idiopathic multifocal choroiditis: a comment on present and past nomenclature. *Retina*. 2013;33(1):1–4.

Multifocal choroiditis with panuveitis

MFCPU is an idiopathic inflammatory disorder that affects the choroid, retina, and vitreous, most often in young (average age is approximately 30 years but ranges from 10 to 70 years) women with myopia. MFCPU is considered a posterior uveitis because the primary inflammation is in the choroid, and any associated anterior chamber or vitreous inflammation is usually mild. The disease is typically bilateral but may be asymmetric. Although a viral etiology has not been proven for MFCPU, herpes simplex and Epstein-Barr viruses have been implicated in some cases, possibly as triggers of an autoimmune process. Variable findings on histologic examination of affected eyes, such as increased choroidal B and/or T lymphocytes, suggest that different immune pathways may produce similar disease phenotypes.

Manifestations Symptoms of MFCPU include floaters, photopsias, blind-spot enlargement, and decreased vision. Clinical examination shows multiple oval or round lesions typically >125 μm at the level of the RPE or inner choroid in any zone of the fundus, although most are peripapillary. Acute lesions have a white-yellow, opaque appearance. As the lesions transition to atrophic scars, they develop a "punched-out appearance" with a white center and a discrete border that may become pigmented (Fig 9-11). Peripheral streaks or linear arrays of lesions and peripapillary pigmentary atrophy may also occur. In some patients, the disease resembles PIC in one eye and MFCPU in the other. Complications include macular edema, CNV, epiretinal membrane, and macular subretinal fibrosis.

Multimodal imaging is used to assess MFCPU. FA of acute active lesions shows early hypofluorescence with late staining (Fig 9-12). Atrophic scars produce transmission defects (early hyperfluorescence that fades in the late phases of the angiogram). Early hyperfluorescence and late leakage may represent macular edema or CNV.

As with BCR, ICGA of active MFCPU reveals more mid-phase hypocyanescent lesions than are seen on clinical examination or FA (see Fig 9-12). The lesions frequently cluster around the optic nerve and correlate with an enlarged blind spot on visual fields. Most of these hypofluorescent spots fade with resolution of inflammation.

FAF findings in MFCPU vary and are often most useful when correlated with other imaging modalities and followed longitudinally. In active disease, FAF may show fully *hyper*autofluorescent lesions, *hyper*autofluorescent edges associated with *hypo*autofluorescent central lesions, or increase in size of *hypo*autofluorescent lesions compared with their size in the inactive phase. In general, FAF lesions are often smaller and more numerous than those

Figure 9-11 Multifocal choroiditis with panuveitis. Montage of color fundus photographs shows multiple active creamy lesions emanating from the optic nerve. *(Courtesy of Wendy M. Smith, MD.)*

noted on clinical examination (Fig 9-13A, C). OCT of active lesions may show RPE elevation, disruption of the overlying outer retina, subretinal hyperreflective material, and hyperreflectivity of the underlying choroid (Fig 9-13B, D).

Spaide RF, Goldberg N, Freund KB. Redefining multifocal choroiditis and panuveitis and punctate inner choroidopathy through multimodal imaging. *Retina*. 2013;33(7): 1315–1324.

Diagnosis The differential diagnosis of MFCPU includes sarcoidosis, syphilis, OHS, TB, PIC, and BCR. MFCPU lesions are larger than PIC lesions, and PIC usually lacks anterior chamber and vitreous inflammation. Compared with birdshot lesions, those of MFCPU are smaller and more discrete or "punched out"; in addition, patients with MFCPU are typically younger than those with BCR and do not have HLA-A29–positive test results. Similar to OHS, MFCPU may produce peripheral chorioretinal streaks and peripapillary pigment atrophy and hyperplasia; however, OHS typically does not cause anterior segment or vitreous inflammation or substantial subretinal fibrosis unless it is associated with CNV.

Treatment In the typically young patient with MFCPU, the goal of treatment is to minimize the progressive RPE atrophy and macular subretinal fibrosis that leads to vision loss. Because the natural history of untreated disease is poor, an aggressive approach is warranted,

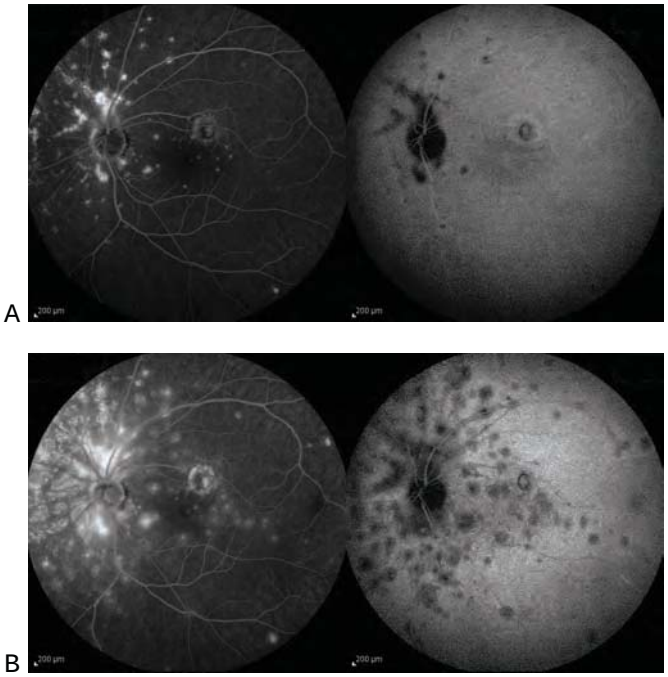

Figure 9-12 Multifocal choroiditis with panuveitis. **A,** Inactive lesions after initiation of systemic IMT. FA *(left)* shows hyperfluorescent window defects. The lesions are hypocyanescent on ICGA *(right)*. Central macular choroidal neovascularization has a hypercyanescent center surrounded by hypocyanescence. **B,** Breakthrough inflammation. FA *(left)* shows increased hyperfluorescent lesions, some leaking on late images. On ICGA *(right)*, the preexisting hypocyanescent lesions are larger, and numerous new hypocyanescent lesions are visible. *(Courtesy of Wendy M. Smith, MD.)*

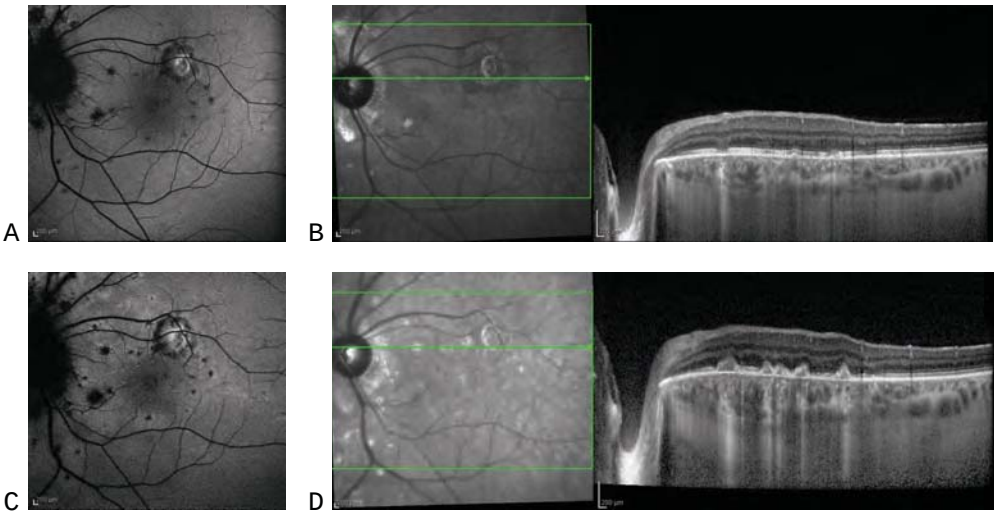

Figure 9-13 Multifocal choroiditis with panuveitis. **A,** Inactive lesions during systemic IMT. FAF shows hypoautofluorescent lesions. Choroidal neovascularization in superior macula has central hyperautofluorescence. **B,** OCT shows irregular patchy outer retinal structures of inactive lesions. **C,** Breakthrough inflammation. FAF shows increased size of hypoautofluorescent lesions compared with that of lesions shown in part A and intervening hyperautofluorescence. **D,** OCT through active lesions shows elevations of the outer retina and thickening of the underlying choroid. *(Courtesy of Wendy M. Smith, MD.)*

including use of systemic IMT. In a large retrospective cohort study of patients with MFCPU, IMT was associated with an 83% reduction in the risk of posterior pole complications and a 92% reduction in the risk of 20/200 vision or worse. Systemic, periocular, and intravitreal corticosteroids often quiet active lesions in the short term; however, antimetabolites, T-cell inhibitors, and/or TNF inhibitors are commonly required for long-term disease control. In some cases, an intravitreal fluocinolone implant may be effective for long-term control of inflammation. Intravitreal anti-VEGF therapy may be used as adjunctive treatment for inflammatory CNV, although use of corticosteroids and/or systemic IMT to control uveitis activity may eliminate the need for ongoing anti-VEGF injections.

de Groot EL, Ten Dam-van Loon NH, de Boer JH, Ossewaarde-van Norel J. The efficacy of corticosteroid-sparing immunomodulatory therapy in treating patients with central multifocal choroiditis. *Acta Ophthalmol.* 2020;98(8):816–821.

Erba S, Cozzi M, Xhepa A, Cereda M, Staurenghi G, Invernizzi A. Distribution and progression of inflammatory chorioretinal lesions related to multifocal choroiditis and their correlations with clinical outcomes at 24 months. *Ocul Immunol Inflamm.* 2022;30(2):409–416.

Papasavvas I, Neri P, Mantovani A, Herbort CP Jr. Idiopathic multifocal choroiditis (MFC): aggressive and prolonged therapy with multiple immunosuppressive agents is needed to halt the progression of active disease. An offbeat review and a case series. *J Ophthalmic Inflamm Infect.* 2022;12(1):2.

Standardization of Uveitis Nomenclature (SUN) Working Group. Classification Criteria for Multifocal Choroiditis With Panuveitis. *Am J Ophthalmol.* 2021;228:152–158.

Thorne JE, Wittenberg S, Jabs DA, et al. Multifocal choroiditis with panuveitis: incidence of ocular complications and loss of visual acuity. *Ophthalmology.* 2006;113(12): 2310–2316.

Punctate inner choroiditis

Punctate inner choroiditis (PIC) is an idiopathic multifocal chorioretinopathy of the outer retina, RPE, and inner choroid that predominantly affects women with myopia. The median age at disease onset is approximately 30 years.

Manifestations Patients with PIC present with metamorphopsia, paracentral scotomas, photopsias, and vision loss. The disease is usually bilateral but often asymmetric. The yellow-white spots of PIC are typically smaller (100–300 μm) than those of MFCPU and are mostly confined to the posterior pole (Fig 9-14). Although inactive lesions may be very subtle on clinical examination, some transition to well-defined, atrophic, variably hyperpigmented chorioretinal scars. In addition, patients with PIC are more likely than those with MFCPU to present with CNV, although they are less likely to have bilateral vision loss.

In patients with active inflammatory lesions of PIC, FA shows hypofluorescence or hyperfluorescence in the early phase and subsequently displays late staining (Fig 9-15). Inactive lesions show transmission hyperfluorescence. CNV produces a zone of early hyperfluorescence, often with a surrounding zone of hypofluorescence. On ICGA, active and inactive lesions are hypocyanescent; during active inflammation, hypocyanescent lesions increase in size, and hypocyanescent mottling may be observed between lesions (see Fig 9-15). On FAF, PIC lesions are *hypo*autofluorescent; when active, they may show a subtle increase in size and/or develop a *hyper*autofluorescent border or halo that recedes as activity resolves.

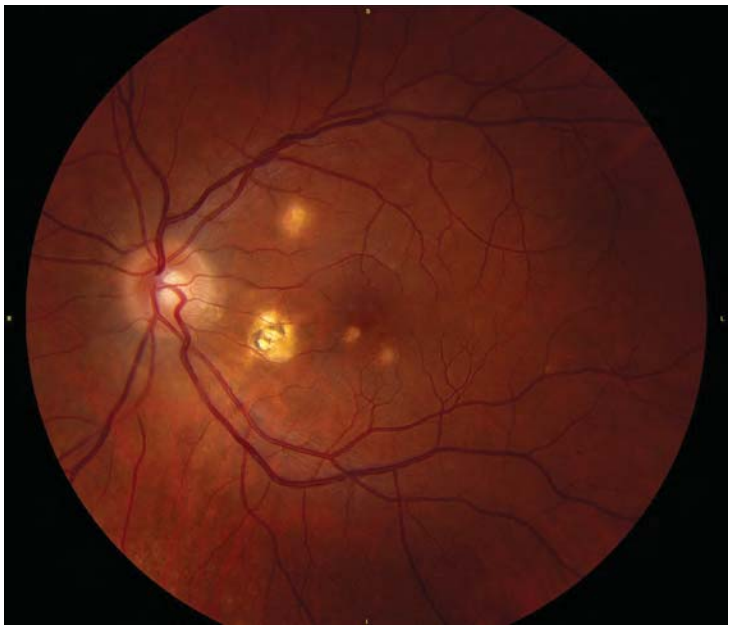

Figure 9-14 Fundus photograph showing punctate inner choroiditis. *(Courtesy of Wendy M. Smith, MD.)*

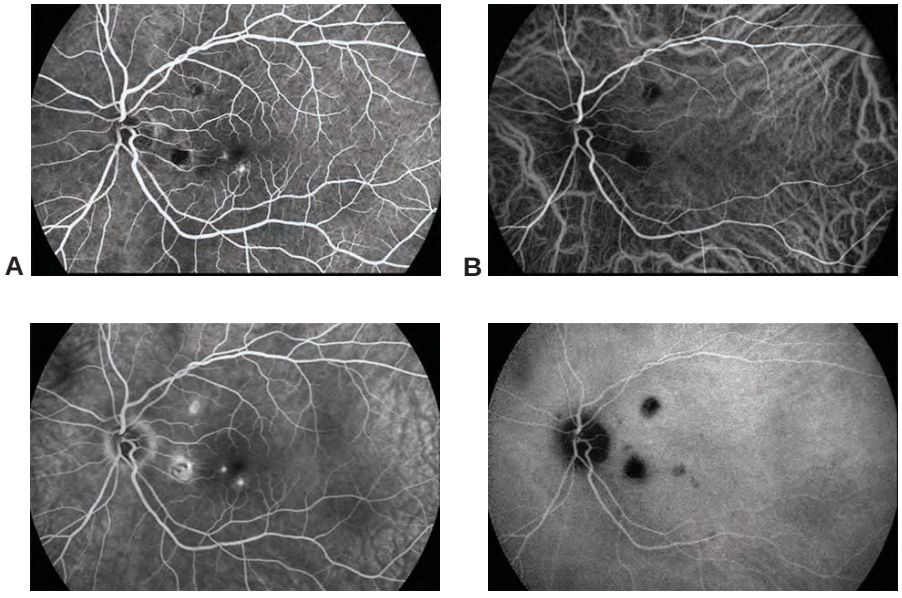

Figure 9-15 Punctate inner choroiditis (PIC). Fluorescein angiograms demonstrating early hyperfluoresence **(A)** and late staining **(C)** of PIC lesions. Corresponding early **(B)** and late **(D)** ICG angiograms demonstrating multiple hypocyanescent spots. *(Courtesy of Wendy M. Smith, MD.)*

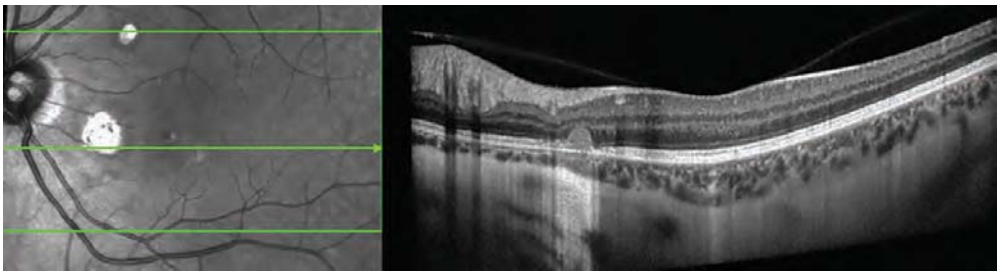

Figure 9-16 Punctate inner choroiditis. OCT scan through an active lesion. *(Courtesy of Wendy M. Smith, MD.)*

OCT of an early, active PIC lesion shows focal hyperreflective elevation of the RPE, often with disruption of the overlying outer retina. The lesion may break through the RPE and form a hump-shaped nodule beneath the outer plexiform layer (Fig 9-16). As the acute lesion regresses, OCT shows tissue loss within the outer retina and inner choroid. A focal choroidal excavation may develop, with V-shaped herniation of the outer plexiform layer and inner retina into the choroid. Active CNV lesions have associated subretinal and intraretinal fluid on OCT. OCT angiography may also help identify CNV lesions.

Ahnood D, Madhusudhan S, Tsaloumas MD, Waheed NK, Keane PA, Denniston AK. Punctate inner choroidopathy: a review. *Surv Ophthalmol*. 2017;62(2):113–126.

Kim H, Woo SJ, Kim Y-K, Lee SC, Lee CS. Focal choroidal excavation in multifocal choroiditis and punctate inner choroidopathy. *Ophthalmology*. 2015;122(7):1534–1535.

Levison AL, Baynes KM, Lowder CY, Kaiser PK, Srivastava SK. Choroidal neovascularisation on optical coherence tomography angiography in punctate inner choroidopathy and multifocal choroiditis. *Br J Ophthalmol*. 2017;101(5):616–622.

Spaide RF, Goldberg N, Freund KB. Redefining multifocal choroiditis and panuveitis and punctate inner choroidopathy through multimodal imaging. *Retina*. 2013;33(7): 1315–1324.

Treatment In some cases, active PIC lesions may regress without anti-inflammatory therapy, and treatment may be limited to intermittent intravitreal anti-VEGF. Indications for corticosteroids and/or systemic IMT include new or persistently active inflammatory lesions in vision-threatening locations or incomplete response to intravitreal anti-VEGF therapy. When inflammatory activity in PIC is controlled with systemic IMT, retinal function and visual acuity may improve even in the presence of perifoveal CNV.

Subretinal fibrosis and uveitis syndrome

Subretinal fibrosis and uveitis (SFU) syndrome is an extremely rare idiopathic panuveitis that has been described in otherwise healthy 20- to 40-year-old women with myopia.

Manifestations and differential diagnosis SFU syndrome is typically bilateral with high-grade anterior chamber inflammation and mild to moderate vitritis. Acute lesions resemble those of early MFCPU: white-yellow lesions (50–500 μm) at the level of the RPE, located from the posterior pole to the midperiphery. Acute lesions may fade with minimal RPE disruption, become atrophic, or coalesce to form multiple large areas of subretinal fibrosis

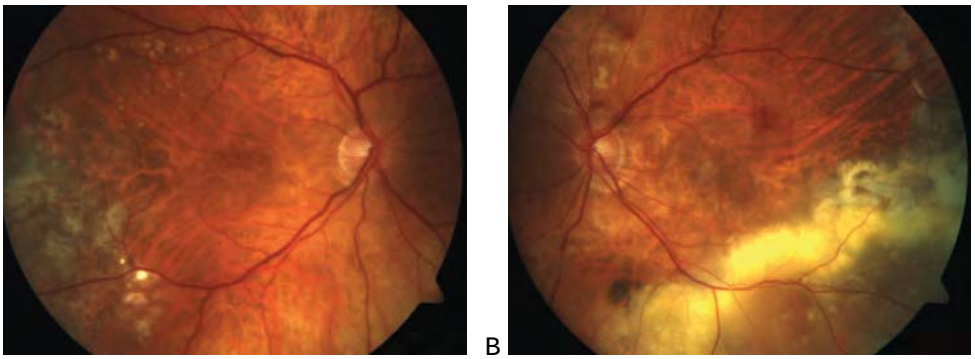

Figure 9-17 Subretinal fibrosis and uveitis syndrome. **A,** Right eye, with white-yellow lesions at the level of the RPE. **B,** Left eye, with confluent lesions signifying more advanced disease. *(Courtesy of Sam S. Dahr, MD, MS.)*

(Fig 9-17). Serous and hemorrhagic retinal detachment, macular edema, and CNV may also occur. Histologic studies reveal a lymphocytic granulomatous infiltration of the choroid with marked gliosis of the retina and subretinal fibrosis, suggesting immune-mediated destruction of the RPE and subsequent fibrosis.

Both FA and OCT are useful for diagnosing SFU. FA may show early alternating areas of blocked choroidal fluorescence and hyperfluorescence, with subsequent late staining, and OCT may show retinal edema, subretinal fluid, and subretinal fibrosis. The differential diagnosis of SFU includes syphilis, TB, sarcoidosis, APMPPE, ampiginous choroiditis, serpiginous choroiditis, sympathetic ophthalmia, toxoplasmosis, OHS, and pathologic myopia.

Treatment SFU may progress over months to years. The prognosis is guarded, but early and aggressive intervention with IMT may slow or stop progression. In recent reports, biologic agents such as rituximab have shown some efficacy in treating SFU.

Adán A, Sanmarti R, Burés A, Casaroli-Marano RP. Successful treatment with infliximab in a patient with diffuse subretinal fibrosis syndrome. *Am J Ophthalmol*. 2007;143(3):533–534.

Cornish KS, Kuffova L, Forrester JV. Treatment of diffuse subretinal fibrosis uveitis with rituximab. *Br J Ophthalmol.* 2015;99(2):153–154.

Kim MK, Chan CC, Belfort R Jr, et al. Histopathologic and immunohistopathologic features of subretinal fibrosis and uveitis syndrome. *Am J Ophthalmol.* 1987;104(1):15–23.

Multiple Evanescent White Dot Syndrome

Multiple evanescent white dot syndrome (MEWDS) is a rare idiopathic posterior uveitis that affects the outer retina and RPE. The typical patient is a young female (mean age at onset, 28 years) with moderate myopia. Patients may report a preceding viral illness.

Manifestations

Presenting symptoms include photopsias, paracentral scotoma, and decreased vision that may be as poor as 20/200. A relative pupillary afferent defect may also be observed.

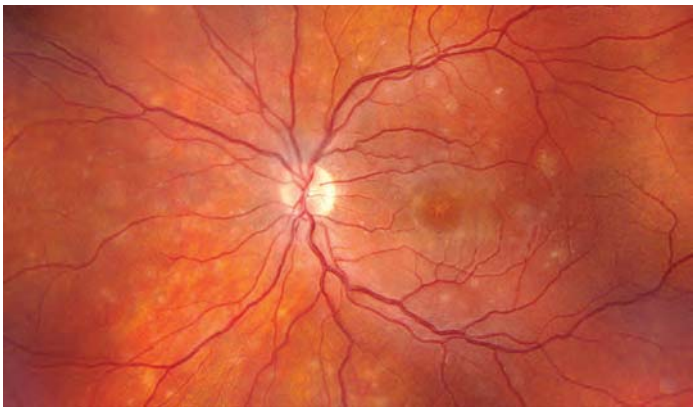

Figure 9-18 Multiple evanescent white dot syndrome. Fundus photograph shows multiple discrete, punctate, yellowish perifoveal dots. *(Courtesy of Wendy M. Smith, MD.)*

Examination may show discrete, white-to-orange spots (100–200 μm) at the deep retina or RPE (Fig 9-18). These lesions, which are transitory and may be subtle, are typically perifoveal and peripapillary, but they may also extend to the periphery. The fovea often has a granular, stippled appearance, termed *peau d'orange*. This appearance may persist even after the retinal lesions have faded. Anterior segment inflammation is minimal or absent, and mild degrees of vitreous cell, optic nerve edema, and vascular sheathing may be present. The lesions and foveal granularity usually resolve over several weeks as vision recovers.

MEWDS lesions are often described as *wreathlike*. For example, when the late-staining punctate hyperfluorescent lesions (Fig 9-19) are viewed under high magnification on FA, the individual lesions look like tiny "wreaths," consistent with the original description of this entity in the literature. In addition, the lesions are often arranged in a wreathlike configuration within the posterior pole. Even when the lesions are very subtle or have resolved on clinical examination, they may still be visualized on FAF (hyperautofluorescence; Fig 9-20) and ICGA (hypocyanescent; see Fig 9-19). ICGA also shows areas of hypocyanescence that are larger and more numerous than the hyperfluorescent lesions seen on FA.

Visual field abnormalities include generalized depression, paracentral or peripheral scotomas, and/or an enlarged blind spot. ERG reveals diminished a-wave and early receptor potential amplitudes, both of which are reversible. Multifocal ERG and electro-oculogram (EOG) localize the disease to the RPE–photoreceptor complex, not the choroid. OCT through the lesions shows photoreceptor inner/outer segment line hyperreflectivity and/or disruption, which also resolves over time (Fig 9-21). In addition, the foveal granularity corresponds to outer retinal structure disruption, and reconstitution of the retinal structures correlates with improvement in vision.

Papasavvas I, Mantovani A, Tugal-Tutkun I, Herbort CP Jr. Multiple evanescent white dot syndrome (MEWDS): update on practical appraisal, diagnosis and clinicopathology; a review and an alternative comprehensive perspective. *J Ophthalmic Inflamm Infect.* 2021; 11(1):45.

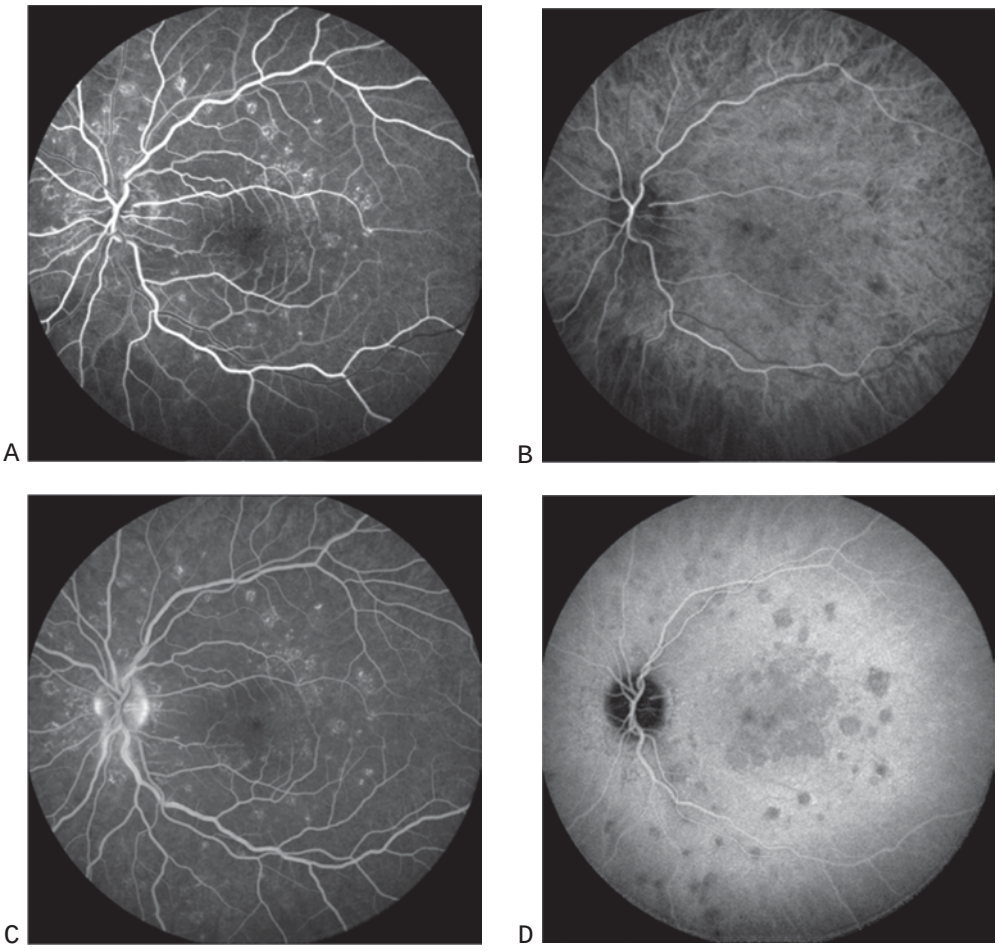

Figure 9-19 Multiple evanescent white dot syndrome (MEWDS). Fluorescein angiograms demonstrating early hyperfluoresence **(A)** and late staining **(C)** of MEWDS lesions. Corresponding early **(B)** and late **(D)** ICG angiograms demonstrating multiple hypocyanescent lesions. *(Courtesy of Wendy M. Smith, MD.)*

Prognosis

No treatment is usually required for MEWDS. After 1 to 2 months, vision typically returns to baseline, and imaging abnormalities mostly resolve, although residual photopsias and blind-spot enlargement may persist for months. Recurrences are rare. When central macular involvement is substantial or multiple recurrences occur, local or systemic treatment or an alternative diagnosis may be considered.

Disease associations

MEWDS has been associated with MFCPU, acute zonal occult outer retinopathy, and acute macular neuroretinopathy (AMN). AMN was previously considered a white dot syndrome because the demographics and symptoms of affected patients matched those of the syndrome. However, multimodal imaging techniques suggest that AMN is a microvascular event in the

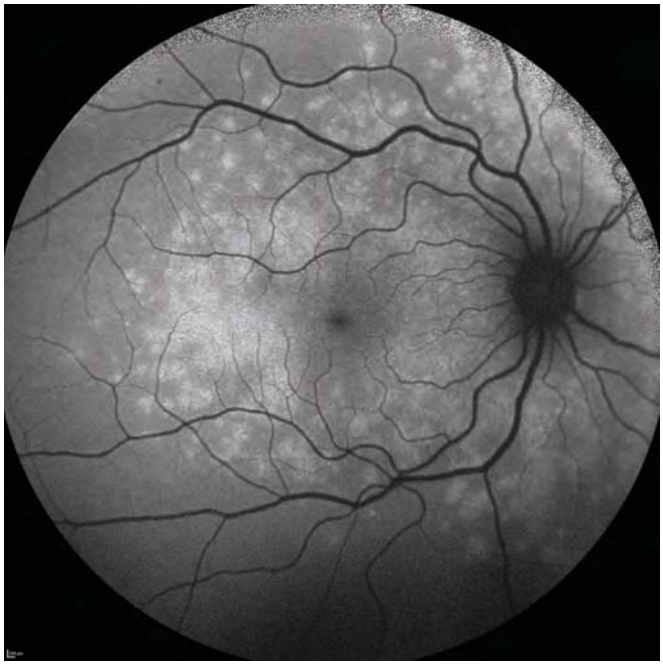

Figure 9-20 Multiple evanescent white dot syndrome. FAF image shows multiple hyperautofluorescent spots. *(Courtesy of Bryn M. Burkholder, MD.)*

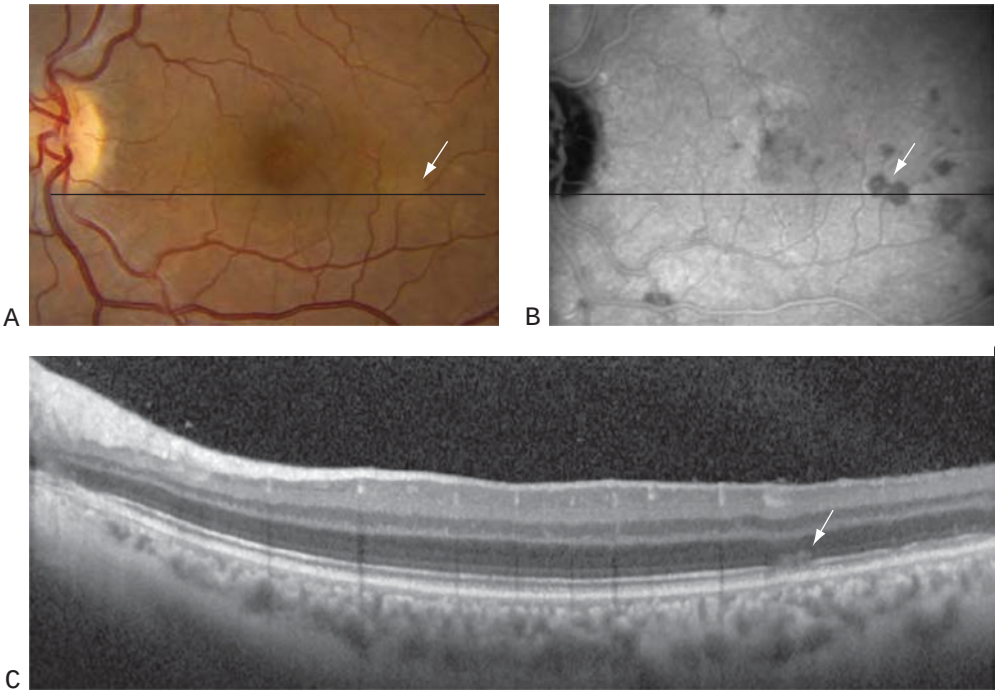

Figure 9-21 Multiple evanescent white dot syndrome. **A,** Color fundus photograph shows subtle spots *(arrow)* and foveal granularity. **B,** ICG angiogram shows more spots *(arrow)* than are apparent on the color photograph. **C,** OCT of the spots (positioned at horizontal lines in **A** and **B**) shows disruption of the inner/outer segment line (ellipsoid zone) *(arrow).* *(Courtesy of Janet L. Davis, MD, and Charles Wycoff, MD.)*

deep capillary plexus of the macula, not a primary inflammatory process. See BCSC Section 12, *Retina and Vitreous*, for further discussion about AMN.

Acute Retinal Pigment Epitheliitis

Acute retinal pigment epitheliitis (ARPE), or Krill disease, is a benign, self-limited inflammation of the RPE with acute onset. ARPE is one of the rarest white dot syndromes. Males and females are affected equally. Affected individuals aged 15–40 years present with vision loss, central metamorphopsia, and scotomas, usually unilaterally (75%). The lesions resolve spontaneously over 6–12 weeks, so patients are usually observed without treatment. The visual prognosis is good.

Manifestations

In patients with ARPE, clusters of small dark-gray or black spots (100–200 μm) with a yellow halo or rim appear in the deep retina, within the posterior pole. Over time, the halo disappears, and pigment clumping may develop. There is mild or no vitritis. FA performed soon after initial onset shows central hypofluorescence of the lesions with a lacy hyperfluorescent rim that creates a honeycomb effect (Fig 9-22). Older lesions may show early and late fluorescein hyperfluorescence without leakage. FAF findings are variable, but hyperautofluorescent lesions are often depicted. ICGA shows early- and mid-phase patchy macular hypercyanescence and a late hypercyanescent halo in the macula. OCT shows transient disruption of the ellipsoid zone and the inner layer of the RPE. Visual field testing reveals a central scotoma. An abnormal EOG after a normal ERG suggests that the disease originated within the RPE.

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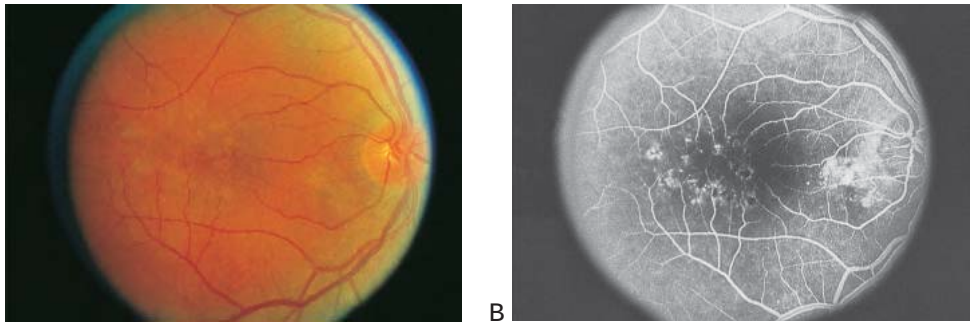

Figure 9-22 Acute retinal pigment epitheliitis. **A,** Fundus photograph shows small yellow-gray lesions in the deep retina. **B,** FA demonstrates honeycomb lesions at the level of the RPE. *(Courtesy of E. Mitchel Opremcak, MD.)*

Acute Zonal Occult Outer Retinopathy

Acute zonal occult outer retinopathy (AZOOR) is an inflammatory outer retinal degeneration that often presents with a clinically normal-appearing fundus. Photopsias are usually prominent and are described as pulsations, windmills, bubbles, sprays, or sparkles. The mean age at disease onset is 37 years, and 76% of patients are female. Diagnosis is often delayed, however, because findings on clinical examination are limited in early disease. At presentation, the disease is commonly unilateral, but fellow eye involvement eventually develops in most cases. Early in the disease, the differential diagnosis of AZOOR includes optic neuritis, optic nerve compressive lesion, a pituitary or intracranial tumor, and paraneoplastic and nonparaneoplastic autoimmune retinopathy. The differential diagnosis also includes MEWDS, DUSN, and inherited retinal degenerations.

Manifestations

In the initial stage of AZOOR, visual acuity is good. Anterior segment inflammation is absent, and mild vitreous cells may occur. The fundus examination is grossly unremarkable at presentation, but eventually a white annular ring (diameter, 3–5 mm) involving the outer retina and centered on the optic disc may be visualized. Later, islands of subtle RPE granularity and/or depigmentation develop in the posterior and midzones of the fundus, sometimes with vessel attenuation or sheathing (Fig 9-23A). FAF shows hypoautofluorescence in zones of RPE and choriocapillary atrophy. Persistent or progressive activity at the lesion border may be hyperautofluorescent secondary to lipofuscin-laden cells that precede RPE cell death (Fig 9-23B). In addition, areas of subacute disease activity may show speckled hyperautofluorescence that evolves into hypoautofluorescence as atrophic changes develop.

Early in the disease, findings on FA are usually normal, but eventually the affected RPE is highlighted as hyperfluorescent window defects. OCT of the involved zones demonstrates

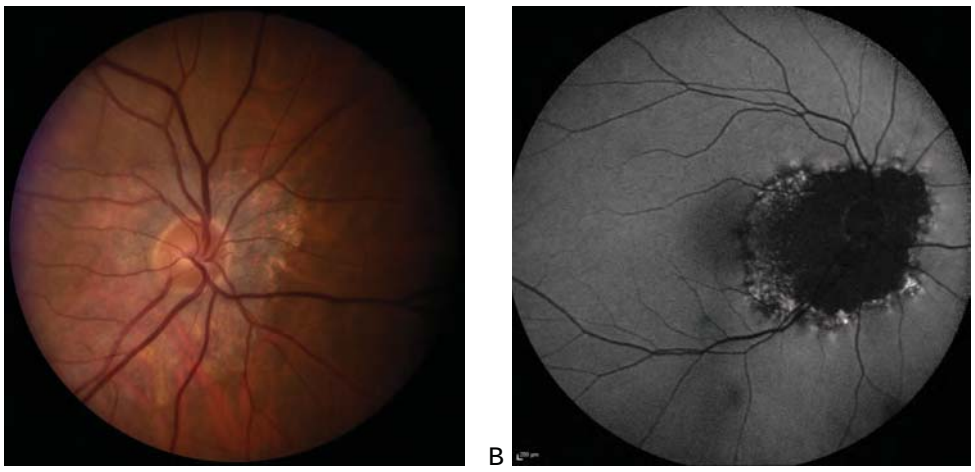

Figure 9-23 Acute zonal occult outer retinopathy. **A,** Fundus photograph demonstrates peripapillary atrophy of the RPE and choriocapillaris. **B,** FAF shows a broad area of peripapillary hypoautofluorescence with a stippled hyperautofluorescent border. *(Courtesy of Bryn M. Burkholder, MD.)*

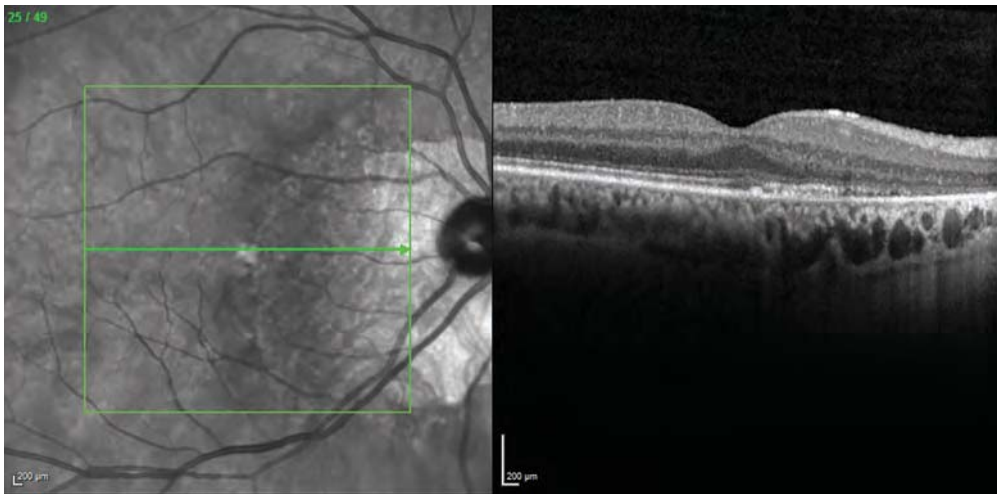

Figure 9-24 Acute zonal occult outer retinopathy. OCT image from the patient in Figure 9-23 demonstrates loss of the peripapillary ellipsoid zone. *(Courtesy of Bryn M. Burkholder, MD.)*

areas of ellipsoid zone loss or irregularity (Fig 9-24). ERG shows dysfunction at both the photoreceptor–RPE complex and the inner retina, including a delayed 30-Hz flicker ERG and a reduction in the EOG light rise. Visual field deficits correspond to the zone of affected retina and may manifest as central, arcuate, or ring scotoma; horizontal or vertical hemianopias; or any combination of these.

Prognosis and treatment

AZOOR evolves over months to years, but visual field loss often stabilizes in approximately 75% of patients. A large case review of long-term outcomes suggests that 68% of eyes retained 20/40 or better vision, but 27% developed 20/200 vision or worse. It is unclear whether treatment with systemic corticosteroids or IMT alters the disease course or visual outcome. However, for a patient with progressive RPE or visual field loss, long-term IMT and/or extended-duration steroid implants may be considered.

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Acute Idiopathic Maculopathy

Acute idiopathic maculopathy (AIM) is typically a unilateral disease (unilateral AIM) that presents with acute central vision loss (ie, 20/200) associated with macular subretinal

fluid. Patients are typically aged 20–40 years and may have a viral prodrome. Some patients concurrently experience hand-foot-and-mouth disease, which is linked to coxsackievirus. Adult patients with AIM may also have a history of exposure to a child with hand-foot-and-mouth disease.

Manifestations and differential diagnosis

Clinical examination of a patient with suspected AIM is notable for turbid yellow subretinal fluid in the macula (Fig 9-25A). The underlying RPE may appear yellow-white-gray and thickened. Minimal intraretinal hemorrhages may also be present, and anterior chamber and vitreous cells are minimal or absent. OCT shows subretinal fluid with hyperreflective debris in the subretinal space (Fig 9-25B). FA of the central lesion shows early hypofluorescence or hyperfluorescence followed by late stippled hyperfluorescent staining of the RPE and pooling of dye in the subretinal space (Fig 9-25C, D). ICGA of the lesion is hypocyanescent.

The differential diagnosis of AIM includes central serous chorioretinopathy, choroidal infarction, CNV, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, serpiginous choroiditis, APMPPE, posterior scleritis, and syphilis.

Prognosis and treatment

The prognosis is variable based on the degree of RPE damage. Macular subretinal fluid typically resolves spontaneously and fairly rapidly. After lesion resolution, residual RPE hypopigmentation and granularity within the macula or a bull's-eye RPE pattern of central

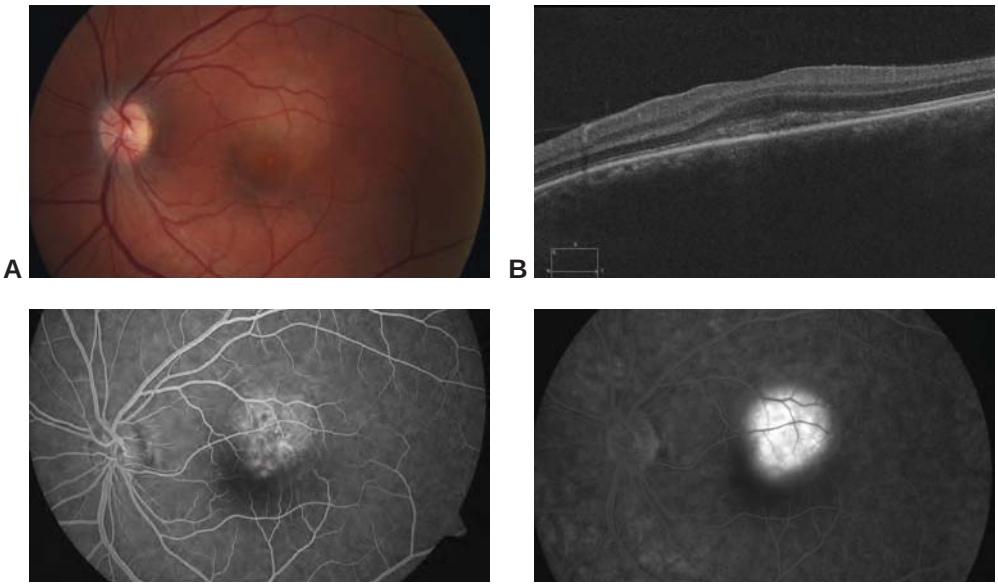

Figure 9-25 Images from a 27-year-old woman with unilateral acute idiopathic maculopathy. **A,** Color fundus photograph shows grayish-yellow discoloration of the RPE. **B,** OCT shows shallow subretinal fluid with hyperreflective material. **C,** FA shows a mixed pattern of early hypofluorescence and hyperfluorescence. **D,** Late FA shows RPE staining and pooling within the neurosensory detachment. *(Courtesy of Sam S. Dahr, MD, MS.)*

hyperpigmentation surrounded by hypopigmentation is typically seen. If subfoveal RPE degeneration or CNV develops, the visual outcome may be poor. Patients are usually monitored without therapy, although oral corticosteroids may be considered in patients with significant vision loss or slow lesion resolution.

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Autoimmune Retinopathy

Autoimmune retinopathy (AIR) is a rare, presumably immune-mediated retinal degeneration characterized by visual field deficits and photoreceptor dysfunction on ERG. Paraneoplastic AIR (pAIR) encompasses cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). In contrast, nonparaneoplastic AIR (npAIR) occurs in the absence of any malignancy and is more common in females than in males (ratio 2:3), typically aged 40–60 years. Approximately 50% of patients with npAIR have a systemic autoimmune disease.

Manifestations

Autoimmune retinopathy presents with progressive, bilateral vision loss; photopsias; scotomas; dyschromatopsia; photoaversion; and nyctalopia. Ophthalmic examination may demonstrate normal findings initially, but vessel attenuation, RPE disruption, optic nerve pallor, and/or diffuse retinal atrophy may develop over time (Fig 9-26). Anterior chamber and vitreous inflammation is absent or very minimal. FA may show macular leakage, whereas OCT reveals macular thinning with ellipsoid zone disruption and thinned outer nuclear and photoreceptor layers (Fig 9-27). FAF may show a parafoveal ring of hyperautofluorescence.

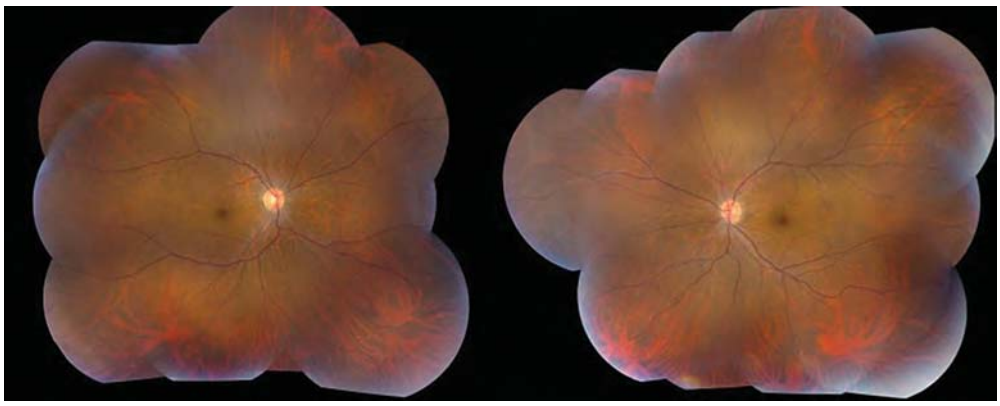

Figure 9-26 Nonparaneoplastic autoimmune retinopathy in a 39-year-old patient. The photographs show mild vascular attenuation, diminished foveal reflex, and mild optic nerve pallor. The electroretinogram (not shown) showed diminished cone and rod responses. *(Courtesy of H. Nida Sen, MD. Autoimmune retinopathy: current concepts and practices (an American Ophthalmological Society thesis).* Trans Am Ophthalmol Soc. *2017;115:T8(1–13). Published with permission of the American Ophthalmological Society.)*

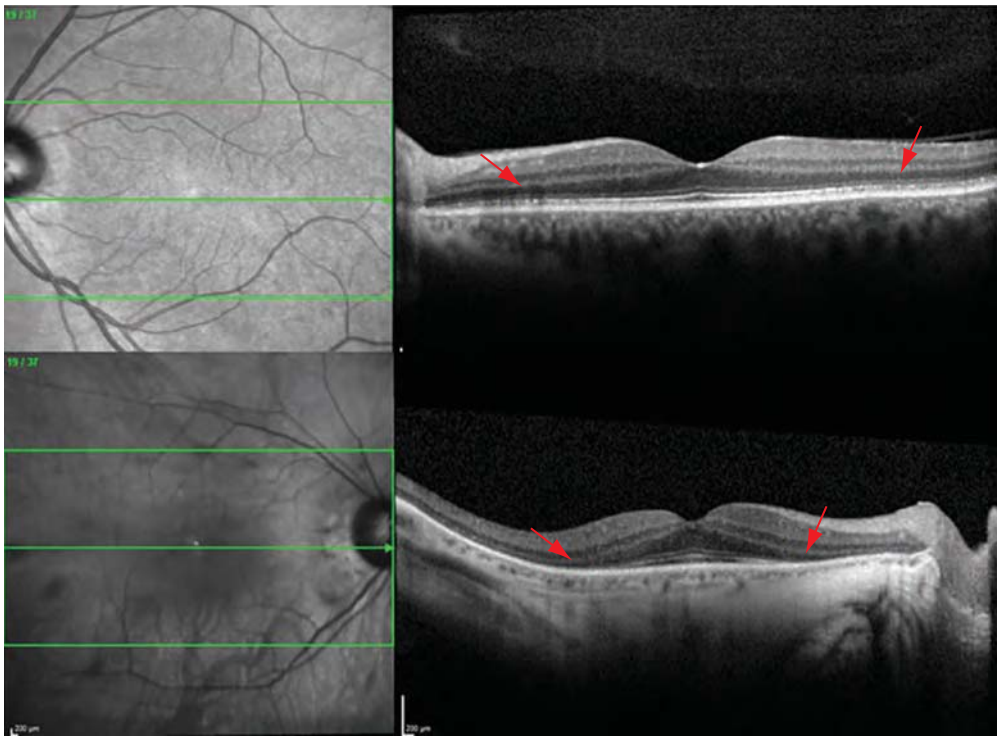

Figure 9-27 Optical coherence tomography images from 2 patients with nonparaneoplastic autoimmune retinopathy. *Top,* Patient with mild disruption of the photoreceptors *(red arrows). Bottom,* Patient with more severe photoreceptor loss *(red arrows). (Courtesy of H. Nida Sen, MD. Autoimmune retinopathy: current concepts and practices (an American Ophthalmological Society thesis).* Trans Am Ophthalmol Soc. *2017;115:T8(1–13). Published with permission of the American Ophthalmological Society.)*

Visual field changes include central scotoma, paracentral scotoma, or constricted fields. ERG findings may be markedly abnormal: In patients with CAR, cone responses are typically depressed, whereas in those with MAR, the photoreceptor response is normal followed by an attenuated b-wave, representing on-bipolar cell dysfunction.

Diagnosis

Diagnosis of AIR is challenging. Traditionally, the major biomarker in diagnosing and managing this disease has been the presence of serum anti-retinal antibodies (ARAs). However, recent research indicating a poor correlation between most serum ARAs and disease phenotype has raised questions about whether the antibodies are a cause or a consequence of retinal degeneration in AIR. Concerns have also arisen with detection of ARAs in healthy controls as well as in patients with systemic autoimmune disease, other uveitic entities such as BCR and AZOOR, age-related macular degeneration, and diabetic retinopathy. Conversely, there are reports of negative serum ARA test results in patients with clinical and ERG findings consistent with AIR. Further complicating diagnosis, techniques for detecting ARAs have not been standardized, leading to widely variable results between laboratories. Taken together, these

findings have led many to conclude that the presence of serum ARAs cannot be automatically equated with the diagnosis of AIR.

Ultimately, the diagnosis of AIR is one of exclusion, with the following criteria warranting consideration:

- compatible symptoms
- positive serum ARA test results
- abnormal ERG results with or without visual field loss
- absence of overt (>1+ grade) intraocular inflammation
- absence of fundus findings or an alternative uveitic diagnosis that explains visual field or ERG loss
- absence of inherited retinal degeneration such as retinitis pigmentosa or cone dystrophy
- absence of malignancy (ie, to diagnose npAIR)

When pAIR is suspected, testing for the presence of anti-recoverin antibodies, which are strongly associated with CAR, can be considered. The most common CAR-associated malignancy is small cell lung cancer. Autoantibodies to transient receptor potential cation channel (TRMP1; expressed in both melanocytes and retinal on-bipolar cells) strongly support a diagnosis of MAR in a compatible clinical context. Nevertheless, the absence of these autoantibodies does not rule out pAIR. When there is strong clinical suspicion for pAIR, obtaining age-, sex-, and risk factor–appropriate cancer screenings may be most expeditious.

Treatment

In addition to uncertainty surrounding the diagnosis of AIR, treatment may also be challenging because the systemic and local strategies used for other types of ocular inflammation may not be as effective for AIR. For patients with npAIR, corticosteroids (local or systemic), conventional IMT, or biologic agents (ie, rituximab) may be considered. In patients with pAIR, therapy for the underlying malignancy is the first step in treatment; additional measures may include systemic or local corticosteroids, intravenous immunoglobulin, and/or plasmapheresis. Treatment response may be assessed with OCT, FAF, visual field evaluations, and ERG. Unfortunately, reversal of retinal damage is unlikely, although stabilization may be possible. See BCSC Section 5, *Neuro-Ophthalmology,* for additional discussion on AIR.

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