CHAPTER 4

# Age-Related Macular Degeneration and Other Causes of Choroidal Neovascularization

*This chapter includes a related activity. Go to www.aao.org/bcscactivity_section12 or scan the QR code in the text to access this content.*

## Highlights

- Age-related macular degeneration (AMD) is a leading cause of permanent vision loss worldwide. It has 2 late-stage manifestations, which may coexist: a nonneovascular form known as *geographic atrophy* and a neovascular form characterized by the presence of macular neovascularization *(choroidal neovascularization)*.
- Risk factors for AMD may be nonmodifiable (eg, age) or modifiable (eg, cigarette smoking and low micronutrient intake).
- According to multiple genome-wide association studies, genetic factors account for at least 55% of total AMD risk, and the pathway most consistently implicated in AMD is the complement cascade.
- Anti–vascular endothelial growth factor agents are the mainstay of treatment for exudative AMD and are typically administered using 1 of 3 broad approaches: fixed-interval dosing, as-needed dosing, or treat-and-extend dosing.
- In addition to AMD, multiple retinal pathologies may lead to choroidal neovascularization; these distinct exudative diseases are also frequently managed with anti–vascular endothelial growth factor drugs.

## Age-Related Macular Degeneration Studies

This glossary provides the abbreviated and full names of age-related macular degeneration studies referenced in this chapter; an updated glossary is available online (www.aao.org/bcscglossary_section12). Only the short names are used in the text.

**ANCHOR** Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD

**AREDS** Age-Related Eye Disease Study

**AREDS2** Age-Related Eye Disease Study 2

**CATT** Comparison of Age-Related Macular Degeneration Treatments Trials

**EXCITE** Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to AMD

**HARBOR** A Study of Ranibizumab Administered Monthly or on an As-Needed Basis in Patients With Subfoveal Neovascular AMD

**HOME** HOme Monitoring of the Eye (HOME) Study

**HORIZON** Open-label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to AMD

**MARINA** Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD

**MESA** Multi-Ethnic Study of Atherosclerosis

**PIER** Phase 3b, Multicenter, Randomized, Double-Masked, Sham Injection–Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects With Subfoveal Choroidal Neovascularization With or Without Classic Choroidal Neovascularization Secondary to AMD

**PLANET** Aflibercept in Polypoidal Choroidal Vasculopathy study

**SUSTAIN** Study of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to AMD

**TREND** TReat and extEND

**VIEW 1 and VIEW 2** VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD 1 and 2

## Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss worldwide among people older than 50 years. In the United States, it is the most common cause of legal blindness, affecting an estimated 2.07 million people in 2010 and projected to affect 3.7 million by 2030. An estimated 71,000 new cases of neovascular AMD develop each year in North America.

This complex disorder has 2 main clinical stages: an intermediate or earlier phase of nonexudative degeneration (often referred to collectively as *dry AMD*) and a late stage (also known as *advanced AMD*). Late-stage AMD is further subdivided into a nonneovascular form, known as *geographic atrophy,* and a neovascular form characterized by macular neovascularization (MNV). These 2 late stages often coexist in the same eye. Historically, the term *choroidal neovascularization (CNV),* or *CNV membrane (CNVM),*

was used to refer to the neovascular complex associated with AMD. However, the term *MNV* is now preferred because in some cases, the neovascularization arises from the retinal vasculature. The terms *neovascular AMD, exudative AMD,* and *wet AMD* are also used for the neovascular form.

Normal aging initiates a spectrum of changes in the macula that affect the outer retina, retinal pigment epithelium (RPE), Bruch membrane, and choriocapillaris (Fig 4-1):

- Photoreceptors, rods more than cones, are reduced in density and distribution.
- In the RPE, ultrastructural changes include loss of melanin granules, formation of lipofuscin granules, and accumulation of residual bodies.
- Basal laminar deposits accumulate between the plasma membrane of the RPE cell and the native RPE basement membrane in AMD; these deposits consist of extracellular matrix proteins, including widely spaced collagen fibers.
- Basal linear deposits accumulate and expand to soft drusen in AMD; this lipid-rich material is attributed to lipoprotein particles that accumulate between the basement membrane of the RPE and the inner collagenous layer of Bruch membrane.
- In the choriocapillaris, progressive involutional changes occur.

All of these changes represent aging and may not be part of AMD pathology.

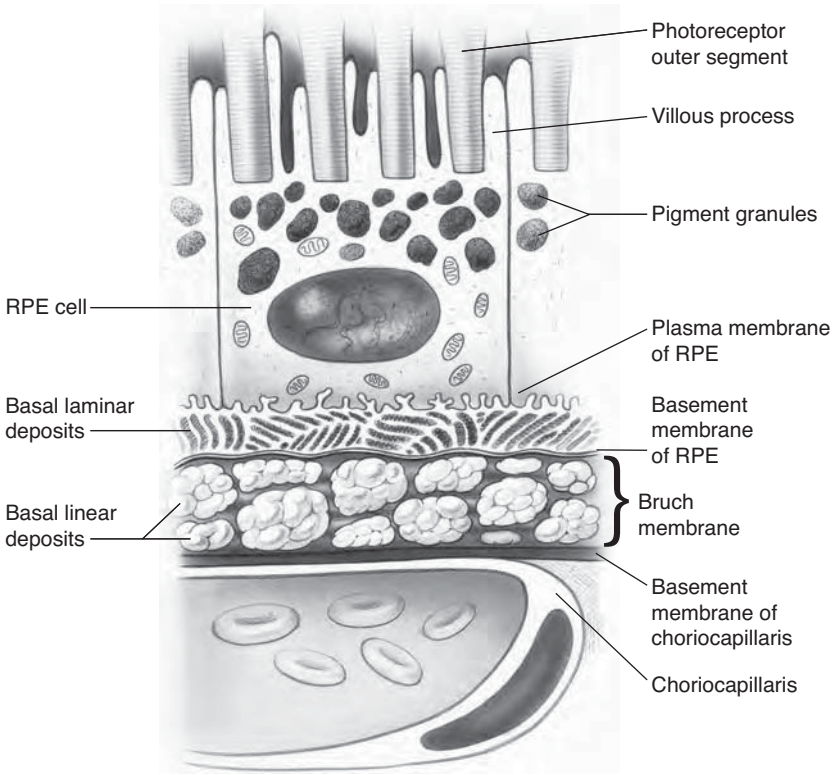


**Figure 4-1** Schematic illustration of basal laminar deposits and basal linear deposits that result in a thickened inner collagenous layer of Bruch membrane. RPE = retinal pigment epithelium. *(Illustration by Christine Gralapp.)*

Abnormalities associated with AMD that are not related to normal aging may be classified as nonneovascular or neovascular.

Population-based studies have demonstrated that age is the foremost risk factor for AMD; in resource-rich countries, approximately 10% of individuals older than 65 years and 25% older than 75 years have AMD. In addition to age, other nonmodifiable risk factors for AMD include female sex, family history of AMD, hyperopia, light iris color, and race. MESA, a 10-year longitudinal study, found that the prevalence of AMD in the United States was highest in White participants (5.4%) and lowest in African American individuals (2.4%); among participants of Asian and Hispanic ethnicity, the prevalence was 4.6% and 4.2%, respectively.

The most common modifiable risk factor for AMD is cigarette smoking. Others include hypertension, hypercholesterolemia, cardiovascular disease, high waist-to-hip ratio in men, and elevated levels of C-reactive protein and other inflammatory markers.

Klein R, Klein BE, Knudtson MD, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the Multi-Ethnic Study of Atherosclerosis. *Ophthalmology*. 2006;113(3):373–380.

## Genetics and AMD

Although the exact etiology of AMD is poorly understood, its development appears to involve an interplay of extrinsic and intrinsic risk factors. Within this context, a genetic predisposition has emerged as one of the most important risk factors for the disorder. According to familial and population-based studies, genetic factors account for an estimated 55% or more of the total variability in AMD risk. Although the emerging association between AMD and genetics is strong, it is also complex. Human genome-wide association studies have identified more than 34 genetic loci for AMD on at least 19 chromosomes.

Although genetic studies have identified multiple biochemical pathways related to AMD pathophysiology, including lipid transport and metabolism (eg, *APOE*), modulation of the extracellular matrix (eg, *COL8A1, COL10A1, MMP9,* and *TIMP3*), clearance of all-*trans*-retinaldehyde from photoreceptors *(ABCA4),* and angiogenesis (eg, *VEGFA*), the pathway most consistently implicated in genetic studies of AMD is the complement cascade. The complement system is a complex, innate immune response that allows a host to clear damaged cells, regulate inflammation, and opsonize foreign cells; polymorphisms within certain complement components, including *CFD, CFH, CFI, C2/CFB, C3, C5,* and *C7,* have been strongly linked to AMD risk.

The 2 major susceptibility genes for AMD are *CFH* (1q31), which codes for complement factor H, and *ARMS2/HTRA1* (10q26). The *CFH* Y402H polymorphism confers a 4.6-fold increased risk for AMD when heterozygous and a 7.4-fold increased risk when homozygous. The A69S *ARMS2/HTRA1* polymorphism confers a 2.7-fold increased risk for AMD when heterozygous and an 8.2-fold increased risk when homozygous. When both genes are homozygous for the aforementioned polymorphisms, the risk for AMD is increased 50-fold.

Although genetic testing is available for AMD, the American Academy of Ophthalmology's official recommendation is to defer this testing until replicable studies have confirmed its value for prognostication or response to therapy.

American Academy of Ophthalmology Preferred Practice Pattern Retina/Vitreous Committee, Hoskins Center for Quality Eye Care. Preferred Practice Pattern Guidelines. *Age-Related Macular Degeneration*. American Academy of Ophthalmology; 2015. www.aao.org/ppp

Frisch LG, Igl W, Cooke Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet.* 2016;48(2):134–143.

## Nonneovascular AMD

In all stages of nonneovascular AMD, the defining lesion is the druse (plural, *drusen*). Because drusen variably affect overlying photoreceptors, they may be associated with mild to moderate vision loss, decreased contrast sensitivity and color vision, and impaired dark adaptation. Other indicators of nonneovascular AMD are abnormalities of the RPE, including hypopigmentation, hyperpigmentation, and atrophy.

### *Drusen*

Clinically, drusen typically are round, yellow lesions located along the basal surface of the RPE, mostly in the postequatorial retina (Fig 4-2). Histologically, this material corresponds to the abnormal thickening of the inner aspect of Bruch membrane, shown in Figure 4-1. Ultrastructurally, basal laminar deposits (granular, lipid-rich material and widely spaced collagen fibers between the plasma membrane and basement membrane of

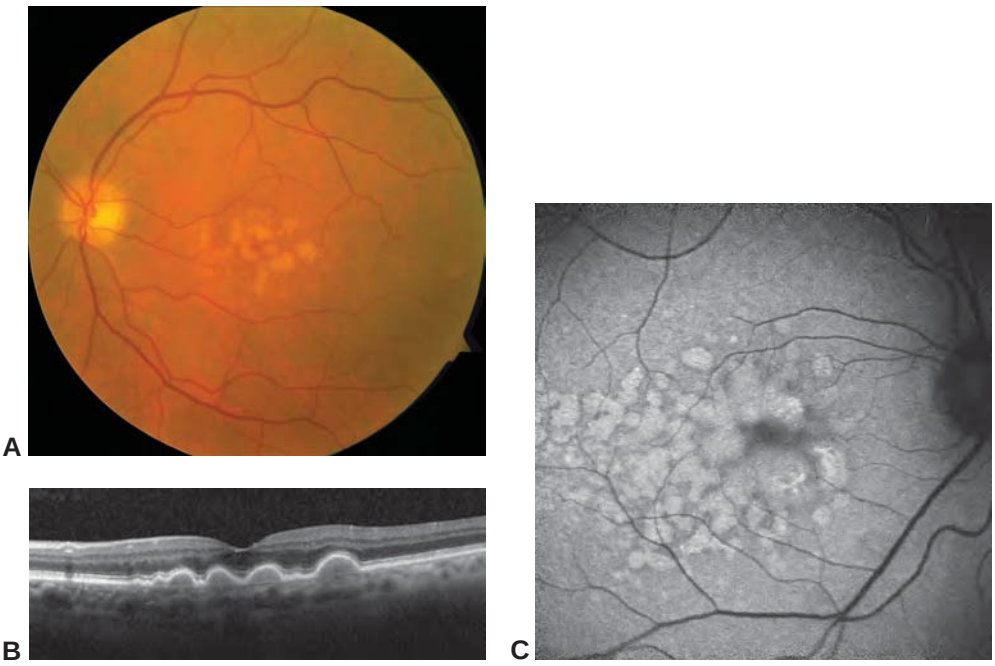


**Figure 4-2** Drusen. **A,** Color fundus photograph shows large soft and confluent drusen in a patient with nonneovascular (dry) age-related macular degeneration (AMD). **B,** Corresponding spectral-domain optical coherence tomography (SD-OCT) image of the soft drusen. **C,** Autofluorescence image of an eye with areas of confluent drusen. *(Courtesy of David Sarraf, MD.)*

the RPE cell) and basal linear deposits (phospholipid vesicles and electron-dense granules within the inner collagenous zone of Bruch membrane) are observed.

The thickened inner aspect of Bruch membrane, along with the RPE, may separate from the rest of the membrane, resulting in a pigment epithelial detachment (PED). When small, such a detachment may be identified as a large or soft druse; when larger (ie, diameter >350 μm), it is recognizable as large confluent drusen that have coalesced into a PED, also known as a *drusenoid PED*.

Drusen are categorized by size as follows, with the typical diameter given within parentheses: small (<63 μm), intermediate (63–124 μm), and large (≥125 μm). Increasing size, number, and confluence of the drusen elevate the risk of progression to MNV or geographic atrophy (GA). In AREDS, among patients with early AMD (ie, with many small drusen or a few intermediate drusen, category 2), the risk of progression to category 4 AMD over a 5-year period was 1.3%. In contrast, for patients with nonsubfoveal GA, many intermediate drusen, or even a single large druse (category 3), the risk was 18%. Patients who progressed to MNV or subfoveal GA were considered to have advanced, or category 4, AMD. Patients with no AMD (a few small or no drusen without pigment changes, category 1) had 0% risk of progression to category 4 AMD.

Drusen are further distinguished by their boundaries: hard (discrete and well demarcated), soft (amorphous and poorly demarcated; see Fig 4-2A, B), or confluent (contiguous drusen without clear boundaries; see Fig 4-2C). Hard drusen are well-defined focal areas of lipidization or hyalinization of the RPE–Bruch membrane complex. Soft drusen are associated with diffuse thickening of the inner aspects of Bruch membrane (ie, basal linear deposits). An eye containing soft, and perhaps confluent, drusen is more likely to progress to atrophy or MNV than an eye containing only hard drusen; consistent with this, drusen volume has emerged as a possible biomarker for increased risk of late AMD development.

Reticular pseudodrusen or subretinal drusenoid deposits are similar in appearance to drusen; however, they are recognizable by their reticular-like network, best seen on fundus autofluorescence and near-infrared imaging (Fig 4-3). These lesions are typically smaller than soft drusen, are located on the apical surface of the RPE, and are commonly distributed in the superior macular region. Although they share some proteins with drusen (eg, apolipoprotein E, complement factor H, and vitronectin), they contain different lipids and do not contain shed disc remnants. Their presence has been associated with progressive atrophy of the photoreceptor layer, GA, and increased risk of MNV.

**Fluorescein angiography of drusen** On fluorescein angiography (FA), drusen appearance may vary. Typically, small hard drusen hyperfluoresce early in FA studies because of a window defect, whereas larger soft and confluent drusen and drusenoid PEDs slowly and homogeneously stain late because of pooling of the fluorescein dye in the sub-RPE compartment.

**Optical coherence tomography of drusen** Spectral-domain optical coherence tomography (SD-OCT) of small and large drusen typically reveals sub-RPE nodular elevations with a notable absence of intraretinal and subretinal fluid (see Fig 4-2). Reticular pseudodrusen are identified above the RPE and beneath the inner segment ellipsoid layer (see Fig 4-3).

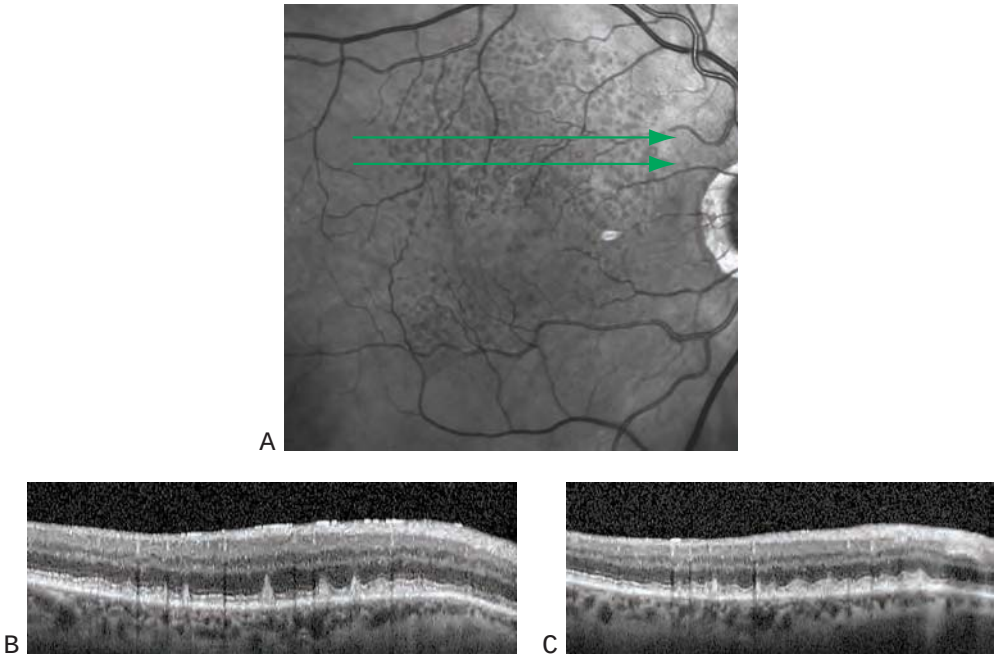


**Figure 4-3** Reticular pseudodrusen. **A,** Near-infrared reflectance image shows the multifocal and typical netlike arrangement of pseudodrusen. *Green arrows* mark locations of **B** *(top arrow)* and **C** *(bottom arrow).* **B,** SD-OCT image demonstrates the location of typical peak-shaped reticular pseudodrusen above the RPE. **C,** SD-OCT image demonstrates the location of undulating reticular pseudodrusen above the RPE. *(Courtesy of Charles C. Wykoff, MD, PhD.)*

Enhanced depth imaging (EDI) OCT provides more details of choroidal architecture and a clearer definition of the choroidal-scleral interface, which is helpful in characterizing AMD. In eyes with AMD, choroidal thickness is often reduced.

### *Abnormalities of the retinal pigment epithelium*

In patients with nonneovascular AMD, characteristic RPE abnormalities include focal hyperpigmentation or hypopigmentation, intraretinal pigment migration, focal atrophy, and GA. Focal RPE hyperpigmentation appears as increased pigmentation at the level of the outer retina. These areas typically block fluorescence on FA and appear as hyperreflective outer retinal foci on SD-OCT. Intraretinal pigment migration within the neurosensory retina may be visualized superficial to drusen or drusenoid PEDs. The incidence of these abnormalities increases with age, and their presence increases the risk of progression to more advanced forms of AMD.

**Geographic atrophy** In the eye, focal atrophy can appear clinically as areas of mottled pigmentation or depigmentation. When these lesions are contiguous and have a diameter greater than 175 μm, they are described as GA of the RPE. In areas of GA, absence or depigmentation of the RPE exposes the choroidal vessels. The overlying outer retina typically appears thin, and the underlying choriocapillaris is attenuated or atrophied. On FA, GA appears as well-circumscribed window defects of varying sizes corresponding to the

area of absent RPE. On SD-OCT, GA manifests as loss of the photoreceptors and RPE. Choriocapillaris loss may also be appreciated. On fundus autofluorescence (FAF), another useful noninvasive technique for monitoring disease progression (Fig 4-4), GA appears as well-demarcated areas of decreased signal intensity; multiple potential FAF patterns involving adjacent tissue have also been described.

GA often spares the fovea until late in the disease course, and affected patients may maintain good vision until then. Although GA was traditionally considered slowly progressive, multiple analyses have highlighted the severe functional impairment and consistent, inexorable rate of annual progression associated with the condition. The average rate of disease progression is approximately 1.79 $mm^2$/year; however, this rate of longitudinal GA enlargement is highly variable and is influenced by multiple factors, including lesion size at baseline and adjacent FAF patterns. When the fovea becomes involved and visual

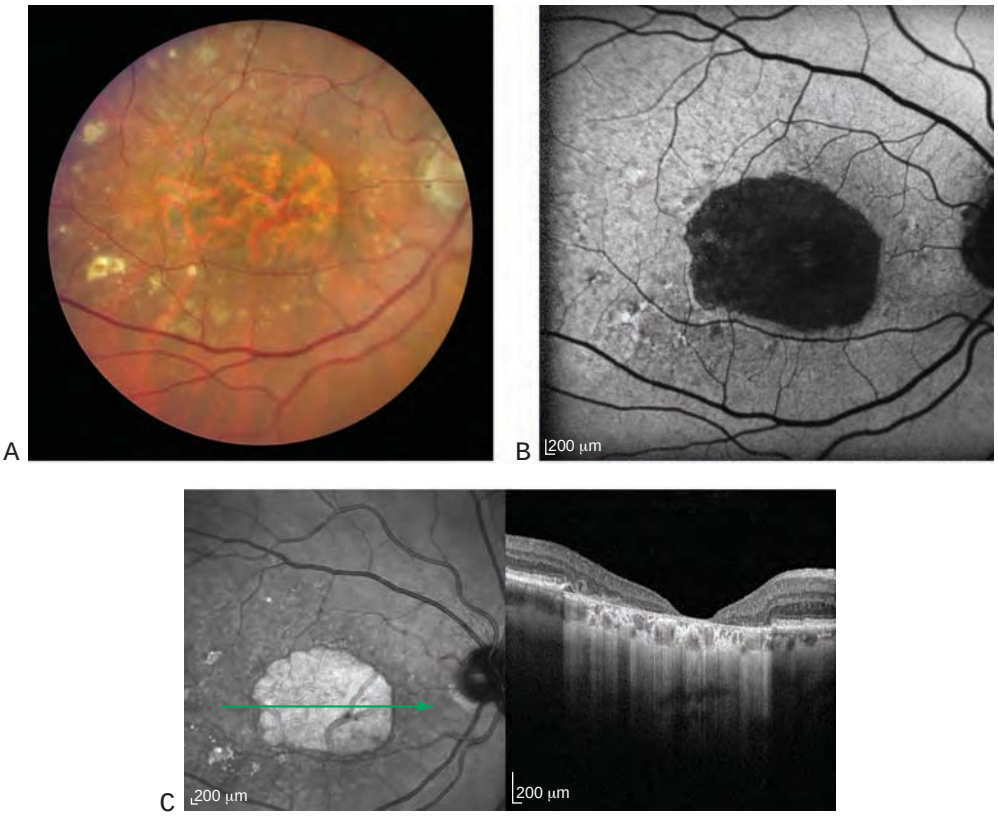


**Figure 4-4** Geographic atrophy (GA). **A,** Color fundus photograph of right eye, demonstrating advanced GA. **B,** Corresponding fundus autofluorescence image from the same patient. The areas of RPE atrophy are hypoautofluorescent *(dark gray or black),* the areas of "sick" RPE are hyperautofluorescent *(brighter than background),* and the areas of healthy RPE are gray. **C,** Corresponding near-infrared reflectance image in the same patient *(left).* Large choroidal vessels are visible through the central area of GA. *Green arrow* marks the location seen in the SD-OCT image *(right)* showing complete atrophy of photoreceptors, RPE, and choriocapillaris. *(Courtesy of Charles C. Wykoff, MD, PhD.)*

acuity (VA) declines, patients are able to read and perform detailed visual tasks by relying on eccentric fixation using the noncentral retina. Among patients with GA, 12%–20% experience severe vision loss.

Although not all eyes with drusen will develop GA, the incidence of atrophy appears to increase with age. In addition, 10% of patients with AMD and a VA of 20/200 or less have GA. Decreased contrast sensitivity and reduced microperimetry sensitivity values reflect the presence of pseudodrusen before progression to GA.

Holekamp N, Wykoff CC, Schmitz-Valckenberg S, et al. Natural history of geographic atrophy secondary to age-related macular degeneration: results from the Prospective Proxima A and B Clinical Trials. *Ophthalmology*. 2020;127(6):769–783.

Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology*. 2018;125(4):537–548. Published correction appears in *Ophthalmology*. 2019;126(1):177.

**Other abnormalities** As drusen resorb over time, atrophy of the RPE may develop. Dystrophic lipidization and calcification may also occur, resulting in the development of refractile or crystalline lesions in the macula (termed *refractile* or *calcific drusen*). Furthermore, pigment or pigment-laden cells (either RPE cells or macrophages that have ingested the pigment) may migrate to the photoreceptor level, causing focal clumps or a reticulated pattern of hyperpigmentation, a proposed prognosticator of progression to late-stage AMD. On OCT, areas of outer retinal tubulation may be misidentified as exudative fluid. These ovoid hyporeflective spaces with hyperreflective borders are located at the outer nuclear layer and represent degenerating photoreceptor rearrangement after retinal injury (Fig 4-5).

### *Differential diagnosis of nonneovascular AMD*

Multiple disorders associated with RPE abnormalities are often misinterpreted as nonneovascular AMD. Central serous chorioretinopathy may produce changes in the RPE and PEDs similar to those in AMD (discussed in Chapter 9). However, in patients with central

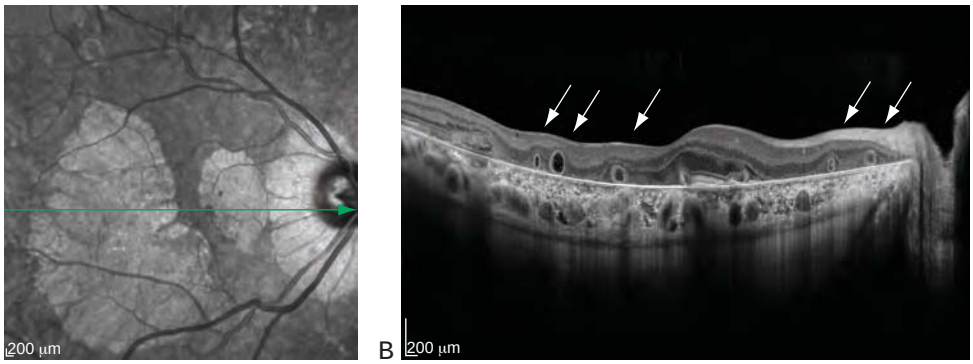


**Figure 4-5** Outer retinal tubulation. **A,** Near-infrared reflectance image with *green arrow* marking the location of the SD-OCT image **(B)** showing multiple areas of outer retinal tubulation, indicated by *white arrows* in the context of extensive macular atrophy. *(Courtesy of K. Bailey Freund, MD.)*

serous chorioretinopathy, EDI-OCT reveals a thickened choroid in the affected and fellow eyes, as opposed to the normal or thin choroid often associated with AMD.

Other differential diagnoses include pattern dystrophies, a group of predominantly autosomal dominant diseases of the RPE that may present with reticular or butterfly-shaped hyperpigmentation of the macula in both eyes, which is often symmetric. Patients with adult-onset foveomacular vitelliform dystrophy (AOFVD) may present with unilateral or bilateral yellow subretinal lesions. On SD-OCT, this condition appears as a hyperreflective, dome-shaped central lesion between the photoreceptor layer and the RPE, often with subretinal fluid that is not responsive to anti–vascular endothelial growth factor (anti-VEGF) therapy (Fig 4-6). However, unlike in AMD, increased subfoveal choroidal thickness is frequently apparent in AOFVD. FAF typically shows decreased central autofluorescence corresponding to the lesion with annular hyperautofluorescence. On FA, early blocked fluorescence is seen, with a surrounding zone of hyperfluorescence; late staining of the vitelliform material may also occur.

Consideration of the patient's concurrent or past pharmaceutical exposure is critical in the differential diagnosis of AMD. For example, a history of drug ingestion and lack of large drusen may help differentiate RPE mottling and macular atrophy from AMD (see Chapter 14).

### *Management of nonneovascular AMD*

See the section 2023 Update at the end of this chapter for further discussion.

**Education and follow-up** Although eyes in early- and intermediate-stage AMD are often minimally symptomatic, they may progress to late AMD with associated severe vision loss. Therefore, patients should be educated about modifiable risk factors, such as low micronutrient levels and tobacco use. Patients with nonneovascular AMD should also be educated about the symptoms of late-stage disease, including metamorphopsia or scotomata, and instructed to promptly seek ophthalmic care when they occur.

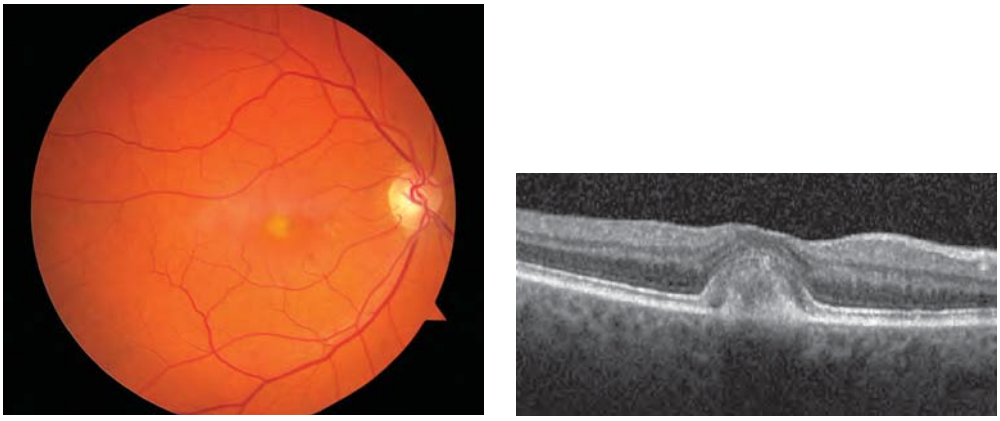

**Figure 4-6** Color fundus photograph *(left)* and corresponding SD-OCT image *(right)* of adult-onset foveomacular vitelliform maculopathy. The foveal region has a yellowish discoloration resembling an egg yolk. OCT demonstrates that the lesion is elevated. *(Courtesy of David Sarraf, MD.)*

**Micronutrients** Ophthalmologists should counsel patients with nonneovascular AMD about epidemiologic studies demonstrating positive associations between the intake of certain micronutrients and decreased risk of the disease.

AREDS first established the benefits of vitamin and zinc supplementation in reducing vision loss in nonexudative AMD. In the study, patients with intermediate or advanced AMD who took antioxidant vitamins C (500 mg) and E (400 IU), beta carotene (15 mg), and the micronutrient zinc (80 mg zinc oxide and 2 mg cupric oxide to prevent zinc-induced anemia) had a 25% reduced risk of progression to more-advanced stages of AMD and a 19% reduced risk of moderate vision loss (≥3 lines of VA) at 5 years. The study defined intermediate (category 3) AMD as the presence of at least 1 large druse (≥125 μm), extensive intermediate drusen (diameter of 63–124 μm), or nonsubfoveal GA. Advanced (category 4) AMD was defined as vision loss due to neovascular AMD or subfoveal GA in only 1 eye. At 10 years, 44% of placebo recipients had advanced AMD compared with 34% of supplement recipients (a 23% risk reduction). In addition, mortality did not increase among patients taking the AREDS-recommended formula. However, among participants with no AMD or with only early-stage AMD (ie, a few small drusen), supplementation provided no measurable benefit.

AREDS investigators developed a simplified 5-step severity scale for classifying the severity of AMD and predicting the disease course based on the following findings:

- presence of 1 or more large (≥125-μm diameter) drusen (1 point)
- presence of any pigment abnormalities (1 point)
- for patients with no large drusen, presence of bilateral intermediate (63- to 124-μm) drusen (1 point)
- presence of neovascular AMD (2 points)

In the study, risk factors were totaled across both eyes to reach a number between 0 and 4, which was used to estimate patients' 5- and 10-year risk of advanced AMD developing in 1 eye (Table 4-1).

AREDS2, a large, prospective, follow-up study, tested whether replacing beta carotene with xanthophylls (lutein and zeaxanthin) and adding omega-3 long-chain polyunsaturated fatty acids (LCPUFAs; docosahexaenoic acid and eicosapentaenoic acid) would further reduce AMD progression. The response of the 4000 participants confirmed the overall risk reduction found in the original AREDS study, leading the authors to conclude that lutein

**Table 4-1 Five- and 10-Year Risks[a] of Advanced AMD in 1 Eye**

| Number of Risk Factor Points | 5-Year Risk, % | 10-Year Risk, % |
|---|---|---|
| 0 | 0.5 | 1 |
| 1 | 3 | 7 |
| 2 | 12 | 22 |
| 3 | 25 | 50 |
| 4 | 50 | 67 |

AMD = age-related macular degeneration.

[a]Risks are based on the number of Age-Related Eye Disease Study (AREDS) risk factors (see chapter text).

and zeaxanthin had effects similar to those of beta carotene but without the increased risk of lung cancer reported in other studies in current and former smokers. It also confirmed that an 80-mg dose of zinc is appropriate for AMD prophylaxis. The addition of LCPUFAs at the dose studied did not decrease the rate of progression to advanced AMD.

The study's final recommendation was to modify the original AREDS supplement, replacing beta carotene with lutein and zeaxanthin (Table 4-2). Currently, patients with category 3 or 4 AMD are advised to take the AREDS2 supplement.

Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005–2015.

Ferris FL, Davis MD, Clemons TE, et al; Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS report no. 18. *Arch Ophthalmol.* 2005;123(11):1570–1574.

**Lifestyle changes** Smoking cessation, obesity reduction, and blood pressure control may reduce the development and progression of AMD. Evidence linking cataract surgery to AMD progression is inconsistent, and evidence linking ultraviolet (UVA or UVB) light exposure to disease progression is weak. In addition, no evidence has linked blue light emitted from electronic devices to increased risk of AMD.

**Amsler grid testing** Patients may use the Amsler grid at home to monitor for visual distortion due to AMD-related retinal architectural distortion, including the development of exudative AMD. The Amsler test card, which contains grid lines and a central dot for fixation, is commonly used to test the central 10° of vision. Each eye is tested individually with reading glasses and at reading distance to check for new or progressive metamorphopsia, scotoma, or other changes in central vision. Any changes noted by the patient should be evaluated promptly. Online and smartphone app versions of the Amsler grid may be more convenient than the test card.

**Hyperacuity testing** Vernier acuity measures a patient's ability to detect deviations in the alignment of visual objects, for example, 2 line segments. Hyperacuity, which helps the viewer discern deviations as small as a single point on a line, is extremely sensitive to any geometric shift in the outer retinal morphology, producing a perception of distortion. In

**Table 4-2 AREDS2 Recommendations for Nutritional Supplementation[a]**

| Nutrient | Daily Dose |
|---|---|
| Vitamin C | 500 mg |
| Vitamin E | 400 IU |
| Lutein | 10 mg |
| Zeaxanthin | 2 mg |
| Zinc | 80 mg |
| Copper[b] | 2 mg |

AREDS2 = Age-Related Eye Disease Study 2.
[a]Recommendations for nutritional supplementation are based on the AREDS2 study (see text).
[b]As cupric oxide; added to avoid zinc-related copper deficiency.

patients with intermediate AMD, preferential hyperacuity perimetry (PHP), which has been studied extensively, can detect recent-onset MNV with high sensitivity (82%) and high specificity (88%). The HOME study, a phase 3 randomized clinical trial with 1520 participants, demonstrated the efficacy and potential benefit of PHP in early detection of MNV.

Shape-discrimination hyperacuity uses a principle similar to that of PHP but instead tests for discrimination of shapes, such as the ability to discern a perfect circle from a distorted contour.

Chew EY, Clemons TE, Harrington M, et al; AREDS2-HOME Study Research Group. Effectiveness of different monitoring modalities in the detection of neovascular age-related macular degeneration: the Home Study, report number 3. *Retina.* 2016;36(8):1542–1547.

## Neovascular AMD

The presence of MNV is the defining characteristic of neovascular AMD. Degenerative changes in Bruch membrane (eg, the accumulation of drusen and progressive thickening of the membrane that characterize nonneovascular AMD) and possibly the choriocapillaris may lead to a proangiogenic environment, with pathologic neovascularization developing from the choriocapillaris or from the neurosensory retina itself. These new vessels, which may be accompanied by fibroblasts, may leak and bleed, disrupting the normal retinal architecture with a degenerate fibrovascular complex; when untreated, this complex ultimately produces a hypertrophic, fibrotic, disciform scar.

### *Signs and symptoms of neovascular AMD*

Patients with neovascular AMD may describe a sudden decrease in vision, metamorphopsia, and/or paracentral scotomata. Amsler grid self-testing by patients is highly effective in detecting early exudative AMD. Clinical signs of MNV may include subretinal or intraretinal fluid (eg, cystoid macular edema [CME]), exudate and/or blood, a pigment ring or gray-green membrane, irregular elevation of the RPE or a PED, an RPE tear, and/or a sea fan pattern of subretinal vessels.

### *Anatomical classification of MNV*

The 3 main subtypes of MNV are based on level of origin:

- In type 1 MNV, also called *occult CNV,* new vessels originating from the choriocapillaris grow through Bruch membrane into the sub-RPE space (Fig 4-7). Fluid leakage and bleeding may produce a vascularized serous or fibrovascular PED. These fibrovascular PEDs typically have an irregular surface contour.
- In type 2 MNV, also called *classic CNV,* new vessels extend into the space between the RPE and the neurosensory retina. On examination, this may appear as a lacy or gray-green lesion. Neovascularization that exists beneath both the neurosensory retina and the RPE is designated as mixed type 1 and type 2 MNV, also termed *minimally classic CNV.*
- In type 3 MNV, the pathologic vessels develop from the deep capillary plexus of the retina and grow downward toward the RPE. Because of their intraretinal origin,

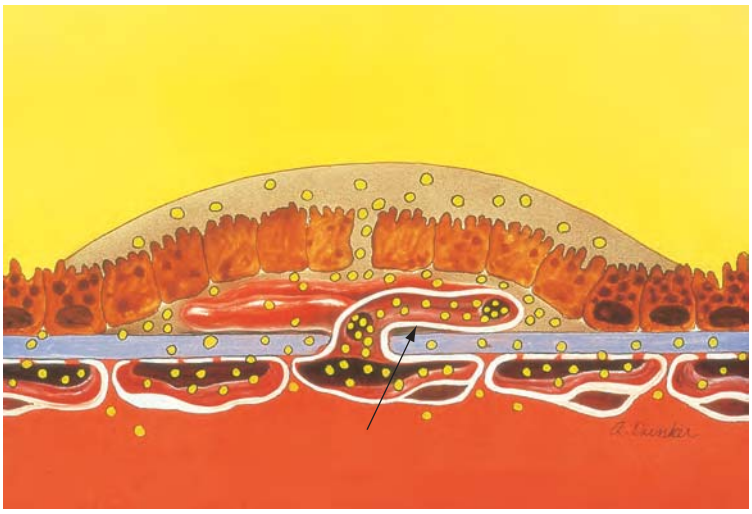

**Figure 4-7** Schematic illustration of type 1 macular neovascularization (MNV) originating from the choriocapillaris, breaking through Bruch membrane (indicated by gray horizontal line bisected by MNV extending up from the choriocapillaris), and proliferating in the subretinal pigment epithelial space. *(Modified with permission from Bressler NM, Bressler SB, Fine SL. Age-related macular degeneration.* Surv Ophthalmol. *1988;32(6):375–413.)*

these lesions were originally called *retinal angiomatous proliferations;* intraretinal pigment migration may occur before the development and maturation of this subtype of MNV. On examination, type 3 MNV often appears as a small area of red discoloration associated with retinal exudate or a bleb of subretinal fluid.

### *Nonexudative neovascular AMD*

Type 1 MNV may manifest without the clinical signs of exudation; that is, MNV may be observed between Bruch membrane and the RPE without associated intraretinal fluid, subretinal fluid, or hemorrhage. This clinical scenario is called *nonexudative neovascular AMD.* These lesions, which have been reported in up to 14% of eyes with intermediate AMD or GA, can be identified with OCT angiography (OCTA) and/or indocyanine green angiography (ICGA). A less reliable finding—a double-layer sign on structural SD-OCT (ie, a low-lying, irregular PED)—may be misdiagnosed as an area of confluent drusen or a drusenoid PED. Clinical recognition of these lesions is relevant because they have been associated with a substantially increased risk of progression to exudative AMD (21%) at 1-year follow-up compared with eyes without these lesions (4%). There may also be a relationship between the presence of nonexudative neovascular AMD and GA progression; type 1 MNV has been hypothesized to be potentially protective against local GA development.

de Oliveira Dias JR, Zhang Q, Garcia JMB, et al. Natural history of subclinical neovascularization in nonexudative age-related macular degeneration using swept-source OCT angiography. *Ophthalmology*. 2018;125(2):255–266.

**Imaging of MNV** Several imaging techniques play an important role in describing, diagnosing, and/or classifying MNV.

**FLUORESCEIN ANGIOGRAPHY OF MNV** Before multimodal imaging–based classification with SD-OCT and OCTA, FA was instrumental in describing types of neovascularization, including classic, occult, and minimally classic patterns. As mentioned previously, *classic MNV* refers to a bright, lacy, and well-defined hyperfluorescent lesion that appears in the early phase of FA and progressively leaks by the late phases. *Occult MNV* refers to more diffuse hyperfluorescence that takes 1 of 2 forms: (1) PED, either fibrovascular PED or vascularized serous PED; or (2) late leakage from an undetermined source. *Minimally classic MNV* refers to a pattern of early hyperfluorescence with late leakage and surrounding stippled hyperfluorescence that also shows late leakage (Fig 4-8).

A fibrovascular PED is an irregular elevation of the RPE with progressive, stippled leakage on FA. Alternatively, the PED may pool dye rapidly in a homogeneous ground-glass pattern that is consistent with a serous PED but has a notch, or hot spot, due to a vascular component, hence the term *vascularized serous PED* (Fig 4-9).

*Late leakage from an undetermined source* describes fluorescence at the level of the RPE that is poorly defined in the early phases of FA, but better appreciated in the late phases.

The angiographic appearance of occult MNV is consistent with that of type 1 neovascularization, whereas the appearance of classic MNV is more often related to that of type 2 neovascularization; however, this is not a hard-and-fast rule. Type 3 neovascularization, or retinal angiomatous proliferations, may appear as a spot of retinal hemorrhage in the macula. It produces a focal hot spot on FA and ICGA with late CME or pooling into a PED.

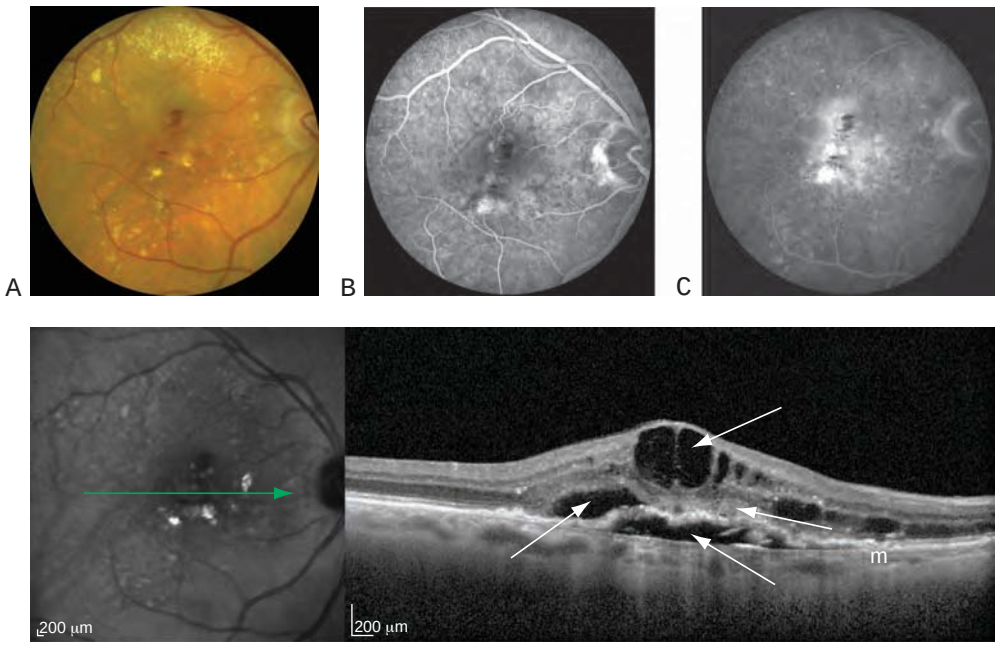


**Figure 4-8** Treatment-naive neovascular AMD. Color fundus photograph **(A)** with early **(B)** and late **(C)** frames of fluorescein angiogram of a minimally classic, fovea-involving, choroidal neovascular membrane. **D,** Near-infrared reflectance image *(left)* with *green arrow* marking the location seen in the SD-OCT image *(right)* showing intraretinal, subretinal, and sub-RPE fluid with subretinal hyperreflective material. *(Courtesy of Charles C. Wykoff, MD, PhD.)*

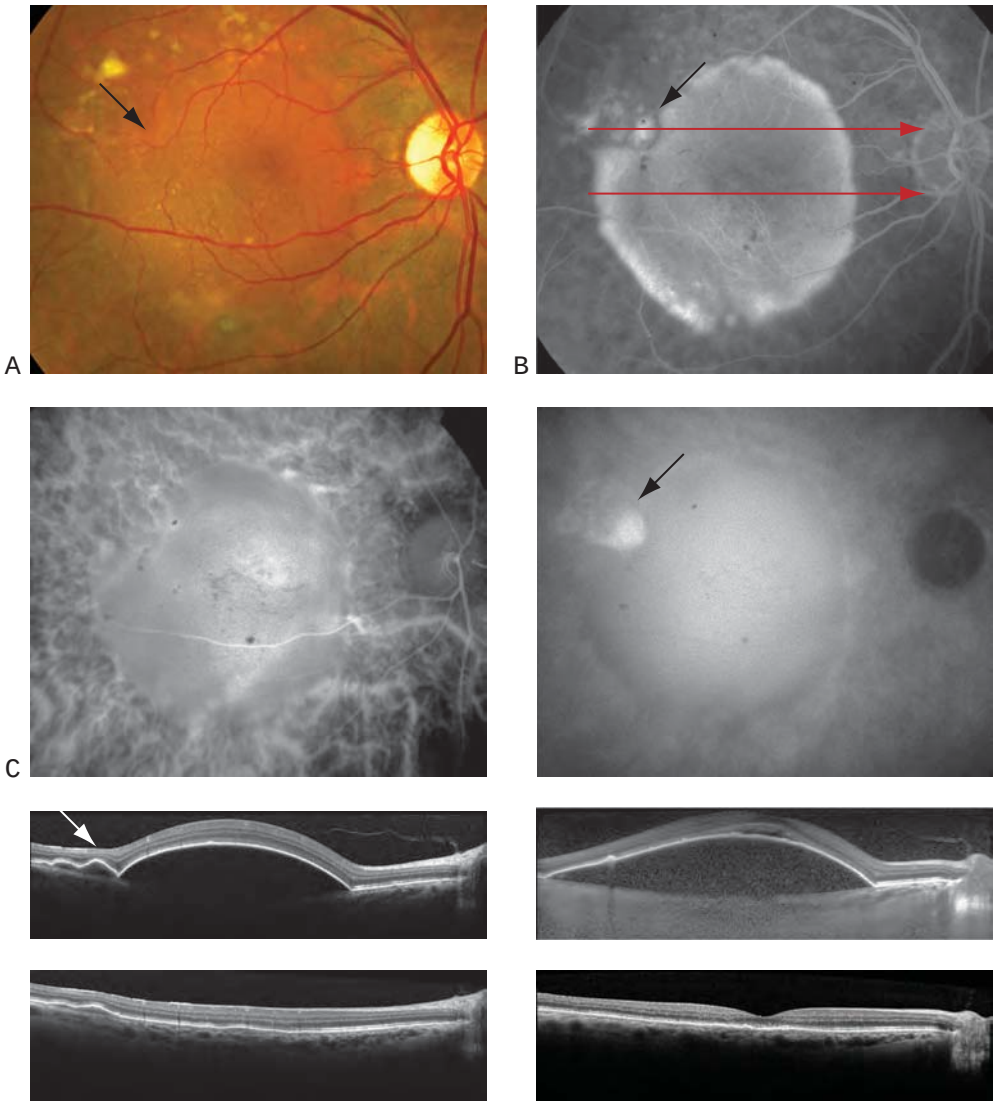


**Figure 4-9** Vascularized serous pigment epithelial detachment (PED). **A,** Color fundus photograph of a vascularized serous PED with a notch *(arrow)* that corresponds to a hot spot on fluorescein angiography (*black arrow* in **B**). *Red letters and arrows* in **B** indicate the SD-OCT scan locations for parts **E** through **H.** Early **(C)** and late **(D)** indocyanine green (ICG) angiography images show pooling of the serous PED and hyperfluorescence of the hot spot (*arrow* in **D**). **E, F,** SD-OCT images of the large serous PED. Note the irregular portion of the PED (*arrow* in **E**), which corresponds to the hot spot and harbors the type 1 neovascular membrane. **G, H,** SD-OCT images show that the PED has resolved after therapy with anti–vascular endothelial growth factor. *(Modified with permission from Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation.* Retina. *2013;33(9):1735–1762.)*

During angiography, thick blood, pigment, scar tissue, or a PED may block fluorescence and obscure an underlying MNV. ICGA, with its longer wavelength fluorescence in the infrared spectrum, may penetrate deeper through heme or pigment to reveal a hot spot that identifies MNV. Because it has 90% protein binding, ICGA may also be able to differentiate between scar tissue and serous RPE fluid to reveal an active vascular lesion.

**SD-OCT OF MNV** SD-OCT is noninvasive and is the most practical visualization technique for diagnosing and classifying MNV as well as monitoring response to treatment. For example, SD-OCT reveals the elevation of the RPE and PEDs produced by type 1 MNV. Serous PEDs appear as sharply elevated, dome-shaped lesions with hollow internal reflectivity and typically no associated subretinal or intraretinal fluid. Fibrovascular PEDs may or may not be sharply elevated and typically demonstrate lacy or polyplike hyperreflective lesions on the undersurface of the RPE, with or without signs of contraction (Fig 4-10; Activity 4-1). Chronic fibrovascular PEDs often have a multilayered appearance because of sub-RPE cholesterol crystal precipitation in an aqueous environment; this appearance has been called the *onion sign*. The fibrotic "bridge arch–shaped" serous PED may develop after anti-VEGF treatment and is associated with a poor visual outcome.

**ACTIVITY 4-1** OCT Activity: OCT of subfoveal pigment epithelial detachment.
*Courtesy of Colin A. McCannel, MD.*

In eyes with MNV, subretinal hyperreflective material (SHRM) may be hyperreflective on SD-OCT. This morphological feature found between the retina and RPE is thought to be a heterogeneous mixture of fluid, fibrin, blood, MNV, and other material. SHRM may have an adverse effect on VA and may cause scarring when it persists. Complex fibrovascular

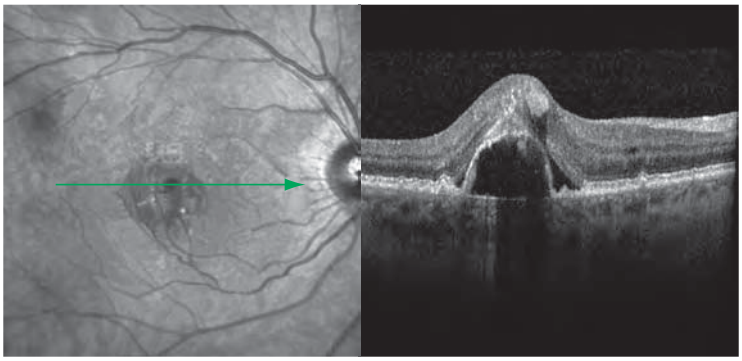

**Figure 4-10** OCT image from a 61-year-old woman who reported progressively decreased vision and onset of waviness of straight lines in the right eye. OCT shows a subfoveal PED with associated subretinal fluid, intraretinal fluid, and intraretinal hyperreflective material. There is also an area of hyperreflective material on the underside of the RPE, likely representing a neovascular complex (see slices 12 and 13 in Activity 4-1). Scrolling through the macula in Activity 4-1 reveals the extent of the lesion, as well as RPE irregularities that resemble small PEDs (drusen). *(Courtesy of Colin A. McCannel, MD.)*

scarring may also be visualized in the sub-PED compartment, with or without associated subretinal and/or intraretinal fluid.

Recognition of MNV patterns on SD-OCT may be helpful for differential diagnosis and for predicting treatment outcomes. Type 1 MNV complexes start from the choroid and are limited to the sub-RPE space, visible as heterogeneous hyperreflective RPE elevations. Type 2 MNV appears as a hyperreflective band or plaque in the subneurosensory space, with associated subretinal and/or intraretinal fluid. Type 3 MNV presents on SD-OCT as hyperreflective foci emanating from the deep capillary plexus of the retina, with or without associated CME and PED.

Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. *Retina.* 2013;33(9):1735–1762.

**OCTA OF MNV** The structural details of MNV can be revealed by OCTA. The fine details of the vascular architecture of each MNV type may be easily visualized, free of the blur caused by fluorescein leakage in FA (Figs 4-11, 4-12, 4-13). In type 1 MNV, OCTA shows abnormal vessels below the RPE. In type 2 MNV, the angiogenic complexes are seen above the RPE. Comparably, downgrowth of new vessels toward the RPE may be seen in type 3 MNV.

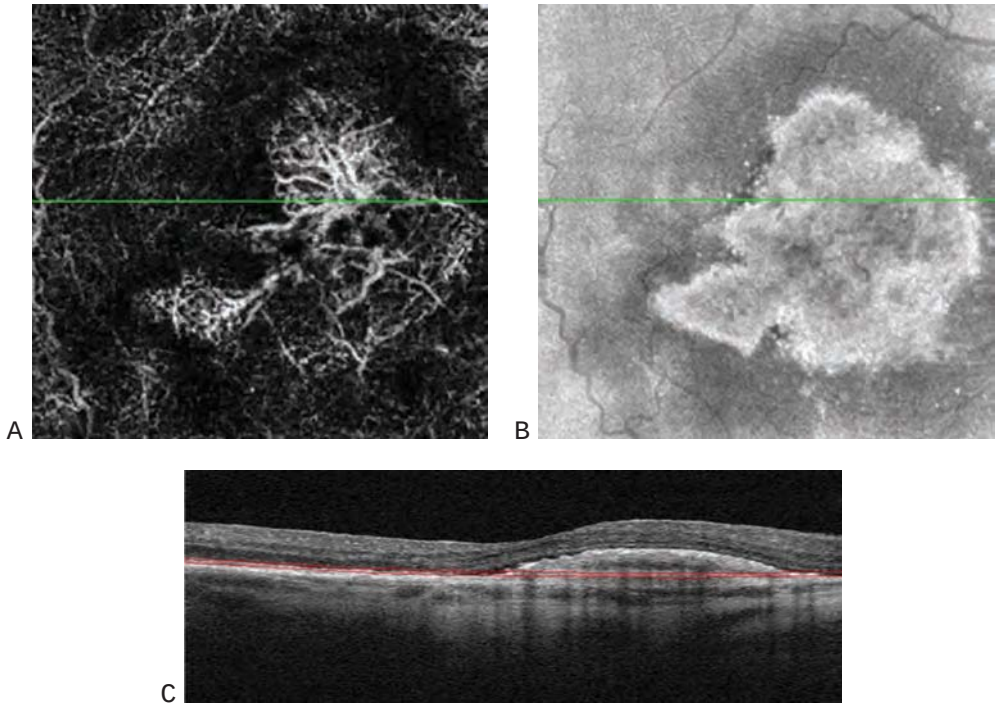


**Figure 4-11** Type 1 MNV. **A,** OCT angiogram (OCTA) of type 1 MNV located beneath the RPE. The lesion has a "sea fan" configuration, with large feeder vessels and large caliper vessels. **B,** En face OCT structural image highlights the hyperreflective dome over the vessels. **C,** Cross-sectional B-scan OCT shows the distortion of the retinal profile caused by the MNV. *(Courtesy of Richard B. Rosen, MD.)*

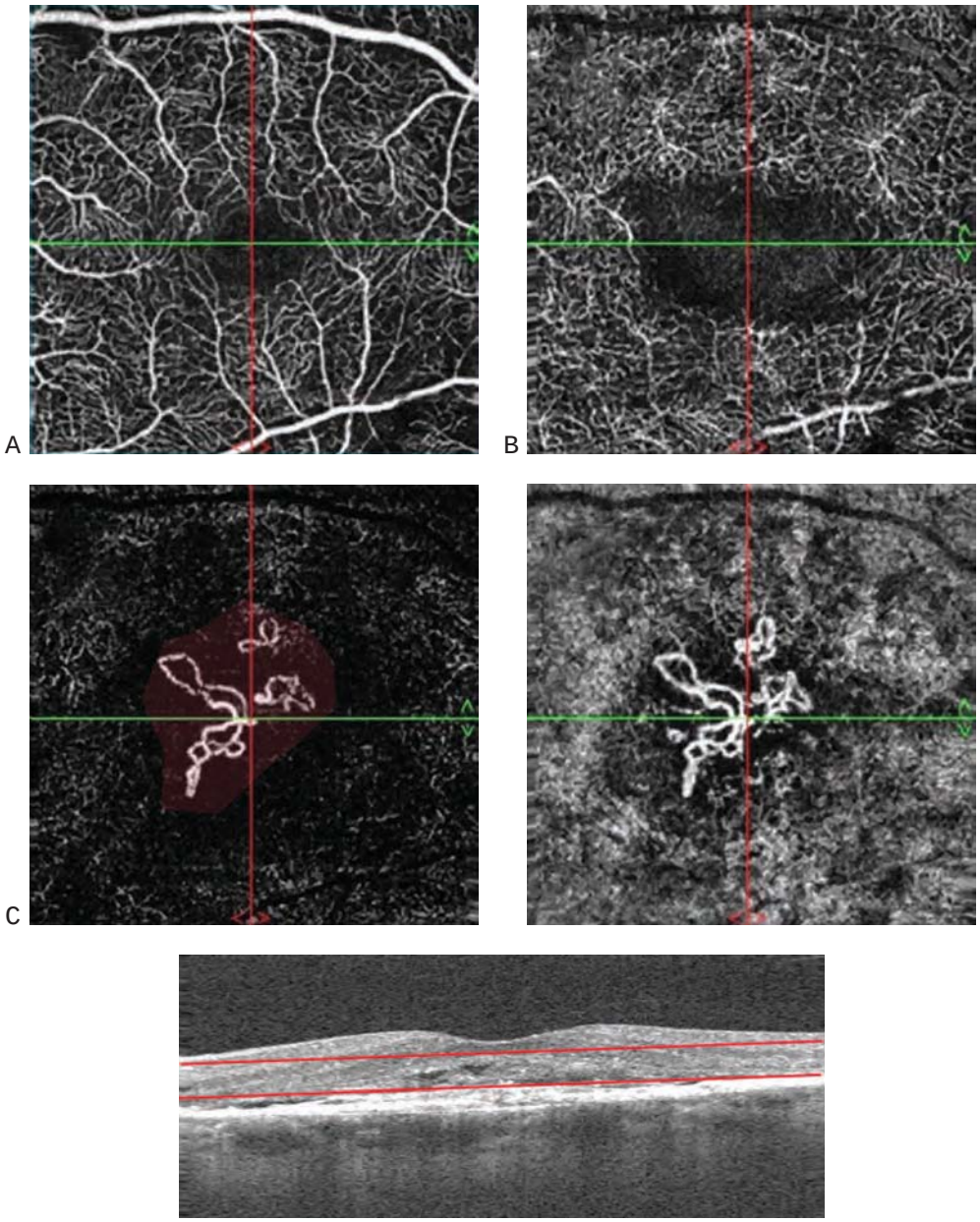


**Figure 4-12** OCTA series of progressively deeper en face slices **(A–D)** of a type 2 MNV located above the RPE in the avascular zone of the retina. **A,** Superficial slab shows the superficial capillary plexus level and large retinal vessels. **B,** Deep capillary plexus level with an expanded foveal avascular zone caused by elevation of the underlying MNV. **C,** Avascular zone of the retina with MNV. **D,** Choriocapillaris level with MNV extending upward in the retina. **E,** Cross-sectional B-scan OCT shows disturbance in the RPE subretinal fluid and fibrosis. *(Courtesy of Bruno Lumbroso.)*

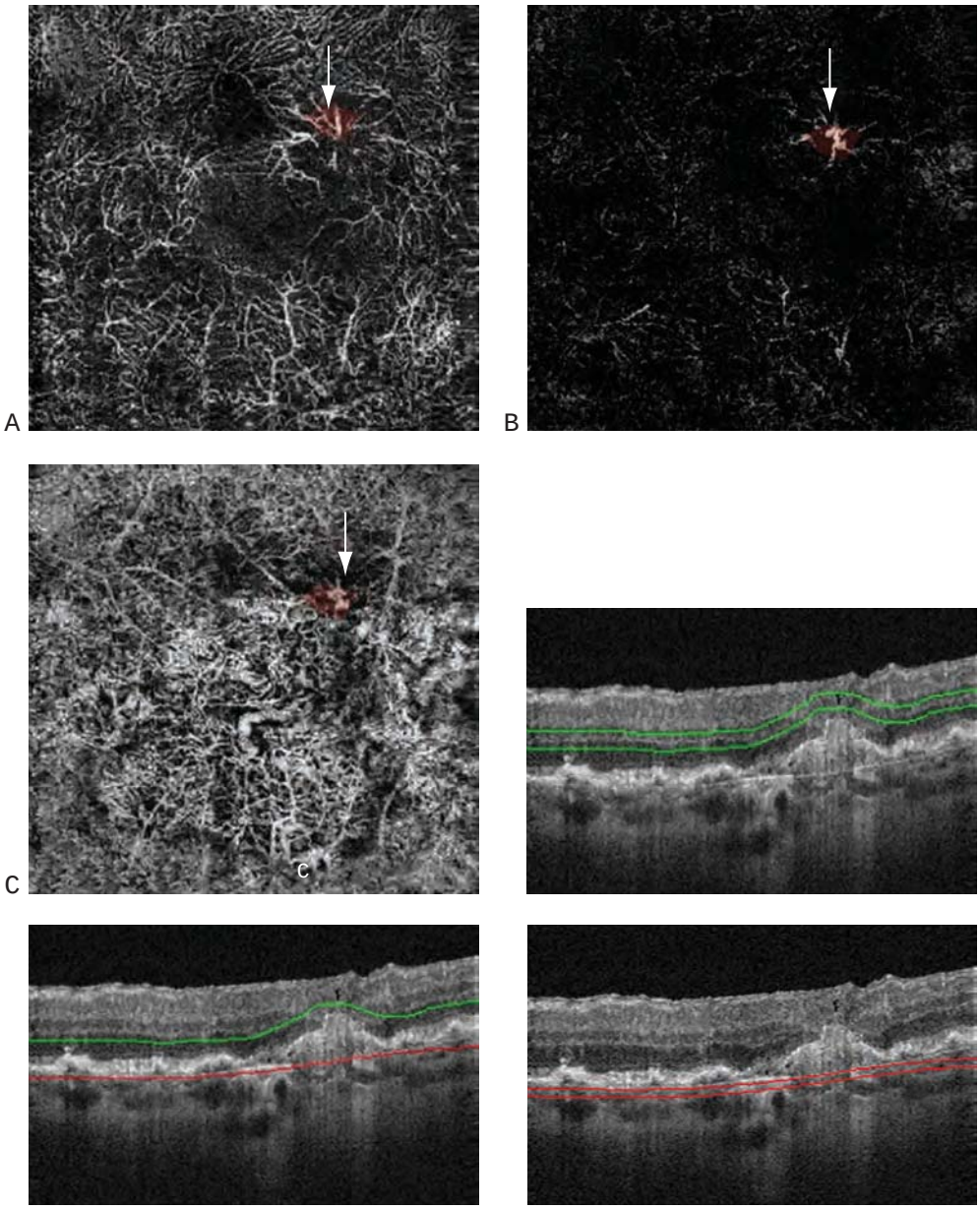


**Figure 4-13** OCTA of type 3 MNV (retinal angiomatous proliferation lesion). **A,** Deep capillary plexus level reveals dilated blood vessels *(arrow)* wider than surrounding capillaries near the edge of the foveal avascular zone. **B,** Avascular zone level shows isolated MNV *(arrow)*. **C,** Choriocapillaris level demonstrates interconnection of dilated deep capillary plexus vessels and choroidal vessels *(arrow)*. **D,** Cross-sectional B-scan OCT shows segmentation of **A. E,** Cross-sectional B-scan OCT shows segmentation of **B. F,** Cross-sectional B-scan OCT shows segmentation of **C.** *(Courtesy of Richard B. Rosen, MD.)*

Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus nomenclature for reporting neovascular age-related macular degeneration data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. *Ophthalmology*. 2020;127(5):616–636. Published correction appears in *Ophthalmology*. 2020;127(10):1434–1435.

**Polypoidal choroidal vasculopathy** Polypoidal choroidal vasculopathy (PCV), initially called *posterior uveal bleeding syndrome,* is a variant of MNV (type 1) and presents with multiple, recurrent serosanguineous RPE detachments. A network of polyps is associated with feeder vessels that adhere to the RPE monolayer of the fibrovascular PED in a "string-of-pearls" configuration. Although PCV was first discovered in middle-aged African American or Asian American women with hypertension, it has since been identified in women and men of all races. In Asian individuals, however, 20%–50% of cases of neovascular AMD are PCV type, whereas in White people, less than 5% of cases of MNV are PCV type.

In PCV, associated serosanguineous detachments are often peripapillary and multifocal but may be peripheral, and there may be associated nodular, orange, subretinal lesions. Vitreous hemorrhage occurs more frequently in PCV AMD than in the non-PCV form. Soft drusen, typical in AMD, may or may not be present, whereas a thickened or so-called *pachychoroid* is often observed on EDI-OCT. ICGA, SD-OCT, and OCTA are all useful for identifying polyps.

Natural history and VA outcomes of PCV may be better than those of MNV associated with AMD, except in cases with severe subretinal hemorrhage (Figs 4-14, 4-15; see also Chapter 2, Fig 2-13). PCV is less responsive to anti-VEGF therapy than other types of MNV. Although the EVEREST studies demonstrated that photodynamic therapy with verteporfin with or without ranibizumab provided better response than ranibizumab alone for PCV, the PLANET study found that aflibercept monotherapy was noninferior to aflibercept plus photodynamic therapy with verteporfin for treatment of the disorder.

Koh A, Lai TYY, Takahashi K, et al; EVEREST II study group. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2017;135(11):1206–1213.

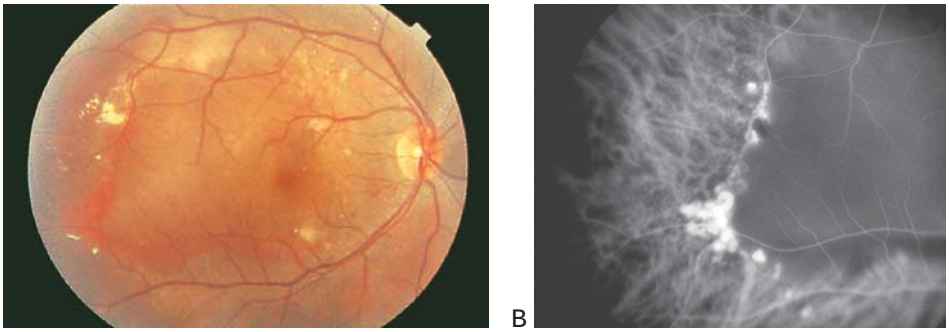


**Figure 4-14** Polypoidal choroidal vasculopathy. **A,** Fundus photograph shows a large RPE detachment with multiple yellow-orange nodular lesions temporally. **B,** ICG angiogram demonstrates the characteristic polypoidal lesions temporally. *(Courtesy of Lawrence A. Yannuzzi, MD.)*

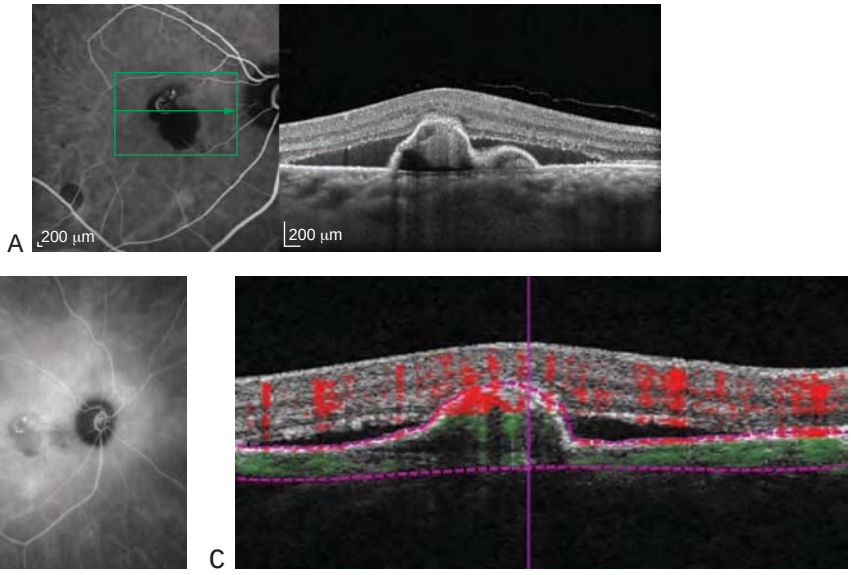


**Figure 4-15** Polypoidal choroidal vasculopathy (PCV). **A,** Near-infrared reflectance image *(left)* showing ring-shaped PCV lesion within a retinal PED. *Green arrow* marks the location of the SD-OCT image *(right)* showing PED and subretinal fluid with PCV polyp visible just under the RPE monolayer. **B,** Corresponding wide-field ICG angiography. PCV complex is visible in the central macula with diffuse hyperpermeability in the macula and peripapillary regions. **C,** Corresponding OCTA. Red-highlighted area within the PED illustrates the polypoidal lesion with high vascular flow. *(Courtesy of Gregg T. Kokame, MD.)*

Lee WK, Iida T, Ogura Y, et al; PLANET Investigators. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(7):786–793. Published correction appears in *JAMA Ophthalmol*. 2018;136(7):840.

### *Differential diagnosis of neovascular AMD*

Many conditions associated with disruption of Bruch membrane complex and secondary CNV can mimic the MNV of AMD (see the section Other Causes of Choroidal Neovascularization later in this chapter). For example, central serous chorioretinopathy (CSC) may be confused with AMD, as subretinal fluid may be seen in both conditions; however, eyes with CSC typically do not have associated subretinal hemorrhage unless secondary CNV has developed. In addition, the choroidal layer, readily visualized using EDI-OCT, is frequently thick in eyes with CSC compared with the typical thin choroidal layer in eyes with AMD.

Macular telangiectasia, especially the most common variant type 2, may also be misdiagnosed as neovascular AMD (see Chapter 7).

### *Management of neovascular AMD*

When neovascular AMD is suspected clinically, OCT can help establish the diagnosis and monitor response to therapy.

**Laser photocoagulation ("thermal laser")** Thermal laser treatment is now used only in exceptionally rare instances of neovascular AMD because of poor outcomes from high recurrence rates, as revealed in the Macular Photocoagulation Study trials.

**Photodynamic therapy ("cold laser")** Photodynamic therapy (PDT) was introduced in 2000 as a less-destructive phototherapy for treating MNV. Treatment involves intravenous administration of the photosensitizing drug verteporfin followed by the application of light of a specific wavelength. The light incites a localized photochemical reaction in the targeted area, resulting in MNV thrombosis. Although PDT slows progression, it does not prevent major vision loss in most eyes with MNV and has been shown to upregulate VEGF in the treatment area. Use of PDT to manage exudative AMD is now rare, except in eyes with PCV.

**Antiangiogenic therapies** Angiogenesis is the sprouting of new blood vessels from existing vessels. The first events in this complex cascade are vasodilation of existing vessels and increased vascular permeability. Next, degradation of the surrounding extracellular matrix occurs, facilitating migration and proliferation of endothelial cells. As endothelial cells join to create lumen, new capillaries develop and then mature, remodeling into stable vascular networks. To date, the most important activator of angiogenesis in retinal diseases is VEGF, originally known as vascular permeability factor.

VEGF is a homodimeric glycoprotein with a heparin-binding domain with specificity for vascular endothelial cells. In addition to angiogenesis and vascular permeability, it induces lymphangiogenesis, and it acts as a survival factor for endothelial cells by preventing apoptosis. VEGF is actually a family of 5 distinct cytokines: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. Because the latter 4 were discovered after VEGF-A, VEGF-A is often referred to simply as *VEGF.*

Most anti-angiogenesis research has focused on the inhibition of VEGF-A (hereafter called VEGF unless specification is warranted), which has multiple isoforms. Elevated concentrations of VEGF in excised MNV and vitreous samples from patients with AMD have suggested a causal role for the glycoprotein in the pathologic neovascularization of AMD.

To date, 4 anti-VEGF pharmaceuticals given by intravitreal injection have been approved by the US Food and Drug Administration (FDA) for the treatment of exudative AMD; an additional drug is widely used but is not FDA approved for ophthalmic use. Overall, this class of therapeutics has been incredibly valuable, changing the epidemiology of blindness in some countries after its clinical introduction. In general, the earlier that conversion to exudative AMD is diagnosed and anti-VEGF therapy is initiated, the better the long-term outcomes.

Although antiangiogenic therapies are effective in AMD, the biggest challenge with their clinical application is the need for repeated doses to achieve optimal long-term outcomes. When exudative AMD is treated with anti-VEGF pharmacotherapy, a variety of clinical approaches may be used. Broadly, these include 1 of 3 strategies or a hybrid of them: (1) fixed dosing; (2) as-needed dosing, also referred to as *pro re nata (PRN)* dosing; and (3) treat-and-extend dosing, also referred to as *TAE, T&E,* or *TREX*. In the following subsections, these management approaches are discussed in the context of the pharmaceutical agent(s) used in key studies.

**Pegaptanib** In 2004, the FDA approved pegaptanib as the first intravitreal anti-VEGF therapy. Studies showed that pegaptanib, an RNA oligonucleotide ligand (or aptamer) that inhibits the human $VEGF_{165}$ isoform without inhibiting all VEGF isoforms, slowed vision loss; however, it has since been supplanted by more effective agents that inhibit all VEGF isoforms.

**Ranibizumab** Ranibizumab is a recombinant humanized antibody fragment that binds VEGF. Monthly ranibizumab dosing was assessed in 2 studies, MARINA and ANCHOR. At 12 months, a loss of fewer than 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters was reported in 95% of ranibizumab-treated patients compared with 62% of sham-treated patients and 64% of PDT-treated patients. In addition, VA improvement of 15 letters or more was reported in 30%–40% of ranibizumab-treated patients compared with 5% or less of control participants (Fig 4-16, Table 4-3). At 24 months, approximately 90% of ranibizumab-treated eyes had lost fewer than 15 ETDRS letters, and the VA gains achieved in the first year were maintained.

Multiple studies have analyzed less-frequent dosing of ranibizumab. VA improvements similar to those seen in the MARINA and ANCHOR studies over the first 3 months were also reported in the PIER and EXCITE studies. However, treatment effects declined in participants undergoing quarterly (ie, every 3 months) ranibizumab dosing as opposed to monthly dosing.

With PRN dosing, ranibizumab is administered until signs of exudation are resolved on OCT and clinical examination; after that, patients are followed up monthly, and treatment

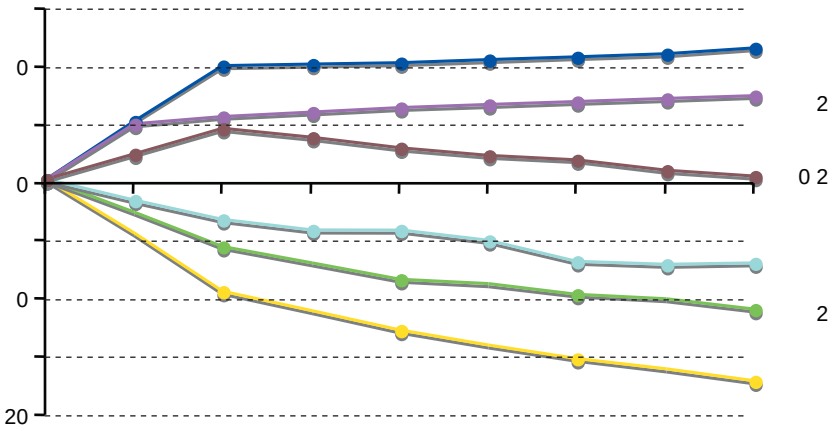


**Figure 4-16** Graph illustrates the mean change in visual acuity (number of letters read) from several phase 3 clinical trials. Comparison of data between different trials should be interpreted with caution; the potentially different study inclusion criteria and baseline characteristics of eyes for different studies may affect the stated visual acuity gains. ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; PC = predominantly classic; PIER = Phase 3b, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects With Subfoveal Choroidal Neovascularization With or Without Classic Choroidal Neovascularization Secondary to AMD; TAP = Treatment of AMD with Photodynamic Therapy; VISION = VEGF Inhibition Study in Ocular Neovascularization. *(Courtesy of Peter K. Kaiser, MD.)*

**Table 4-3 Selected Clinical Trials, Treatments, and Outcomes**

| Clinical Trial | Treatment | Outcome |
|---|---|---|
| ANCHOR | Ranibizumab monthly vs photodynamic therapy as needed quarterly | Increase of 11.3 letters in ranibizumab monthly group vs decrease of 9.5 letters in verteporfin group ($P < 0.001$ at 2 years) |
| MARINA | Ranibizumab monthly vs sham treatment | Increase of 7.2 letters in ranibizumab monthly group vs loss of 10.4 letters in sham group ($P < 0.001$ at 2 years) |
| VIEW 1 | Ranibizumab monthly vs aflibercept monthly and bimonthly | Increase of 8.1 letters in ranibizumab monthly group (94.4% lost <15 letters)<br>Increase of 10.9 letters in aflibercept monthly group (95.1% lost <15 letters)<br>Increase of 7.9 letters in aflibercept bimonthly group (95.1% lost <15 letters)<br>Aflibercept deemed noninferior to ranibizumab |
| VIEW 2 | Ranibizumab monthly vs aflibercept monthly and bimonthly | Increase of 9.4 letters in ranibizumab monthly group (94.4% lost <15 letters)<br>Increase of 7.6 letters in aflibercept monthly group (95.6% lost <15 letters)<br>Increase of 8.9 letters in aflibercept bimonthly group (95.6% lost <15 letters)<br>Aflibercept deemed noninferior to ranibizumab |

Data from Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology.* 2013;120(11):2292–2299.

is resumed only when there are signs of recurrent exudation. Several clinical trials have evaluated PRN approaches to anti-VEGF therapy: SUSTAIN, HORIZON, and HARBOR. In each of these studies, participants were administered 3 monthly injections of ranibizumab, followed by various as-needed treatment regimens according to clinical and OCT-guided criteria. In these studies, visual acuity improvements were comparable to or less favorable than those reported in MARINA and ANCHOR. In the HORIZON study, which involved patients enrolled in prior ranibizumab AMD trials, eyes that had gained 10.2 letters on the ETDRS eye chart after 2 years of monthly injections during ANCHOR or MARINA lost VA, ending with a mean letter gain of only 2.0 compared with baseline (ie, they lost nearly 8 letters once the regimen was switched from monthly injections to an as-needed protocol). HORIZON did not offer any re-treatment guidelines for investigators, resulting in a mean of only 3.6 ranibizumab injections in the 12 months of the extension trial. The phase 3 HARBOR study compared higher-dose (2.0 mg) with standard-dose (0.5 mg) ranibizumab using both monthly and PRN dosing with specific predefined re-treatment criteria. Subjects randomly assigned to PRN dosing were evaluated monthly to determine their need for re-treatment. Study authors reported no differences in VA or anatomical outcomes between the fixed monthly and PRN dosing and noted a very wide range of dosing needs among individual patients.

In patients with MNV, the goal of TAE management is to suppress exudative activity using as few re-treatments as possible. This typically involves 3 phases. First, monthly anti-VEGF therapy is administered until exudation is resolved. Second, treatment continues at progressively increasing intervals, with intervals between doses often lengthened by 2-week

increments, until recurrent exudation is identified. Third, a fixed-interval dosing strategy is initiated using an interval just less than the interval at which signs of exudation recurred. In the TREND study, 650 patients with exudative AMD were randomly assigned to either monthly or TAE management with ranibizumab. At 1 year, TAE management was associated with a mean of 8.7 injections and was found to be noninferior to monthly management, which was associated with a mean of 11.1 injections. In addition, TAE and monthly regimens were associated with mean gains of 6.6 and 7.9 ETDRS letters, respectively, and 62% of eyes managed with TAE were receiving injections at intervals of 8 weeks or longer.

Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J; TREND Study Group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. *Ophthalmology.* 2018;125(1):57–65.

**Aflibercept** Aflibercept is a soluble VEGF receptor decoy; it combines the ligand-binding elements of the extracellular domains of *VEGFR1* and *VEGFR2* and the constant region (Fc) of immunoglobulin G and binds VEGF-A, VEGF-B, and placental growth factor. In the paired VIEW 1 and VIEW 2 studies, patients received aflibercept monthly or every second month after 3 monthly loading doses, while a comparison group received monthly ranibizumab. Both aflibercept regimens demonstrated noninferiority to monthly ranibizumab, with each of the 6 arms gaining between 7.6 and 10.9 letters at 1 year (ie, primary endpoint; see Table 4-3). At 96 weeks, VA gains were maintained with both aflibercept dosing regimens; in addition, 3-line VA increases were seen in 30%–33% of patients in each arm, comparable to results with monthly ranibizumab. In addition, OCT-measured anatomical response was similar among the 3 randomized arms through 2 years, as were safety profiles for both aflibercept and ranibizumab. Among patients with persistent exudative disease activity through the first 3 monthly doses, transition to every-second-month dosing was associated with maintenance of the VA gains achieved during the 3 monthly doses; however, among these incomplete responders, continued monthly dosing appeared to achieve better visual and anatomical outcomes than every-second-month dosing. For more on aflibercept, see the section 2023 Update at the end of this chapter.

Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology.* 2012;119(12):2537–2548.

Jaffe GJ, Kaiser PK, Thompson D, et al. Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. *Ophthalmology.* 2016;123(9):1856–1864.

**Bevacizumab** Bevacizumab is a full-length monoclonal antibody against VEGF that is FDA approved for the intravenous treatment of multiple types of systemic cancer. It is also widely used "off-label" for the intravitreal treatment of exudative AMD. Ranibizumab is derived from bevacizumab, although there are key differences between the drugs. First, with 2 antigen-binding domains, bevacizumab is larger than ranibizumab, which has a single domain. Because full-length antibodies are not cleared as rapidly as antibody fragments, intravitreal injections of bevacizumab have a longer systemic half-life (as well as longer intravitreal half-life) than intravitreal injections of ranibizumab. Second, the repackaged bevacizumab used to treat exudative retinal diseases costs substantially less than ranibizumab.

Several large, prospective, randomized studies on neovascular AMD have demonstrated comparable efficacy between bevacizumab and ranibizumab (Table 4-4). CATT, a multicenter trial funded by the US National Eye Institute, studied 1208 patients and found that bevacizumab and ranibizumab had similar effects on VA over a 2-year period and that PRN treatment provided lower VA gains than fixed monthly dosing. Mean gains from baseline were 8.8 letters in the ranibizumab-monthly group, 7.8 letters in the bevacizumab-monthly group, 6.7 letters in the ranibizumab PRN group, and 5.0 letters in the bevacizumab PRN group. Although the proportion of patients with 1 or more systemic adverse events was significantly greater in the bevacizumab group (39.9%) than in the ranibizumab group (31.7%), death and arteriothrombotic events were not statistically different between the 2 drugs. At 5 years, vision gains in the first 2 years were not sustained, but 50% of eyes maintained VA of 20/40 or better.

**Brolucizumab** Brolucizumab is a single-chain antibody fragment with a molecular weight of 26 kDa, compared with 48 kDa for ranibizumab, 115 kDa for aflibercept, and 149 kDa for bevacizumab. In the HAWK and HARRIER paired trials, the largest phase 3 exudative AMD program to date, 2824 eyes were randomly assigned to aflibercept given every second month after 3 monthly doses or brolucizumab. Patients taking brolucizumab received 3 monthly doses and then transitioned to injections every 12 weeks, with dosing shortened to every 8 weeks when exudative disease activity worsened at multiple prespecified assessment visits. At 48 weeks, VA noninferiority between the drugs, the primary study endpoint, was achieved. At the final study visit at 96 weeks, fewer than half of patients receiving brolucizumab remained on quarterly dosing. Anatomically, brolucizumab appeared to be a statistically significant superior drying agent. However, during the phase 3 program, intraocular inflammation developed in 4.6% of brolucizumab-treated patients, with retinal vasculitis and/or vascular occlusion also developing in some of these patients; in contrast, intraocular inflammation developed in 1.1% of aflibercept-treated patients.

Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;128(1):89–99.

**Complications of intravitreal antiangiogenic therapy** Intravitreal antiangiogenic therapy has been associated with a range of potential adverse effects. The rate of endophthalmitis is approximately 1 in 2000 patients who use anti-VEGF agents (see also Chapter 19). With or without anti-VEGF therapy, eyes with fibrovascular PEDs may be at increased risk for the development of an RPE tear, especially with PEDs greater than 600 μm in height. The mechanism of the tear is thought to be contraction of the underlying type 1 MNV, which may occur after anti-VEGF dosing. Use of bevacizumab to treat cancer has also increased the risk of hypertension; thromboembolic events, especially myocardial infarctions and cerebral vascular accidents; gastrointestinal perforations; and bleeding. However, evidence that intravitreal anti-VEGF agents increase the rate of systemic complications is conflicting.

Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev.* 2014;8(8):CD005139.

**Table 4-4 Clinical Trials Comparing Bevacizumab With Ranibizumab**

| Study Abbreviation | Study Name | Location | Patients Enrolled | Treatment Regimen | Major Outcome |
|---|---|---|---|---|---|
| BRAMD | Comparing the Effectiveness of Bevacizumab to Ranibizumab in Patients With Exudative Age-Related Macular Degeneration | The Netherlands | 327 | Fixed-interval dosing | Bevacizumab noninferior to ranibizumab with regard to visual acuity outcomes |
| CATT | Comparison of Age-Related Macular Degeneration Treatments Trials | United States | 1208 | As-needed, fixed-interval dosing | Bevacizumab noninferior to ranibizumab with regard to visual acuity outcomes |
| GEFAL | Groupe d'Evaluation Français Avastin vs Lucentis | France | 501 | As-needed dosing | No significant difference in outcomes between drugs |
| IVAN | Randomised Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation | United Kingdom | 610 | As-needed, fixed-interval dosing | No statistically significant differences in visual or anatomical outcomes between drugs |
| LUCAS | Lucentis Compared to Avastin Study | Norway | 432 | Treat-and-extend dosing | No significant differences in outcomes between drugs |
| MANTA | A Randomized Observer and Subject Masked Trial Comparing the Visual Outcome After Treatment With Ranibizumab or Bevacizumab in Patients With Neovascular Age-Related Macular Degeneration Multicenter Anti-VEGF Trial in Austria | Austria | 321 | As-needed dosing | Groups had similar visual acuity and anatomical outcomes |

Data from CATT Research Group; Martin DF, Maguire MG, Ying G, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011;364(20):1897–1908; and from CATT Research Group; Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* 2012;119(7):1388–1398.

**Combination treatment** To address the complex interactions between inflammation, angiogenesis, and fibrosis that are thought to play a role in exudative AMD pathogenesis, combinations of therapies have been explored. Trials have shown that combining PDT with ranibizumab may reduce re-treatment rates compared with ranibizumab monotherapy. Combination strategies may be particularly beneficial for patients with PCV that is refractive to anti-VEGF monotherapy. In those with exudative AMD, cytokines and molecular pathways beyond VEGF-A are also being evaluated to improve outcomes and reduce treatment frequency.

Lim TH, Lai TYY, Takahashi K, et al; EVEREST II Study Group. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II randomized clinical trial. *JAMA Ophthalmol*. 2020;138(9):935–942.

**Surgical treatments** In cases of thick submacular hemorrhage, injection of intravitreal or subretinal tissue plasminogen activator with pneumatic displacement may be considered. In contrast, both submacular surgery, with removal of the MNV from beneath the fovea, and macular translocation surgery involve complex techniques developed before the introduction of anti-VEGF agents and have been abandoned.

**Low-vision therapies and low-vision rehabilitation** Despite the success of intravitreal anti-VEGF pharmacotherapy, a substantial number of patients with AMD will ultimately progress to bilateral central blindness. However, for some of these patients, the use of optical and nonoptical devices may improve functional status and quality of life (see BCSC Section 3, *Clinical Optics and Vision Rehabilitation*). For example, an implantable miniature telescope can provide magnification up to a factor of 2.7, although corneal decompensation due to endothelial cell loss is a known risk of this technology. Even simple strategies such as magnification (eg, high-plus lenses, video magnifiers), optimal lighting, and contrast enhancement techniques may be beneficial and warrant discussion with patients.

**Social determinants of neovascular AMD treatment** A lack of caretakers and the financial burden of treatment may play a major role in patient nonadherence with treatment visits.

## Other Causes of Choroidal Neovascularization

A number of conditions other than AMD can produce degenerative changes within the macula, with central vision loss caused by CNV, atrophy, or scarring. Although historically focused on laser therapies or PDT, CNV management now involves primarily the use of intravitreal anti-VEGF agents.

### Ocular Histoplasmosis Syndrome

*Histoplasma capsulatum* fungus is endemic to the Mississippi and Ohio River valleys. Humans become infected by inhaling the yeast form of this fungus, which then disseminates throughout the bloodstream. Although the systemic infection eventually subsides, the individual may be left with chorioretinal scars that produce visual symptoms years later.

Ocular histoplasmosis syndrome (OHS), a disease associated with *H capsulatum* infection, is also referred to as *presumed OHS* because the causality has not been definitively confirmed. OHS is most prevalent among individuals with the greatest percentage of positive skin reactors; more than 90% of patients with the characteristic OHS fundus appearance react positively to the histoplasmin skin test. The organism has been identified histologically in the choroid of 5 patients with OHS. Nevertheless, other etiologies besides *H capsulatum* may produce a similar phenotype (see also the section "Multifocal choroiditis, including inner punctate choroiditis" in Chapter 11).

Clinically, OHS presents with small, atrophic, "punched-out" chorioretinal scars in the midperiphery and posterior pole ("histo spots"), linear peripheral atrophic tracks, and juxtapapillary chorioretinal scarring with or without CNV in the macula (Fig 4-17). Lesions are bilateral in more than 60% of patients, and characteristically, vitreous inflammation is

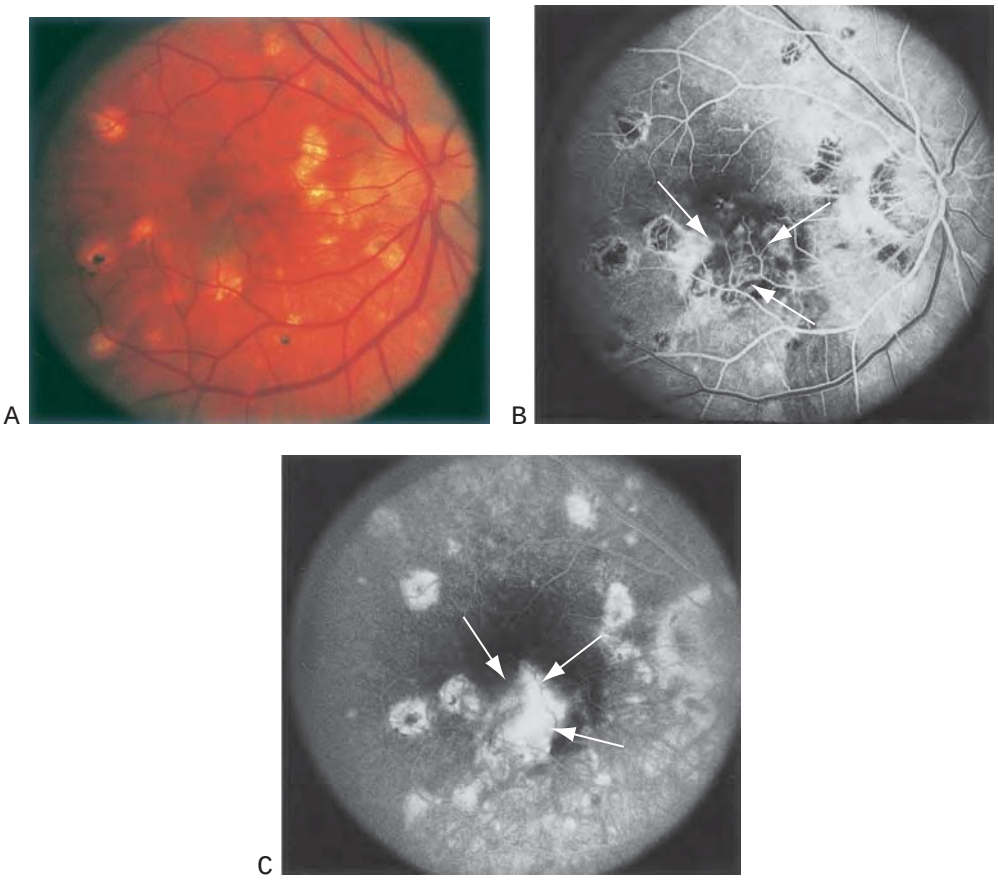


**Figure 4-17** Ocular histoplasmosis syndrome with CNV. **A,** Fundus photograph shows peripapillary atrophy and numerous atrophic scars. **B,** Transit frame of the angiographic study reveals blocked fluorescence from blood and pigment as well as hyperfluorescence resulting from the CNV *(arrows)* and choroidal transmission in areas of atrophy. **C,** Leakage from the choroidal neovascular membrane *(arrows)* late in the study, as well as staining of the sclera beneath atrophic scars.

absent. Most patients with OHS are asymptomatic until the development of CNV, which may cause vision loss, metamorphopsia, and paracentral scotomata. Diseases with features similar to those of OHS include panuveitis and multifocal choroiditis; see also BCSC Section 9, *Uveitis and Ocular Inflammation*.

## Angioid Streaks

Irregular dark red or brown lines radiating from a ring of peripapillary atrophy surrounding the optic nerve head are referred to as *angioid streaks* because they mimic the appearance of blood vessels. On FA, characteristic window defects with late staining are noted, resulting from dehiscences or cracks in the thickened and calcified Bruch membrane (Fig 4-18).

The systemic disease most commonly associated with angioid streaks is pseudoxanthoma elasticum (PXE), or Grönblad-Strandberg syndrome, a predominantly autosomal recessive disorder inherited through mutation in the *ABCC6* gene, which is located on band 16p13.11. Additional fundus findings associated with PXE include optic disc drusen, peripheral round atrophic scars with a "comet" sign, and a mottled RPE appearance referred to as *peau d'orange* ("skin of an orange"). Paget disease of bone, β-thalassemia, sickle cell anemia, and Ehlers-Danlos syndrome may also be associated with angioid streaks. When the ophthalmologist establishes a new diagnosis of angioid streaks and the patient has none of the aforementioned conditions, the patient should be referred for evaluation and management of possible underlying systemic diseases.

Unless they are subfoveal, angioid streaks usually are asymptomatic. Visual disturbances may develop owing to submacular hemorrhage resulting from trauma, but these disturbances may resolve spontaneously when there is no CNV. The most relevant visual complication is the development of CNV. Safety glasses are an advisable precaution for patients with angioid streaks, who may be highly susceptible to choroidal rupture after even

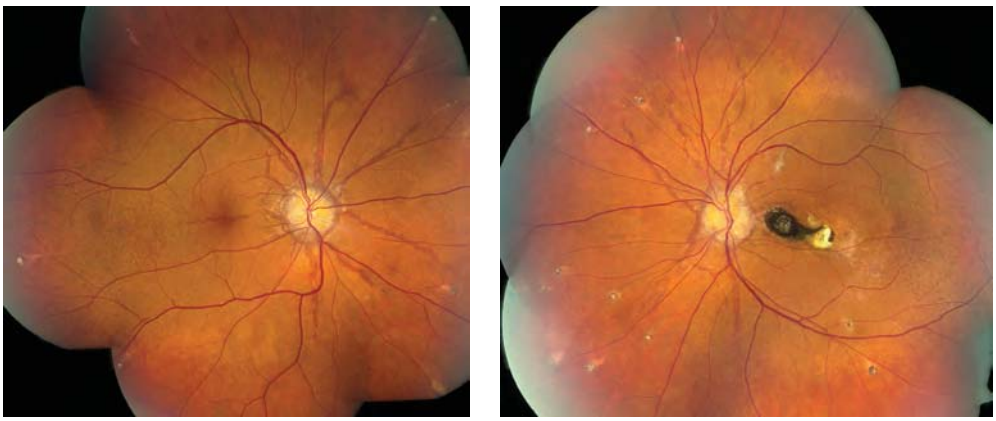

**Figure 4-18** Color montages of fundus photographs from a patient with pseudoxanthoma elasticum showing, in both eyes, angioid streaks radiating from the optic nerve head; a "peau d'orange" appearance of the fundus temporal to the macula; optic disc drusen; midperipheral comet lesions; and in the left eye, an old, inactive CNV. *(Courtesy of Stephen J. Kim, MD.)*

minor blunt injury. Medical consultation is indicated to evaluate for systemic manifestations of PXE, including benign features such as "plucked chicken" skin appearance and more serious life-threatening findings such as calcific arteriosclerosis of coronary arteries and gastrointestinal and cerebrovascular bleeding.

## Pathologic Myopia

Choroidal neovascularization may develop in 5%–10% of adult eyes with an axial length of 26.5 mm or more, with or without lacquer cracks or widespread chorioretinal degeneration (Fig 4-19; see also Chapter 10). Laser therapy is typically not used because of the risk of laser scar expansion through the foveal center over time (so-called *atrophic creep*). Although PDT has been shown to be beneficial, the mainstay of treatment currently is intravitreal anti-VEGF therapy. Several studies have demonstrated sustained regression of myopic CNV after anti-VEGF treatment, with stabilization or improvement of VA after as

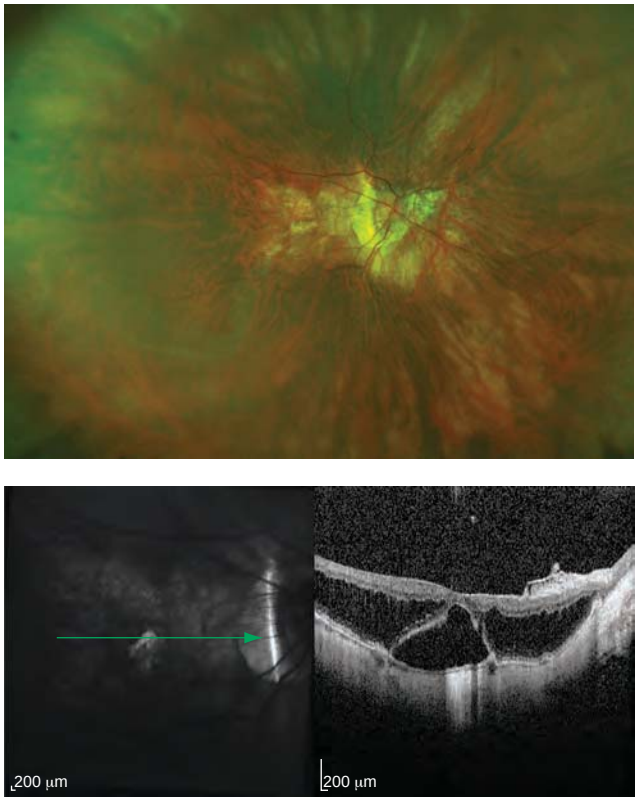


**Figure 4-19** Pathologic myopia. **A,** Color fundus photograph of the right eye demonstrating myopic macular degeneration with a posterior staphyloma, prominent peripapillary atrophy of the RPE, and extensive pigment mottling centrally. **B,** Near-infrared reflectance image *(left)* with *green arrow* marking the location of the SD-OCT image *(right)* showing extensive intraretinal fluid with myopic macular schisis as well as central subretinal fluid and a mild epiretinal membrane. *(Courtesy of Charles C. Wykoff, MD, PhD.)*

**Table 4-5 Conditions Associated With Choroidal Neovascularization**

| | |
|---|---|
| **Degenerative** | **Neoplastic** |
| Age-related macular degeneration | Choroidal hemangioma |
| Angioid streaks | Choroidal nevus |
| Myopic degeneration | Hamartoma of the RPE |
| **Heredodegenerative** | Metastatic choroidal tumors |
| Fundus flavimaculatus | **Traumatic** |
| Optic disc drusen | Choroidal rupture |
| Vitelliform maculopathy | Intense photocoagulation |
| **Inflammatory** | **Idiopathic** |
| Behçet disease | |
| Multifocal choroiditis | |
| Ocular histoplasmosis syndrome | |
| Rubella | |
| Serpiginous-like choroiditis (also called *multifocal serpiginoid choroiditis*) | |
| Sympathetic ophthalmia | |
| Toxocariasis | |
| Toxoplasmosis | |
| Vogt-Koyanagi-Harada syndrome | |

RPE = retinal pigment epithelium.

few as 1 or 2 injections and no need for ongoing repeated injections in many patients, in contrast to management of exudative AMD.

Wolf S, Balciuniene VJ, Laganovska G, et al; RADIANCE Study Group. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. *Ophthalmology*. 2014;121(3):682–692.e2.

### Idiopathic CNV and Miscellaneous Causes of CNV

Choroidal neovascularization may complicate any of the conditions known to damage Bruch membrane, including inflammatory chorioretinopathies, choroidal neoplasms, traumatic choroidal rupture, and optic nerve head abnormalities (Table 4-5). It may also develop in eyes with no apparent risk factors or predisposing lesions (eg, idiopathic CNV).

Heier JS, Brown D, Ciulla T, et al. Ranibizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration: a phase I clinical trial. *Ophthalmology.* 2011;118(1):111–118.

## 2023 Update

### Management of Nonneovascular AMD: Anti-Complement Therapy

In 2023, *pegcetacoplan*, a cyclic peptide that inhibits C3, became the first FDA-approved treatment for GA due to AMD. In 2 phase 3 studies, OAKS and DERBY, patients were assigned to pegcetacoplan or sham treatment monthly or every other month (EOM). A statistically significant reduction in GA growth was seen at 24 months in both studies: 22% in

OAKS and 19% in DERBY for the monthly arms, and 18% in OAKS and 16% in DERBY for the EOM arms. Adverse effects of note included choroidal neovascularization (12% in monthly arm, 7% in EOM arm, 3% in sham arm); intraocular inflammation (4% monthly, 2% EOM, <1% sham); and ischemic optic neuropathy (1.7% monthly, 0.2% EOM, 0% sham). FDA approval for intravitreal *avacincaptad pegol*, a second treatment for GA due to AMD, was also granted in 2023. The GATHER1 and GATHER2 trials showed monthly injections of this C5 complement inhibitor led to a statistically significant reduction in the rate of GA at 6 months. Adverse events included transient IOP elevations in 9% of patients and an increased rate of neovascular AMD (7% in treatment arm, 4% in sham arm).

Khanani AM, Patel SS, Staurenghi G, et al; GATHER2 Trial Investigators. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. *Lancet.* 2023;402(10411):1449–1458.

## Management of Neovascular AMD

In 2023, a high-dose formulation of *aflibercept* (8.0 mg/0.07 mL) was approved by the FDA. The PULSAR trial demonstrated the noninferiority of aflibercept 8 mg given at 12-week and 16-week dosing intervals compared with an 8-week dosing interval for aflibercept 2 mg in patients with neovascular AMD. At the end of 2 years, 88% of patients were maintained on a ≥12-week dosing interval.

*Faricimab*, a bispecific antibody targeting both angiopoietin-2 and VEGF, was approved by the FDA in 2022. The pivotal trials TENAYA and LUCERNE demonstrated the non-inferiority of faricimab 6 mg compared with aflibercept 2 mg for treatment of neovascular AMD based on the primary outcome measure of mean change in BCVA averaged over weeks 40, 44, and 48. At 1 year, 46% of patients treated with faricimab in TENAYA and 45% in LUCERNE were maintained on a 16-week dosing interval. At 2 years, 59% of patients in TENAYA and 67% in LUCERNE were treated on a 16-week dosing regimen with faricimab.

Heier JS, Khanani AM, Quezada Ruiz C, et al; TENAYA and LUCERNE Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet.* 2022;399(10326):729–740.

CHAPTER 5

# Diabetic Retinopathy

*This chapter includes a related activity. Go to www.aao.org/bcscactivity_section12 or scan the QR code in the text to access this content.*

## Highlights

- Systemic control of hyperglycemia, hypertension, and hyperlipidemia is the foundation of care for all diabetic eye diseases.
- For treating proliferative diabetic retinopathy, both panretinal photocoagulation and intravitreal anti-VEGF therapy are effective. Panretinal photocoagulation may also be considered for eyes with severe nonproliferative diabetic retinopathy, especially in patients with type 2 diabetes. Anti–vascular endothelial growth factor (anti-VEGF) agents frequently reduce the severity of diabetic retinopathy and the risk of vision-threatening complications in eyes with nonproliferative disease but may not improve long-term visual outcomes.
- Intravitreal anti-VEGF is first-line therapy for most eyes with center-involved diabetic macular edema and vision loss. In contrast, treatment can generally be deferred in eyes with good vision despite center-involved diabetic macular edema.
- When anti-VEGF treatment is inappropriate or ineffective for diabetic macular edema, intravitreal corticosteroid therapy and macular focal/grid laser photocoagulation may be used as alternative or adjunctive therapy.

## Introduction

Diabetic retinopathy is a leading cause of vision loss worldwide among patients aged 25–74 years, especially in resource-rich countries such as the United States. This chapter provides a foundation for the evaluation and treatment of diabetic retinopathy. See BCSC Section 1, *Update on General Medicine,* for discussion of diabetes mellitus. The following glossary provides the abbreviated and full names of diabetic retinopathy and diabetic and macular edema studies referenced in this chapter. Only the short names are used in the text.