CHAPTER 8

Retinopathy of Prematurity

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Highlights

- Retinopathy of prematurity (ROP) is the arrest of normal retinal vascular development in the preterm infant, with compensatory mechanisms that produce aberrant vascularization of the retina.
- In most infants, ROP follows a predictable course of onset, progression, and resolution that is closely tied to gestational age, not postnatal (also called *chronologic*) age.
- The level of ROP for which treatment is recommended is currently termed *type 1 ROP*.

Introduction

Retinopathy of prematurity is a complex disease process in preterm infants initiated in part by incomplete or abnormal retinal vascularization. When normal vascular growth (ie, *vasculogenesis*) is disturbed, new vessels proliferate (ie, *angiogenesis*) into the vitreous cavity at the border of the vascular and avascular retina. Left untreated, ROP culminates in the development of a dense, white, fibrovascular plaque behind the lens and complete traction retinal detachment (this end stage is reflected in the former name for ROP, *retrolental fibroplasia*).

The main risk factors for ROP are prematurity and low birth weight. See BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* for additional discussion of ROP.

Epidemiology

Premature birth is defined as any delivery before 37 weeks of gestation, whereas delivery before 32 weeks of gestation is generally associated with the development of retinal disease. In the United States, according to the National Institutes of Health, approximately 80,000 infants are at risk for ROP each year, and approximately 1100–1500 have disease that is severe enough to require treatment. Among these infants, 400–600 will never achieve visual acuity better than 20/200. Globally, an estimated 50,000 children younger

than 15 years are blind because of complications of ROP. The prevalence is highest in the poorest countries of Latin America, southeast Asia, and Africa. In these resource-limited regions, the rise in cases of ROP corresponds to increased survival rates among at-risk preterm infants.

In a study by the Cryotherapy for Retinopathy of Prematurity Cooperative Group, some signs of ROP were present in 66% of infants with a birth weight of ≤1250 g and in 82% of infants with a birth weight of <1000 g. Progression to treatment-requiring ROP occurred in approximately 10% of infants with a birth weight of ≤1250 g, but up to 50% of infants with a birth weight of ≤500 g.

Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology.* 1991;98(11):1628–1640.

Classification, Terminology, and Clinical Features

Normal retinal vascularization begins at approximately week 16 of gestation, with vessel growth proceeding from the optic nerve head to the periphery. Vascularization is completed nasally by approximately 36 weeks' gestation and temporally by 40 weeks' gestation. Thus, a child born prematurely (typically before 32 weeks of gestation) is at risk for ROP.

To formalize discussion of the clinical aspects of ROP and to standardize and support research into ROP, a necessary lexicon of clinical descriptors was developed. This lexicon, the International Classification of ROP (ICROP), was introduced in 1984 and revised in 2005 and most recently in 2021. The original ICROP group introduced 4 defining concepts for ROP: the *location,* or zone, of involvement; the *extent* of disease (measured in clock-hours); the disease *severity,* or stage; and the presence or absence of *plus disease,* which is defined as the presence of dilatation and tortuosity of vessels in zone I (see Table 8-1 and accompanying Figs 8-1 through 8-8).

As an extension of these concepts, the following diagnostic terminology can be used to further classify ROP, which can help clinicians optimize management and treatment decisions (Table 8-2):

- The term *threshold ROP* was coined in the mid-1980s by investigators in the Cryotherapy for ROP (CRYO-ROP) study to define disease with equal chances of spontaneous regression or progression to an unfavorable outcome. Threshold disease is characterized by at least 5 contiguous clock-hours of extraretinal neovascularization or 8 cumulative clock-hours of extraretinal neovascularization with plus disease as well as retinal vessels ending in zone I or II.
- The term *prethreshold disease* was introduced in the early 2000s with the Early Treatment for Retinopathy of Prematurity (ETROP) study. Prethreshold disease is further divided into high-risk prethreshold, or type 1, ROP and lower-risk prethreshold, or type 2, ROP (see Table 8-2 for a detailed description). In current practice, type 1 ROP is the point at which treatment is indicated (Activity 8-1).

Table 8-1 Classification of Acute Retinopathy of Prematurity

Location

Zone I: posterior retina within a circle (the radius of which is twice the estimated distance between the optic nerve head center and foveal center) centered on the optic nerve

Zone II: annulus centered on the nerve extending from zone I to the nasal ora serrata

Zone III: remaining crescent of temporal peripheral retina

Extent: number of clock-hours involved (from 1 to 12)

Severity

Stage 0: immature retinal vasculature without pathologic changes (see Fig 8-1)

Stage 1: a flat, thin, white *demarcation line* between vascularized and avascular retina (see Fig 8-2); abnormal branching or dilatation of the retinal vessels may lead up to the line

Stage 2: a demarcation line that has height, width, and volume *(ridge);* small, isolated tufts of neovascular tissue lying on the surface of the retina, commonly called *popcorn,* may be seen posterior to the ridge (see Fig 8-3)

Stage 3: a ridge with extraretinal fibrovascular proliferation infiltrating the vitreous (see Fig 8-4)

Stage 4: a partial retinal detachment (see Fig 8-5)

- A: extrafoveal
- B: retinal detachment including the fovea

Stage 5: total retinal detachment (see Fig 8-6)

- A: optic nerve head is visible by ophthalmoscopy (suggesting open-funnel configuration of retinal detachment
- B: optic nerve head is not visible by ophthalmoscopy (due to retrolental fibrosis or a closed-funnel retinal detachment)
- C: abnormalities of the anterior segment accompanying stage 5B

Plus disease: vascular dilatation (venous) and tortuosity (arteriolar or venous) of the retinal vessels within zone I; iris vascular dilatation and vitreous haze may be present (see Fig 8-7; see also Fig 8-4B)

Aggressive ROP (also referred to as *Rush disease* and *aggressive posterior ROP*): a rapidly progressive, severe form of ROP often (but not always) characterized by posterior location, prominent plus disease, and sometimes iris rubeosis; the peripheral retinopathy may be ill-defined (see Fig 8-8)

ROP = retinopathy of prematurity.

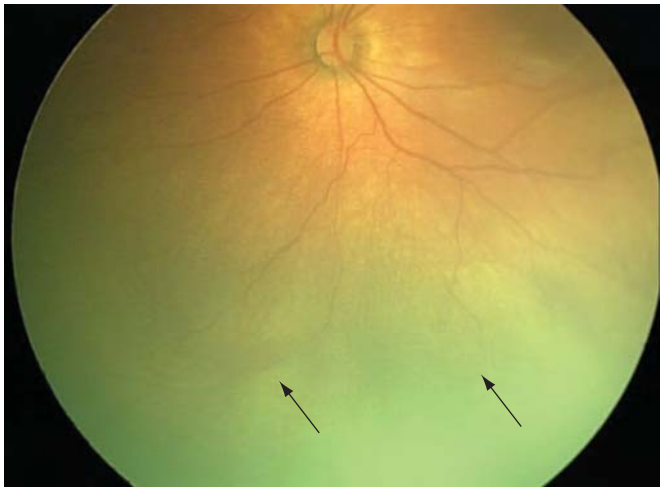

Figure 8-1 Fundus photograph demonstrating immature retinal vascularization (stage 0 ROP). Note the progressive tapering and eventual disappearance of retinal vessels *(arrows)* as they course peripherally. ROP = retinopathy of prematurity. *(Courtesy of Franco M. Recchia, MD.)*

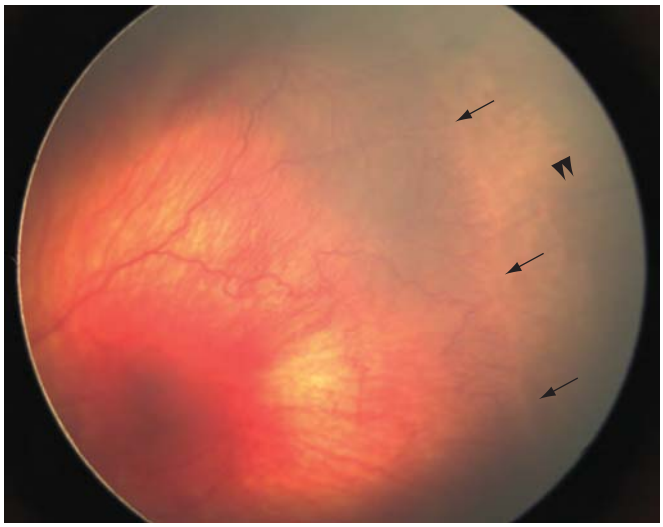

Figure 8-2 Stage 1 ROP. Fundus photograph reveals a faint white demarcation line temporally *(arrows)*. Arborizing, dilated vessels approach the line, and a choroidal vessel is seen extending to the periphery *(arrowheads)*. *(Courtesy of Franco M. Recchia, MD.)*

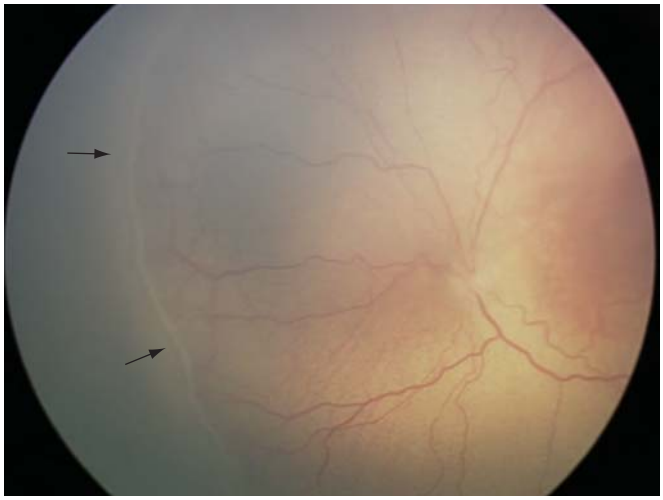

Figure 8-3 Stage 2 ROP. Fundus photograph shows an elevated gray-white ridge *(arrows)* at the border of the vascularized *(rosy)* and avascular *(grayish)* retina. *(Courtesy of Franco M. Recchia, MD.)*

- *Aggressive ROP* (*A-ROP*; previously referred to as *Rush disease* and *aggressive posterior ROP [AP-ROP]*) is characterized by the rapid development of pathologic neovascularization and severe plus disease without progression through the typical stages of ROP. Hemorrhages at the junction of the vascular and avascular retina, as well as iris rubeosis, may be seen (see Fig 8-8). The vascular–avascular junction

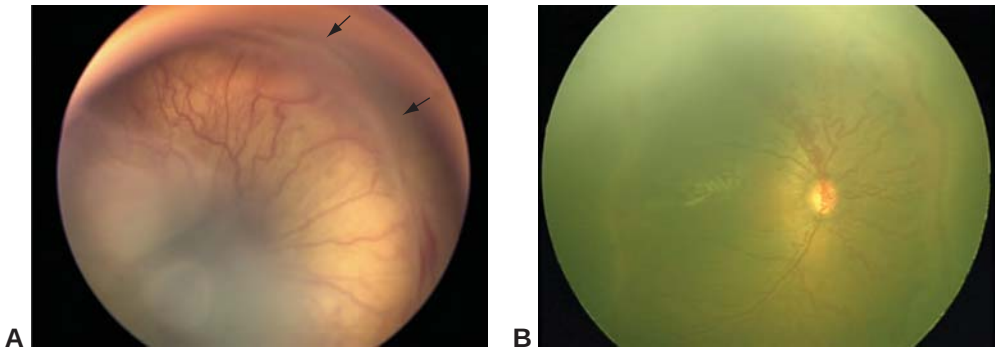

Figure 8-4 Stage 3 ROP. **A,** Fundus photograph shows fibrovascular tissue *(arrows)* extending from the surface of the retina into the vitreous and preretinal hemorrhage *(lower right)*. **B,** Fundus photograph shows an elevated circumferential fibrovascular ridge and marked plus disease (dilation and tortuosity of all posterior vessels). *(Part A courtesy of Colin A. McCannel, MD; part B courtesy of Franco M. Recchia, MD.)*

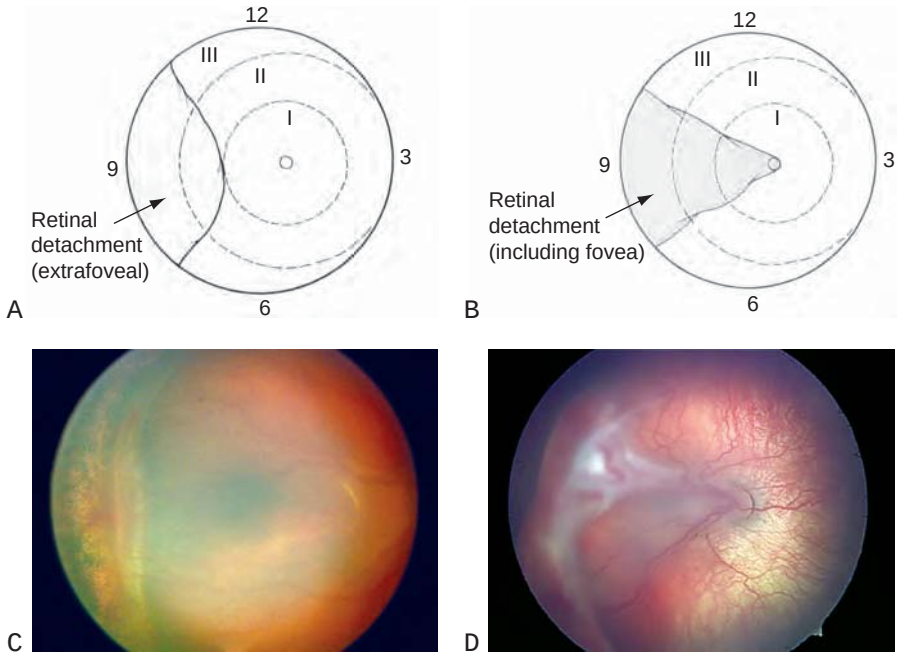

Figure 8-5 Stage 4 ROP. Schematic representations show stage 4A **(A)** and stage 4B **(B).** The roman numerals in each circle indicate the zones, per the international classification, and the arabic numerals indicate clock-hours. Wide-angle clinical photographs of stage 4A **(C)** and stage 4B **(D)** correspond to the schematic diagrams. *(Parts A and B courtesy of J. Arch McNamara, MD; parts C and D courtesy of Audina Berrocal, MD.)*

may be deceptively featureless, with neovascularization appearing only as a flat network of fine vessels that may be confused with underlying choroid (Fig 8-9). This phenomenon is not restricted to the posterior retina or to the smallest infants, as originally thought.

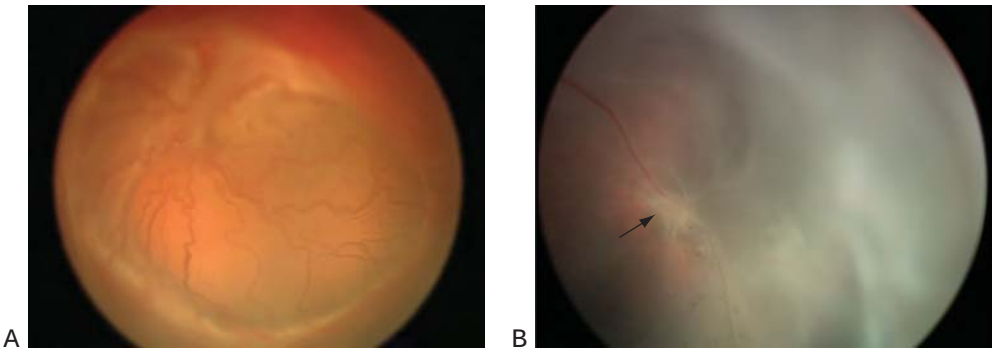

Figure 8-6 Stage 5 ROP. Wide-angle fundus photographs show total ROP retinal detachment (RD). **A,** Total RD with visible optic nerve head is now defined as stage 5A. Persistent vascular activity accompanies the preretinal fibrovascular ridge that contracts circumferentially, acting like a purse string. **B,** Eventually, the vascular activity subsides, and the fibrosis starts to close the funnel anteriorly (evolution into stage 5B). The *arrow* denotes the optic nerve head, which is almost completely obscured. *(Part A courtesy of Audina Berrocal, MD; part B courtesy of Franco M. Recchia, MD.)*

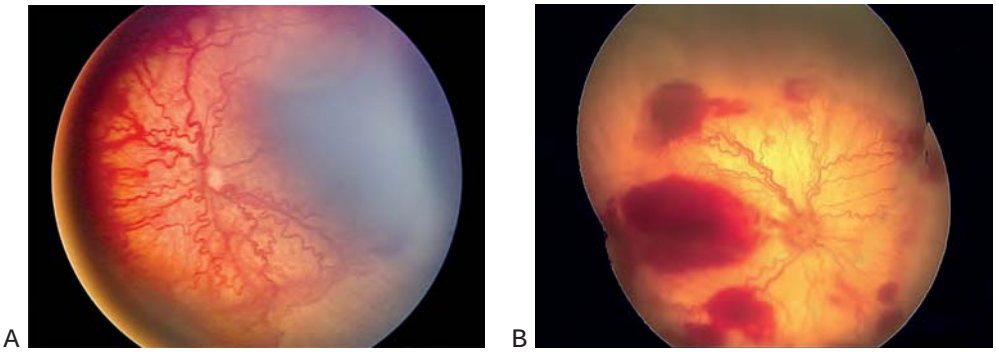

Figure 8-7 Fundus photographs show pronounced plus disease in eyes with ROP. The retinal arteries and veins are dilated and tortuous. **A,** The avascular retina and preretinal proliferations can be seen inferiorly and inferotemporally *(bottom right)*. **B,** Preretinal hemorrhages are visible, originating from the proliferative disease. *(Part A courtesy of Colin A. McCannel, MD; part B courtesy of Audina Berrocal, MD.)*

According to the ICROP, an eye is classified on the basis of the most advanced disease noted. However, documentation should reflect all affected zones and stages observed, including their relative extent.

ACTIVITY 8-1 Interactive schematic for type 1 ROP.
Developed by Franco M. Recchia, MD.

Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, 3rd ed [epub ahead of print, July 8, 2021]. *Ophthalmology.* 2021;128(10):e51–e68. doi:10.1016/j.ophtha.2021.05.031

Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol.* 2003;121(12):1684–1694.

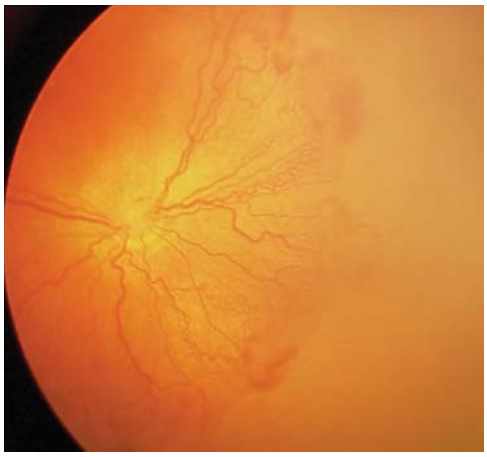

Figure 8-8 Aggressive ROP (A-ROP). Fundus photograph shows prominent plus disease and ill-defined retinopathy in zone I, accompanied by blot hemorrhages. *(Courtesy of Franco M. Recchia, MD.)*

Table 8-2 Common Terms Used in Clinical Trials to Describe Acute Retinopathy of Prematurity (ROP)

Threshold disease (all 3 features must be present)
Extraretinal neovascularization (stage 3 disease): EITHER 5 contiguous clock-hours OR 8 cumulative clock-hours
Retinal vessels ending within zone I or zone II
Plus disease
Prethreshold disease
All zone I and zone II changes, except zone II stage 1 and zone II stage 2 without plus disease, that do not meet threshold treatment criteria; subdivided into type 1 and type 2 disease
Type 1 ROP
Zone I, any stage ROP with plus disease, or
Zone I, stage 3 ROP without plus disease, or
Zone II, stage 2 or 3 ROP with plus disease
Type 2 ROP
Zone I, stage 1 or 2 ROP without plus disease, or
Zone II, stage 3 ROP without plus disease

International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol.* 2005; 123(7):991–999.

Pathophysiology of ROP

A link between excessively exuberant perinatal oxygen supplementation and severe ROP was well recognized by the 1950s. After substantial reductions in oxygen use in neonatal intensive care units (NICUs), the incidence of ROP decreased dramatically. However, many infants experienced adverse neurologic outcomes as an unintended consequence of that oxygen restriction, and infant death rates rose. Once oxygen was again used more liberally, neurologic outcomes and survival improved, with the consequence of a resurgence of ROP.

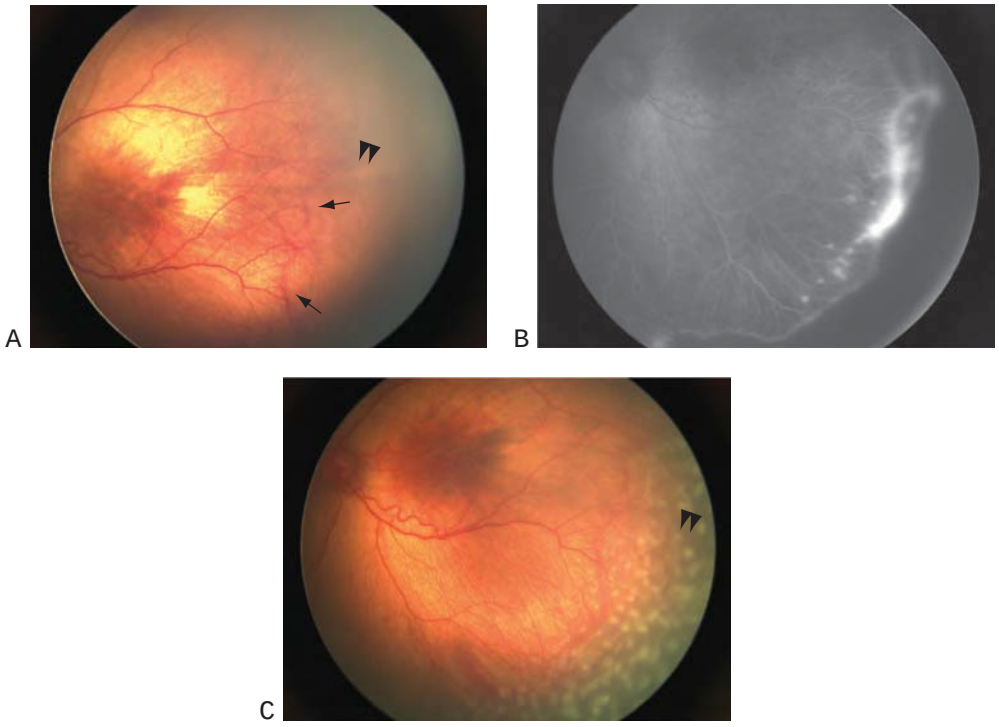

Figure 8-9 Type 1 ROP (stage 3, zone II) treated with peripheral laser photocoagulation. **A,** Color fundus photograph shows the long posterior ciliary nerve *(arrowheads)* and flat neovascularization in posterior zone II temporally *(arrows)*, which is identified definitively by the areas of leakage on the corresponding fluorescein angiogram **(B). C,** Color photograph taken immediately after laser treatment. Note that treatment abuts the ridge and is intentionally more sparse in the region of the long posterior ciliary nerve *(arrowheads)* to minimize damage to the nerve. *(Courtesy of Franco M. Recchia, MD.)*

Since then, converging lines of experimental and clinical evidence suggest that the disease proceeds in 2 phases linked in large part to fluctuations in retinal oxygenation:

- *Phase 1* of ROP occurs from birth until approximately 31 weeks of gestational age, when there is relative hyperoxia compared with the typical intrauterine environment. The relative hyperoxia leads to a lower demand for retinal oxygenation and a subsequent arrest in retinal blood vessel growth. This cessation in vessel growth is largely due to a decrease in the levels of hormones and growth factors that govern normal vascular development in the eye, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1).
- *Phase 2* of ROP begins over the ensuing weeks (typically by 32–34 weeks' gestational age). Increased metabolic demands in the retina coupled with insufficient oxygenation (due to the suppression of vessel growth in phase 1) lead to relative hypoxia, which then induces increased retinal production of growth factors (particularly VEGF). This leads to the proliferation of abnormal blood vessels, and oxidative damage to endothelial cells, which leads to disorganized vascular growth.

The onset of phase 2 corresponds to the clinical appearance of ROP on ophthalmoscopy and is closely correlated with the infant's gestational age, rather than his or her postnatal age. Initially, this process causes the formation of visible flat or raised whitish tissue (ROP stages 1 [flat line] and 2 [ridge]). As the disease progresses, vascular growth proliferates into the vitreous cavity (ROP stage 3). In this vasoproliferative phase, new vessels varying widely in size and extent arise from retinal vessels just posterior to the peripheral ridge. These abnormal new vessels easily bleed, leading to vitreous hemorrhage, and may induce contracture of the firmly attached vitreous gel. Eventually, growth factor and hormonal changes cause involution and fibrosis of the blood vessels with cicatricial contraction that may lead to traction (also called *tractional*) retinal detachment (ROP stages 4 and 5).

Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. *N Engl J Med*. 2012;367(26):2515–2526.

Natural Course

Although the precise systemic and/or local tissue factors that influence progression and regression of ROP are not known, the time course is predictable. ROP is typically a transient disease that regresses spontaneously in most infants, particularly those with heavier birth weights (closer to 1500 g) and older gestational age (closer to 32 weeks) at birth. In general, eyes with ROP in zone III have a good visual prognosis. In contrast, the more posterior the zone at the time of diagnosis, the greater the area of nonperfused retina and thus the more worrisome the prognosis.

Screening Recommendations

Screening for ROP consists of a dilated fundus examination using binocular indirect ophthalmoscopy. Use of a topical anesthetic and an eyelid speculum facilitates examination. The pupils should be examined for failure to dilate and the iris inspected for vessel engorgement or frank rubeosis, as these may be signs of aggressive disease. In addition, the optic nerve should be evaluated for plus disease and the periphery examined with scleral depression to establish the extent of vessel growth.

Alternatively, telemedicine (ie, photographic) screening approaches may replace the indirect ophthalmoscopic examination (see the section Fundus Photographic Screening of ROP). However, clinicians should be aware that telemedicine screening criteria developed in one country may not apply in another country, especially when the level or quality of available medical or perinatal care is not comparable.

Screening Criteria

All infants with a birth weight <1500 g or a gestational age of ≤30 weeks should be screened for ROP. Infants with a birth weight between 1500 and 2000 g or a gestational age >30 weeks who have an unstable clinical course and are considered by their attending pediatrician or neonatologist to be at high risk for the disease should also be screened. The

first examination is generally performed at a postnatal age of between 4 and 6 weeks or, alternatively, between 31 and 33 weeks' gestational or postmenstrual age, whichever is later.

Newer neonatal algorithms, such as WINROP (Weight, Insulin-like growth factor-I, Neonatal, ROP), can identify infants at highest risk for ROP as early as 6 weeks before the onset of clinical findings of ROP through a calculation using birth weight, rate of postnatal weight gain, levels of IGF-1 and IGF-binding proteins, and other factors. Conversely, they may also predict which infants will not develop ROP and may not require examination despite meeting the conventional screening criteria. These algorithms are a useful adjunct to standard screening criteria and are being used with increasing frequency worldwide.

Screening Intervals

After each patient evaluation for ROP, disease features dictate the follow-up interval (eg, more severe disease indicates a shorter follow-up interval).

Follow up in 1 week or less

- zone I: immature vascularization only (stage 0);
- zone I: stage 1 or stage 2 ROP;
- immature retina (stage 0) extending into posterior zone II, near the boundary of zone I and zone II;
- suspected A-ROP; and
- stage 3 ROP: zone I requires treatment not observation

Follow up in 1–2 weeks

- posterior zone II: immature vascularization (stage 0);
- zone II: stage 2 ROP; and
- zone I: unequivocally regressing ROP

Follow up in 2 weeks

- zone II: stage 1 ROP;
- zone II: immature vascularization (stage 0); and
- zone II: unequivocally regressing ROP

Follow up in 2–3 weeks

- zone III: stage 1 or 2 ROP; and
- zone III: regressing ROP

Retinal screening examinations are usually discontinued when any one of the following criteria is met:

- full retinal vascularization (ie, vascularization ending within 1 disc-diameter of the ora serrata; this criterion should be used for all patients with ROP treated with intravitreal anti-VEGF medications alone)
- zone III retinal vascularization attained without previous zone I or II ROP
- postmenstrual age of 45 weeks and no type 1 ROP (ie, as stage 3 ROP in zone II or any ROP in zone I) or more severe ROP

- postmenstrual age of at least 65 weeks in patients for whom intravitreal anti-VEGF medications caused regression of ROP (ie, this treatment alters the natural history of the disease); because very late recurrences of proliferative ROP have been reported, clinical judgment and caution should be used on a case-by-case basis to determine when surveillance can be safely terminated in these patients
- regression of ROP (care must be taken to confirm the absence of abnormal vascular tissue that could reactivate)

Fierson WM; American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics.* 2018;142(6). doi:10.1542/peds.2018-3061 [Published correction appears in *Pediatrics*. 2019;143(3):320183810.]

Fundus Photographic Screening of ROP

Ultra-wide-angle (120°) fundus photography is useful for documenting disease in premature infant eyes, for assessing disease progression, and for screening. Given shortages of willing examiners skilled in indirect ophthalmoscopy and ROP screening, remote screening of photographic fundus images (ie, telemedicine) has efficiently and cost-effectively improved access to eye care for premature infants at high risk for ROP, providing real-time diagnosis and improving documentation. For detection of plus disease and disease requiring treatment, photoscreening by experienced personnel is comparable to binocular indirect ophthalmoscopy, which is considered the gold standard for ROP screening examinations.

To help identify patients who require an in-person examination after photoscreening, the Photographic Screening for Retinopathy of Prematurity (Photo-ROP) Cooperative Group established a definition of *clinically significant ROP* based on features detectable by photography:

- zone I, any ROP without plus disease
- zone II, stage 2 with no plus disease or up to 1 quadrant of plus disease
- zone II, stage 3 with no plus disease or up to 1 quadrant of plus disease

In addition, more advanced approaches to interpretation of fundus photographs, such as electronic image recognition and deep learning algorithms, are under study.

Daniel E, Quinn GE, Hildebrand PL, et al; e-ROP Cooperative Group. Validated system for centralized grading of retinopathy of prematurity: telemedicine approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) study. *JAMA Ophthalmol.* 2015;133(6):675–682.

Prevention and Risk Factors

Preventing ROP begins with preventing prematurity through optimal prenatal, perinatal, and postnatal care. During the postnatal clinical course, factors that appear to increase the risk of severe ROP include sepsis, blood transfusion, intraventricular hemorrhage, necrotizing enterocolitis, and slow weight gain.

Alteration of oxygenation levels as the infant grows is thought to modify the course of ROP. In keeping with the two-phase pathophysiology of ROP (discussed earlier), some researchers have suggested that oxygen saturation should be decreased during phase 1 ROP, when the infant's oxygen requirements are lower, whereas oxygenation should be increased during phase 2 to meet the infant's growing demands. Aggressive parenteral nutrition has reduced the risk of less severe ROP but not severe ROP. Supplementation with vitamins A and E, inositol, or breast milk also appears to reduce the incidence of ROP but only in observational studies, whereas use of transfusion guidelines, erythropoietin, and antifungal agents showed no benefit.

Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions to prevent retinopathy of prematurity: a meta-analysis. *Pediatrics*. 2016;137(4):e20153387. doi:10.1542/peds.2015-3387

Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. *Surv Ophthalmol*. 2018;63(5):618–637.

Treatment of Acute ROP

In 1988, the multicenter CRYO-ROP study demonstrated that ablation of the avascular anterior retina reduced the incidence of unfavorable outcomes by approximately one-half in eyes with threshold ROP (Table 8-3). Although this finding represented a major advance, nearly one-fourth of eyes still experienced unfavorable outcomes with treatment; eyes with posterior disease had the worst outcomes. Also in the late 1980s, the introduction of portable laser units coupled with an indirect ophthalmoscope offered a promising alternative for treating the peripheral retina with photocoagulation.

To examine whether early ablation of the avascular retina improves visual and structural outcomes in infants with bilateral, high-risk, prethreshold ROP, the ETROP trial randomly assigned 1 eye to early laser photocoagulation and the fellow (ie, control) eye to conventional management per the CRYO-ROP study. High-risk disease was determined using a computational model based on the natural history cohort of the CRYO-ROP study. The ETROP group determined that in infants with high-risk prethreshold ROP, earlier treatment was associated with reduced rates of unfavorable functional and structural outcomes. For risk assessment of prethreshold eyes, the study also determined that clinical categorization of eyes as having either type 1 or type 2 ROP achieved results very similar to those of the computational model. The authors concluded that treatment should be initiated in eyes with the following retinal findings characteristic of type 1 ROP:

- zone I ROP: any stage with plus disease;
- zone I ROP: stage 3, no plus disease; and
- zone II ROP: stage 2 or 3 with plus disease

The authors also suggested that eyes meeting the criteria for type 1 ROP should be considered for peripheral retinal laser treatment, whereas those meeting the criteria for type 2 ROP may be monitored at short intervals. When eyes with type 2 ROP progress to type 1 ROP or to threshold ROP, laser ablative treatment may be considered.

Table 8-3 Summary of Multicenter Clinical Trials That Guide Current Treatment of Acute ROP

Study Name (Year Enrollment Completed)	Outcome Measure(s)	Number of Eyes Assessed for Primary Outcome	Randomization Point	Treatment Arms	Main Conclusions	Comments
Trials of Peripheral Retinal Ablation						
Cryotherapy for Retinopathy of Prematurity; CRYO-ROP (1987)	(1) Unfavorable structural outcome at 1 year (defined as the presence of a macular fold, RD involving zone I, or obscuration of the posterior pole by cataract or retrolental fibrosis) (2) Unfavorable functional outcome at 1 year (Snellen equivalent of 20/200 or worse)	291	Threshold disease	(a) Observation (b) Peripheral cryotherapy	Unfavorable structural outcomes occurred in 48% of observed eyes vs 26% of treated eyes. Unfavorable functional outcomes occurred in 56% of observed eyes vs 35% of treated eyes.	Findings were consistent through 15 years of follow-up. Long-term risk of RD increased in all eyes throughout follow-up.
The Early Treatment for Retinopathy of Prematurity Study; ETROP (2002)	(1) Unfavorable functional outcome at 9 months (2) Unfavorable structural outcome at 9 months	657 (718 randomized enrolled)	High-risk prethreshold disease[a]	(a) Immediate laser photocoagulation to peripheral retina (361 eyes) (b) Conventional treatment (delay of laser until reaching threshold disease) (357 eyes)	Earlier treatment was associated with a reduction in unfavorable visual acuity outcomes (from 19.5% to 14.5%) and a reduction in unfavorable structural outcomes (from 15.6% to 9.1%).	The rate of cardiopulmonary complications was higher among infants treated earlier, but there was no difference in mortality between the two groups. The greatest benefit from early treatment was seen in eyes with zone I disease.

(Continued)

Table 8-3 *(continued)*

Study Name (Year Enrollment Completed)	Outcome Measure(s)	Number of Eyes Assessed for Primary Outcome	Randomization Point	Treatment Arms	Main Conclusions	Comments
Trials of Intravitreal Anti-VEGF Agents						
Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity; BEAT-ROP (2010)	Recurrence of ROP requiring re-treatment by 54 weeks of postconceptional age	143 (150 enrolled)	Stage 3+ ROP in zone I or posterior zone II	(a) Laser retinal ablation (b) Intravitreal bevacizumab, 0.625 mg in 0.025 mL	Recurrence of ROP was significantly higher in zone I eyes treated with laser than in eyes treated with bevacizumab (42% vs 6%, respectively). The difference for zone II eyes was not statistically significant (12% vs 5%, respectively).	The recurrence rate in the laser arm was higher than rates in previous studies. Two-thirds of study sites were in Texas. Median time to recurrent ROP was 16 weeks after injection and 6 weeks after laser therapy. The follow-up period was short (≈6 months after treatment).
Ranibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity study; RAINBOW (2017)	Treatment success was defined as no active retinopathy, no unfavorable structural outcomes, and no need for a different treatment modality by 24 weeks after therapy.	214 (225 enrolled)	Bilateral ROP as follows: Zone I, stage 1+, 2+, 3, or 3+ ROP Zone II, stage 3+ AP-ROP	(a) Laser retinal ablation (b) Bilateral intravitreal ranibizumab, 0.1 mg (c) Bilateral intravitreal ranibizumab, 0.2 mg	Treatment was successful in 80% of eyes receiving ranibizumab 0.2 mg, 75% of eyes receiving ranibizumab 0.1 mg, and 66% of eyes undergoing laser therapy.	The RAINBOW study cohort was not identical to the BEAT-ROP study cohort. Inclusion criteria were closer to the clinical profile of eyes typically treated in modern practice. There was no reduction in circulating serum levels of VEGF in any of the groups.

AP-ROP = aggressive posterior retinopathy of prematurity; RD = retinal detachment; ROP = retinopathy of prematurity; VEGF = vascular endothelial growth factor.

[a] The term *high-risk prethreshold*, which was coined by the ETROP investigators, required 2 findings: (1) clinical evidence of prethreshold ROP; AND (2) >15% computed risk of progression to unfavorable outcome if untreated. This risk was calculated using an algorithm incorporating demographic and clinical variables from the natural history arm of the CRYO-ROP study.

Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol.* 2003;121(12):1684–1694.

Shulman JP, Hobbs R, Hartnett ME. Retinopathy of prematurity: evolving concepts in diagnosis and management. *Focal Points: Clinical Modules for Ophthalmologists.* American Academy of Ophthalmology; 2015, module 1.

Laser and Cryoablation Surgery

Ablation of ROP should be performed with a laser rather than cryoablation because laser surgery is associated with less treatment-related morbidity. A diode red (810-nm) laser is preferred, as its energy will not be absorbed by prominent iris vessels or a persistent tunica vasculosa lentis. The conventional treatment pattern is best described as nearly confluent, with burns placed 0.5- to 1-burn width apart starting at the ridge and proceeding anteriorly to the ora serrata for 360° to treat all avascular retina (see Fig 8-9 earlier in the chapter). In the horizontal meridians, laser treatment should be applied in a lighter pattern to avoid damaging the long ciliary vessels and nerves, as damage to these structures may cause severe anterior segment ischemia. Although retinal cryoablation surgery is now rare in the United States, the technique may still be used when laser or intravitreal therapy is unavailable. Because respiratory or cardiorespiratory arrest occurs in up to 5% of infants treated with cryotherapy, treatment should be performed in conjunction with systemic monitoring. To minimize stress and risk to the infant, use of systemic analgesia may be considered. Some neonatologists prefer that infants undergo treatment with general anesthesia in an operating room.

Follow-up is recommended at 1 week after laser treatment. At that time, some reduction in the level of plus disease, but not necessarily regression of neovascularization, is expected. The primary purpose of this follow-up visit is to confirm that the disease has not worsened. By 1 month after laser therapy, obvious improvement, and even complete regression, of peripheral disease is expected.

Simpson JL, Melia M, Yang MB, Buffenn AN, Chiang MF, Lambert SR. Current role of cryotherapy in retinopathy of prematurity: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2012;119(4):873–877.

Anti-VEGF Drugs

Intravitreal bevacizumab monotherapy for zone I or posterior zone II stage 3 ROP with plus disease was studied by the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) group. In eyes with zone I ROP, recurrent neovascularization was observed significantly less often with bevacizumab treatment than with laser therapy by 54 weeks' gestational age. In contrast, in eyes with zone II disease, outcomes were similar with either treatment. Interestingly, normal peripheral retinal vascularization continued after treatment with intravitreal bevacizumab, though at gestational ages several months older than normally seen. Recurrence of ROP requiring treatment was noted in 6% of all infants treated with bevacizumab, at a median interval of 16 weeks after injection. On average, ROP recurred sooner in eyes with zone II disease than in eyes with zone I disease.

The authors concluded that the sample size was too small and the follow-up period too short to allow proper evaluation of the systemic safety of intravitreal bevacizumab or to assess the true incidence of late recurrence of ROP.

More recent trials have evaluated the efficacy of anti-VEGF agents ranibizumab 0.2 mg (RAINBOW study) and intravitreal aflibercept 0.4 mg (BUTTERFLEYE and FIREFLEYE studies) in eyes with zone I or posterior zone II, stage 3+ ROP. Both agents were comparable to laser retinopexy in avoiding unfavorable structural outcome and eliminating active ROP by 24 weeks posttreatment. Intravitreal ranibizumab 0.2 mg and aflibercept 0.4 mg are now approved for treatment of ROP in Europe and the United States, respectively.

VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-vascular endothelial growth factor therapy for primary treatment of type 1 retinopathy of prematurity: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2017;124(5):619–633.

Indications

For most cases of type I ROP, laser therapy remains the mainstay of treatment, given its proven safety, efficacy, predictable outcomes, and high probability of long-term success. Nevertheless, anti-VEGF treatment may be preferred in cases of iris rubeosis with poor dilation and very posterior disease and in infants who cannot tolerate the anesthesia associated with laser treatment.

Intravitreal injection technique

Intravitreal injections may be performed in the NICU (Video 8-1). A topical anesthetic and 5% betadine solution are applied first, and a sterile eyelid speculum is used to retract the eyelids. The injection site should be no more than 1.5 mm posterior to the corneal limbus, through the pars plicata. Given that infants have a proportionally larger crystalline lens than adults, the direction of the injection should be parallel to, rather than oblique to, the visual axis. Injection volume is typically 0.03 mL or less (approximately half the volume used in adults). Risks associated with the injection include ocular hypertension, cataract, endophthalmitis, bleeding, and retinal detachment.

VIDEO 8-1 Intravitreal injection in an infant.
Courtesy of Franco M. Recchia, MD.

Follow-up

Follow-up is recommended within 1 week of injection to assess therapeutic response and to determine the need for additional treatment. Because late reactivation of major proliferative disease is possible in infants whose ROP was treated with an intravitreal injection of bevacizumab or ranibizumab alone, continued close follow-up is crucial. This is particularly important between 2 and 4 months after injection, when the risk of ROP reactivation is highest.

In addition, special caution is urged before suspending regular retinal examinations in infants receiving anti-VEGF medications for ROP. Initial ROP regression (as with laser treatment) or achievement of 45 weeks' postmenstrual age (as with untreated type 2 ROP) is not sufficient to discontinue monitoring. Although full retinal vascularization is the

only clear criterion for terminating examinations, full retinal vascularization is not always achieved in infants treated with anti-VEGF monotherapy. Thus, many experts recommend definitive treatment with peripheral retinal laser photocoagulation before these patients are discharged from the NICU.

Safety profile

The results of the BEAT-ROP, RAINBOW, and other studies have dramatically changed how zone I ROP, and probably all ROP, is treated. However, substantive long-term data on systemic safety are limited.

Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3^{+} retinopathy of prematurity. *N Engl J Med.* 2011;364(7):603–615.

Stahl A, Lepore D, Fielder A, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet*. 2019;394(10208):1551–1559.

Vitrectomy and Scleral Buckling Surgery

Eyes with stage 4 ROP (ie, progressive, active-phase ROP) require surgical intervention using scleral buckling or a lens-sparing vitrectomy to alleviate the vitreoretinal traction causing retinal detachment. Eyes undergoing surgical intervention at stage 4A have more favorable outcomes than those undergoing surgery at later stage 4B or 5; in addition, lens-sparing vitrectomy at stage 4A ROP may reduce progression to stage 4B and 5 disease. Given the improved visual outcome, this is the preferred approach.

In one study of infants with stage 5 ROP, vitrectomy combined with dissection of the fibrovascular membranes and adherent vitreous resulted in full or partial reattachment of the retina in approximately 30% of eyes (Video 8-2). Nevertheless, only 25% of retinas in eyes with initial partial or total reattachment after surgery remained fully attached at a median follow-up of 5 years. When a drainage retinotomy is performed or an iatrogenic retinal break occurs during a vitrectomy for ROP, the prognosis for that eye is uniformly poor.

VIDEO 8-2 Stage 5 ROP surgery.
Courtesy of Audina M. Berrocal, MD.

Capone A Jr, Trese MT. Lens-sparing vitreous surgery for tractional stage 4A retinopathy of prematurity retinal detachments. *Ophthalmology.* 2001;108(11):2068–2070.

Quinn GE, Dobson V, Barr CC, et al. Visual acuity of eyes after vitrectomy for retinopathy of prematurity: follow-up at 5 1/2 years. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology.* 1996;103(4):595–600.

Associated Conditions and Late Sequelae of ROP

Following resolution of the acute phase of ROP, the infant should be examined by a pediatric ophthalmologist (typically within 6–12 months) for myopia, strabismus, and amblyopia.

In the ETROP study, high myopia (minus 5 diopters or greater) among children receiving laser treatment for ROP was observed in approximately one-fourth within 1 year of age and one-half by 6 years of age.

Conditions that are more likely to occur over time in eyes with regressed ROP include

- myopia with astigmatism
- anisometropia
- strabismus
- amblyopia
- cataract
- glaucoma
- macular dragging (Fig 8-10)
- retinal pigmentary changes
- retinal tears
- abnormal vitreoretinal interface/adhesions
- retinal detachment (rhegmatogenous, traction, and/or exudative) (Figs 8-11, 8-12, 8-13, respectively)
- anomalous foveal anatomy (Fig 8-14)

Figure 8-10 Montage color fundus photograph from an adult who had untreated ROP as an infant, showing severe dragging of retinal vessels and a macular fold extending to the temporal periphery. Diffuse pigmentary changes are also visible. *(Courtesy of Franco M. Recchia, MD.)*

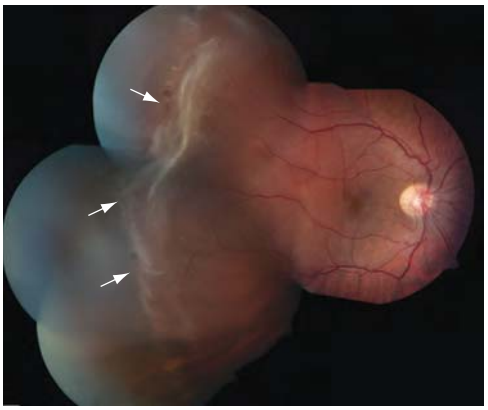

Figure 8-11 Rhegmatogenous retinal detachment in a 16-year-old male who was born at 26 weeks of gestational age. Avascular retina with numerous atrophic retinal holes *(arrows)* are seen peripheral to an old demarcation line in the temporal periphery. Subretinal fluid extends into the temporal macula. *(Courtesy of Franco M. Recchia, MD.)*

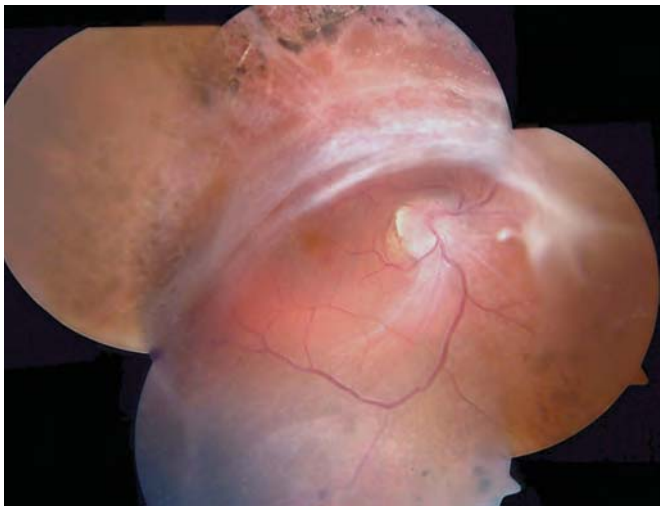

Figure 8-12 Traction retinal detachment in a 19-year-old male with a history of severe prematurity. Circumferential contraction of the posterior hyaloid has led to superior traction detachment. Scattered old laser photocoagulation scars are seen in the periphery. *(Courtesy of Franco M. Recchia, MD.)*

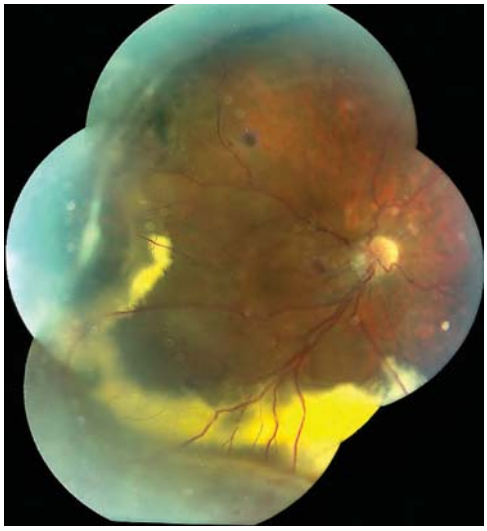

Figure 8-13 Montage of color fundus photographs showing exudative (also termed *Coats-like*) retinopathy in the right eye of a 22-year-old woman who was born at 24 weeks of gestation. Dense lipid exudate and subretinal fluid are present in the inferior and temporal preequatorial retina. Macular dragging and residual white fibrotic ridge tissue are also present in the superotemporal quadrant. *(Courtesy of Franco M. Recchia, MD.)*

Medicolegal Aspects of ROP

Several unique aspects of ROP care contribute to the risk of liability. The protracted hospital stay of premature infants requires complex coordination of multiple services, practitioners, caregivers, and specialists, of whom the ophthalmologist is just one of many and may be forgotten. Miscommunication between care coordinators and the ophthalmologist may delay scheduling or performance of eye examinations. If the narrow treatment window is missed, adverse outcomes may result. In addition, given the shortage of

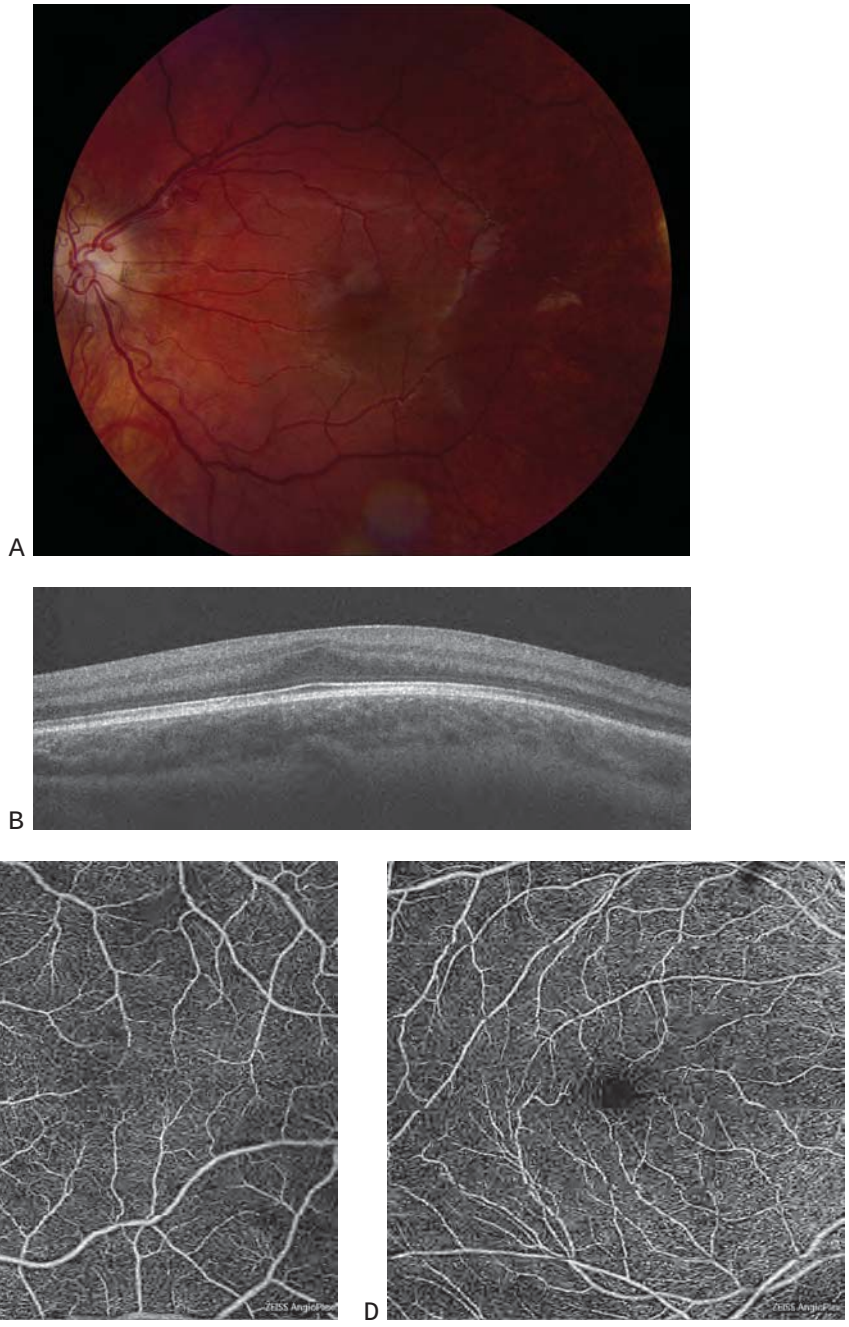

Figure 8-14 **A–C:** Images from a 10-year-old boy who was referred for evaluation because visual acuity was correctable only to 20/40. Pertinent medical history was his birth at 28 weeks' gestation. Color photograph **(A)** shows macular dragging and a blood vessel entering the foveal area. Optical coherence tomography (OCT) **(B)** through the anatomical center of the macula shows absence of a foveal depression and persistence of all retinal layers. OCT angiography (OCTA) **(C)** shows absence of a foveal avascular zone. **D,** OCTA from a 10-year-old child born at full term is shown for comparison. The finding of a blunted or absent foveal depression (also termed *fovea plana*) is a biomarker of premature birth. Normally, the foveal depression forms embryologically by a patterned centrifugal regression of inner retinal layers by the 30th week of gestation. Although the finding of foveal dysplasia or fovea plana, as seen here, indicates a premature birth, it is still compatible with good vision. *(Courtesy of Eric W. Schneider, MD.)*

experienced ROP screeners, management of ROP in some hospitals becomes the responsibility of ophthalmologists who may be uncomfortable or unfamiliar with the nuances and complexities of ROP care.

Poor outcomes from ROP may be perceived as medical malpractice and therefore pose a risk for litigation by patients or their families. Malpractice claims alleging mismanagement of ROP rank among the highest in ophthalmology and indeed all of medicine. Indemnity payments have exceeded 20 million dollars and are rationalized by the young age of the plaintiff and the lifelong duration of irreversible vision loss.

Patient safety can be promoted and liability minimized through implementation of an "ROP safety net," offered through the Ophthalmic Mutual Insurance Company (OMIC). See the following reference for toolkits that detail every step in the care process.

Menke AM. ROP Safety Net: Risk Analysis. Version 8/15/18. Ophthalmic Mutual Insurance Company; 2018. https://www.omic.com/rop-safety-net/

CHAPTER 9

Choroidal Disease

Highlights

- Pachychoroid is an entity with an evolving definition but is generally thought of as abnormally dilated choroidal vessels abutting the retinal pigment epithelium (with or without choroidal thickening).
- Fluorescein angiography can contribute to the diagnosis of arteritic anterior ischemic optic neuropathy.
- Hypertensive choroidopathy can be diagnosed by means of multimodal imaging because of its unique characteristics on optical coherence tomography and fundus autofluorescence.

Scope of Chapter

This chapter describes noninflammatory choroidal diseases that also involve the retina. Inflammatory disorders of the retina and choroid are discussed in Chapter 11. See also BCSC Section 9, *Uveitis and Ocular Inflammation*. Intraocular tumors such as melanoma are covered in BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors*.

Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC; also called *central serous retinopathy [CSR])* causes an idiopathic serous detachment of the retina related to leakage at the level of the retinal pigment epithelium (RPE) secondary to hyperpermeability of the choriocapillaris, as seen on indocyanine green angiography (ICGA). While the condition was originally described in 1866 by von Graefe as recurrent central retinitis, it was Maumenee who first performed fluorescein angioscopy on patients with CSC and found a leak at the level of the RPE, not from retinal vessels (the previously hypothesized source of leakage). Gass subsequently described the findings seen on fluorescein angiography (FA) and suggested that laser photocoagulation could be used to treat affected patients. Gass also stated that the disease was secondary to hyperpermeability of the choriocapillaris, a hypothesis that was confirmed decades later via ICGA.

Demographics and Features

Central serous chorioretinopathy occurs primarily in persons between the ages of 35 and 55 years, with a male-to-female ratio of 3:1; at present, there are no reliable statistics

suggesting any association with race. Patients describe a variety of symptoms, including sudden onset of blurred or dim vision, micropsia, metamorphopsia, paracentral scotomata, decreased color vision, and prolonged afterimages. Visual acuity ranges from 20/20 to 20/200, but in most patients, it is better than 20/30. Decreased visual acuity can often be improved with a small hyperopic correction.

CSC has several clinical variations. In an acute manifestation, the retina has a round or oval elevation in the macular region; it often involves the fovea. FA shows leaks from the RPE that may appear early in the angiographic sequence as a dot (the *dot* form) or as a tree-shaped movement of dye in the subretinal space (the *smokestack* form) (Fig 9-1). In some circumstances, vigorous leaks can cause deposition of a grayish-white, feathered-edge subretinal material that is generally believed to be fibrin. In chronic CSC, the RPE

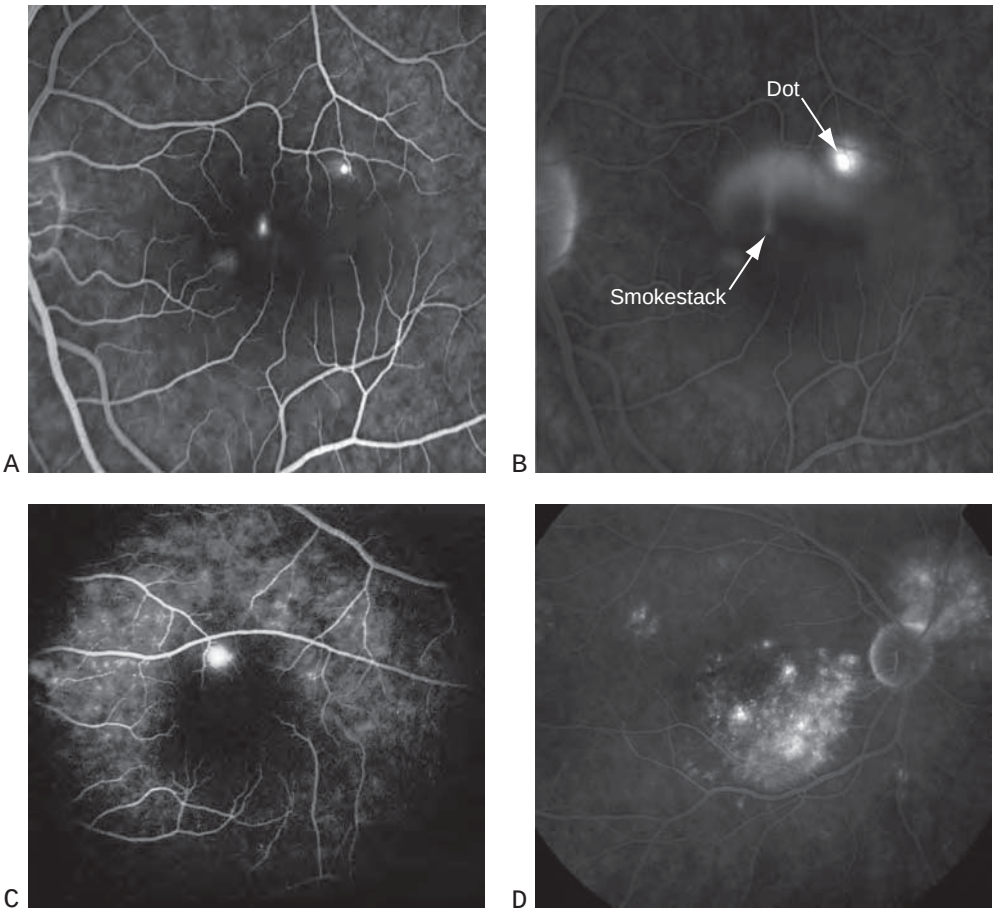

Figure 9-1 Fluorescein angiographic (FA) patterns of the leaks in central serous chorioretinopathy (CSC). **A,** In the early phase, the patient was seen to have 2 main leaks. **B,** Later in the angiogram, the leaks show 2 different morphologies: the *smokestack* and the *dot* varieties. **C,** Acute CSC generally presents with 1 leak or a few leaks. **D,** Chronic forms of CSC exhibit many small leaks, as demonstrated in this image from a different patient. *(Courtesy of Richard F. Spaide, MD.)*

shows granular pigmentation; FA reveals many small, sometimes inconspicuous leaks; and there is widespread shallow detachment with areas of atrophy of the photoreceptors (see Fig 9-1D).

CLINICAL PEARL

Retinal pigment epithelial changes on optical coherence tomography (OCT) or fundus autofluorescence (FAF) may suggest previous episodes of CSC and resolved subretinal fluid.

Systemic Associations

Central serous chorioretinopathy is associated with stress and with a tense, driven personality. Systemic associations include endogenous hypercortisolism (Cushing syndrome), hypertension, sleep apnea, use of psychopharmacologic medications, and pregnancy. Use of systemic corticosteroids, which may be administered through intramuscular, topical, inhalational, epidural, or even intra-articular routes, is associated with CSC; but, curiously, use of intraocular corticosteroids does not appear to be associated with the condition. Organ transplant recipients and patients with autoimmune disease requiring long-standing, high-dose steroids are particularly vulnerable to the more severe and chronic variants.

Fawzi AA, Holland GN, Kreiger AE, Heckenlively JR, Arroyo JG, Cunningham ET Jr. Central serous chorioretinopathy after solid organ transplantation. *Ophthalmology.* 2006;113(5): 805–813.e5.

Mrejen S, Balaratnasingam C, Kaden TR, et al. Long-term visual outcomes and causes of vision loss in chronic central serous chorioretinopathy. *Ophthalmology.* 2019;126(4): 576–588.

Imaging

The extent of the detachment can be documented with color fundus photographs. FAF imaging shows the accumulation of shed photoreceptor outer segments in the subretinal space, as well as distributed defects of the RPE. It has been theorized that the white dots seen under the retina are macrophages with fluorophores from phagocytized outer segments (Fig 9-2). Eyes with chronic CSC can display descending tracts during both FA and FAF imaging (Fig 9-3). Enhanced depth imaging OCT (EDI-OCT) shows thickening of the choroid and, in areas where thickening is most prominent, posterior loculation of fluid in the deep choroid. Figure 9-4 shows the internal structure of a healthy choroid, and Figure 9-5 shows the choroid in 1 healthy eye and in 3 eyes with CSC.

Although ICGA can reveal choroidal vascular hyperpermeability (Fig 9-6), it has largely been supplanted by OCT, even for detecting possible coexisting choroidal neovascularization (CNV), which may be present in up to 20% of cases in individuals older than 50 years. OCT angiography seems to be adept at detecting secondary CNV that may develop in these patients.

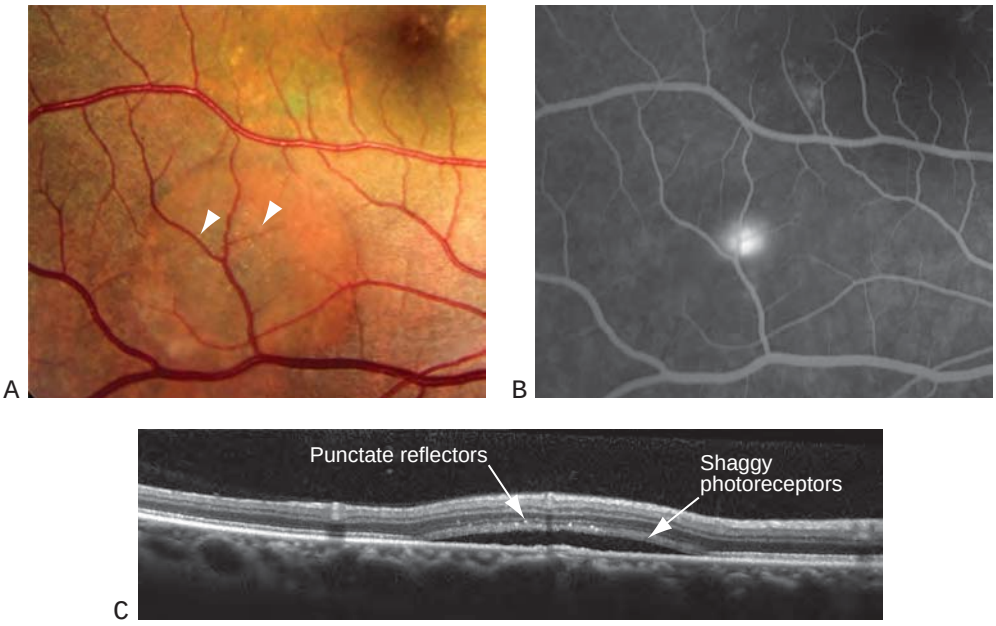

Figure 9-2 Central serous chorioretinopathy with white dots. **A,** Fundus photograph shows an ovoid elevation of the retina with white dots on the undersurface *(arrowheads)*. **B,** FA reveals a single leakage point. **C,** The elevated retina, seen in cross section, has a thick coat on its inner surface that has autofluorescent characteristics consistent with retinal outer segment–derived fluorophores. These fluorophores are therefore considered to be derived from the outer segments that could not be phagocytized by the retinal pigment epithelium (RPE) because of the physical separation, caused by the fluid, between the retina and RPE. The region of shaggy photoreceptors contains punctate dots that are highly reflective; it has been theorized that these dots are macrophages. *(Courtesy of Richard F. Spaide, MD.)*

Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina.* 2009;29(10): 1469–1473.

Spaide RF, Klancnik JM Jr. Fundus autofluorescence and central serous chorioretinopathy. *Ophthalmology.* 2005;112(5):825–833.

Differential Diagnosis

Other entities that may be considered in the differential diagnosis of CSC include type 1 CNV and polypoidal choroidal vasculopathy (PCV; see Chapter 4), which is a variant of type 1 CNV. The FA findings can overlap significantly; both entities show leakage of fluorescein, and the visualization of the structures underlying the RPE is poor. If CNV is present, OCT demonstrates an irregular wavy, shallow elevation of the RPE by a layer of material with heterogeneous reflectivity. The neovascularization seen in association with CSC is generally easy to detect with OCT angiography. What complicates the issue, particularly regarding treatment, is that type 1 CNV and PCV appear to be associated with CSC; they may be its sequelae.

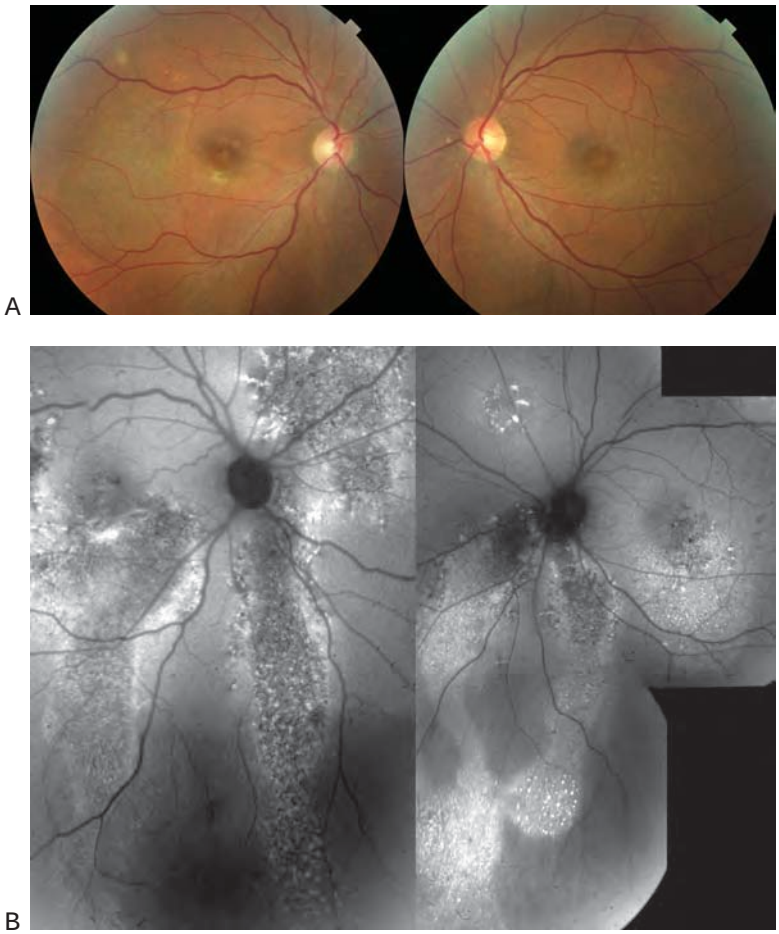

Figure 9-3 Autofluorescence abnormalities in CSC. **A,** Fundus photographs show the right and left eyes of a patient with CSC. Although subtle pigmentary changes are visible, it can be difficult to discern where fluid has accumulated. **B,** Autofluorescent images show widespread abnormalities induced by the presence of subretinal fluid, particularly the descending tracts created by the fluid. *(Reproduced with permission from Elsevier. Imamura Y, Fujiwara T, Spaide RF. Fundus autofluorescence and visual acuity in central serous chorioretinopathy.* Ophthalmology. *2011;118(4):700–705. Copyright 2011.)*

Pachychoroid spectrum and its evolving nomenclature

The widespread utilization of EDI-OCT has facilitated quantitative evaluation of the choroid and, with it, the recognition of a thick, or *pachy,* choroid phenotype, which is commonly seen in CSC. The spectrum of disease encompassed in this entity ranges from pigment epithelial changes in the setting of thick, poorly tessellated choroid *(pachychoroid pigment epitheliopathy)* to *pachyvessels,* which on cross-sectional OCT appear to compress and obliterate the overlying choriocapillaris, to PCV (see Chapter 4 for further discussion). Ophthalmologists have recently recognized that increased choroidal thickness may not be universally present in these eyes and have moved toward a more pathogenesis-based definition, with the understanding that these pachyvessels are actually dilated anastomotic

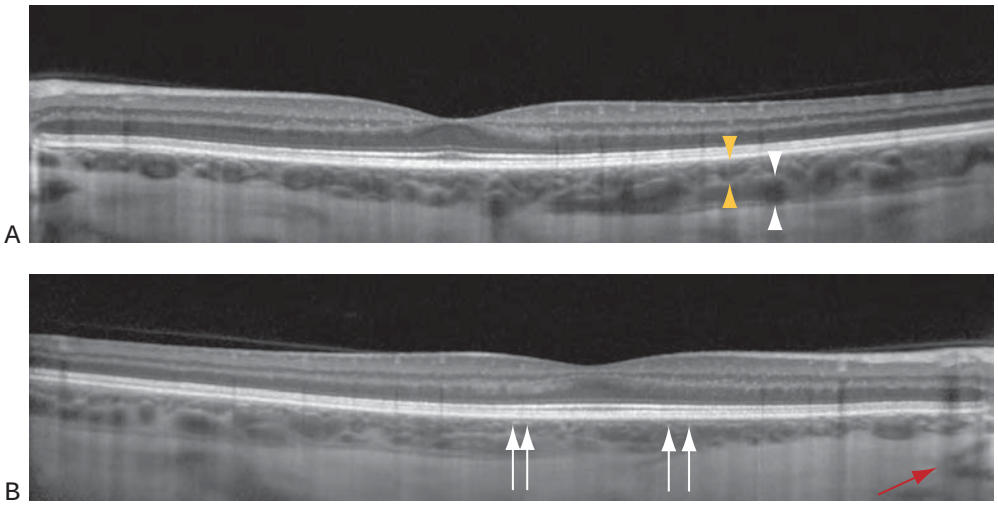

Figure 9-4 The internal structure of the healthy choroid, depicted on enhanced depth imaging optical coherence tomography (EDI-OCT). The choroidal vessels decrease in diameter from the outer to the inner choroid. **A,** The larger vessels *(white arrowheads)* are dark in the center with a thick hyperreflective wall. The medium-sized vessels *(yellow arrowheads)* have a smaller hyporeflective area in the center and a hyperreflective wall. **B,** As vessel diameter decreases, the central hyporeflective area decreases until it is not visible. At that size, the vessel appears as a white hyperreflective structure *(white arrows)*. Note the delineation of the hyporeflective line near the junction with the inner sclera, which appears to be in the suprachoroidal space. The *red arrow* points to a vessel coursing through the sclera. *(Reproduced with permission from Elsevier. Mrejen S, Spaide RF. Optical coherence tomography: imaging of the choroid and beyond.* Surv Ophthalmol. *2013;58(5):387–429. Copyright 2013.)*

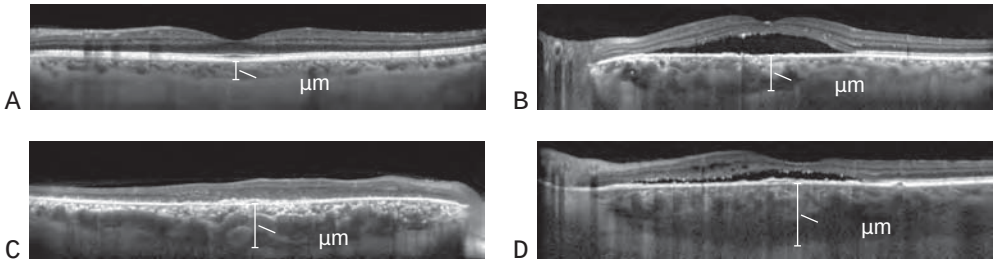

Figure 9-5 The choroid is seen in cross section using EDI-OCT. Subfoveal choroidal thickness was measured vertically from the outer border of the RPE to the inner border of the sclera *(brackets)* in a healthy eye in a 55-year-old man **(A)** and in 3 representative eyes with CSC: in a 44-year-old man **(B),** a 57-year-old man **(C),** and a 63-year-old man **(D).** *(Reproduced with permission from Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy.* Retina. *2009;29(10):1469–1473. doi:10.1097/IAE.0b013e3181be0a83)*

venous channels that run across the choroidal watershed zones, traversing the macula. These observations signal choroidal venous insufficiency as the potential unifying underlying pathogenesis of these entities.

Cheung CMG, Lee WK, Koizumi H, Dansingani K, Lai TYY, Freund KB. Pachychoroid disease. *Eye (Lond).* 2019;33(1):14–33.

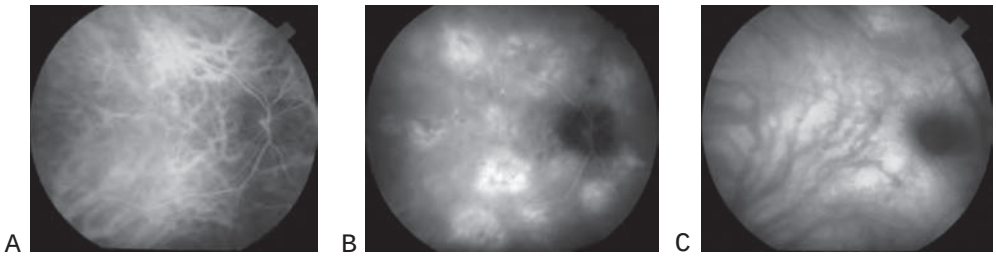

Figure 9-6 Stages of indocyanine green angiography (ICGA) in CSC. **A,** Early after injection, the dye can be seen within the choroidal vessels. **B,** During the middle phase of the angiogram, choriocapillaris hyperpermeability results in the appearance of multiple hyperfluorescent clouds. **C,** Later in the angiogram, the dye has largely been removed from the choroidal vessels. Dye that has leaked into the stroma has diffused posteriorly, silhouetting the larger choroidal vessels. *(Reproduced with permission from Spaide RF, Hall L, Haas A, et al. Indocyanine green videoangiography of older patients with central serous chorioretinopathy.* Retina. *1996;16(3):203–213. doi:10.1097/00006982-199616030-00004)*

Matsumoto H, Hoshino J, Mukai R, et al. Vortex vein anastomosis at the watershed in pachychoroid spectrum diseases. *Ophthalmol Retina.* 2020;4(9):938–945.

Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. *Retina.* 2013;33(8):1659–1672.

Treatment

Central serous chorioretinopathy is generally self-limited and resolves spontaneously, with the majority of patients attaining excellent visual results. However, it can be destructive in some chronic cases, causing visually significant scotomata. *Verteporfin photodynamic therapy (PDT),* whether at full fluence or, more commonly, reduced fluence, has been shown to decrease or eliminate subretinal fluid, decreases choroidal thickness, and reduces choroidal vascular hyperpermeability. Treatment is guided by either FA or ICGA, and a sufficiently large spot size is used to cover the main leakage point(s) with a surrounding safety margin of 1000 μm. This therapy (at full fluence, in studies of age-related macular degeneration) is associated with a 4% risk of vision decrease. CSC may recur after successful PDT, and therapy can be repeated safely, especially if lower fluence is used and the lesion is extrafoveal.

Laser photocoagulation therapy is no longer preferred for CSC, as secondary CNV occurred in the immediate postoperative period in up to 2% of eyes treated with this modality. Moreover, unlike PDT, photocoagulation has no effect on choroidal thickness.

Use of mineralocorticoid receptor antagonists (eplerenone or spironolactone) has shown some benefit in anecdotal reports. However, a recent randomized placebo-controlled trial using eplerenone in chronic CSC demonstrated no benefit with the medication (25 mg/day for 1 week, increasing to 50 mg/day for up to 12 months).

Lotery A, Sivaprasad S, O'Connell A, et al. Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2020;395(10220):294–303.

Maruko I, Iida T, Sugano Y, Ojima A, Ogasawara M, Spaide RF. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. *Ophthalmology.* 2010;117(9):1792–1799.

Choroidal Perfusion Abnormalities

The choroid receives its arterial supply from approximately 20 short posterior ciliary arteries and 2 anterior ciliary arteries. A network of branching arterioles distributes the blood throughout the choroid in a segmental fashion, ultimately leading to the choriocapillaris, and helps reduce the blood pressure as well. Although the vessels in the choriocapillaris exhibit relatively uniform patterns in any given region of the eye, the pressure gradients imposed by the feeding arterioles and draining venules establish a lobular perfusion pattern. Abnormalities in choroidal blood flow can be divided into several main categories based on the underlying disease process.

Arteritic Disease

In arteritic diseases such as *giant cell arteritis* (Figs 9-7, 9-8) or *granulomatosis with polyangiitis* (formerly called *Wegener granulomatosis;* Fig 9-9), inflammatory occlusion can cause sectorial areas of nonperfusion. FA or ICGA is typically performed in cases in which an arteritic cause of vision loss is suspected; flow defects in the choroid are often undetected by ophthalmoscopy alone. Patchy and delayed choroidal filling, especially around the optic nerve, is characteristic of arteritic ischemic optic neuropathy (see Fig 9-7).

Nonarteritic Disease

Nonarteritic problems with blood flow can occur as a result of embolic or systemic disease or as a manifestation of severe hypertension. Emboli from the heart, injection of corticosteroids or calcium hydroxylapatite, and intravascular coagulation all have the potential to occlude choroidal vessels. Vascular occlusion can also occur in patients with lupus anticoagulants.

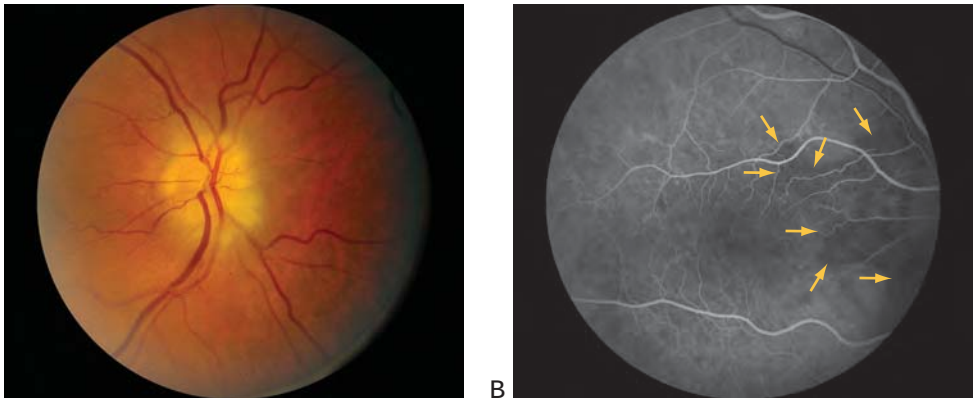

Figure 9-7 Arteritic anterior ischemic optic neuropathy with delayed choroidal filling. **A,** Color fundus photograph showing pallid edema of the right optic nerve head. **B,** Early venous phase of the angiogram showing incomplete filling of the choroidal lobule surrounding the optic nerve *(arrows)*. Normally, choroidal filling is complete by the early venous to mid-venous phase. *(Courtesy of Nicholas J. Volpe, MD.)*

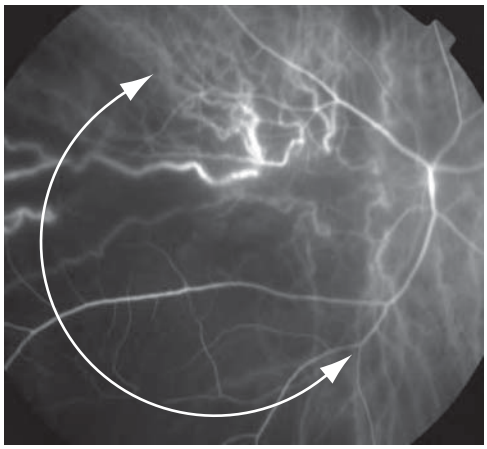

Figure 9-8 Giant cell arteritis. ICGA image taken 1 day after this patient had severe vision loss secondary to arteritic anterior ischemic optic neuropathy. A wedge-shaped area of choroidal nonperfusion is apparent *(curved arrow)*. The apex of the wedge of nonperfusion points toward the area of the occluded short posterior ciliary artery. *(Courtesy of Richard F. Spaide, MD.)*

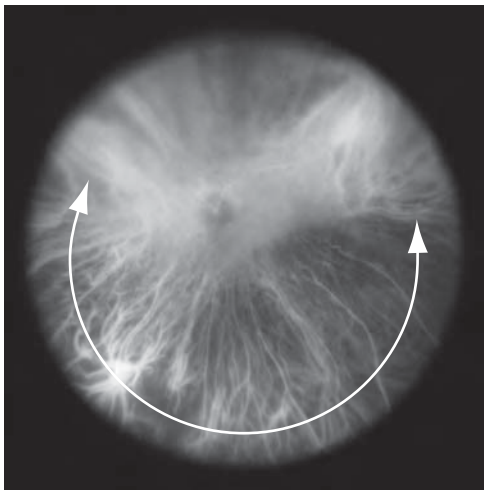

Figure 9-9 Granulomatosis with polyangiitis (formerly, Wegener granulomatosis). The early phase of wide-angle ICGA of the left eye reveals a widespread filling defect of the arterioles and choriocapillaris in the inferior fundus *(curved arrow)* and in a segmental area of the superior fundus *(asterisk)*. *(Reproduced with permission from Elsevier. Iida T, Spaide RF, Kantor J. Retinal and choroidal arterial occlusion in Wegener's granulomatosis.* Am J Ophthalmol. *2002;133(1):151–152. Copyright 2002.)*

Thrombotic thrombocytopenic purpura causes a classic pentad of findings: (1) microangiopathic hemolytic anemia, (2) thrombocytopenia, (3) fever, (4) neurologic dysfunction, and (5) renal dysfunction. Patients with this condition may have multifocal yellow placoid areas and associated serous detachment of the retina. Similar fundus findings may occur in patients with *disseminated intravascular coagulation,* in which consumption of coagulation proteins, involvement of cellular elements, and release of fibrin degradation products lead to hemorrhage from multiple sites and ischemia from microthrombi.

Similar fundus findings also occur in patients with acute hypertension, such as malignant hypertension or eclampsia. In addition to causing retinal and optic nerve head abnormalities, these disorders commonly lead to serous detachment of the retina associated with areas of yellow placoid discoloration of the RPE (Fig 9-10). The perfusion

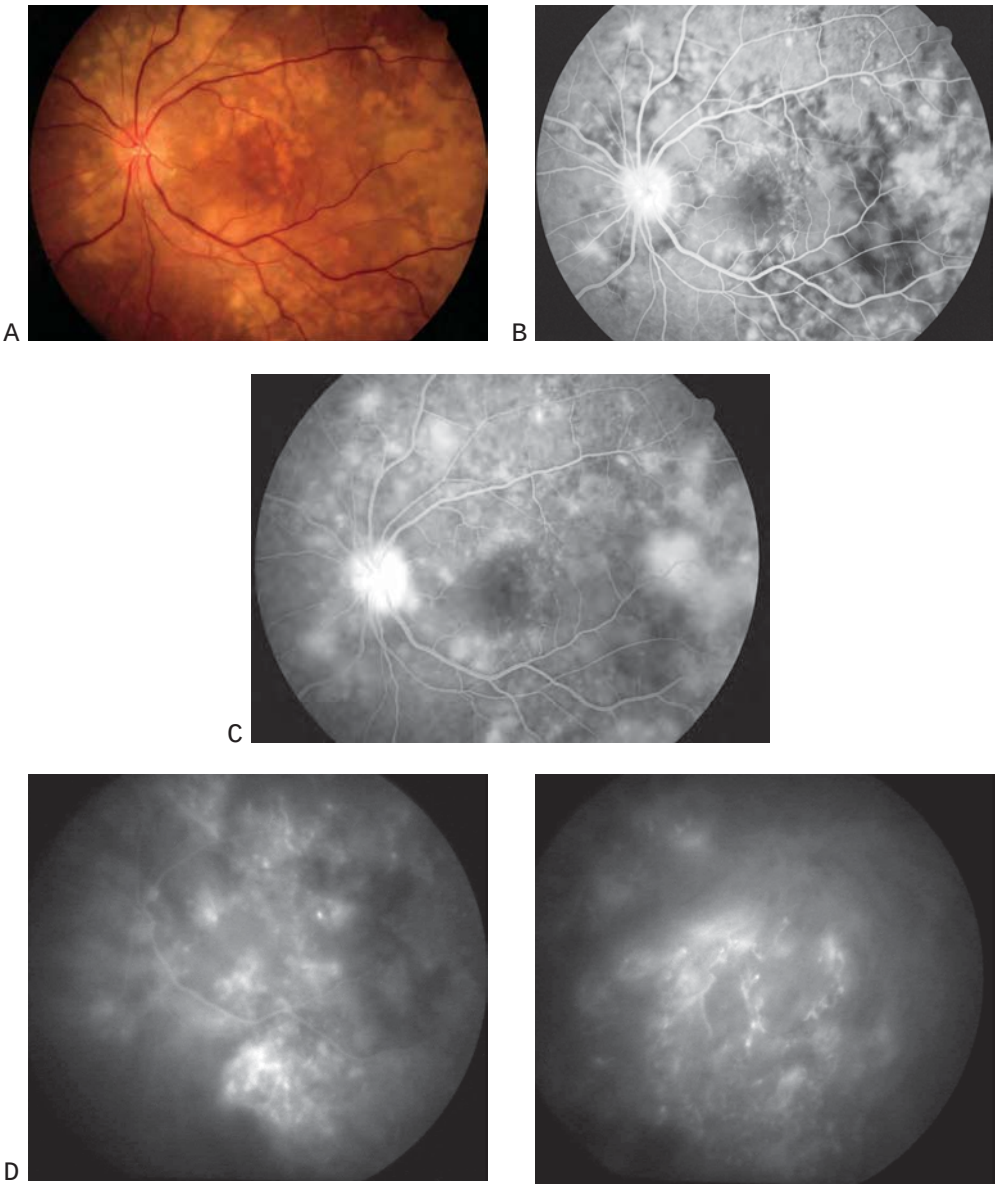

Figure 9-10 Preeclampsia with hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. **A,** Fundus photograph reveals a serous detachment of the retina and multiple yellowish placoid areas at the level of the RPE and inner choroid. **B,** Early-phase FA image shows reticular patterns of decreased choroidal perfusion bordering areas of hyperfluorescence. Early leakage from the level of the RPE is evident and becomes more apparent in the later phases of the study **(C).** There is also staining of and leakage from the optic nerve. **D,** ICGA image shows profound choroidal vascular filling defects alternating with areas of abnormal vessel leakage and staining, a rare finding. **E,** In the late phase, numerous arterioles show staining of their walls, indicating severe vascular damage. *(Reproduced with permission from Spaide RF, Goldbaum M, Wong DW, Tang KC, Iida T. Serous detachment of the retina.* Retina. *2003;23(6):820–846.)*

abnormalities may range from focal infarction of the choriocapillaris to fibrinoid necrosis of larger arterioles. Resolution of smaller infarcts, which initially appear tan in color, produces small patches of atrophy and pigmentary hyperplasia called *Elschnig spots* (Fig 9-11). Infarction of an arteriole can lead to *Siegrist streaks,* which are hyperpigmented flecks arranged linearly along choroidal vessels. Posterior ciliary artery occlusions can result in wedge-shaped zones of choroidal infarction called *Amalric triangles*.

Choriocapillaris Blood Flow Abnormalities

Choroidal blood flow defects affect lobule-sized areas of the choroid or areas supplied by arterioles and therefore affect 1 to several choroidal lobules. Many ocular diseases (eg, acute

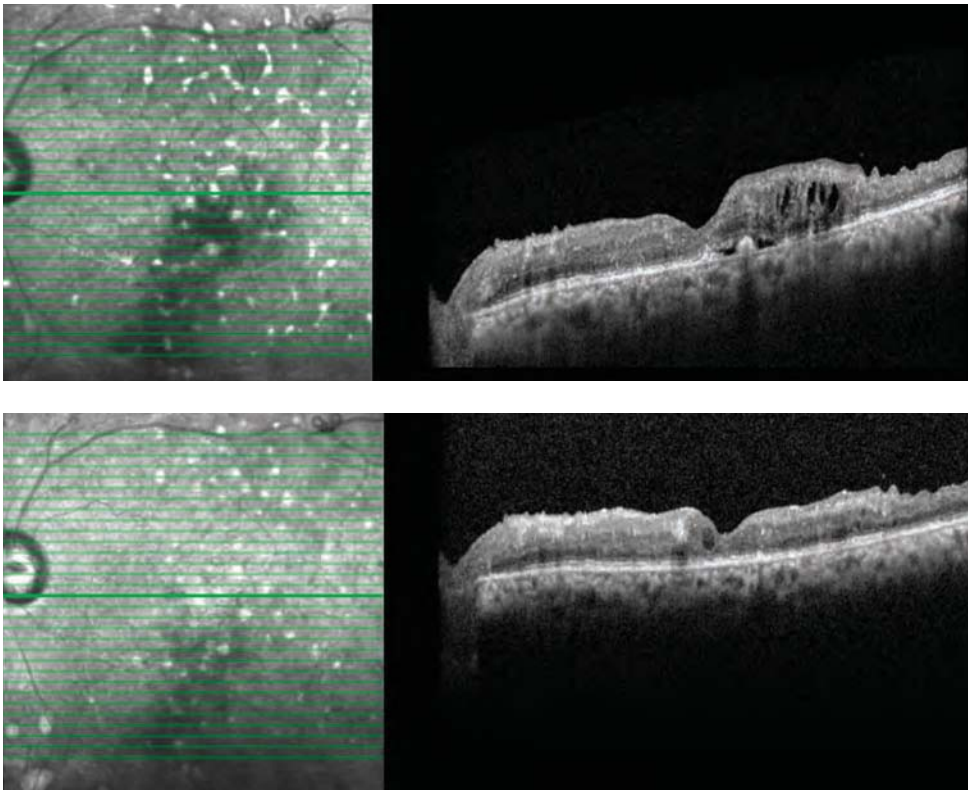

Figure 9-11 OCT images from a 43-year-old man with a history of hypertension, type 2 diabetes, chronic kidney disease, and proliferative diabetic retinopathy who had previously undergone vitrectomy for bilateral traction retinal detachment. He presented to the emergency department with a hypertensive urgency requiring admission and initiation of dialysis for acute renal failure. **A,** Imaging performed 2 months after these events. Notably, hyperreflective lesions on the infrared (IR) image *(to the right of the OCT image)* were new and not present at prior ophthalmologic visits. OCT shows sub-RPE deposits and subretinal and intraretinal fluid, consistent with hypertensive choroidopathy, and Elschnig spots. The patient was observed without retinal intervention while blood pressure and renal issues resolved. **B,** Vision stabilized and fluid resolved without further ocular intervention, with some fading of the IR hyperreflective lesions and inner retinal thinning over the following 18 months. *(Courtesy of Amani Fawzi, MD.)*

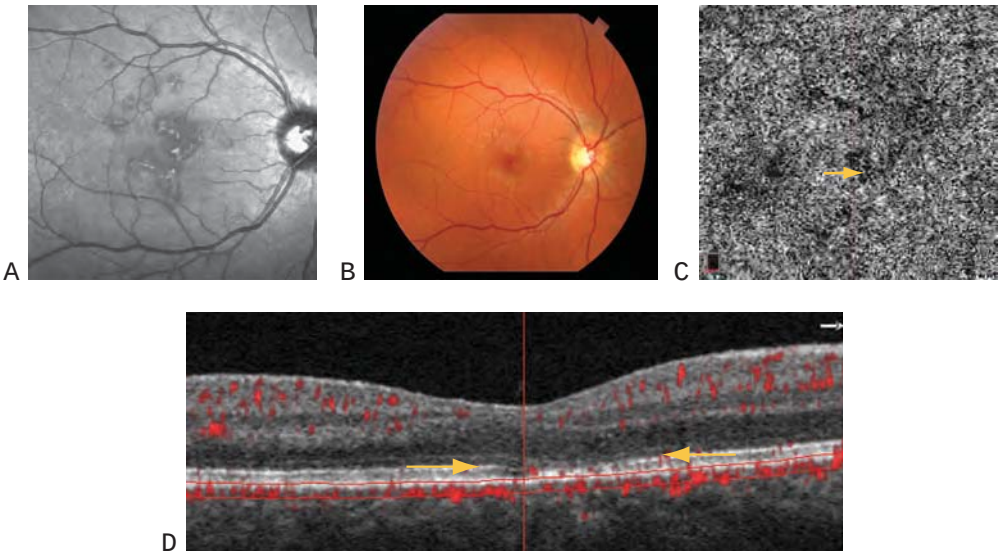

Figure 9-12 Resolving case of acute posterior multifocal placoid pigment epitheliopathy (APMPPE). **A,** Infrared image shows the hallmark jigsaw pattern pigmentary changes. **B,** These changes are visible as hyporeflective lesions on the fundus photograph. **C,** OCT angiography focused on the choriocapillaris shows focal flow deficit *(arrow)*. **D,** Corresponding outer retinal lesion on OCT is seen as thinning and disruption of the ellipsoid zone *(between arrows)*. *(Courtesy of Amani Fawzi, MD.)*

posterior multifocal placoid pigment epitheliopathy; Fig 9-12) characteristically produce lesions that are the putative size of a choroidal lobule. On OCT angiography at the level of the choriocapillaris, multiple areas of signal voids are frequently seen and are consistent with decreased perfusion, which is best depicted by this modality. These areas increase in size and number with age; they are also larger and more numerous in patients with hypertension, pseudodrusen, or, interestingly, late age-related macular degeneration in the *fellow* eye. These characteristic OCT angiographic findings are consistent with histologic studies showing a growing number of ghost vessels in the choriocapillaris (a sign of vessel death), basal linear deposits, and subretinal drusenoid deposits with increasing age. Some diseases are known to be associated with both RPE atrophy and geographic atrophy; they include pseudoxanthoma elasticum and maternally inherited diabetes mellitus and deafness. Even in the absence of RPE atrophy, patients with these diseases can exhibit remarkable loss of the choriocapillaris (Fig 9-13).

Hayreh SS. Posterior ciliary artery circulation in health and disease: the Weisenfeld lecture. *Invest Ophthalmol Vis Sci.* 2004;45(3):749–757; 748.

Increased Venous Pressure

In rare cases, choroidal blood flow abnormalities may be related to venous outflow problems, including those caused by *dural arteriovenous malformations* or *carotid-cavernous*

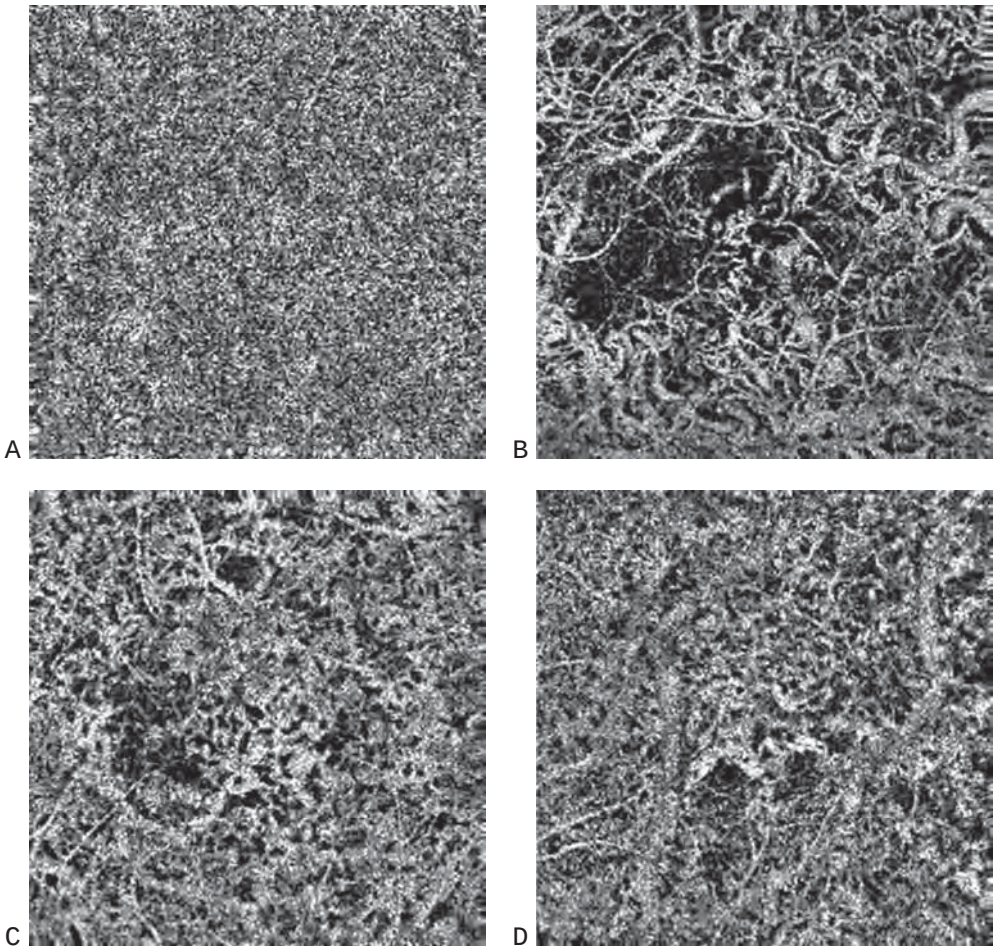

Figure 9-13 OCT angiography images of the choriocapillaris in a healthy patient and in patients with pseudoxanthoma elasticum (PXE). **A,** Healthy 63-year-old patient with no ocular disease. **B–D:** Three different patients with PXE: a 55-year-old patient **(B)** and two 63-year-old patients **(C, D).** The eyes with PXE show no evidence of RPE atrophy but have remarkable loss of the choriocapillaris. *(Reproduced with permission from Spaide RF. Choriocapillaris signal voids in maternally inherited diabetes and deafness and in pseudoxanthoma elasticum.* Retina. *2017;37(11):2008–2014. doi:10.1097/IAE.0000000000001497)*

fistulas (Fig 9-14). Diagnosis of choroidal blood flow abnormalities often requires dye-based angiography and occasionally a stethoscope (to detect a bruit). These patients should be referred for appropriate medical evaluation.

Age-Related Choroidal Atrophy

The thickness of the choroid decreases with higher levels of myopia and increasing age. In some older patients, the choroid is much thinner than expected. The eyes of these

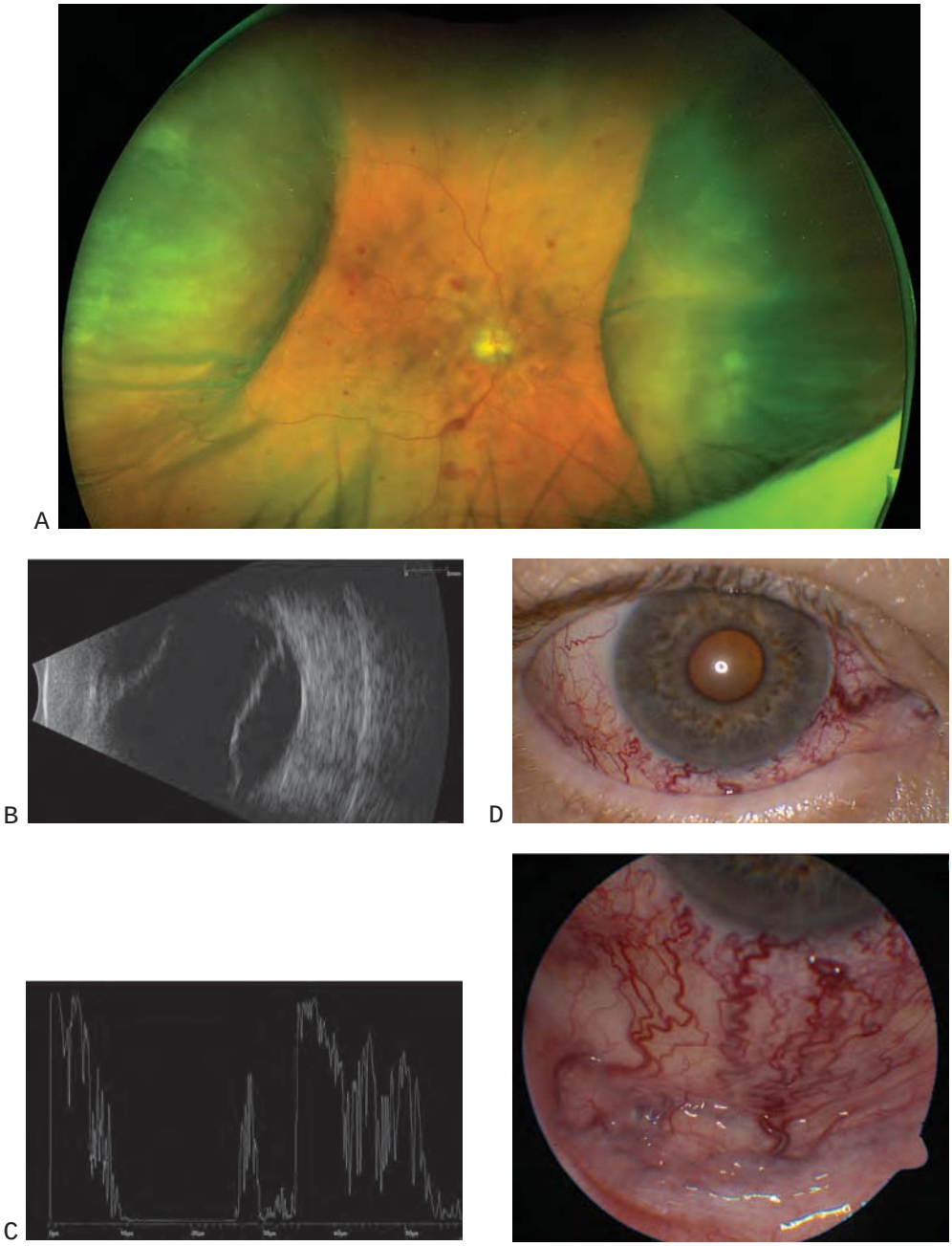

Figure 9-14 Constellation of classic findings with carotid-cavernous fistulas. **A,** Wide-angle color photograph from an older adult patient who was referred for "multiple choroidal melanomas" found incidentally on examination. **B,** B-scan shows large choroidals. **C,** Diagnostic A-scan shows very low internal reflectivity, consistent with serous choroidals rather than tumor masses. **D, E,** The patient was noted to have a red eye. On very specific questioning, he revealed that he had fallen and hit his head approximately 9 months earlier, and the eye began to turn red approximately 1–2 months after the fall. The patient was hypertensive. These images show classic corkscrew vessels. Patients with a carotid-cavernous fistula can also have a hyporeactive pupil from anterior segment ischemia, as was the case with this patient. *(Courtesy of Anthony B. Daniels, MD, MSc.)*

individuals tend to have *pseudodrusen,* which resemble drusen in appearance but are caused by collections of subretinal drusenoid deposits above the RPE. Like eyes with drusen, eyes with subretinal drusenoid deposits have an increased risk of CNV, particularly types 2 and 3, and geographic atrophy. More than 90% of eyes with geographic atrophy also have pseudodrusen. In contrast with patients with drusen, patients with subretinal drusenoid deposits perform more poorly on microperimetry, and dark adaptation is markedly prolonged in this group (Figs 9-15, 9-16).

Spaide RF. Disease expression in nonexudative age-related macular degeneration varies with choroidal thickness. *Retina.* 2018;38(4):708–716.

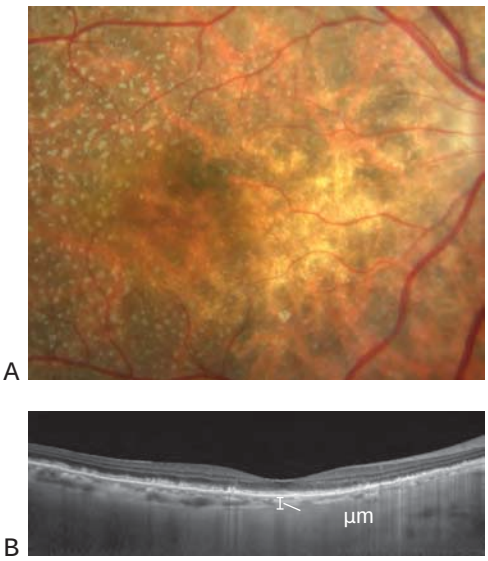

Figure 9-15 Pseudodrusen and the choroid. **A,** Fundus photograph shows an eye with prominent pseudodrusen. **B,** The true nature of the pseudodrusen is seen as subretinal drusenoid deposits. The subfoveal choroidal thickness is 121 µm. The choroid is thinner in eyes with pseudodrusen than in those with drusen. *(Reproduced with permission from Spaide RF. Disease expression in nonexudative age-related macular degeneration varies with choroidal thickness.* Retina. *2018;38(4):708–716. doi:10.1097/IAE.0000000000001689)*

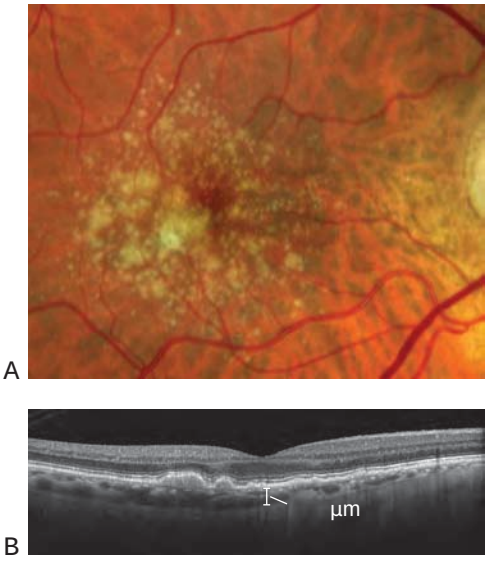

Figure 9-16 Drusen and the choroid. **A,** An eye with typical soft drusen. **B,** The subfoveal choroidal thickness is 162 µm. *(Reproduced with permission from Spaide RF. Disease expression in nonexudative age-related macular degeneration varies with choroidal thickness.* Retina. *2018;38(4):708–716. doi:10.1097/IAE.0000000000001689)*

Choroidal Folds

Folds in the choroid, sometimes called *chorioretinal folds,* occur for various reasons, including secondary to disease. Forces external to the eye, such as an indenting tumor or thyroid eye disease, can cause choroidal folds. The sclera may be thickened by posterior scleritis, thereby crowding the choroid (Fig 9-17). A relatively common phenomenon, which is poorly characterized, is the development of choroidal folds in middle-aged adults, with acquired hyperopia occurring in some of these individuals. Engorgement of the choroid causes an expansion of the tissue, which is limited by the sclera. Reduced intraocular pressure, occurring most commonly as a postoperative complication, can cause ciliochoroidal effusions and curvilinear choroidal folds in the posterior pole, a condition known as *hypotony maculopathy*. Use of medications such as topiramate can cause idiopathic swelling of the choroid resulting in chorioretinal folds and ciliochoroidal effusions without hypotony. Increased intracranial pressure can cause papilledema resulting in fine folds that course circumferentially around the optic nerve head; these folds are called *Patton lines*. Localized choroidal folds can be seen in association with CNV, choroidal neoplasms, and scleral buckles (Table 9-1).

Spaide RF, Goldbaum M, Wong DW, Tang KC, Iida T. Serous detachment of the retina. *Retina.* 2003;23(6):820–846.

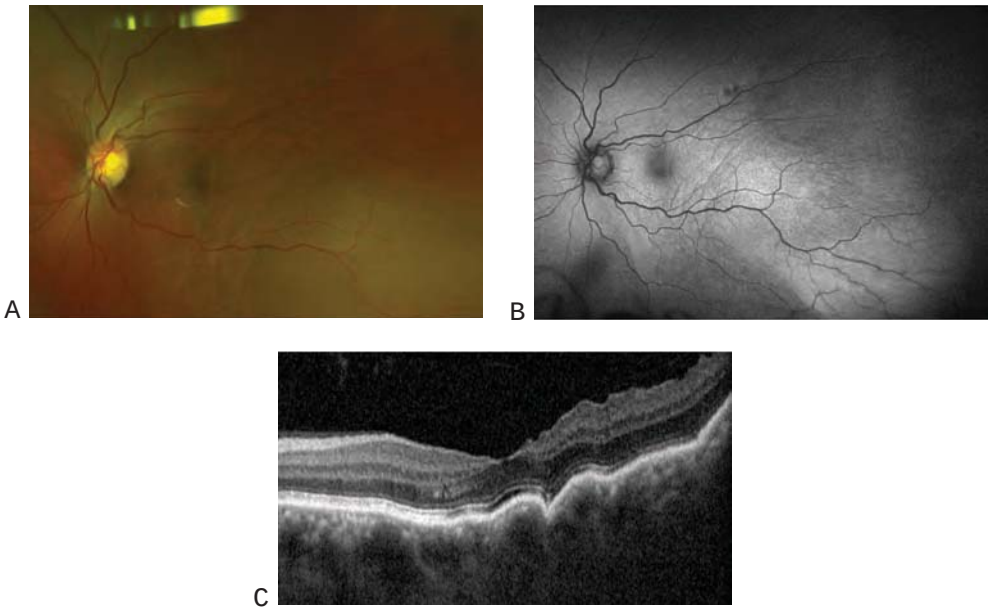

Figure 9-17 Choroidal folds in a patient with nodular posterior scleritis. **A,** Fundus photograph shows subtle striae associated with choroidal folds extending through the temporal macula. **B,** Fundus autofluorescence highlights the striae of folds with alternating hyper- and hypoautofluorescent changes emanating from the inferotemporal area of posterior nodular scleritis. **C,** Spectral-domain OCT shows characteristic undulations of RPE consistent with choroidal folds and a thickening choroid consistent with posterior scleritis. *(Courtesy of Avni P. Finn, MD, MBA.)*

Table 9-1 Differential Diagnosis of Choroidal Folds

Etiology of Choroidal Folds	Characteristic
Focal choroidal mass/neovascularization	Usually radiating from center of the lesion
Hyperopia	Usually horizontal in posterior pole/papillomacular bundle; extreme example in posterior microphthalmia
Hypotony	Ciliochoroidal effusions and curvilinear choroidal folds in the posterior pole
Idiopathic; theories include scleral calcification and/or inflammation	Oblique, along the insertion of the oblique muscles
Medications (eg, topiramate)	Ciliochoroidal effusions without hypotony
Papilledema	Patton lines, concentric with optic nerve head
Retrobulbar mass/orbital hardware	Varies according to indent location
Thyroid eye disease	Nonspecific

Choroidal Hemangiomas

Isolated choroidal hemangiomas are reddish-orange, well-circumscribed tumors of varying thickness that can affect the macula either directly or through subretinal fluid (Fig 9-18). Circumscribed hemangiomas transilluminate readily and exhibit highly echographic patterns on ultrasonography. During dye-based angiography, hemangiomas show very early filling of large vessels.

Sturge-Weber syndrome (encephalofacial hemangiomatosis) causes a diffuse hemangioma that, in children, may present first as glaucoma or amblyopia. The areas corresponding to the hemangioma typically appear reddish orange on ophthalmoscopy, a pattern referred to as "tomato ketchup fundus"; the underlying choroidal markings are not visible. The choroidal hemangiomas in Sturge-Weber syndrome are sometimes overlooked because they are diffuse and may blend imperceptibly into adjacent normal choroid. An ipsilateral facial nevus flammeus (port-wine birthmark) is also typically present in patients with this syndrome. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* and Section 6, *Pediatric Ophthalmology and Strabismus,* for further discussion.

Hemangiomas have been treated with laser photocoagulation, cryopexy, external beam and plaque radiation, and PDT.

Blasi MA, Tiberti AC, Scupola A, et al. Photodynamic therapy with verteporfin for symptomatic circumscribed choroidal hemangioma: five-year outcomes. *Ophthalmology.* 2010;117(8):1630–1637.

Madreperla SA, Hungerford JL, Plowman PN, Laganowski HC, Gregory PT. Choroidal hemangiomas: visual and anatomic results of treatment by photocoagulation or radiation therapy. *Ophthalmology.* 1997;104(11):1773–1778.

Uveal Effusion Syndrome

Uveal effusion syndrome is a rare condition in which abnormal scleral composition or thickness reduces transscleral aqueous outflow, inhibiting net fluid movement through

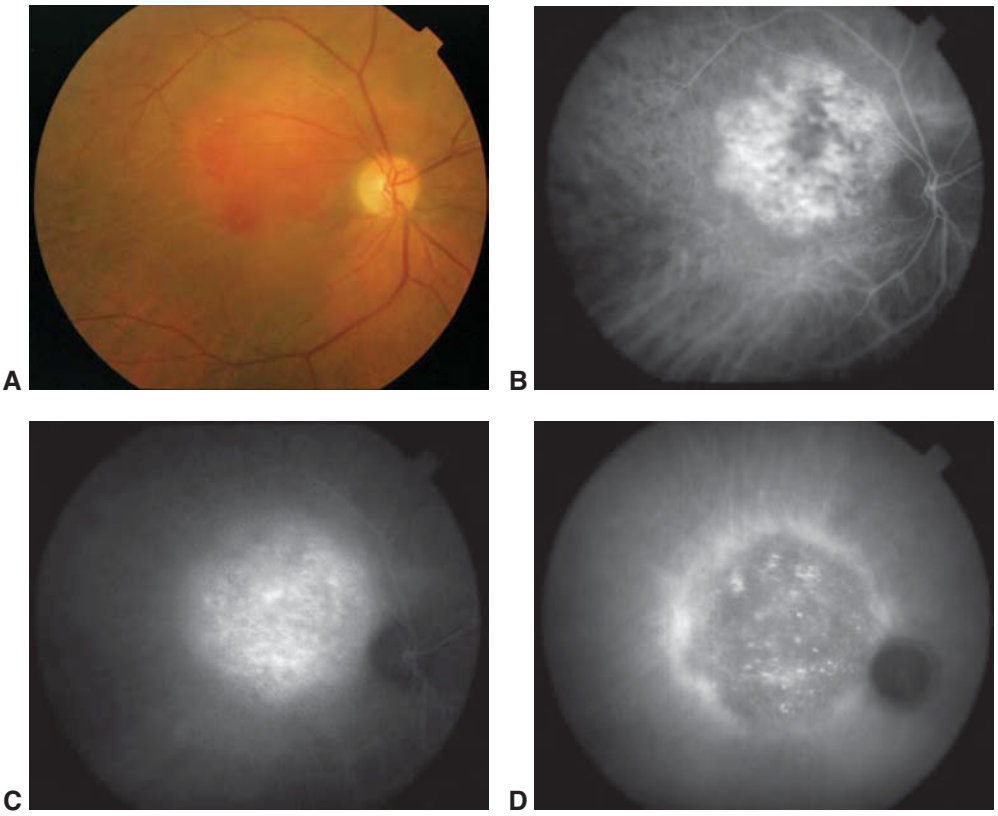

Figure 9-18 Choroidal hemangioma. **A,** Fundus photograph of the typical reddish-orange elevation of a circumscribed choroidal hemangioma. **B,** Soon after injection of ICG dye, the vascular composition of the hemangioma is revealed. **C,** Hyperfluorescence of the tumor occurs in the middle phase of the angiographic study from a combination of dye within and leakage from the vessels of the hemangioma. **D,** In the late phase of the study, the dye "washes out" of the lesion, leaving hyperfluorescent staining in the adjacent tissues. *(Reproduced with permission from Spaide RF, Goldbaum M, Wong DW, Tang KC, Iida T. Serous detachment of the retina.* Retina. *2003;23(6):820–846.)*

the posterior eye wall. Choroidal and ciliary body thickening, RPE alterations, and exudative retinal detachment may occur. The choroid is often so thick that OCT imaging is not possible, but the gross thickening can be imaged with ultrasonography. FA usually shows a leopard-spot pattern of hypofluorescence without focal leakage (Fig 9-19). Uveal effusion syndrome is a diagnosis of exclusion, usually made after ruling out all of the more common entities, such as posterior scleritis, and other etiologies of exudative detachments. A high index of suspicion for uveal effusion syndrome should be maintained for young patients with hyperopia. Scleral window surgery may yield anatomical restoration.

Elagouz M, Stanescu-Segall D, Jackson TL. Uveal effusion syndrome. *Surv Ophthalmol.* 2010;55(2):134–145.

Johnson MW, Gass JD. Surgical management of the idiopathic uveal effusion syndrome. *Ophthalmology.* 1990;97(6):778–785.

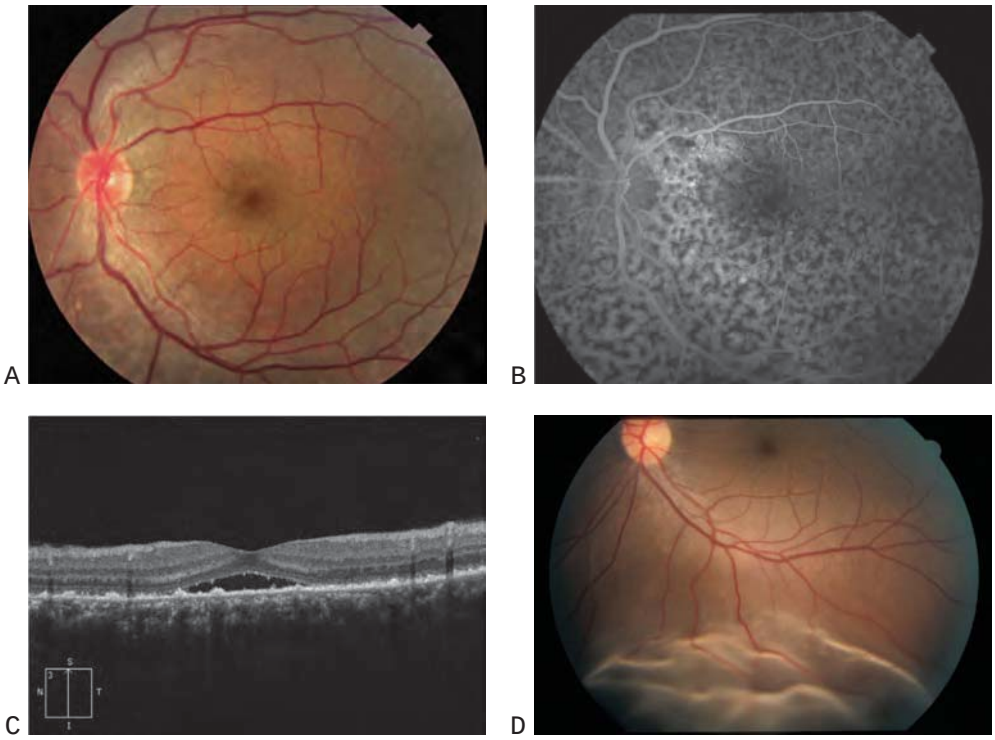

Figure 9-19 Idiopathic uveal effusion syndrome. **A–C:** In this patient's left eye, visual acuity was reduced to 20/70, and results of the systemic workup were negative. **A,** Fundus photograph demonstrates a blunted foveal reflex and irregular, subtle subretinal deposits. **B,** Corresponding FA image reveals a diffuse leopard-spot pattern of blocking with intervening window defects involving the entire posterior pole. **C,** OCT scan reveals a small amount of subfoveal fluid and outer retinal deposits. Not shown is a peripheral serous retinal detachment. **D,** Fundus photograph from a different patient with recent-onset uveal effusion shows the typical appearance of serous retinal detachment syndrome as well as an underlying choroidal detachment, which is common for this condition. *(Parts A–C courtesy of Ronald C. Gentile, MD; part D courtesy of Colin A. McCannel, MD.)*

Bilateral Diffuse Uveal Melanocytic Proliferation

A rare paraneoplastic disorder affecting the choroid, *bilateral diffuse uveal melanocytic proliferation (BDUMP)* causes diffuse thickening of the choroid, "giraffe skin" reddish or brownish choroidal discoloration, serous retinal detachment, and cataracts (Fig 9-20). The bilateral proliferation of benign melanocytes is usually associated with or often heralds systemic cancer. These proliferations can look like large nevi.

Most patients with BDUMP also exhibit nummular loss of the RPE, an anatomical change that differs distinctly from large nevi or thickening of the choroid. These areas of RPE loss are hypoautofluorescent during FAF but hyperfluorescent during FA. OCT shows mounds of residual material, presumed to be persistent RPE cells, between areas of loss. Tumors commonly associated with BDUMP are cancers of the ovary, uterus, and

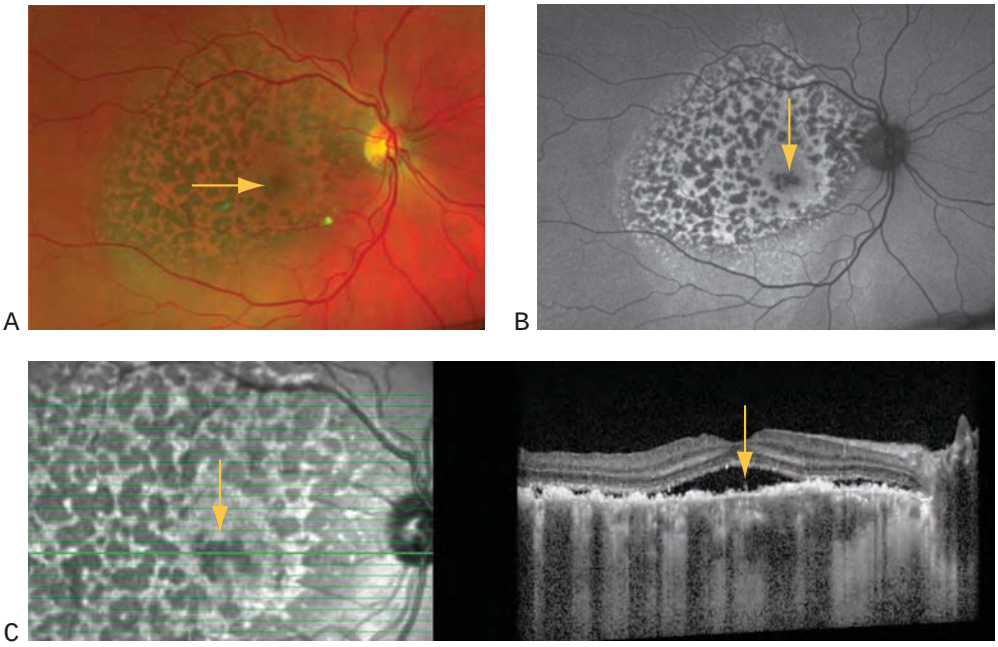

Figure 9-20 Multimodal imaging of bilateral diffuse uveal melanocytic proliferation (BDUMP). **A,** Pseudocolor image (Optos) shows the "giraffe skin" pattern of hypopigmentation and hyperpigmentation *(arrow)*. **B,** Autofluorescence (530 nm) shows that the hyperpigmented areas *(arrow)* correspond to hypoautofluorescence (green autofluorescence) and hyporeflectivity on IR imaging (**C,** *left*). These areas correspond to attenuation of the RPE on OCT (**C,** *right*). In addition, the hyperautofluorescent areas around the attenuation correspond to the hypopigmented areas on the color photograph. **C,** The OCT image highlights the thickened, disorganized choroidal architecture and the thickened RPE (thickened RPE corresponds to the hypopigmented, hyperautofluorescent, and hyperreflective areas on the color, autofluorescence, and IR images, respectively). *(Courtesy of Amani Fawzi, MD.)*

lung, although BDUMP may also occur with cancers of the kidney, colon, pancreas, gallbladder, breast, and esophagus.

Gass JD, Gieser RG, Wilkinson CP, Beahm DE, Pautler SE. Bilateral diffuse uveal melanocytic proliferation in patients with occult carcinoma. *Arch Ophthalmol.* 1990;108(4):527–533.

Wu S, Slakter JS, Shields JA, Spaide RF. Cancer-associated nummular loss of the pigment epithelium. *Am J Ophthalmol.* 2005;139(5):933–935.