CHAPTER 7

Other Retinal Vascular Diseases

Highlights

- Proliferative sickle cell retinopathy occurs most commonly with sickle cell–hemoglobin C disease.
- All Black patients presenting with a traumatic hyphema should be screened for a sickling hemoglobinopathy.
- Cerebellar hemangioblastoma and renal cell carcinoma are the leading causes of death in patients with von Hippel–Lindau syndrome.

Sickle Cell Disease and Retinopathy

Sickle Cell Disease

Sickle cell anemia is the most common inherited blood disorder in the United States. The sickle cell hemoglobinopathies of greatest ocular importance are those in which mutant hemoglobins S, C, or both are inherited instead of hemoglobin A, which is normally predominant in adults (see Part III, Genetics, in BCSC Section 2, *Fundamentals and Principles of Ophthalmology*). Sickle cell hemoglobinopathies are most prevalent in the Black population and affect approximately 10% of African American people (Table 7-1). Thalassemia, in which the α- or β-polypeptide chain is defective, is rare but frequently causes retinopathy.

Table 7-1 Incidence of Sickle Cell Hemoglobinopathies in North America

Hemoglobinopathy	Incidence in Population, %	Incidence of Proliferative Retinopathy in Subgroups
Any sickle hemoglobin	10	—
Sickle cell trait (HbAS)	8	Uncommon
Hemoglobin C trait (HbAC)	2	Uncommon
Homozygous sickle cell (HbSS)	0.4	3%[a]
Sickle cell–hemoglobin C (HbSC)	0.2	33%[a]
Sickle cell–thalassemia (SThal)	0.03	14%[a]
Homozygous C (HbCC)	0.016	Unknown

[a] Approximate.

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Although sickling and solubility tests (sickle cell preparations) are reliable indicators of the presence of hemoglobin S and therefore are excellent for sickle cell anemia screening, these tests do not distinguish between heterozygous and homozygous states in the hemoglobinopathies. Patients who test positive on sickle cell preparations should also undergo hemoglobin electrophoresis testing. See BCSC Section 1, *Update on General Medicine,* for further discussion of sickle cell disease.

Scott AW, Lutty GA, Goldberg MF. Hemoglobinopathies. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Ryan's Retina.* Vol 1. 6th ed. Elsevier/Saunders; 2018:chap 60.

Stages of Sickle Cell Retinopathy

Sickle cell retinopathy has been classified into 5 stages based on the following pathogenetic sequence (stages 1 through 3 are depicted in Fig 7-1):

- peripheral arteriolar occlusions *(stage 1)* leading to
- peripheral nonperfusion and peripheral arteriovenular anastomoses *(stage 2),* which are dilated, preexisting capillary channels
- peripheral sea fan neovascularization *(stage 3),* which may occur at the posterior border of areas of nonperfusion and lead to
- vitreous hemorrhage *(stage 4)* and
- traction (also called *tractional*) retinal detachment *(stage 5)*

Nonproliferative Sickle Cell Retinopathy

The retinal changes in nonproliferative sickle cell retinopathy are caused by arteriolar and capillary occlusion. Anastomosis and remodeling occur in the periphery, as does the resorption of blood around the infarct (see Fig 7-1). Salmon-patch hemorrhages represent areas of intraretinal hemorrhage that occur after a peripheral retinal arteriolar occlusion (Fig 7-2A). Refractile spots are old, resorbed hemorrhages with hemosiderin deposition within the inner retina just beneath the internal limiting membrane (ILM) (Fig 7-2B). Black "sunburst" lesions are localized areas of retinal pigment epithelial hypertrophy, hyperplasia, and pigment migration in the peripheral retina, probably caused by hemorrhage.

Occlusion of parafoveal capillaries and arterioles is one cause of decreased vision in patients with sickle cell retinopathy (Fig 7-3). These changes can be detected on angiography, particularly with optical coherence tomography angiography (OCTA), and may be subtle (Fig 7-4) or catastrophic (Fig 7-5). Spontaneous occlusion of the central retinal artery may also develop in patients with sickle cell hemoglobinopathies.

Proliferative Sickle Cell Retinopathy

Proliferative sickle cell retinopathy (PSR) occurs most commonly with sickle cell–hemoglobin C (also called *HbSC*) disease, with an incidence of approximately 33% (see Table 7-1). It occurs less commonly with sickle cell–thalassemia (SThal), the incidence of which is approximately 14%. Homozygous sickle cell disease (also called *HbSS disease*) results in more systemic complications than the other types of sickle cell disease but has a

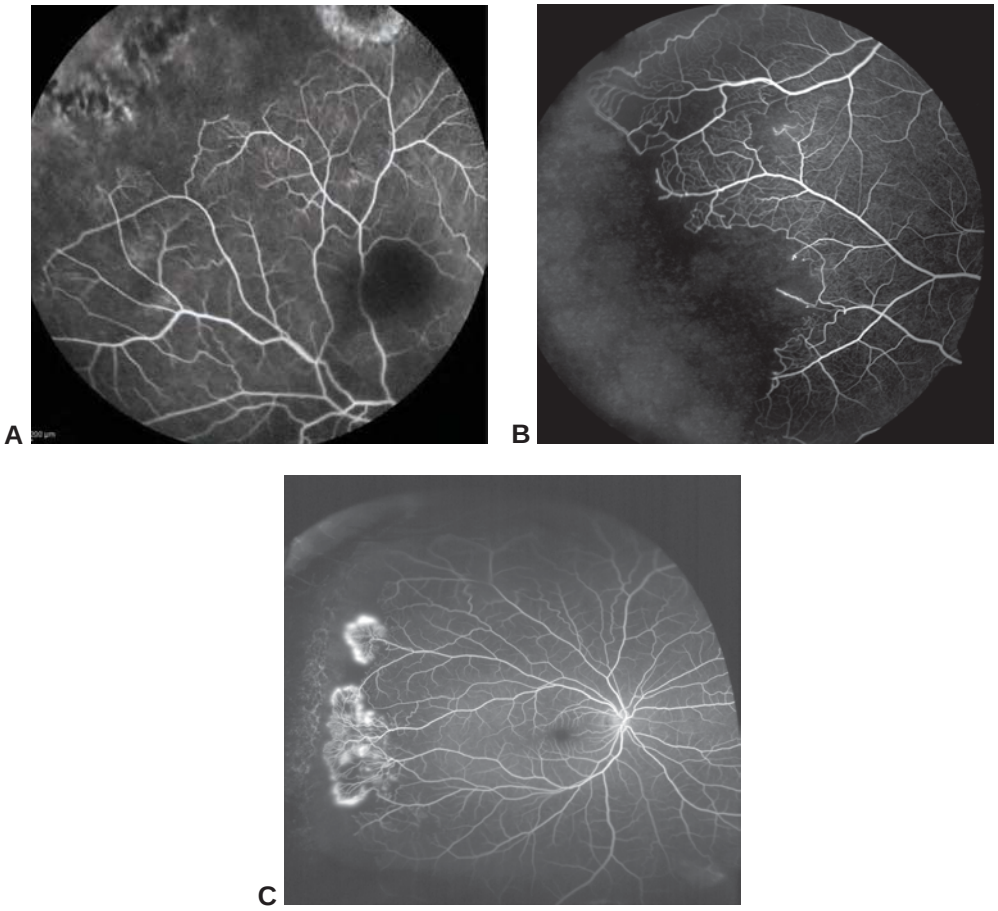

Figure 7-1 Fluorescein angiograms (FAs) showing the first 3 stages of sickle cell retinopathy. **A,** Stage 1: The image shows normal vessels posteriorly but severe capillary dropout throughout the periphery. **B,** Stage 2: FA shows peripheral nonperfusion and dilated arteriovenular anastomosis. **C,** Stage 3: The image shows peripheral retinal neovascularization, consistent with proliferative sickle cell retinopathy. *(These images were originally published in the Retina Image Bank. Part A: Thomas A. Ciulla, MD, MBA. Photograph by Thomas Steele. Sickle Cell Retinopathy. Retina Image Bank, 2015; image number 2566. Parts B and C: Michael P. Kelly, FOPS. Sickle Cell Retinopathy. Retina Image Bank, 2012; image numbers 949, 721. © American Society of Retina Specialists.)*

very low incidence of proliferative retinopathy at approximately 3%. Proliferative retinopathy is rare with sickle cell trait (also called *HbAS*). The ocular complications result from ischemia secondary to infarction of the retinal tissue by means of arteriolar, precapillary arteriolar, capillary, or venular occlusions; they include retinal neovascularization, preretinal or vitreous hemorrhage, and traction retinal detachment.

PSR is one of many retinal vascular diseases in which extraretinal fibrovascular proliferation occurs in response to retinal ischemia. While the neovascularization in eyes with proliferative diabetic retinopathy (PDR) generally begins postequatorially, the neovascularization in PSR is located more peripherally (Fig 7-6). Another way in which PSR

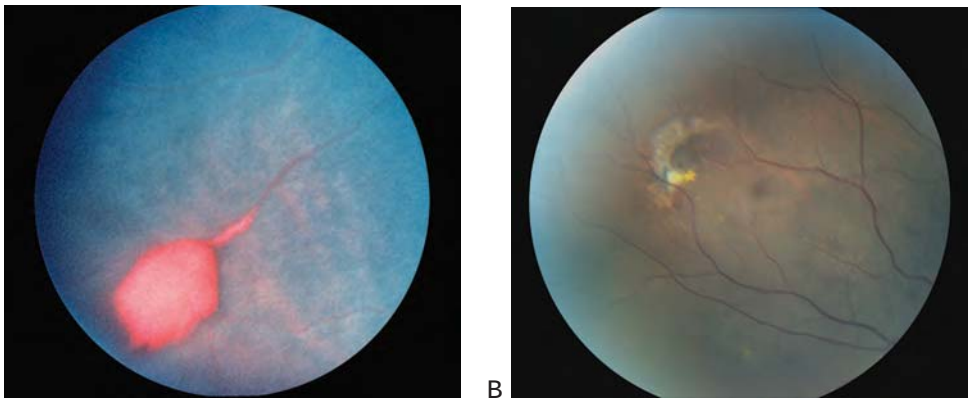

Figure 7-2 Salmon-patch hemorrhage in sickle cell retinopathy. **A,** Peripheral fundus photograph from a patient with sickle cell disease shows a retinal hemorrhage unrelated to proliferation; instead, it is the result of infarction of the retina from a vascular occlusion—a *salmon patch*. **B,** Peripheral fundus photograph of an iridescent, or refractile, patch that represents an area of previous, now resorbed, retinal hemorrhage (salmon patch). *(Part A: This image was originally published in the Retina Image Bank. Larry Halperin, MD. Sickle Salmon-Patch Hemorrhage. Retina Image Bank, 2012; image number 1789. © American Society of Retina Specialists. Part B courtesy of G. Baker Hubbard III, MD.)*

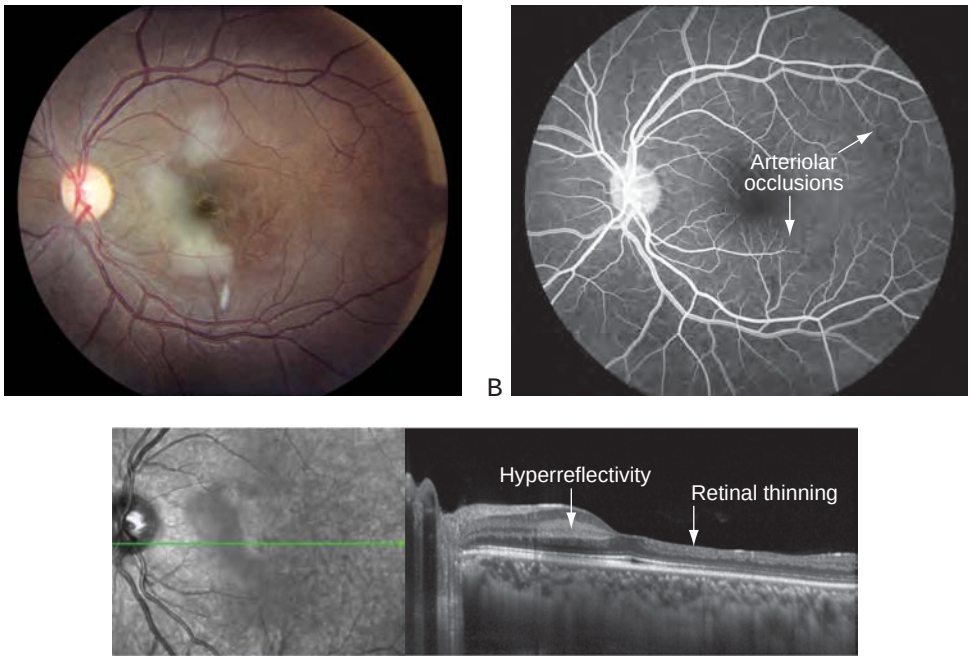

Figure 7-3 Retinal arteriolar occlusions in nonproliferative sickle cell retinopathy. **A,** Fundus photograph of patchy, creamy parafoveal retinal infarctions in the left eye of a 21-year-old woman with sickle cell (HbSS) disease; the sickling crisis was dehydration induced. **B,** FA demonstrates occlusion of multiple small retinal arterioles *(arrows);* however, none correspond to the areas of opacified retina. Similar findings were present in the other eye. Note that unlike embolic events, these occlusions do not occur at a bifurcation. The patient maintained good central visual function. **C,** Optical coherence tomography (OCT) demonstrates *hyperreflectivity* in the middle retina corresponding to an area of creamy retinal infarction, suggesting ischemia of the deep capillary plexus. There is temporal *retinal thinning* with loss of the inner retinal layers, indicating previous infarctions in that area. *(Courtesy of Michael Dollin, MD.)*

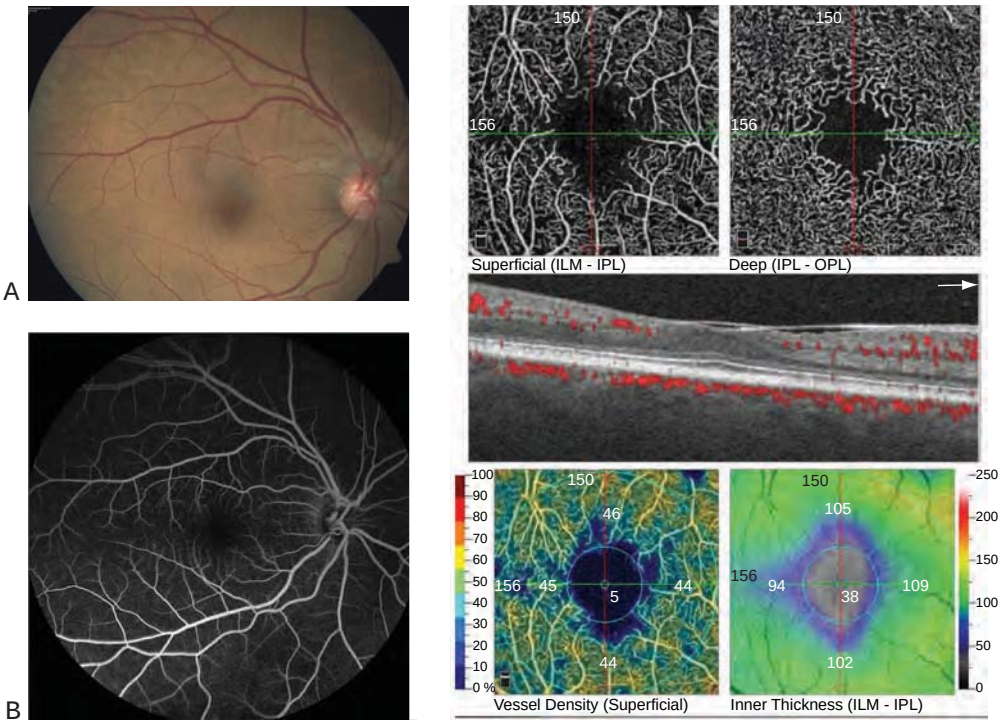

Figure 7-4 **A,** Fundus photograph of the right eye of a 47-year-old woman with sickle cell–hemoglobin C (HbSC) disease and 20/20 vision. **B,** FA is unremarkable. **C,** *Top row:* OCT angiography (OCTA) of the superficial and deep capillary plexus shows an enlarged foveal avascular zone (FAZ) that is especially prominent in the superficial, pruned capillaries. *Middle row:* Cross-sectional OCT with flow overlay, showing widened foveal depression, vitreomacular adhesion, and expanded vascular FAZ boundaries. *Bottom row: S*uperficial vessel density *(right)* and inner retinal thickness *(left)* maps. *Left* image shows central thinning consistent with an enlarged FAZ, while the capillary density map highlights decreased density in areas outside the FAZ (pseudocolored in deeper shades of blue). *(Courtesy of Jennifer Irene Lim, MD.)*

can be differentiated from PDR is that in PSR, spontaneous regression of the peripheral neovascularization by autoinfarction frequently occurs, resulting in a white sea fan neovascularization (Fig 7-7). Table 7-2 presents a differential diagnosis for peripheral retinal neovascularization.

Elagouz M, Jyothi S, Gupta B, Sivaprasad S. Sickle cell disease and the eye: old and new concepts. *Surv Ophthalmol.* 2010;55(4):359–377.

Other Ocular Abnormalities in Sickle Cell Hemoglobinopathies

Many patients with HbSS or HbSC disease exhibit segmentation of blood in the conjunctival blood vessels. Numerous comma-shaped thrombi dilate and occlude capillaries, most often in the inferior bulbar conjunctiva and fornix (referred to as the *comma sign*). Similarly, small vessels on the surface of the optic nerve head can exhibit intravascular occlusions, manifested as dark red spots (called *the nerve head sign of sickling*). Angioid streaks

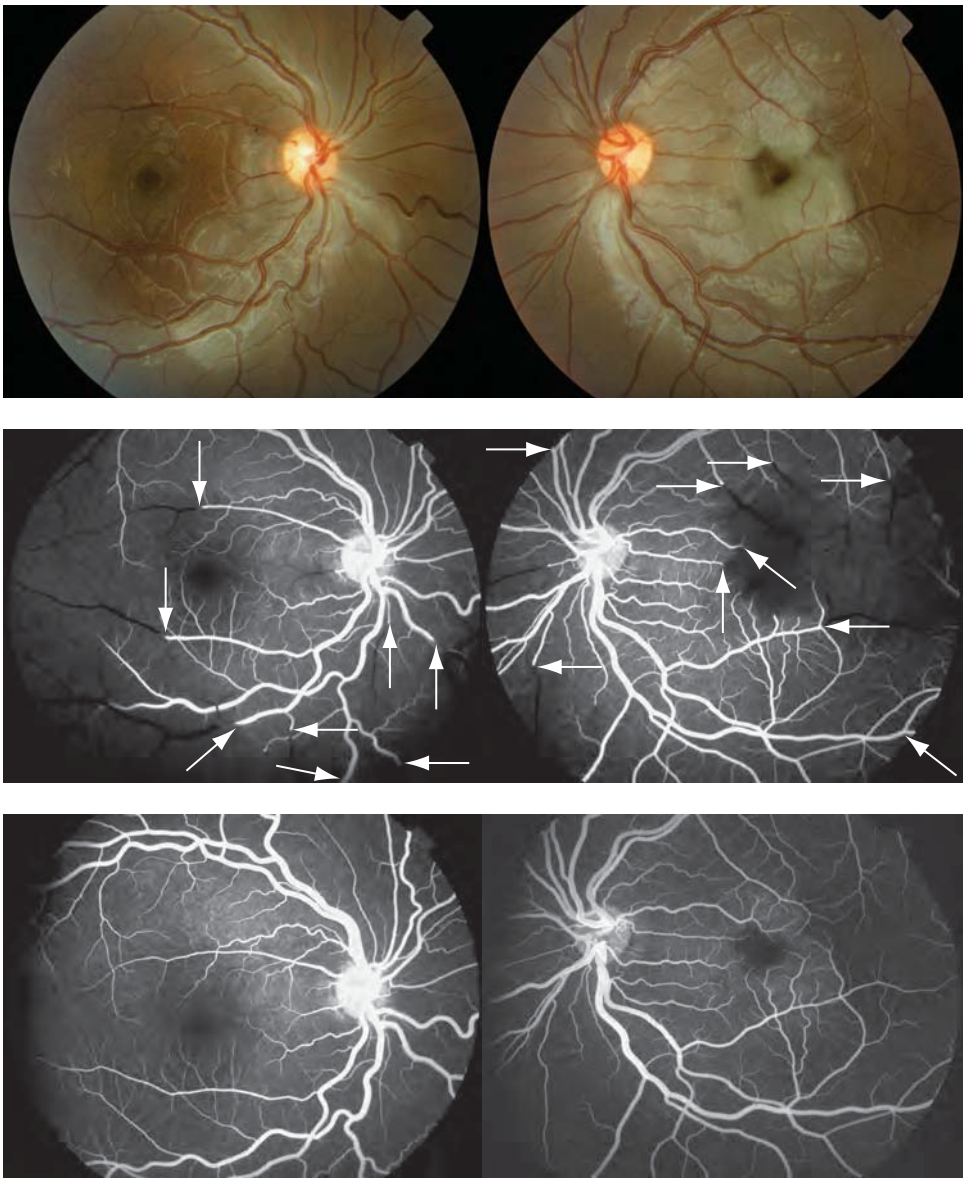

Figure 7-5 Bilateral, multiple branch retinal artery occlusions (BRAOs) in nonproliferative sickle cell retinopathy. **A,** Fundus photographs from a 5½-year-old boy with HbSS disease (sickle cell anemia) show multiple acute BRAOs during a massive sickling episode. **B,** FA images show numerous medium and large arteriolar vessel occlusions *(arrows),* notably not located at bifurcations. **C,** The patient was treated promptly following a hypertransfusion protocol, which resulted in dramatic reperfusion of the retina. However, the corrected distance visual acuity did not improve beyond 20/200 in either eye. *(Courtesy of Brian Leonard, MD.)*

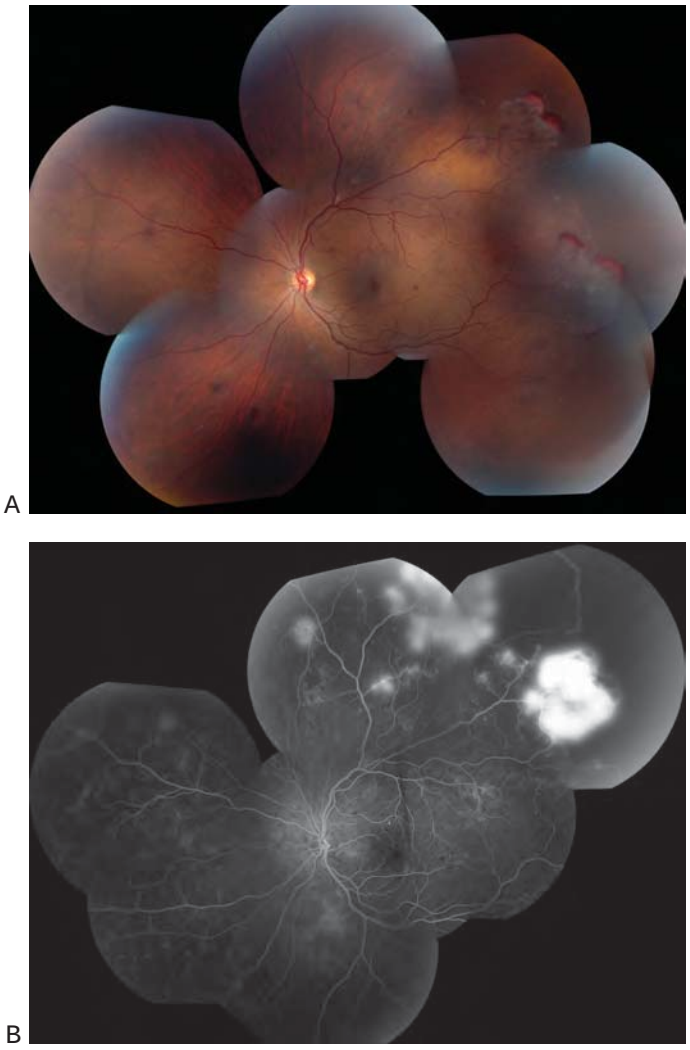

Figure 7-6 Wide-field fundus image montages of the left eye of a 26-year-old African American man with a history of HbSC disease. **A,** Hemorrhaging has occurred at the anterior border of the proliferative lesions. **B,** FA imaging shows leakage from the sea fan lesions in the periphery and peripheral nonperfusion anterior to the sea fans. *(Courtesy of Asheesh Tewari, MD.)*

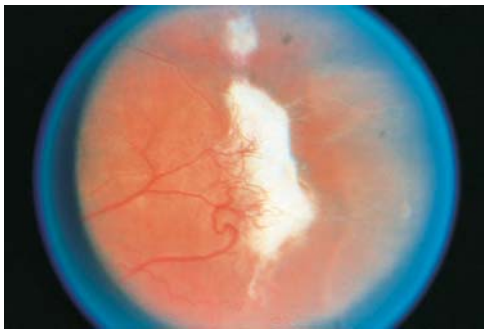

Figure 7-7 Fundus photograph of peripheral neovascularization (sea fan neovascularization) with autoinfarction, as illustrated by the white atrophic vessels. *(Courtesy of Harry W. Flynn Jr, MD.)*

Table 7-2 Differential Diagnosis of Peripheral Retinal Neovascularization

Vascular diseases with ischemia
Aortic arch syndromes/ocular ischemic syndromes
Branch retinal artery occlusion (BRAO)
Branch retinal vein occlusion (BRVO)
Carotid-cavernous fistula
Central retinal artery occlusion
Central retinal vein occlusion
Coats disease
Eales disease
Familial exudative vitreoretinopathy (FEVR)
Hyperviscosity syndromes (eg, chronic myelogenous leukemia)
Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN)
Proliferative diabetic retinopathy (PDR)
Retinal embolization (eg, talc emboli)
Retinopathy of prematurity (ROP)
Sickling hemoglobinopathies (eg, SC, SS) and other hemoglobinopathies (eg, HbAC, HbAS)
Inflammatory diseases with possible ischemia
Birdshot chorioretinopathy
Multiple sclerosis
Retinal vasculitis (eg, systemic lupus erythematosus)
Sarcoidosis
Susac syndrome
Toxoplasmosis
Uveitis, including pars planitis
Miscellaneous conditions
Choroidal melanoma
Chronic retinal detachment
Incontinentia pigmenti
Radiation retinopathy
Retinitis pigmentosa
Retinoschisis

Modified with permission from Elsevier. Jampol LM, Ebroon DA, Goldbaum MH. Peripheral proliferative retinopathies: an update on angiogenesis, etiologies, and management. *Surv Ophthalmol*. 1994;38(6): 519–540.

have been reported clinically in up to 6% of cases of HbSS disease and in persons with sickle cell trait (HbAS).

Management of Sickle Cell Retinopathy and Its Complications

Traumatic hyphema

All Black patients presenting with a traumatic hyphema should be screened for a sickling hemoglobinopathy (including HbAS) because of the increased risk of rigid sickled erythrocytes inducing high intraocular pressure (IOP). For patients with hyphema and increased IOP, early anterior chamber washout is recommended in order to control the IOP and prevent corneal blood staining. In general, carbonic anhydrase inhibitors should be avoided in patients with sickle cell disease as these drugs may worsen sickling through the production of systemic acidosis.

CLINICAL PEARL

Always remember to test for sickle cell disease in patients with traumatic hyphema (especially in Black patients).

McLeod DS, Merges C, Fukushima A, Goldberg MF, Lutty GA. Histopathologic features of neovascularization in sickle cell retinopathy. *Am J Ophthalmol.* 1997;124(4):455–472.

Proliferative sickle cell retinopathy: photocoagulation

Peripheral scatter photocoagulation applied to the ischemic peripheral retina generally causes regression of neovascular fronds and thus decreases the risk of vitreous hemorrhage. The decision to treat PSR with scatter photocoagulation should be made cautiously, however, because retinal tears can occur and do so more commonly after such treatment in PSR than in PDR.

Proliferative sickle cell retinopathy: vitreoretinal surgery

Surgery may be indicated for nonclearing vitreous hemorrhage and for rhegmatogenous, traction, schisis, or combined retinal detachment. Retinal detachment usually begins in the ischemic peripheral retina. The tears typically occur at the base of sea fans and can be precipitated by photocoagulation treatment. Anterior segment ischemia or necrosis has been reported in association with 360° scleral buckling procedures, particularly when combined with extensive diathermy or cryopexy.

Vasculitis

Retinal vasculitis from any cause may progress through the stages of inflammation, ischemia, neovascularization, and subsequent hemorrhagic and tractional complications. The early clinical manifestations are generally nonspecific, consisting of perivascular infiltrates and sheathing of the retinal vessels (vascular wall thickening with vessel involution; Fig 7-8). Veins tend to become inflamed earlier and more frequently than arterioles, but involvement of both arteries and veins is the rule. A variety of inflammatory uveitides may cause retinal vasculitis; see Chapter 5 in BCSC Section 9, *Uveitis and Ocular Inflammation.* Masquerade

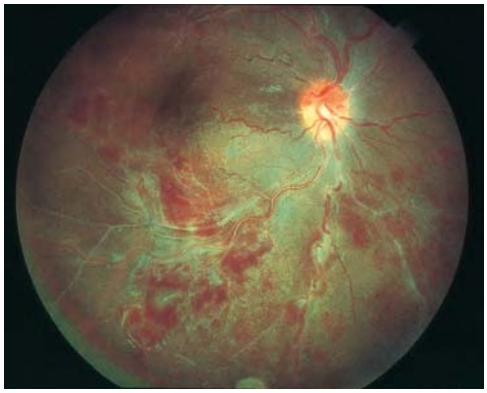

Figure 7-8 Fundus photograph of retinal vasculitis in an eye of a patient with Crohn disease. Retinal hemorrhages and edema are present, as is prominent sheathing of the retinal vessels. *(Courtesy of Gary C. Brown, MD.)*

syndromes should also be considered as possible causes. See Section 9 for further discussion of most of these conditions and Section 5, *Neuro-Ophthalmology,* for discussion of multiple sclerosis and giant cell arteritis.

A primary occlusive retinal vasculopathy for which no cause can be found is termed *Eales disease.* This condition usually involves the peripheral retina of both eyes and often results in extraretinal neovascularization with vitreous hemorrhage. It typically occurs in males and may be associated with tuberculin hypersensitivity. There is also a possible association between tuberculosis and Eales disease.

Susac syndrome is characterized by multiple branch retinal artery occlusions and can be associated with hearing loss and, in rare cases, with strokes. It is most commonly diagnosed in women in their third decade of life, and there is no known cause. Treatment of Susac syndrome includes corticosteroids and generally requires long-term immunosuppression.

Chronic embolism or thrombosis without inflammation may result in a clinical picture that is indistinguishable from previous retinal vasculitis. Evaluation includes a search for possible causes: cardiac valvular disease, cardiac arrhythmias, ulcerated atheromatous disease of the carotid vessels, and hemoglobinopathies.

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) describes a syndrome characterized by the presence of retinal vasculitis, multiple macroaneurysms, neuroretinitis, and peripheral capillary nonperfusion. Systemic investigations are generally noncontributory, and oral prednisone has demonstrated little benefit. Capillary nonperfusion is often sufficiently severe to warrant panretinal photocoagulation.

Cystoid Macular Edema

Cystoid macular edema (CME) is characterized by intraretinal edema contained in honeycomb-like cystoid spaces. The source of the edema is abnormal perifoveal retinal capillary permeability, which in many cases is visible on fluorescein angiography (FA) as multiple small focal leaks and late pooling of the dye in extracellular cystoid spaces. OCT findings in CME include diffuse retinal thickening with cystoid areas that are more prominent in the inner nuclear and outer plexiform layers. On occasion, a nonreflective cavity that is consistent with subretinal fluid accumulation is present beneath the neurosensory retina (see Chapter 5, Fig 5-11B, and Chapter 6, Fig 6-8A). Because of the radial foveal arrangement of both the glia and Henle inner fibers, this pooling classically forms a "flower petal" (petaloid) pattern (Fig 7-9).

Etiologies of CME

Abnormal permeability of the perifoveal retinal capillaries may occur in a wide variety of conditions, including diabetic retinopathy, central retinal vein occlusion, branch retinal vein occlusion, any type of uveitis, and retinitis pigmentosa (RP). CME can also be triggered or worsened by drugs. In addition, CME may occur after any ocular surgery. Cataract surgery is one of the most common etiologies of CME from any cause and is discussed in detail in BCSC Section 11, *Lens and Cataract*. CME occurring after cataract extraction is called *Irvine-Gass syndrome*. There is no uniform definition of pseudophakic CME, the reported

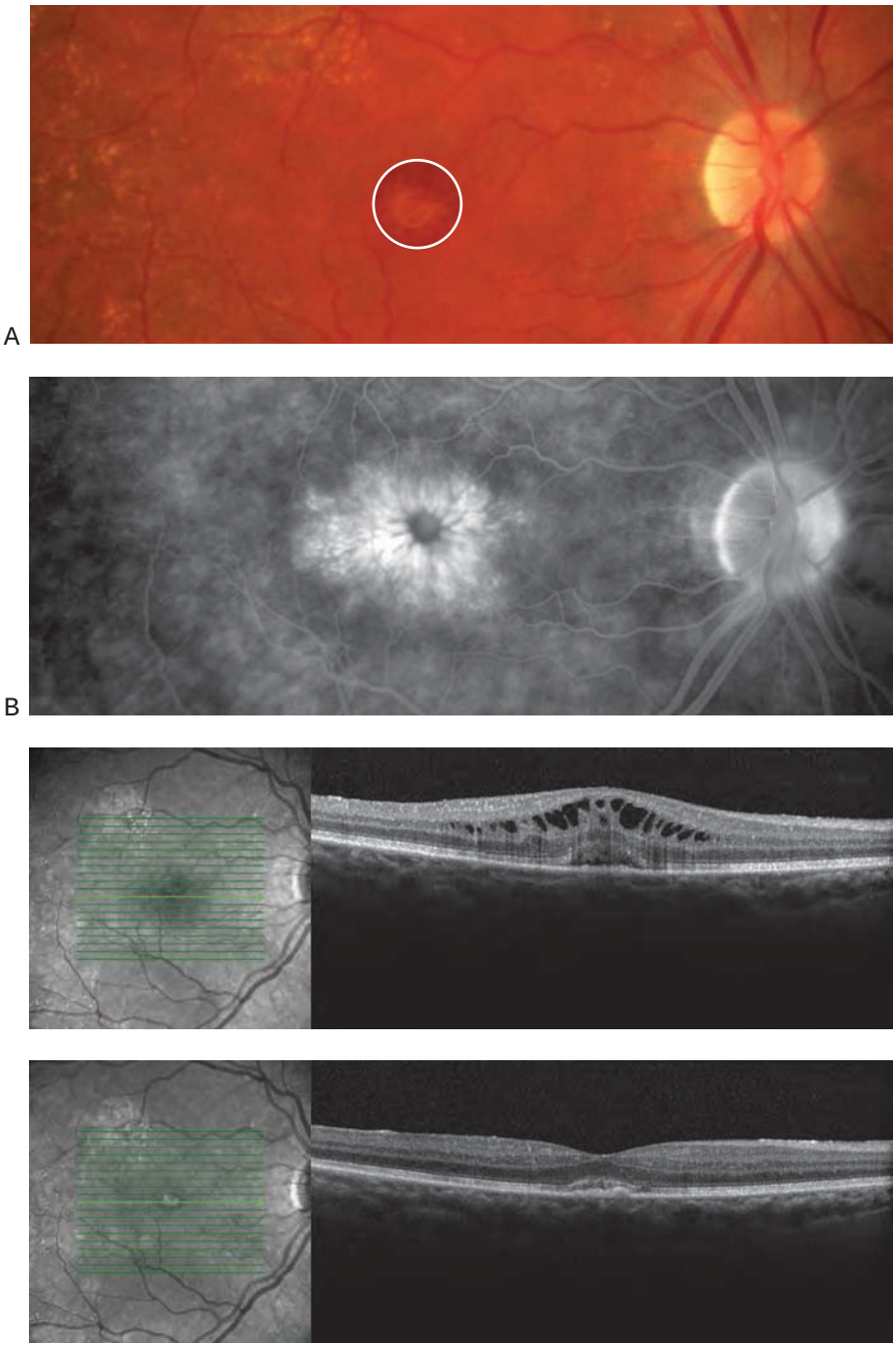

Figure 7-9 Pseudophakic cystoid macular edema (CME). **A,** Fundus photograph of an optic nerve head and macula 3 months after complex cataract surgery. A small incidental grayish-yellow adult vitelliform dystrophy lesion is present in the subfoveal region *(circled)*. **B,** A mid-phase FA image demonstrates cystoid hyperfluorescence, with a classic petaloid pattern. As is typical in eyes with pseudophakic CME, there is mild hyperfluorescence of the nasal portion of the optic nerve head. **C,** OCT image shows cystoid retinal thickening and a subfoveal vitelliform lesion. **D,** After 8 weeks of topical steroidal and nonsteroidal anti-inflammatory therapy, OCT shows that the CME has fully resolved. *(Courtesy of Brian Leonard, MD.)*

incidence of which ranges from approximately 1% to over 30% following extracapsular cataract extraction. The incidence of clinically relevant pseudophakic CME, which includes reduced vision in the presence of CME, is 1%–2%. The differential diagnosis of CME in which FA fails to show leakage includes conditions such as X-linked hereditary retinoschisis, Goldmann-Favre disease, and RP. Angiographically silent CME may also occur as an adverse effect of treatment with nicotinic acid and taxanes (see also Chapter 14 in this volume).

Johnson MW. Etiology and treatment of macular edema. *Am J Ophthalmol.* 2009;147(1):11–21.

Treatment of CME

Treatment of CME is generally directed toward the underlying etiology (eg, branch retinal vein occlusion, uveitis). To reduce the risk of postoperative pseudophakic CME, a combination of topical corticosteroids and nonsteroidal anti-inflammatory drugs is commonly used as prophylactic treatment. If CME is severe or refractory to topical therapy, periocular (eg, posterior sub-Tenon triamcinolone acetonide) or intraocular injection of steroid preparations is an appropriate escalation of therapy. Oral and/or topical acetazolamide may be successful for treatment of CME, especially in chronic cases (eg, associated with RP).

If CME is associated with vitreous adhesions to the iris or a corneoscleral wound, vitrectomy or Nd:YAG laser treatment to interrupt the vitreous strands may be helpful. In cases of CME caused by epiretinal membranes or vitreomacular traction, surgical intervention may be appropriate (see Chapter 19).

Kim SJ, Schoenberger SD, Thorne JE, Ehlers JP, Yeh S, Bakri SJ. Topical nonsteroidal anti-inflammatory drugs and cataract surgery: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2015;122(11):2159–2168.

Coats Disease

Coats disease is characterized by the presence of vascular abnormalities (retinal telangiectasia), such as ectatic arterioles, microaneurysms, venous dilatations (phlebectasias), and fusiform capillary dilatations, which are often associated with exudative retinal detachment (Fig 7-10). Age at onset is 6–8 years, usually only 1 eye is involved, and there is a marked male predominance (85% of cases). Researchers have not yet identified an associated gene or chromosome or any hereditary pattern, and no association between Coats disease and systemic disease has been found.

In an eye with Coats disease, the abnormal vessels are compromised, resulting in the leakage of serum and other blood components, which accumulate in and under the retina. Any portion of the peripheral and macular capillary system may be involved. Although angiography demonstrates the presence of retinal capillary nonperfusion, posterior segment neovascularization is unusual. The clinical findings vary widely, ranging from mild retinal vascular abnormalities and minimal exudation to extensive areas of retinal telangiectasia associated with massive leakage and exudative retinal detachment. The severity and rate of progression appear greater in children younger than 4 years, in whom massive exudative retinal detachment with the retina juxtaposed to the lens may simulate retinoblastoma or other causes of leukocoria (called *Coats reaction*) or xanthocoria (yellow pupil). See BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* for the differential diagnosis of leukocoria.

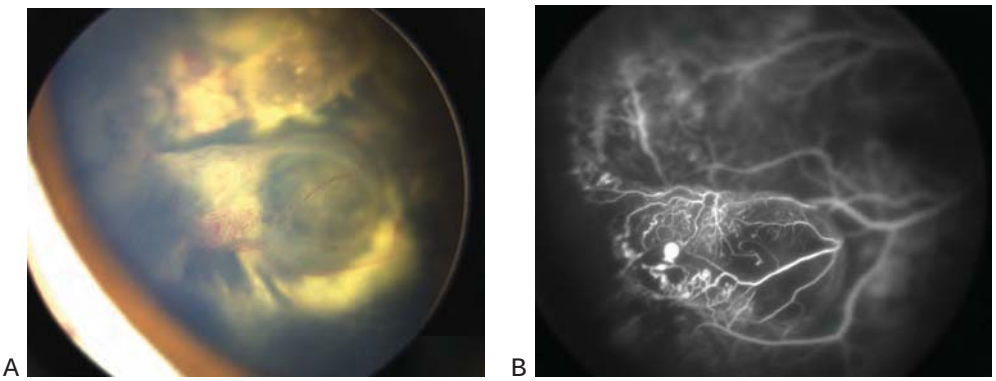

Figure 7-10 Photograph **(A)** and FA image **(B)** from a boy who presented with unilateral leukocoria. The patient had extensive vascular changes, telangiectatic vessels, and an exudative retinal detachment with extensive lipid deposition characteristic of Coats disease. FA highlights the peripheral telangiectasias and characteristic aneurysms. *(Courtesy of Safa Rahmani, MD.)*

Pediatric patients with peripheral involvement typically present with lipid deposition in an otherwise angiographically normal macula, because hard exudate tends to accumulate in the macula. Similar findings in adults probably represent late decompensation of preexisting vascular anomalies. Occasionally, the initial finding is a submacular lipogranuloma or subretinal fibrosis. The differential diagnosis for Coats disease may include

- dominant (familial) exudative vitreoretinopathy
- facioscapulohumeral muscular dystrophy
- retinopathy of prematurity (ROP)
- retinal hemangioblastomas (von Hippel–Lindau syndrome)

For milder cases of lipid exudation, additional considerations are diabetic retinopathy, branch retinal vein occlusion, juxtafoveal retinal telangiectasia, and radiation retinopathy.

Treatment of Coats disease generally consists of direct ablation of the vascular anomalies with photocoagulation or cryotherapy and, in severe cases, retinal reattachment surgery. Intravitreal anti–vascular endothelial growth factor (VEGF) therapy may be a useful adjunctive treatment for cases that are resistant to ablative therapy alone.

Coats-like Reaction in Other Retinal Conditions

Certain forms of RP may be associated with a "Coats-like" reaction, characterized by telangiectatic, dilated vessels and extensive lipid exudation. Most well documented among these forms is *CRB1*-associated RP1 (preserved para-arteriolar retinal pigment epithelium phenotype). Other retinopathies that may present with a unilateral Coats-like phenotype include retinal vasoproliferative tumor (VPT; also known as *reactive retinal astrocytic tumor*), which is distinguished by a preretinal fibrotic mass, disorganized vasculature, and isolated temporal location.

Sigler EJ, Randolph JC, Calzada JI, Wilson MW, Haik BG. Current management of Coats disease. *Surv Ophthalmol*. 2014;59(1):30–46.

Macular Telangiectasia

Macular telangiectasia is divided into 3 general types:

- type 1: unilateral parafoveal telangiectasia, congenital or acquired
- type 2: bilateral parafoveal telangiectasia
- type 3: bilateral parafoveal telangiectasia with retinal capillary obliteration

Macular Telangiectasia Type 1

Macular telangiectasia type 1 (MacTel 1; also called *aneurysmal telangiectasia*), typically occurs unilaterally, predominantly in young males, and with characteristic aneurysmal dilatations of the temporal macular vasculature with surrounding CME and yellowish exudates. MacTel 1 is considered a macular variant of Coats disease. Peripheral vascular changes may also occur. Anti-VEGF therapy is generally ineffective.

Macular Telangiectasia Type 2

Macular telangiectasia type 2 (MacTel 2; also called *juxtafoveal telangiectasis*), the most common form of macular telangiectasis, is a rare, progressive bilateral idiopathic neurodegenerative disease of the macular, parafoveal, retina. Characteristic findings begin to appear in affected individuals in the fifth to seventh decades of life and include a reduced foveolar reflex, loss of retinal transparency (retinal graying), superficial retinal crystalline deposits, mildly ectatic capillaries, slightly dilated blunted venules, progression to pigment hyperplasia, and foveal atrophy (Fig 7-11). Subretinal neovascularization may occur during the natural disease course and can be difficult to differentiate from the anomalous vasculature, requiring multimodal imaging and clinical suspicion. Many of the clinical features of MacTel 2 are characterized by dysfunction of both neural and vascular retinal elements, suggesting that a macular Müller cell defect plays an essential role in the pathogenesis of this disease (see Fig 7-11).

The telangiectatic vessels are readily apparent on FA and usually leak. OCT imaging typically shows a thinned central macular retina, including the fovea; within the inner foveal layers, oblong cavitations are present in which the long axis is parallel to the retinal surface (Fig 7-12; also see Fig 7-11). OCTA visualizes the deep capillary plexus changes of MacTel 2 (Fig 7-13).

To date, there is no FDA-approved, effective treatment of MacTel 2. Intravitreal anti-VEGF therapy is used for the management of active subretinal neovascularization with associated hemorrhage or exudation. The MacTel Project (www.lmri.net/mactel/the-mactel-project/) is an important ongoing international collaboration that aims to better understand MacTel 2 and find new therapeutic targets and therapies.

Chew EY, Clemons TE, Jaffe GJ, et al. Effect of ciliary neurotrophic factor on retinal neurodegeneration in patients with macular telangiectasia type 2: a randomized clinical trial. *Ophthalmology*. 2019;126(4):540–549.

Clemons TE, Gillies MC, Chew EY, et al; MacTel Research Group. Baseline characteristics of participants in the natural history study of macular telangiectasia (MacTel). MacTel Project report no. 2. *Ophthalmic Epidemiol.* 2010;17(1):66–73.

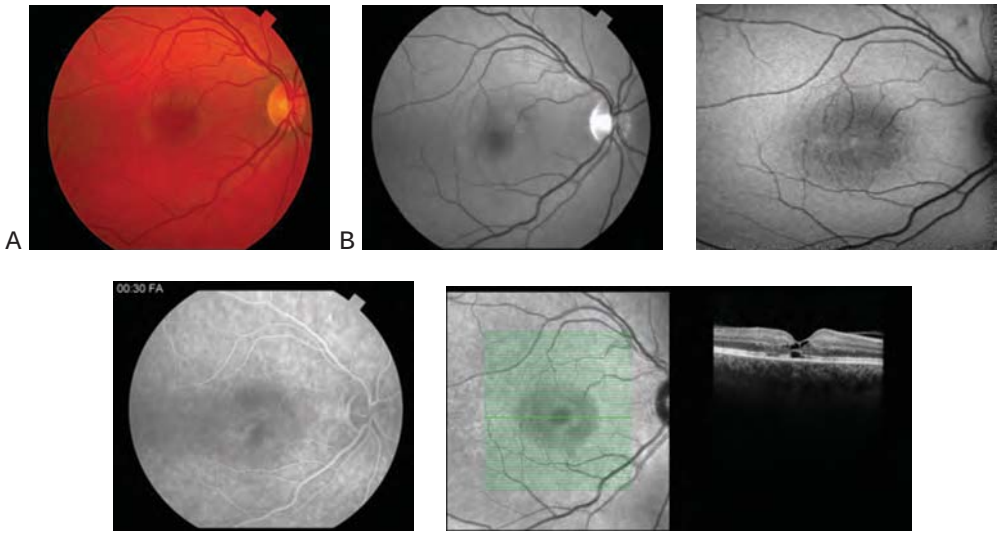

Figure 7-11 Early MacTel 2. **A,** Color photograph shows a subtle parafoveal halo and a few crystals in the temporal parafovea, highlighted in the red-free image **(B). C,** Fundus autofluorescence (488 nm) shows loss of foveal pigment, apparent as a hyperautofluorescent signal. **D,** Early frames of FA show the telangiectatic vessels around the FAZ. **E,** OCT *(right)* shows characteristic central cavitary lesions in the inner retina and loss of the ellipsoid zone in the fovea and temporally. Corresponding infrared image *(left)* highlights the parafoveal halo. *(Courtesy of Amani Fawzi, MD.)*

Gantner ML, Eade K, Wallace M, et al. Serine and lipid metabolism in macular disease and peripheral neuropathy. *N Engl J Med.* 2019;381(15):1422–1433. doi:10.1056/NEJMoa1815111

Yannuzzi LA, Bardal AM, Freund KB, Chen KJ, Eandi CM, Blodi B. Idiopathic macular telangiectasia. *Arch Ophthalmol.* 2006;124(4):450–460.

Macular Telangiectasia Type 3

Macular telangiectasia type 3 is an extremely rare vaso-occlusive process that affects the parafoveal region and is distinct from macular telangiectasia types 1 and 2.

Phakomatoses

Conventionally, many of the syndromes referred to as phakomatoses ("mother spot") are grouped loosely by the common features of ocular and extraocular or systemic involvement of a congenital nature. Most, but not all, are hereditary. Except for Sturge-Weber syndrome, the phakomatoses involve the neuroretina and its circulation. The phakomatoses discussed in this chapter are those most commonly associated with retinal vascular disease. For further discussion of the phakomatoses, see BCSC Section 5, *Neuro-Ophthalmology,* and Section 6, *Pediatric Ophthalmology and Strabismus.*

Von Hippel–Lindau Syndrome

Von Hippel–Lindau (VHL) syndrome (also called *familial cerebelloretinal angiomatosis,* among other names) is caused by a tumor suppressor gene mutation on the short arm of

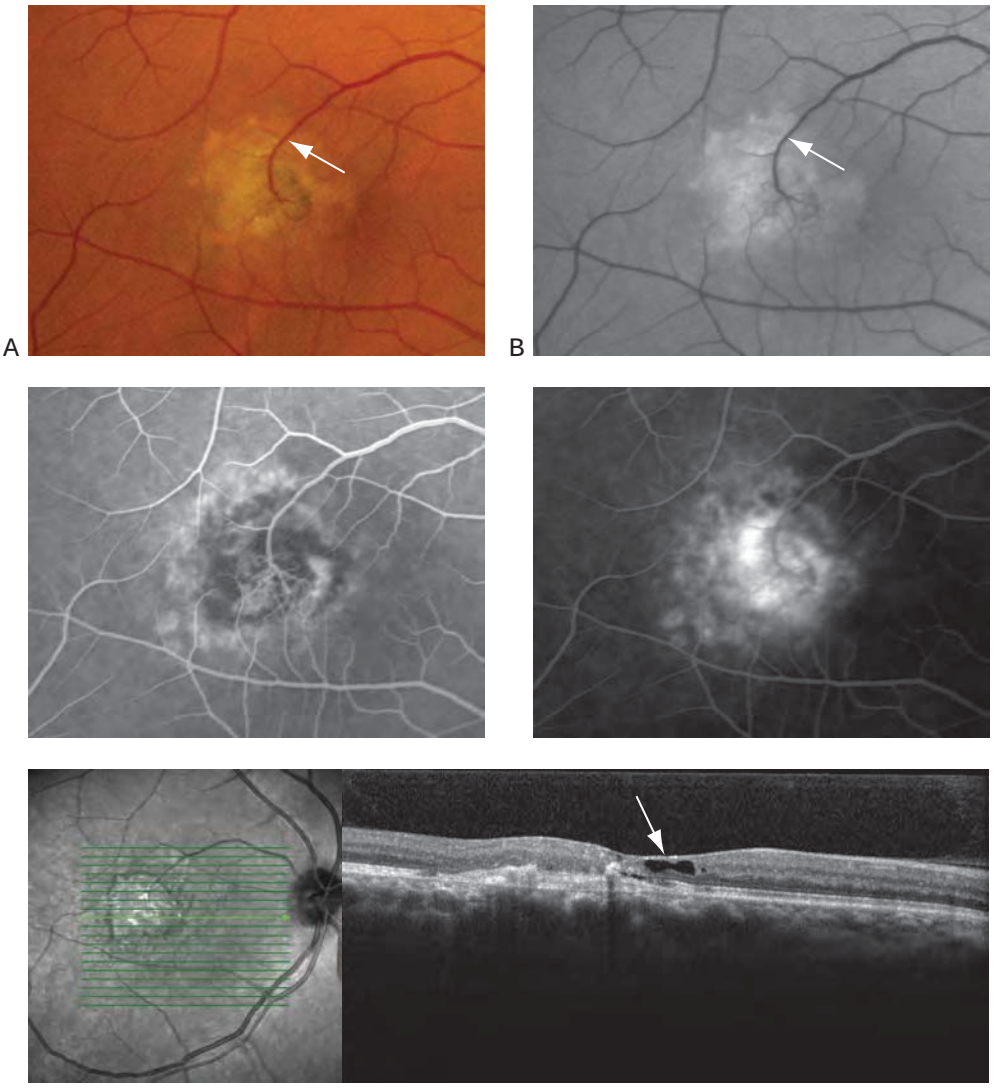

Figure 7-12 Advanced MacTel 2. **A,** Fundus photograph of the right eye shows the chorioretinal venous shunt vessel *(arrow).* This patient receives recurring intravitreal anti–vascular endothelial growth factor (VEGF) treatments for a subretinal neovascular membrane. **B,** Red-free image of the eye shown in **A. C,** Mid-phase FA image demonstrates subretinal neovascularization with superficial and deep components. **D,** Later-phase FA image shows late staining of the neovascular membrane complex. **E,** OCT demonstrates the neovascular membrane complex and MacTel 2–like hyporeflective cavities within the inner foveal layers *(arrow).* *(Courtesy of Brian Leonard, MD.)*

chromosome 3 (3p26–p25), the inheritance of which is autosomal dominant with incomplete penetrance and variable expression. The disease is characterized by retinal and central nervous system hemangioblastomas and visceral manifestations (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*). Central nervous system tumors include hemangioblastomas of the cerebellum, medulla, pons, and spinal cord in 20% of patients with VHL syndrome. Systemic manifestations include renal cell carcinoma; pheochromocytomas;

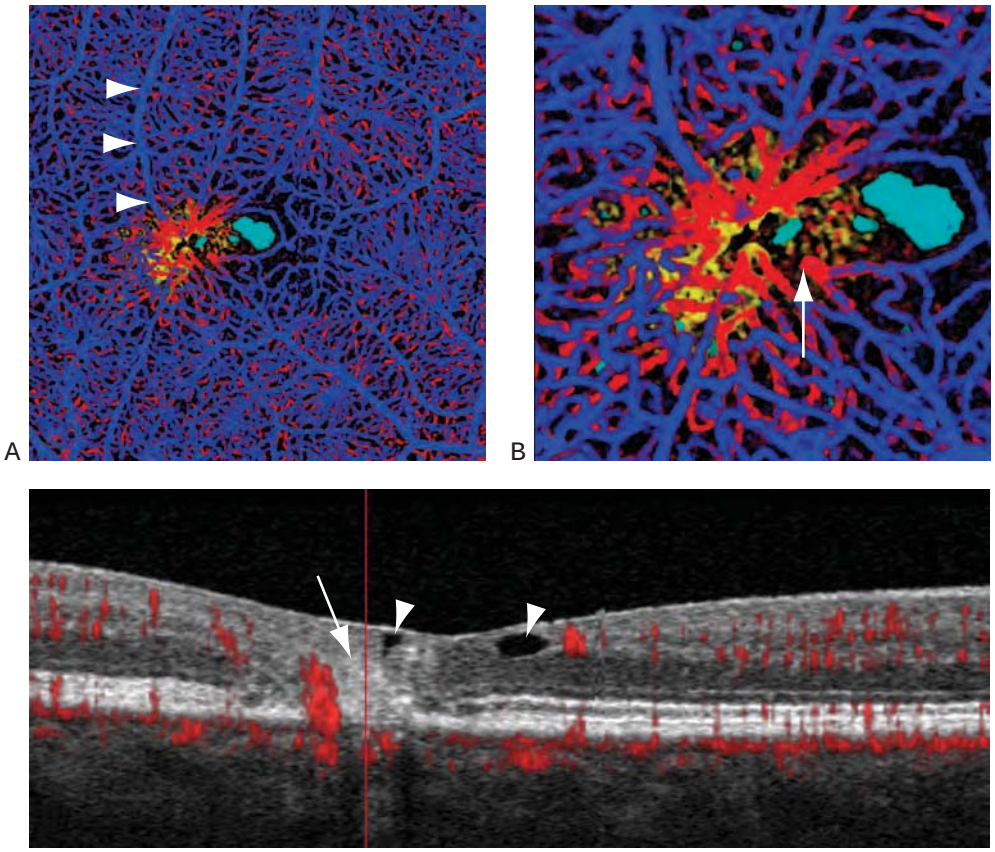

Figure 7-13 MacTel 2 OCT and OCTA imaging. OCTA images do not show leakage and thus can better reveal the complex vascular pathology. **A,** Volume-rendered OCTA image of a right eye. At the level of the superficial vascular plexus, the vessels are *blue;* at the deep plexus they are *red;* and external to the deep plexus, they are *yellow*. Retinal cavitations are *cyan*. A contraction in the temporal juxtafoveal region causes a dragging of the perifoveal capillary ring temporally. Note the dragging of vessels such as the large retinal vein *(arrowheads),* producing an appearance of a right-angle vein. **B,** OCTA image shows enlargement of the area of contracture in the temporal juxtafoveal macula. Note the angled capillary segments *(arrow)* that point toward the epicenter of the contracture. **C,** This B-scan structural OCT shows a flow overlay in red. The scan was taken at the fovea. The hyperreflective material extends nearly the full thickness of the retina *(arrow)*. Note the considerable flow *(red color)* on the temporal side, which is suggestive of retinochoroidal anastomotic vessels. Nasal to the hyperreflective region are cavitations *(arrowheads)*. Over time, cavitations may change in size, shape, and number. *(Courtesy of Richard F. Spaide, MD.)*

endolymphatic sac tumors; cysts of the kidney, pancreas, and liver; and bilateral papillary cystadenomas of the epididymis (men) or broad ligament of the uterus (women). Diagnosis of a retinal hemangioblastoma warrants a systemic workup and genetic testing, the results of which can confirm the diagnosis of VHL syndrome. Cerebellar hemangioblastoma and renal cell carcinoma are the leading causes of death in patients with VHL syndrome.

A fully developed retinal lesion is a spherical orange-red tumor fed by a dilated, tortuous retinal artery and drained by an engorged vein (Fig 7-14). Hemangioblastomas of the optic nerve head and peripapillary region are often flat and difficult to recognize.

Multiple hemangioblastomas may be present in the same eye, and bilateral involvement occurs in 50% of patients. Leakage from a hemangioblastoma may cause decreased vision from macular exudates (Fig 7-15) with or without exudative retinal detachment. Vitreous hemorrhage or traction detachment may also occur.

Ocular management includes destructive treatment of all identified retinal hemangioblastomas with careful follow-up to detect recurrence or the development of new lesions. Successful treatment is facilitated by early diagnosis, because the lesions usually enlarge with time and require repeated sessions for complete ablation. Laser photocoagulation or cryotherapy is used to treat and destroy the angiomatous lesions directly, with an end point of blanching of the vascular structure. Photodynamic therapy with verteporfin can also be used (Fig 7-16). Successful treatment results in shrinkage of the hemangioblastoma,

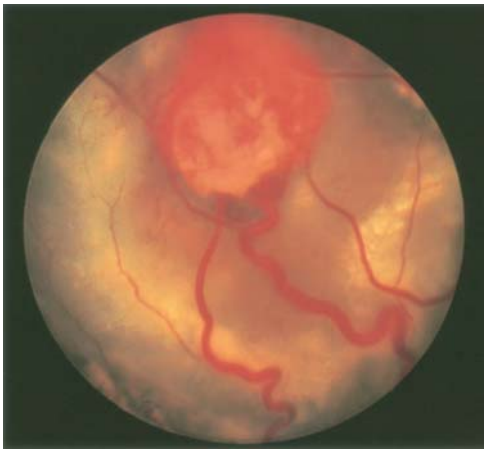

Figure 7-14 Fundus photograph from a patient with von Hippel–Lindau syndrome shows a peripheral retinal hemangioblastoma with surrounding exudate and retinal detachment. The feeder arteriole and draining venule are dilated.

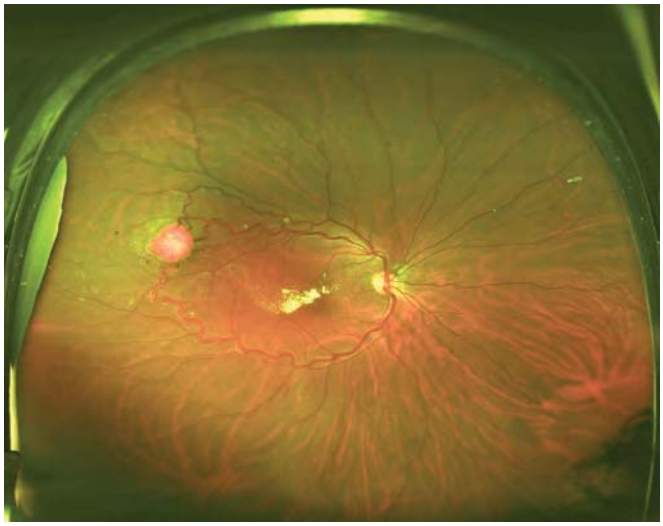

Figure 7-15 Ultra-wide-field fundus photograph from a patient with von Hippel–Lindau syndrome, showing a retinal hemangioblastoma in the near periphery and associated exudative maculopathy. *(Courtesy of Colin A. McCannel, MD.)*

attenuation of the afferent vessels, and resorption of the subretinal fluid. Cryotherapy may be used to treat larger, especially more peripheral, lesions but can cause a temporary and marked increase in the amount of exudation and sometimes exudative retinal detachment. Anti-VEGF therapy does not usually result in a meaningful, long-term treatment effect.

Retinal hemangioblastomas may also occur sporadically without systemic involvement; these have been called *von Hippel lesions.* Another form of retinal lesions, VPTs (discussed earlier in the chapter), are thought to be reactive astrocytic in nature and may present as a large peripheral vascular mass with surrounding exudation/Coats-like reaction. These acquired lesions do not have the dilated feeder and draining vessels seen with hemangioblastomas. Generally, vasoproliferative lesions are idiopathic and isolated; in rare cases, they may be present as a late complication of ROP, RP, uveitis, or other conditions.

Gaudric A, Krivosic V, Duquid G, Massin P, Giraud S, Richard S. Vitreoretinal surgery for severe retinal capillary hemangiomas in von Hippel–Lindau disease. *Ophthalmology.* 2011;118(1): 142–149.

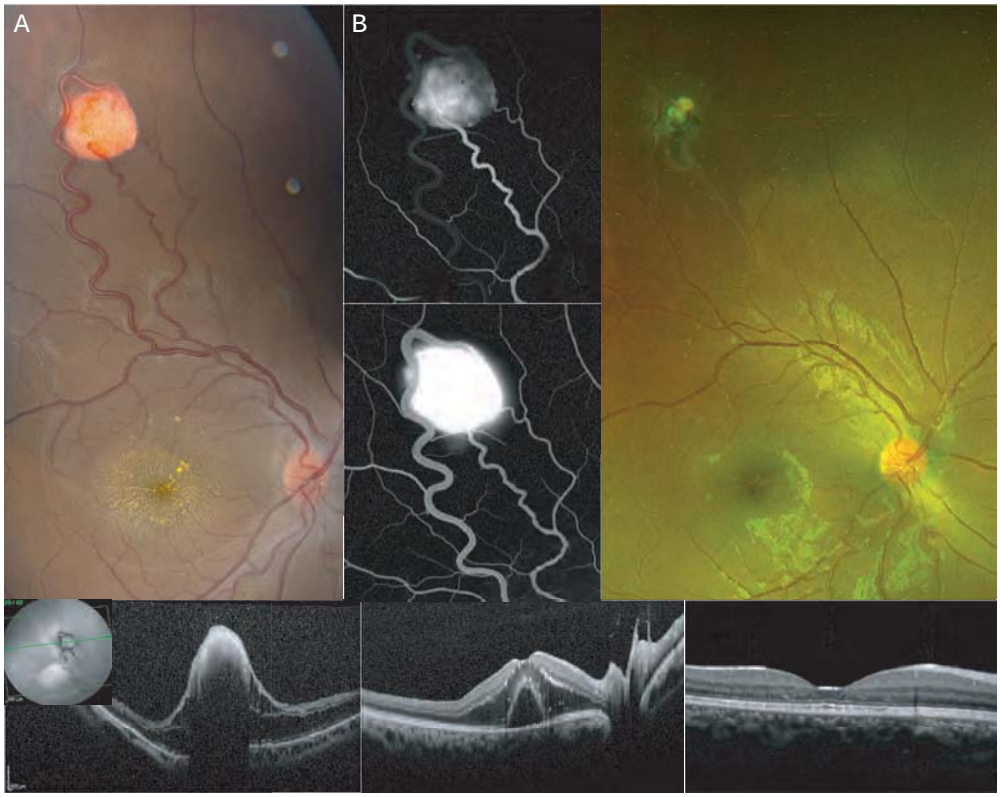

Figure 7-16 Retinal hemangioblastoma (RH). **A,** Classic appearance with dilated feeder vessels, along with hard exudates. Note the large area of fluid in the macula. Classic early-phase **(B)** and late-phase **(C)** FA images showing RH leakage. **D,** Appearance of this tumor after a single photodynamic therapy (PDT) session. Note that the vessel caliber and tortuosity normalize after treatment. **E,** OCT of the tumor itself (*inset* depicts the location of the OCT slice). **F,** Intraretinal and subretinal fluid in the macula at presentation. **G,** Resorption of the fluid following PDT. *(Courtesy of Anthony B. Daniels, MD, MSc.)*

Wyburn-Mason Syndrome

In Wyburn-Mason syndrome, congenital retinal arteriovenous malformations occur in conjunction with similar ipsilateral vascular malformations in the brain, face, orbit, and mandible. The lesions are composed of blood vessels without an intervening capillary bed (racemose hemangioma). The abnormalities may range from a single arteriovenous communication to a complex anastomotic system. In the eye, the lesions are usually located in the retina and optic nerve and are unilateral and asymptomatic. Typically, they do not show leakage on FA. Intraosseous vascular malformations that may occur in the maxilla and mandible can lead to unexpected hemorrhaging during dental extractions. Most commonly, racemose hemangiomas in the retina are isolated and are not part of the full syndrome (Fig 7-17).

Retinal Cavernous Hemangioma

Although most cases of cavernous hemangioma are sporadic and restricted to the retina or optic nerve head, they may occur in a familial (autosomal dominant) pattern and may be associated with intracranial and skin hemangiomas. For this reason, cavernous hemangioma may be considered one of the phakomatoses.

Retinal cavernous hemangioma is characterized by the formation of grapelike clusters of thin-walled saccular angiomatous lesions in the inner retina or on the optic nerve head (Fig 7-18). The blood flow in these lesions is derived from the retinal circulation and is relatively stagnant, producing a characteristic picture on FA. These dilated saccular lesions fill slowly during angiography, and the sluggish blood flow results in plasma-erythrocyte layering, which is pathognomonic. Fluorescein leakage is characteristically absent, correlating with the absence of subretinal fluid and exudate in the retinal cavernous hemangioma and serving to differentiate the condition from retinal telangiectasia, retinal hemangioblastomas, and racemose hemangioma of the retina.

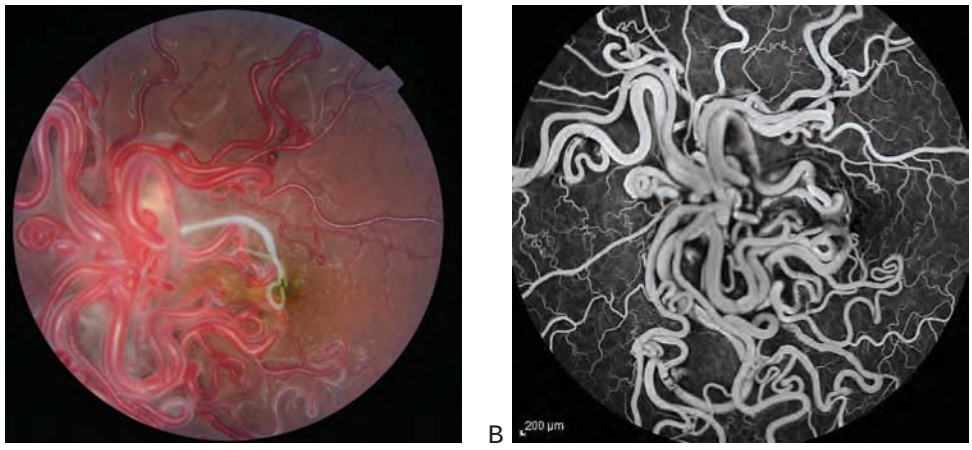

Figure 7-17 **A,** Fundus photograph from a 16-year-old female patient with poor vision in one eye demonstrates racemose angiomatosis as seen in Wyburn-Mason syndrome. **B,** FA highlights the vascular lesion without fluorescein leakage. *(These images were originally published in the Retina Image Bank. Caesar K. Luo, MD. Photographs by Joseph Trabucco. Wyburn Mason. Retina Image Bank, 2018; image numbers 28305, 28304. © American Society of Retina Specialists.)*

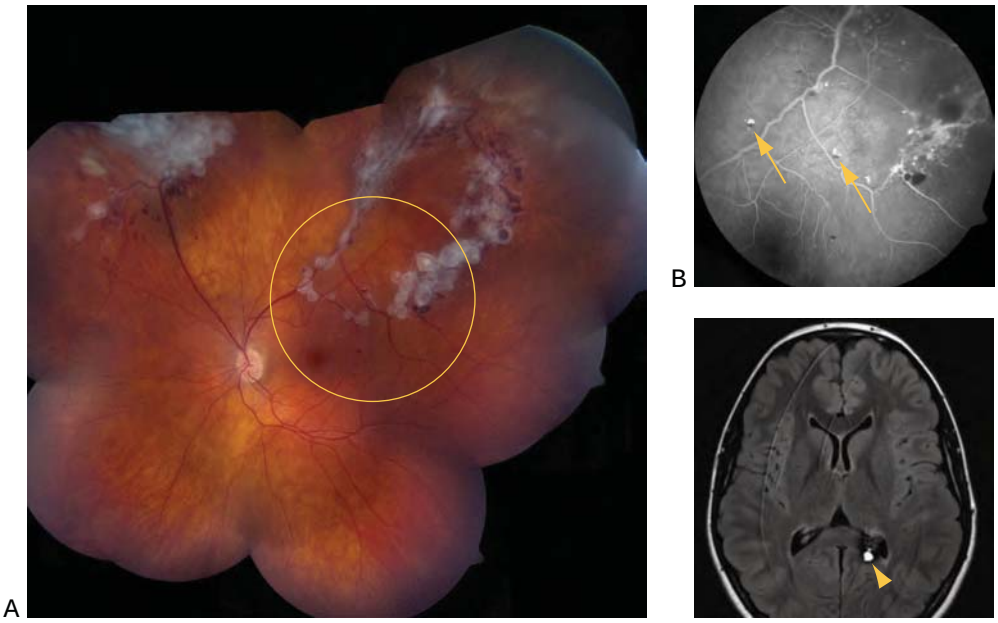

Figure 7-18 Retinal cavernous hemangioma in a 13-year-old girl. **A,** Color fundus image montage of the left eye (right eye was normal) shows superficial gliosis and grapelike clusters of thin-walled saccular angiomatous lesions in the inner retina. **B,** FA (of the area circled in **A**) shows characteristic findings of dilated saccular lesions and plasma-erythrocyte layering *(arrows)* but no leaking because of stagnant blood flow. **C,** Magnetic resonance image (T2 fluid-attenuated inversion recovery) demonstrates an associated left-sided cerebral cavernous hemangioma *(arrowhead)*. The patient underwent stereotactic image-guided resection to reduce the risk of intracranial hemorrhage. *(Courtesy of Kenneth Taubenslag, MD, and Stephen J. Kim, MD.)*

These hemangiomas usually remain asymptomatic but may bleed into the vitreous in rare instances. Treatment of retinal cavernous hemangiomas is usually not indicated unless vitreous hemorrhage recurs, in which case photocoagulation or cryotherapy may be effective. Intracranial hemangiomas may lead to seizures, intracranial hemorrhages, and even death (see Fig 7-18). Neuroimaging should always be done to rule out intracranial involvement. See also BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors.*

Radiation Retinopathy

Exposure to ionizing radiation can damage the retinal vasculature. Radiation retinopathy typically has a delayed onset, is slowly progressive, and causes microangiopathic changes that clinically resemble diabetic retinopathy. The development of radiation retinopathy depends on dose fractionation and can occur after either external beam or local plaque brachytherapy, typically within months to years after radiation treatment. In general, radiation retinopathy is noted around 18 months after treatment with external beam radiation and earlier after treatment with brachytherapy. Because radiation retinopathy appears very similar to other vascular diseases, eliciting a history of radiation treatment is important in establishing the diagnosis. An exposure to doses of 30–35 grays (Gy) or more is usually

necessary to induce clinical symptoms; occasionally, however, retinopathy may develop after as little as 15 Gy of external beam radiation. Studies have shown retinal damage in 50% of patients receiving 60 Gy and in 85%–95% of patients receiving 70–80 Gy. The total dose, volume of retina irradiated, and fractionation scheme are important in determining the threshold dose for radiation retinopathy. See BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors,* for further discussion of external beam radiation and brachytherapy.

CLINICAL PEARL

Remember to inquire about previous radiation treatment in patients who present with microvascular changes that mimic diabetic retinopathy.

Clinically, affected patients may be asymptomatic or may describe decreased vision. Ophthalmic examination may reveal signs of retinal vascular disease, including cotton-wool spots, which are foci of axoplasmic stasis in the nerve fiber layer (Fig 7-19); retinal hemorrhages; microaneurysms; perivascular sheathing; capillary telangiectasis; macular edema; and optic nerve head edema. Capillary nonperfusion, documented by FA, is commonly present, and extensive retinal ischemia can lead to neovascularization of the retina, iris, or optic nerve head. Other possible complications include optic atrophy, central retinal artery occlusion, central retinal vein occlusion, choroidal neovascularization, vitreous hemorrhage, neovascular glaucoma, and traction retinal detachment. Visual outcome is primarily related to the extent of the macular involvement with CME, exudative maculopathy, or capillary nonperfusion. Occasionally, vision loss may be caused by acute optic neuropathy.

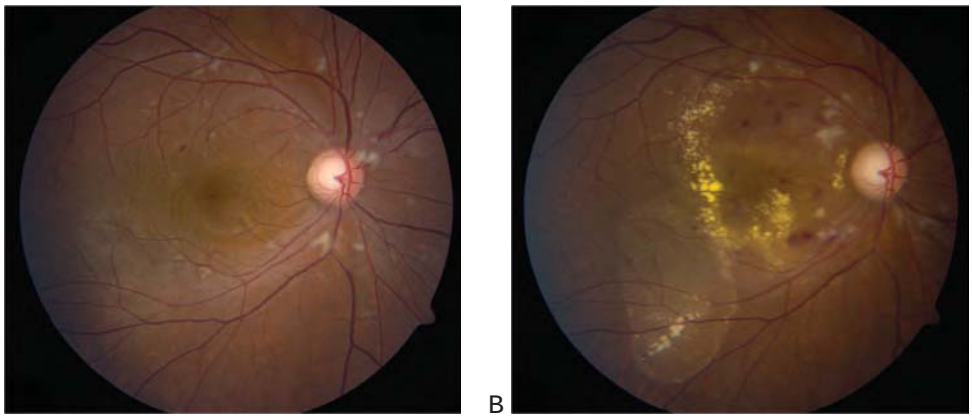

Figure 7-19 Radiation retinopathy following plaque brachytherapy for choroidal melanoma. Progression of retinopathy over time. **A,** Image shows intraretinal hemorrhages and cotton-wool spots. Compared with other entities (such as diabetes) that can cause intraretinal hemorrhages and cotton-wool spots, radiation retinopathy causes many more of these spots relative to the extent of the hemorrhages. **B,** Eight months later, there is substantial progression of the retinopathy, with increased exudation and subretinal and intraretinal fluid in the macula. Visual acuity declined in the interim. *(Courtesy of Anthony B. Daniels, MD, MSc.)*

Anti-VEGF agents or steroids may be effective (off-label) treatments for radiation retinopathy. Laser photocoagulation is less effective because it results in retinal atrophy and laser scar expansion.

Patel SJ, Schachat AP. Radiation retinopathy. In: Albert DM, Miller JW, Azar DT, Blodi BA, eds. *Albert & Jakobiec's Principles and Practice of Ophthalmology.* 3rd ed. Saunders; 2008:chap 175.

Valsalva Retinopathy

A sudden rise in intrathoracic or intra-abdominal pressure (eg, as during coughing, vomiting, lifting, or straining for a bowel movement) may increase intraocular venous pressure sufficiently to rupture small superficial capillaries in the macula. The hemorrhage is typically located under the ILM, where it may create a hemorrhagic detachment of the ILM (Fig 7-20), but patients can present with hemorrhage in any layer of the retina. Vitreous hemorrhage

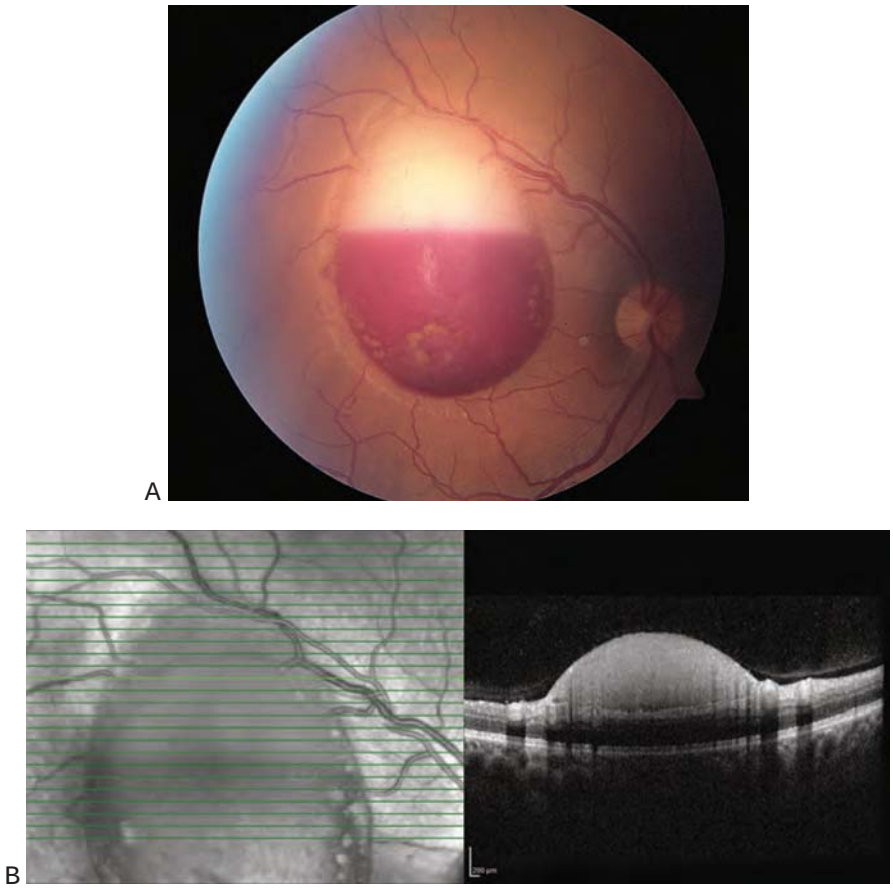

Figure 7-20 Valsalva retinopathy. **A,** Fundus photograph from a 30-year-old man who experienced sudden vision loss after receiving the Heimlich maneuver. **B,** Spectral-domain OCT demonstrates classic hemorrhagic detachment of the internal limiting membrane with corresponding shadowing effect. *(Courtesy of Kenneth Taubenslag, MD, and Edward Cherney, MD.)*

and subretinal hemorrhage may be present. Vision is usually only mildly reduced, and the prognosis is excellent, with spontaneous resolution usually occurring within months after onset. The differential diagnosis of Valsalva retinopathy includes posterior vitreous separation or a macroaneurysm, which may cause an identical hemorrhage. Therefore, in all cases, a peripheral retinal tear or an aneurysm along an arteriole must be ruled out.

Purtscher Retinopathy and Purtscher-like Retinopathy

After acute compression injuries to the thorax or head, a patient may experience vision loss associated with Purtscher retinopathy in 1 or both eyes (Table 7-3). This retinopathy is characterized by cotton-wool spots, polygonal areas of retinal whitening (Purtscher flecken), hemorrhages, and retinal edema, which are found most commonly surrounding the optic nerve head. FA reveals evidence of arteriolar obstruction and leakage. Occasionally, patients present with optic nerve head edema and an afferent pupillary defect. Vision may be permanently lost from infarction, and optic atrophy may develop.

Purtscher retinopathy is thought to be a result of injury-induced complement activation, which causes granulocyte aggregation and leukoembolization. This process in turn can occlude small arterioles. When the occlusion of a precapillary arteriole affects the radial peripapillary capillary network, cotton-wool spots develop; these areas of retinal whitening have indistinct borders and can obscure or partially overlie retinal blood vessels. When capillaries in lamina deeper than the radial peripapillary network are blocked, the ophthalmoscopic correlate is instead Purtscher flecken, which manifest as intraretinal whitening with a clear zone on either side of the retinal arterioles, venules, and precapillary arterioles.

Various other conditions may activate complement and produce a similar fundus appearance. Purtscher's original description involved trauma; cases not involving trauma but with similar fundus findings are therefore termed *Purtscher-like retinopathy* (Fig 7-21; see Table 7-3).

Table 7-3 Conditions Associated With Purtscher or Purtscher-like Retinopathy

Acute pancreatitis
Amniotic fluid embolism
Autoimmune diseases
Chest compression
Chronic renal failure
Dermatomyositis
Early postpartum state
Head injury
Long-bone fractures (fat embolism syndrome)
Orbital steroid injection
Retrobulbar anesthesia
Scleroderma
Sjögren syndrome
Systemic lupus erythematosus
Thrombotic thrombocytopenic purpura
Trauma

Modified with permission from Regillo CD. Posterior segment manifestations of systemic trauma. In: Regillo CD, Brown GC, Flynn HW Jr, eds. *Vitreoretinal Disease: The Essentials.* Thieme; 1999:538. www.thieme.com

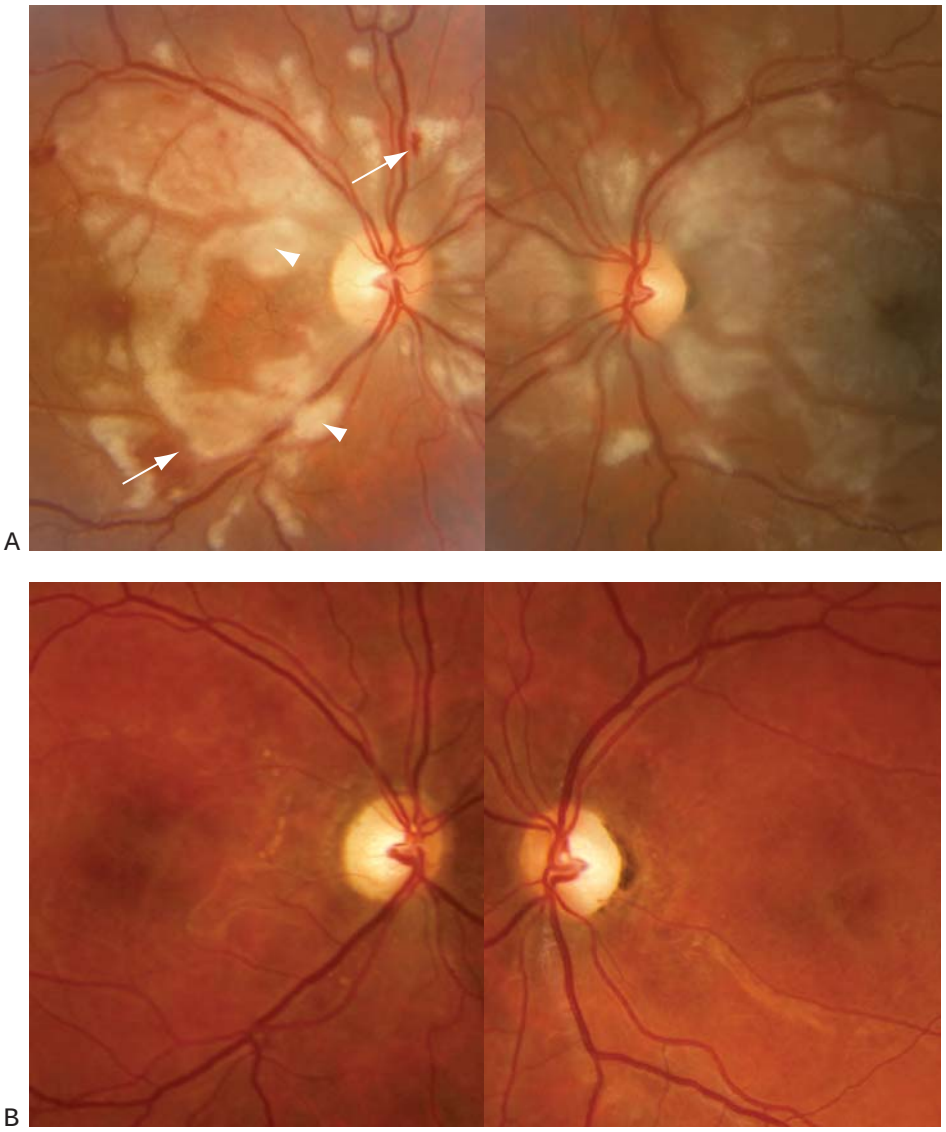

Figure 7-21 Purtscher-like retinopathy. **A,** Fundus photographs from a 20-year-old woman were taken 1 day after an uncomplicated delivery of a healthy baby. The patient had noted profound, persistent bilateral vision loss beginning 1 hour after parturition. Intraretinal hemorrhages *(arrows)* and bright, superficial cotton-wool spots *(arrowheads)* were present, in addition to extensive areas of well-demarcated Purtscher flecken *(asterisk)* with characteristic sparing of the perivascular retina. The flecken are likely the result of occlusion of the precapillary arterioles. The location of these flecken and cotton-wool spots surrounding the optic nerve head is characteristic and distinguishes this entity from other ischemic conditions. **B,** Corresponding fundus photographs taken 4 years later demonstrate optic atrophy and deep macular pigmentary atrophy. Visual acuity was 20/200 OD and 20/800 OS. *(Courtesy of Brian Leonard, MD.)*

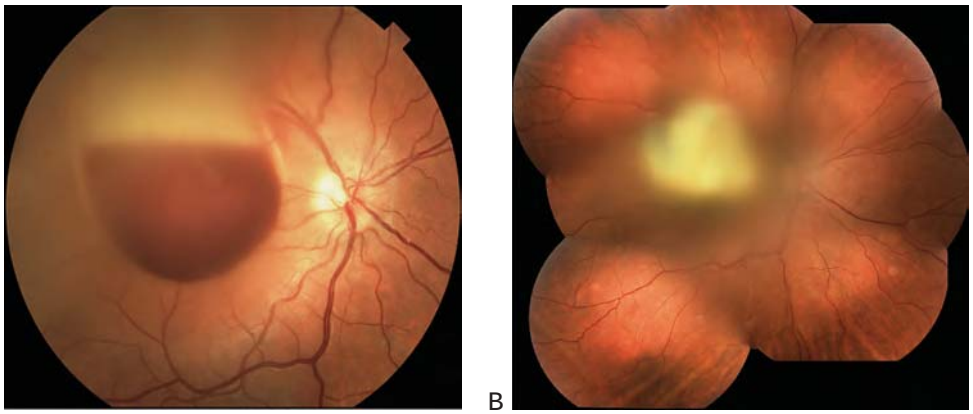

Figure 7-22 Fundus photographs from an 18-year-old male who presented with central blurred vision in his right eye after traumatic brain injury (due to a skateboarding accident), occipital skull fracture, and right-sided subdural and epidural hematoma. **A,** Image from the initial presentation shows a premacular (subhyaloid) hemorrhage. **B,** Over the following 3 weeks, the hemorrhage dispersed into the vitreous cavity. *(Courtesy of Brian C. Joondeph, MD, MPS.)*

For example, the retinopathy associated with acute pancreatitis, which appears identical to traumatic Purtscher retinopathy, is probably also caused by complement-mediated leukoembolization. Other conditions that may cause these changes include collagen vascular diseases (such as systemic lupus erythematosus), early postpartum state, and amniotic fluid embolism. Fat embolism following crush injuries or long-bone fractures may cause similar retinal findings.

Terson Syndrome

Terson syndrome is recognized as a vitreous and sub-ILM or subhyaloid hemorrhage caused by an abrupt intracranial hemorrhage (Fig 7-22). Although the exact mechanism is not known, it is suspected that the acute intracranial hemorrhage causes an acute rise in the intraocular venous pressure, resulting in a rupture of peripapillary and retinal vessels. Approximately one-third of patients with subarachnoid or subdural hemorrhage have associated intraocular hemorrhage, which may include intraretinal and subretinal bleeding. In most cases, visual function is unaffected once the hemorrhage clears. Spontaneous improvement generally occurs, although vitrectomy is occasionally required to clear the ocular media.

Agarwal A. *Gass' Atlas of Macular Diseases.* 5th ed. Saunders; 2012:724–726.