Retina Atlas
Series Editors:
Sandeep Saxena · Richard F. Spaide · Eric H. Souied · Timothy Y. Y. Lai

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Retinal Vascular Disease

Springer

Retina Atlas

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Retinal Vascular Disease

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Contents

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Central Retinal Artery Occlusion

1

Fabio Scarinci

Introduction

Retinal Artery Occlusion (RAO) is a vascular disease caused by the temporary blockage of retinal arterioles, leading to retinal infarction, and significant visual loss. RAO was first described by von Graefe's report as multiple systemic emboli in a patient affected by endocarditis that caused an obstruction of the central retinal artery (von Graefes 1859).

RAO is most commonly due to an embolic source, even though coagulopathies, vasculitis, and other systemic disease may be implicated in other forms of acute RAO (Hayreh et al. 2009).

The occlusion can affect either the central retinal artery (CRAO), or a branch of this vessel, leading to Branch Retinal Artery Occlusion (BRAO); in some cases, only the cilioretinal artery may be involved (with or without concomitant retinal venous occlusions).

Patients usually present with sudden and complete visual loss in the affected eye with a CRAO, or with altitudinal or sectoral visual field defect in BRAO.

Epidemiology

The incidence of CRAO is estimated to be 8.5 cases per 100,000 in the general population (Rumelt et al. 1999). It is most common in older men, although occlusions in children and young adults have been described, usually in association with familial history of vascular diseases such as hyperhomocysteinemia or factor V Leiden (Chen and Lee 2008).

Etiopathogenesis and Classification

The central retinal artery (CRA) is a branch of the ophthalmic artery, which is the first branch of the internal carotid artery. The CRA supplies the superficial layer of the optic disc and upon leaving the disc, divides into four branches that supply the four quadrants of the retina (Singh and Dass 1960).

The CRA mainly supplies the inner retinal layers, while the outer retina is nourished by the choriocapillaris via the ciliary artery, branching from the ophthalmic artery.

The cilioretinal artery originates from the short posterior ciliary artery, and when present, is an important anatomical variation that supplies the papillo-macular bundle.

Although the correct anatomical location of retinal occlusion is still debated, several studies have shown that the most common location for a CRAO is at the narrowest part of the CRA, where the CRA perforates the dural sheath of the optic nerve (Hayreh 1971).

Cholesterol, calcium, and platelet–fibrin emboli are considered the three main types of emboli that are associated with RAO. Both cholesterol and platelet–fibrin emboli arise from atheroma in the carotid arteries. On the other hand, calcium emboli usually arise from the cardiac valves. On fundus examination, both calcium and platelet–fibrin emboli appear white, calcium being brighter, while cholesterol emboli appear orange (Farris and Waymack 2019).

Currently, four main types of CRAO can be differentiated (Hayreh and Zimmerman 2005).

- *Non-arteritic permanent CRAO*

  Non-arteritic permanent CRAO is the most common form of CRAO, and is usually associated with platelet–fibrin emboli. Systemic diseases, such as diabetes or hypertension, represent the main risk factors for non-arteritic permanent CRAO (Chen and Lee 2008) (Figs. 1.1, 1.2, and 1.3).

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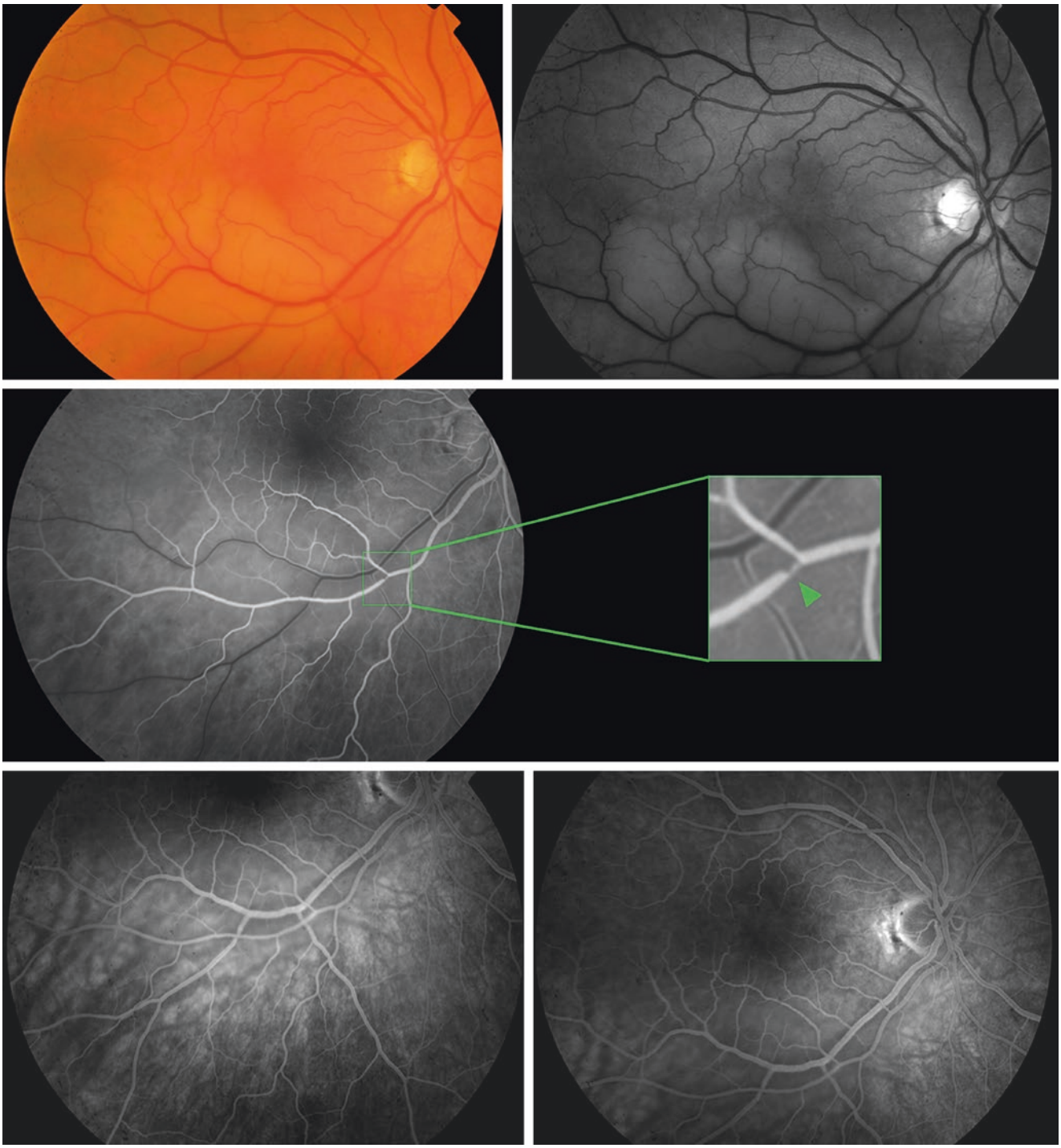

Fig. 1.1 Color fundus photograph, infrared, and fluorescein angiography imaging show a non-arteritic branch retinal artery occlusion. A platelet fibrin embolus is visible at the site of the occlusion (inset box) at the level of the inferior temporal arcade

- *Non-arteritic Transient CRAO*

  Non-arteritic transient CRAO is considered a form of transient ischemic attack of the retina and represents the subtype of CRAO with the best visual prognosis. As soon as the blood flow is restored, symptoms can resolve (Hayreh et al. 1997) (Fig. 1.4).
- *Non-arteritic CRAO with cilioretinal sparing.*

  Almost 50% of patients with CRAO are found to have a cilioretinal artery on fundus examination which can be extremely advantageous in preserving blood supply to the fovea and papillo–macular bundle, and hence, preserving central visual acuity (Justice Jr. and Lehmann 1976) (Figs. 1.5 and 1.6).
- *Arteritic CRAO*

This is the rarest form of CRAO. It is reported in 4.5% of patients and is frequently associated with giant cell arteritis or other autoimmune vasculopathies (Hayreh and Zimmerman 2005).

Clinical Features

Patients with acute CRAO complain of painless, monocular sudden, and severe visual loss. Episodes of amaurosis fugax can be considered as premonitory signs (Recchia and Brown 2000).

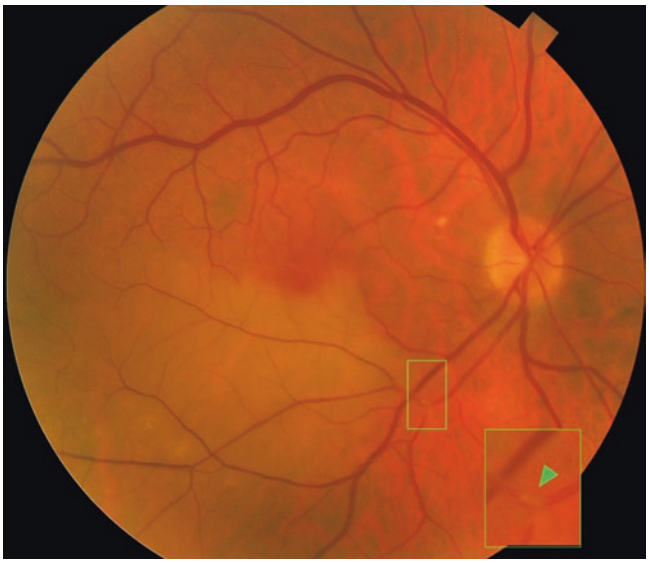

Fig. 1.2 Color fundus photography shows a non-arteritic branch retinal artery occlusion along with platelet fibrin embolus at the level of the inferior temporal arcade

At the time of presentation, visual acuity usually ranges from counting fingers to light perception.

On examination, an afferent pupillary defect may be observed after CRAO. Because of the ischemic process caused by the artery occlusion, the genesis of new vessels may lead to rubeosis iridis.

Intraocular pressure (IOP) is usually normal, but in the case of rubeosis iridis, higher values of IOP may be reported.

In CRAO, clinical findings are usually located in posterior pole with sparing of the periphery.

On fundus examination, several clinical findings are described in acute CRAO:

- Optic nerve pallor and edema of optic disc.
- Whitish or opaque posterior pole with the typical cherry-red spot described in 90% of cases, which represents the earliest finding in CRAO.
- Arterial attenuation.
- Emboli, which are observed in 20% of patients on fundus evaluation.

Optic nerve edema is a result of a frequently associated anterior ischemic neuropathy of the optic nerve; pallor of the nerve is frequently associated with arteritic CRAO.

Neovascularization of the optic nerve has been described in some cases (Mason et al. 2015).

The cherry-red spot and the whitish appearance of the posterior pole are reported as a consequence of the ischemic retinal tissue where the fovea is preserved because of its direct nourishment from choroidal blood vessels (Hildebrand and Fielder 2011).

Finally, emboli and arterial attenuation represent respectively the cause and effect of arterial obstruction. In the

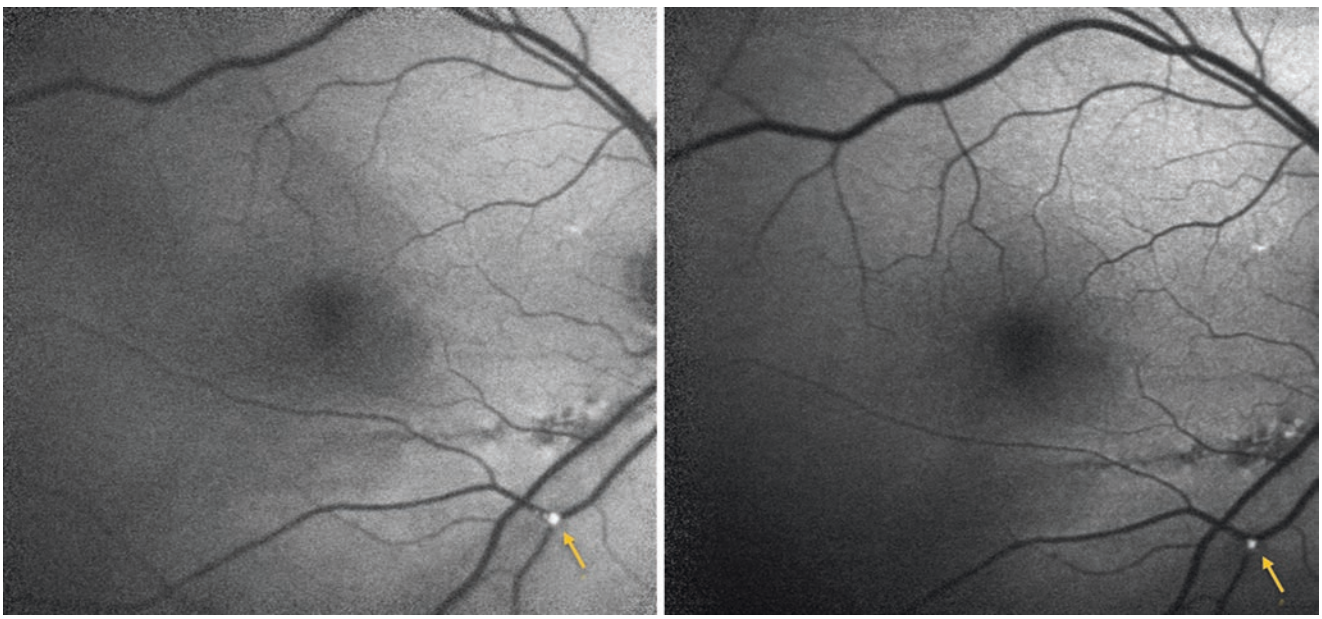

Fig. 1.3 Fundus autofluorescence shows the platelet–fibrin embolus (orange arrow) as a hyperautofluorescent dot at the site of the occlusion

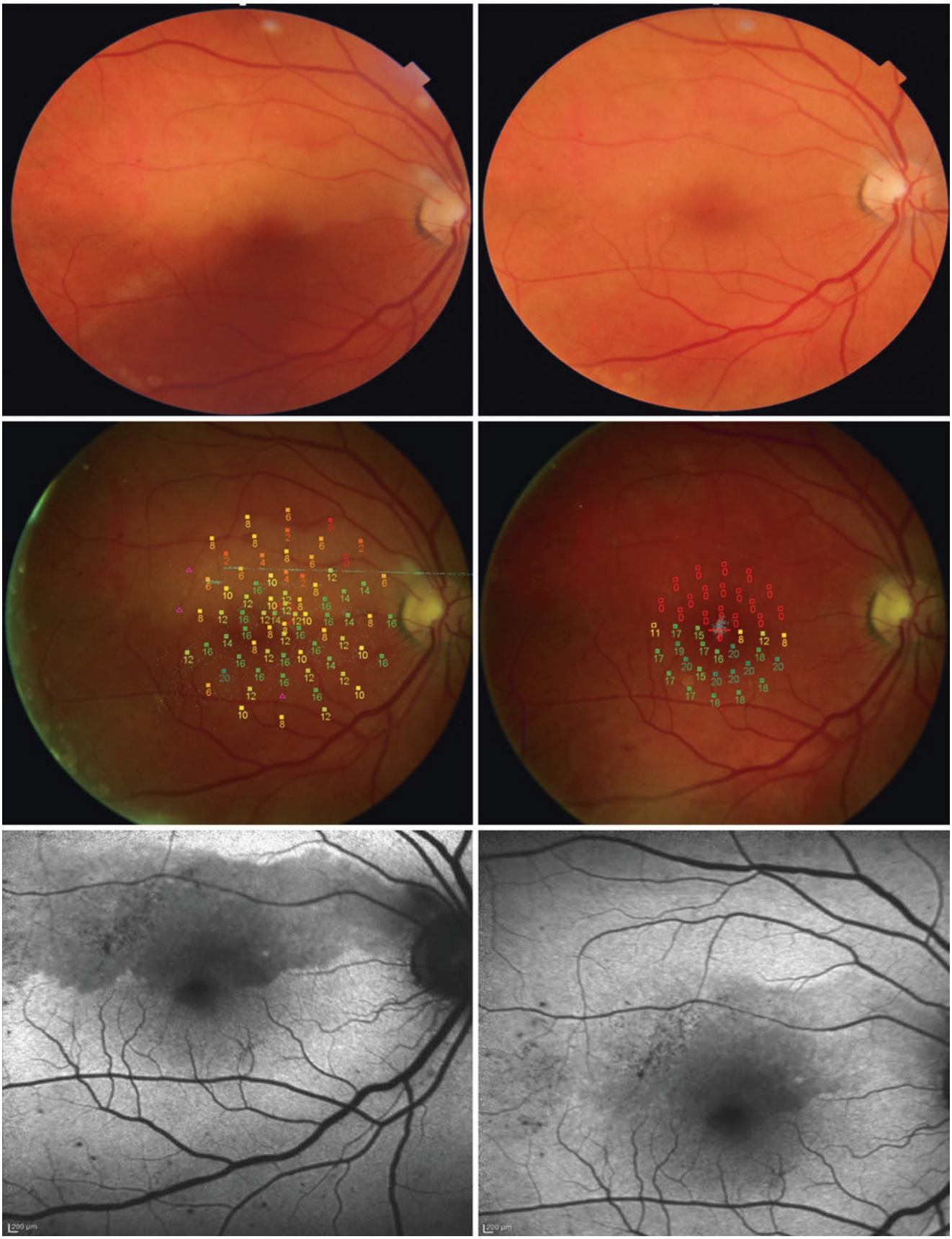

Fig. 1.4 Color figures, microperimetry maps, and fundus autofluorescence show non-arteritic transient branch retinal artery occlusion

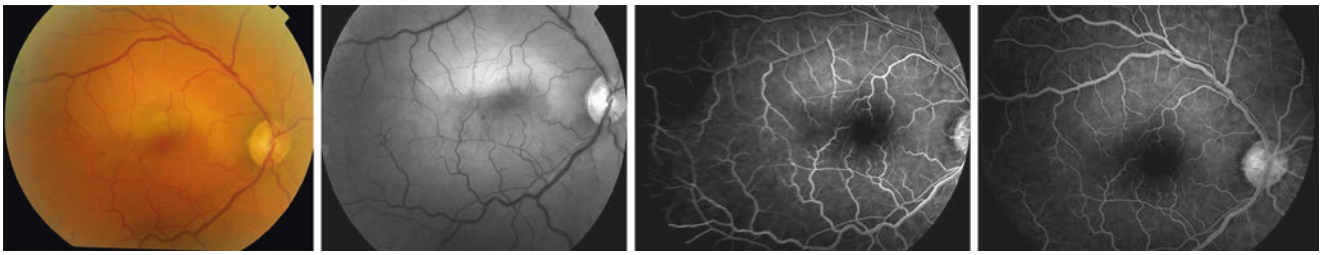

Fig. 1.5 Color fundus photograph, infrared, and fluorescein angiography show a non-arteritic branch retinal artery occlusion with foveal sparing

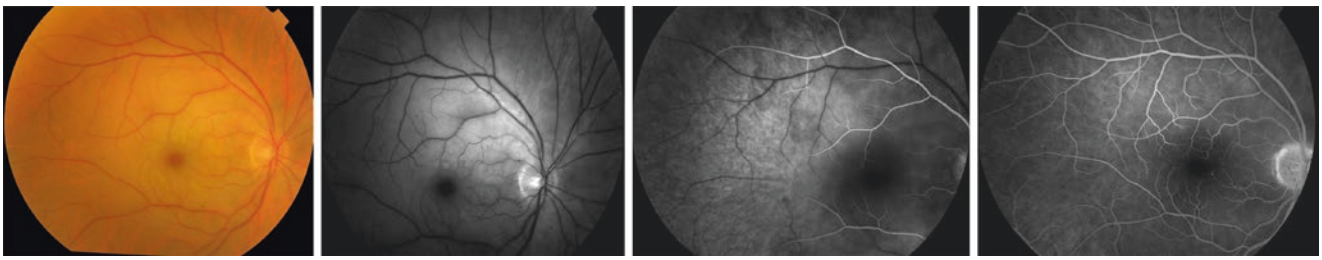

Fig. 1.6 Color fundus photograph, infrared, and fluorescein angiography show a non-arteritic branch retinal artery occlusion with foveal involvement

chronic stages of CRAO, optic atrophy, retinal pigmented epithelium (RPE) changes and cotton wool spots can be found.

Retinal Imaging

Fluorescein angiography (FA) usually shows delayed filling with the dye slowly filling arterioles in a laminar pattern (similar to normal retinal venous flow). The delayed filling of the central retinal artery may vary from 5 to 20 s, but arterial branches may show even more delay. Staining of retinal vessels and leakage of fluorescein dye into the RPE are quite rare with the exclusion of the arteritic/vasculitis forms (David et al. 1967).

In the acute stage of CRAO, optical coherence tomography (OCT) shows an increased reflectivity of the inner nuclear layers, starting from the retinal nerve fiber layer down to the outer plexiform layer, which corresponds with the cellular ischemia and whitening seen on fundus evaluation. In contrast, the outer retinal layers are not opacified, though the outer retinal reflectivity is acutely decreased due to inner retinal hyper-reflectivity. No retinal thickening or edema is usually reported (Karacorlu et al. 2006) (Figs. 1.7 and 1.8).

Other examinations, such as visual field, electroretinography, and fundus autofluorescence may be helpful in the management and follow up of patients affected by CRAO. On visual field examination, a central scotoma is the most common defect in eyes with CRAO, followed by paracentral scotoma. Cases of cilioretinal sparing show a preserved area of central visual field (Hayreh and Zimmerman 2005).

Autofluorescence can be performed as a noninvasive alternative way to fluorescein angiography to better evaluate the fundus and help in the diagnosis of CRAO. Accepting that lipofuscin is present at high level in atherosclerotic plaques, hyperautofluoroscent emboli may help in the diagnosis of an atherosclerotic form with calcium emboli (Bacquet et al. 2017).

Optical coherence tomography angiography (OCTA) may reveal different stages of vascular perfusion in both inner and outer vascular plexus in eyes with CRAO. In the case of acute CRAO, both plexuses' show an equal decrease of vascular perfusion. In the case of CRAO with cilioretinal sparing, a wider area of decreased perfusion in the superficial plexus has been described (Bonini Filho et al. 2015) (Fig. 1.9).

Electroretinography (ERG) can also be performed in these patients and it usually shows a wider attenuation of the b-wave than the a-wave, due to more important involvement of the inner retinal layers. A typical pattern of ERG in patients with CRAO is represented by a negative waveform in the scotopic white stimulus phase (Henkes 1954).

Evaluation and Treatment

Patients with CRAO may not present promptly to the ophthalmologist and it has been demonstrated in experimental models that retinal tissue can suffer irreversible

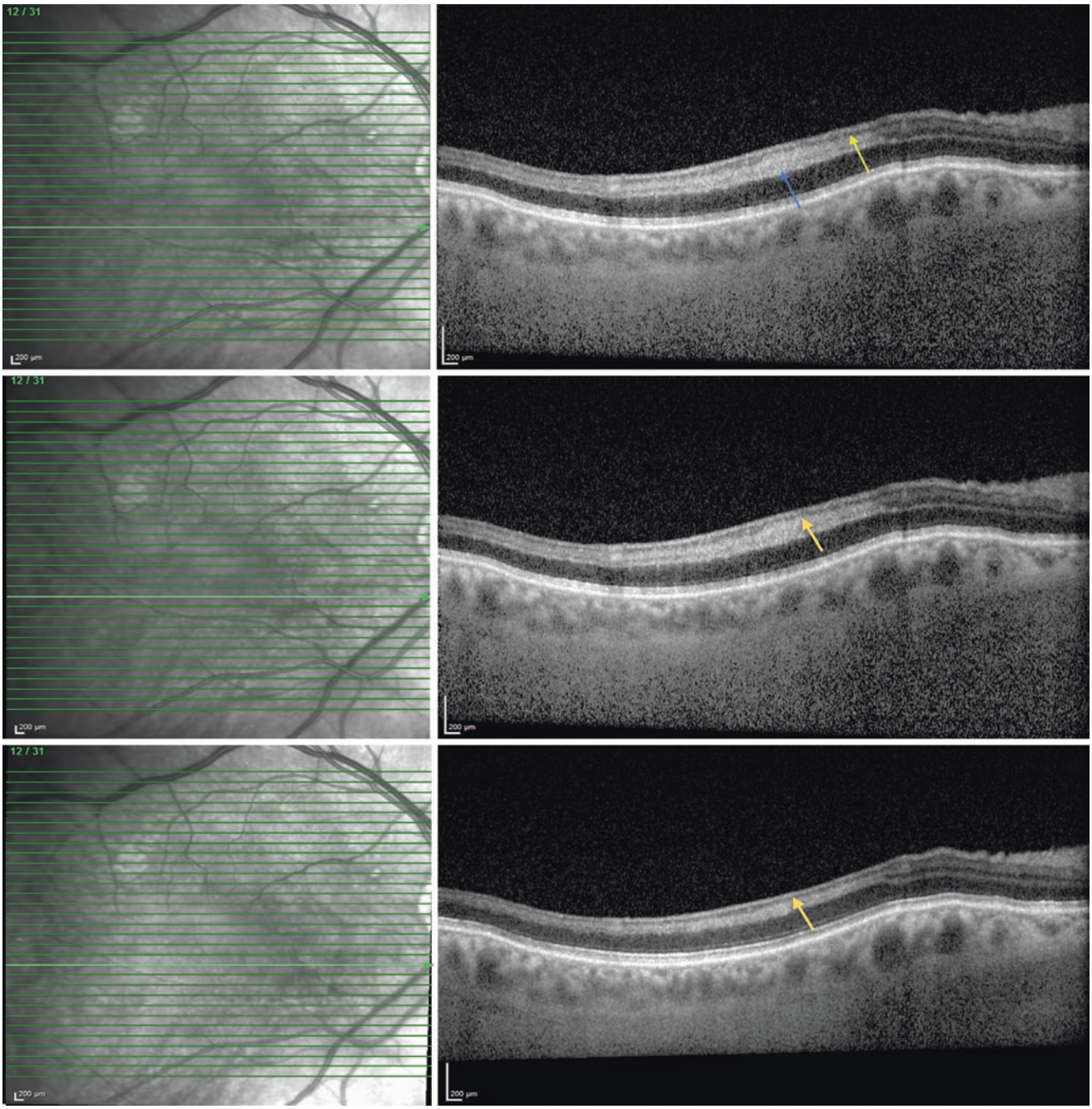

Fig. 1.7 The B scan optical coherence tomography shows the increased reflectivity of the inner nuclear layers at the level of the occlusion in a case of incomplete branch retinal artery occlusion

ischemic damages after 4 h from the onset of acute CRAO (Hayreh et al. 1980).

In patients who present within the first hours from the onset of symptoms, it is important to rule out giant cell arteritis in patients over 50 years of age by C-reactive protein, erythrocyte sedimentation rate, and complete blood count. These patients should be urgently treated with steroids to prevent contralateral eye visual loss (Proven et al. 2003).

A hypercoagulable workup is needed in patients younger than 50 including antiphospholipid antibody syndrome, autoimmune conditions, inflammatory disorders, and other hypercoagulable states (PPP strong recommendation) (https://www.aao.org/preferred-practice-pattern/retinal-ophthalmic-artery-occlusions-ppp-2019). Susac syndrome should be excluded in a young patient with multiple or recurrent BRAO.

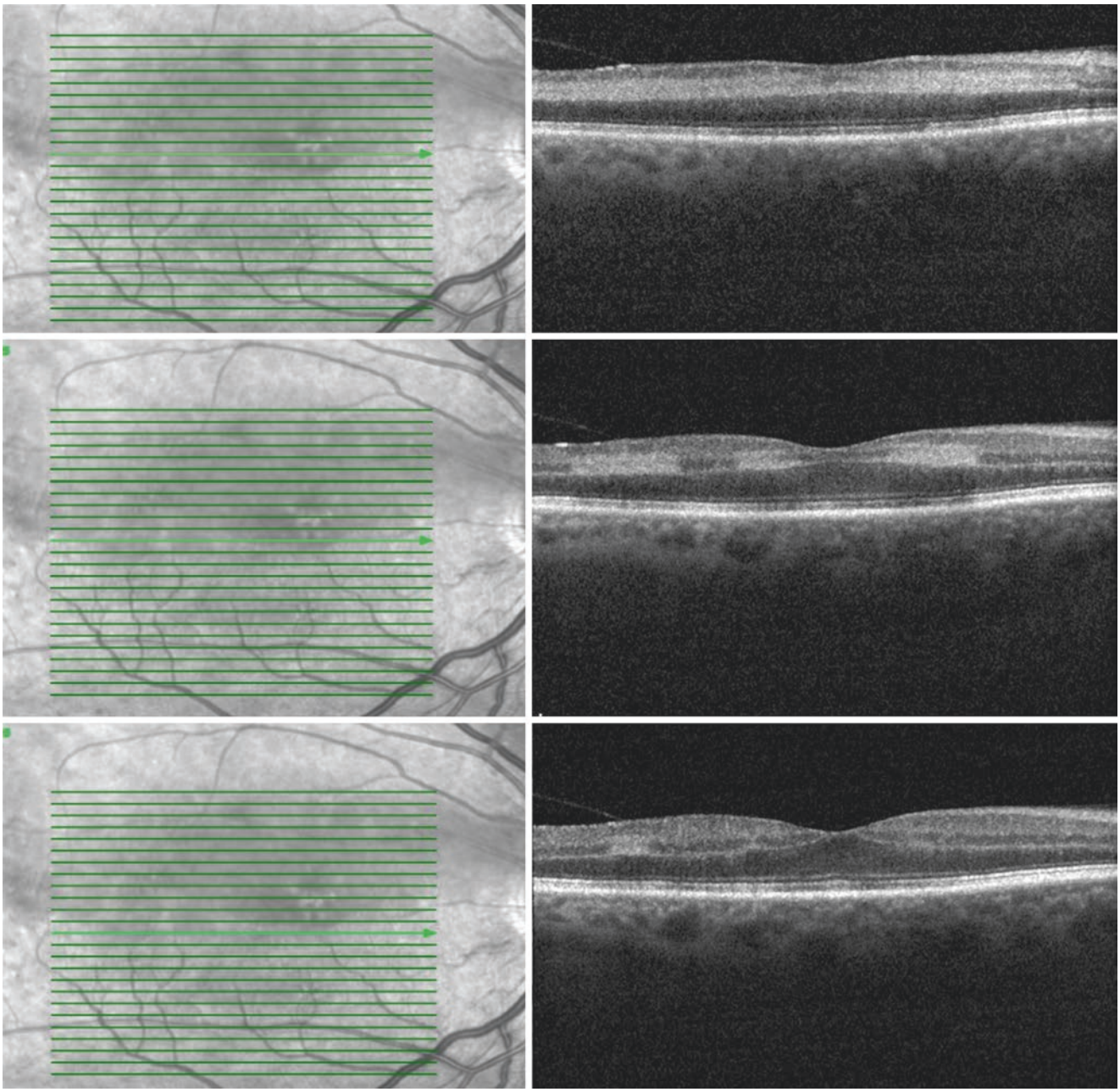

Fig. 1.8 B scan optical coherence tomography shows the increase of reflectivity of the inner retinal layers with the involvement of the foveal depression

In elderly patients, one of the most common causes of the ischemia is atherosclerosis and emboli. Because of this, a cardiac evaluation should be performed to explore cardiac function and defects of the valves, along with echocardiography, electrocardiograms and heart monitoring, which might reveal a rhythm defect. Finally, carotid ultrasound should be performed in order to exclude carotid artery stenosis (https://www.aao.org/preferred-practice-pattern/retinal-ophthalmic-artery-occlusions-ppp-2019).

With regard to this, acute and symptomatic CRAO from embolic etiologies should be immediately referred to the nearest stroke center in order to organize a prompt assessment and eventually an acute intervention (https://www.aao.org/preferred-practice-pattern/retinal-ophthalmic-artery-occlusions-ppp-2019).

In cases of non-arteritic CRAO, there are several approaches that have been proposed but unfortunately none have been evaluated in randomized clinical trials. In order to

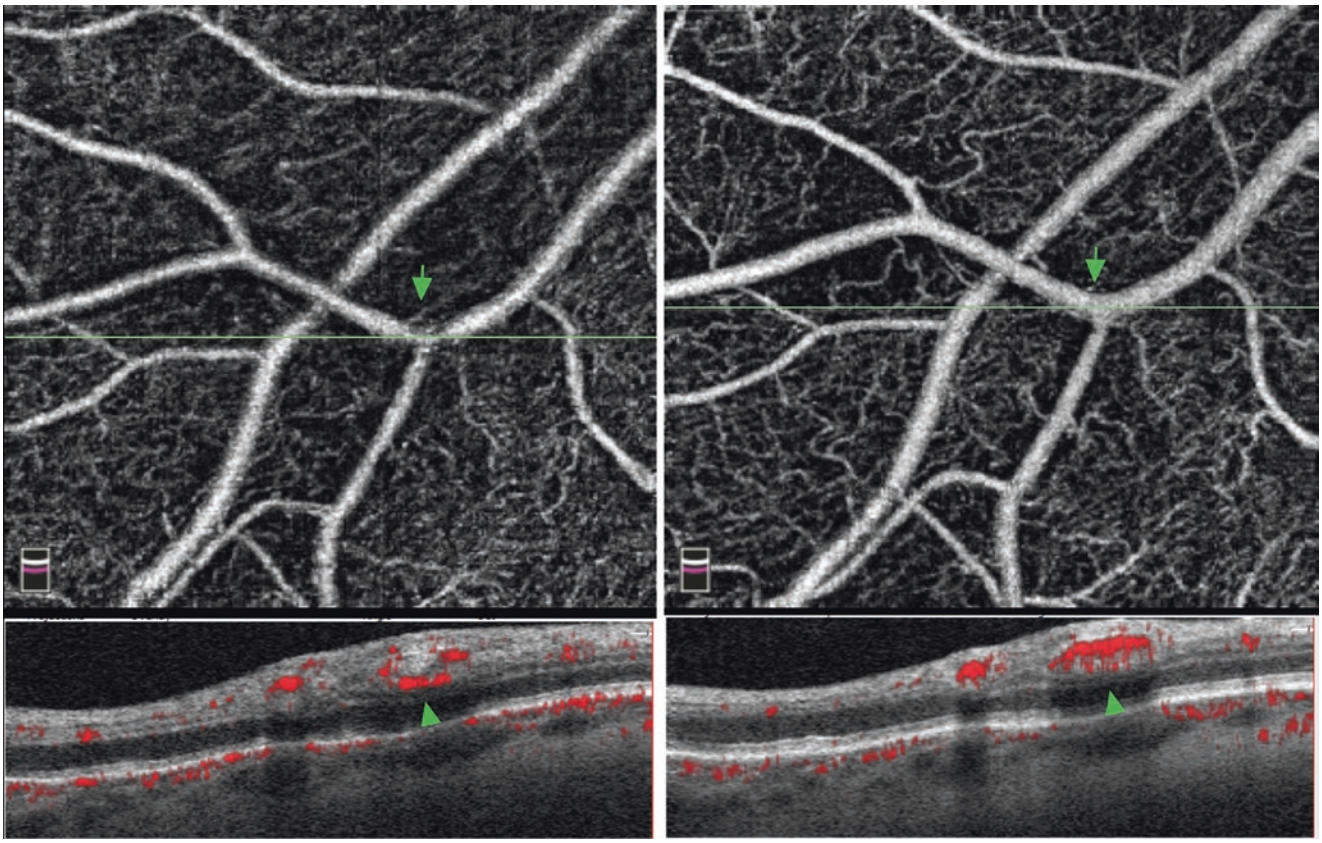

Fig. 1.9 Optical coherence tomography angiography of a branch artery occlusion. The en face images at the level of the superficial capillary plexus show the site of the occlusion at baseline and the same vessel with a wider diameter at the time of the reperfusion (green arrows) after 2 months follow up. The structural B-scan demonstrates the disappearance of the hyperreflective spot, localized in the inner retina, and then reappearance of the red blood cell's motion

dislodge the emboli and produce retinal arterial vasodilation, ocular digital massage has been proposed, using 10–15 s of pressure followed by sudden release. Moreover, anterior chamber paracentesis can be performed in these patients, in order to cause a sudden decrease of IOP and to support the arterial reperfusion.

In addition, the use of vasodilating medication such as sublingual isosorbide dinitrate or inhalation of hyperbaric oxygen has been proposed and could be helpful to restore retinal arterial blood flow (Hayreh 2011).

Intravenous or intra-arterial thrombolysis (Rumelt et al. 1999) can be performed with the aim to dissolve the fibrin occlusion of the involved retinal artery; thrombolytics include streptokinase, urokinase, and tissue plasminogen activator (t-PA) are administered (Hazin et al. 2009). While the intravenous technique via is preferred due to ease and availability, it does present a higher systemic risk of hemorrhage and a generalized hypocoagulable state (Biousse et al. 2007; Biousse 2008).

For this reason, intra-arterial therapy is better tolerated, ensuring a localized delivery of a thrombolytic drug (Hazin et al. 2009).

Although no definite benefit has been shown for using thrombolytic therapy in CRAO, 3 h are considered a window of opportunity for best visual outcome (Arnold et al. 2005).

New reports demonstrated that treatment with hyperbaric oxygen (HBO_2) can be useful in eyes affected by CRAO. The aim is to reoxygenate the ischemic inner retinal layer by hyperoxygenating the choroidal vasculature, trying to recanalize retinal arterial vessels (Butler et al. 2018). In order to obtain the best possible outcome, patients should present to a medical facility with an onset of symptoms no longer than 24 h; these patients may reveal a return to near-normal vision during HBO_2 therapy (Hanley and Cooper 2018).

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Ocular Ischemic Syndrome

2

Judy E. Kim and Eileen S. Hwang

Introduction

Ocular ischemic syndrome (OIS) is defined as the ocular manifestations of severe carotid artery stenosis or occlusion. For some patients, the first indication of carotid disease is OIS. Diagnosing a patient with OIS gives them a poor prognosis for both ocular and systemic morbidity, but may provide the physician with an opportunity to prevent a major stroke (Sivalingam et al. 1989, 1991). Since OIS was first described in 1963 (Hedges 1963; Kearns and Hollenhort 1963), imaging techniques have evolved, improving our ability to characterize the ocular findings of this disease. Although other authors have used the term venous stasis retinopathy, we will use the term ocular ischemic syndrome in this chapter (Brown et al. 2018).

Etiology

In OIS, carotid artery stenosis or occlusion leads to inadequate flow in the ophthalmic artery, the first branch of the internal carotid artery (Fig. 2.1). Inadequate ophthalmic artery perfusion causes ischemia of the choroid, ciliary body, and retina. In contrast, retinal artery occlusions cause only retinal ischemia (Table 2.1) (Mendrinos et al. 2010). Like OIS, orbital infarction syndrome is a result of carotid artery occlusion, but there is additional involvement of the extraocular muscles which are supplied by the ophthalmic artery. Orbital infarction syndrome is far rarer than OIS, probably due to collateral circulation (Bogousslavsky et al. 1991).

Most patients with OIS have at least 80% ipsilateral carotid stenosis (Brown and Magargal 1988), but only 29% of patients with symptomatic total carotid occlusion demonstrate findings consistent with OIS (Klijn et al. 2002). Some patients may be more susceptible to developing OIS because of poor ophthalmic artery perfusion and inadequate collateral circulation.

Carotid stenosis is most frequently caused by atherosclerosis, although cases of OIS caused by carotid dissection and giant cell arteritis have been reported (Duker and Belmont 1988; Hamed et al. 1992). Rarely, an ophthalmic artery occlusion can cause similar ocular findings (Bullock et al. 1972).

Demographics and Incidence

In a series of 43 patients who were diagnosed with OIS, 67% were male and 33% were female. The average age was 65 years old and the youngest age was 52 years old. 49% of the patients had left eye involvement, 32% had right eye involvement, and 19% had bilateral disease (Brown and Magargal 1988).

Clinical Features

Symptoms

Most patients with OIS experience gradual onset vision loss, although a small percentage describe acute loss of vision (Brown and Magargal 1988; Mizener et al. 1997). Visual acuity on presentation varies. In one series, 37% of patients had vision of counting fingers or worse, 43% had vision of 20/50 or better, and 20% had intermediate visual acuity (Sivalingam et al. 1991).

Patients with OIS sometimes describe amaurosis fugax (Hayreh and Zimmerman 2014). Amaurosis is sudden, painless vision loss in one eye that lasts for 2–30 min that may be diffuse or altitudinal (Streifler et al. 1995). Amaurosis is a common symptom of retinal vascular disease.

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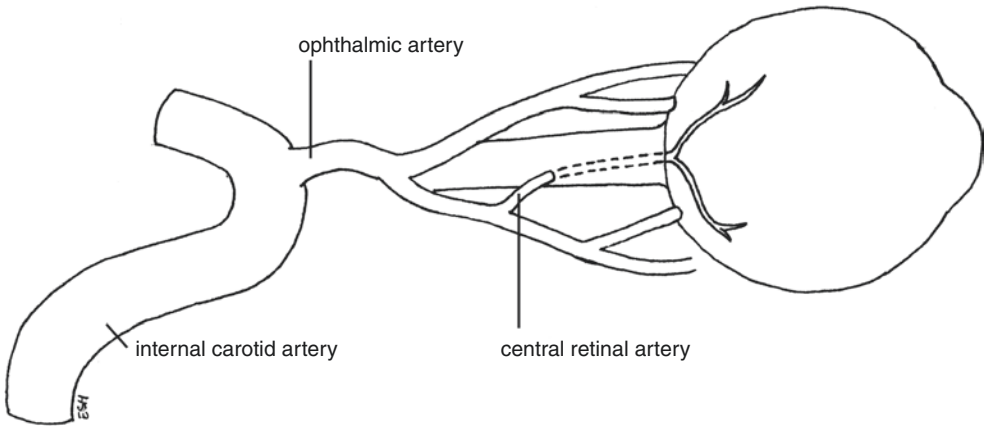

Fig. 2.1 Diagram illustrating blood supply to the eye

Table 2.1 Comparison of central retinal artery occlusion, ocular ischemic syndrome, and orbital infarction syndrome

Disease	Area of vascular occlusion	Ischemic area
Central retinal artery occlusion	Central retinal artery	Retina
Ocular ischemic syndrome	Carotid artery	Retina, choroid, and ciliary body
Orbital infarction syndrome	Carotid artery	Retina, choroid, ciliary body, and extraocular muscles

Fundus Findings

Funduscopic examination in patients with OIS often reveals multiple dot-blot retinal hemorrhages and microaneurysms in the mid-periphery (Fig. 2.2) (Brown and Magargal 1988). In comparison, retinal hemorrhages in diabetic retinopathy are usually largely located in the posterior pole in addition to the mid-periphery. However, the distribution of hemorrhages does not always follow the typical pattern (Fig. 2.3). Another characteristic feature of OIS is the presence of dilated retinal veins without tortuosity (Figs. 2.3 and 2.4), which may occur in response to hypoxia. The lack of venous tortuosity helps to distinguish OIS from central retinal vein occlusion, in which elevated intraluminal pressure leads to venous dilation as well as tortuosity.

Less common funduscopic findings include nerve fiber layer hemorrhages, cotton wool spots, cholesterol emboli, "box-carring" of retinal arteries, cherry-red spots, neovascularization of the disc or elsewhere, and vitreous hemorrhage (Figs. 2.5 and 2.6) (Mizener et al. 1997). Two other findings include choroidal infarcts, which appear as wedge-shaped areas of chorioretinal atrophy, and spontaneous retinal arterial pulsations, which occur due to low perfusion pressure.

The most frequent optic nerve abnormalities are pallor and cupping secondary to neovascular glaucoma (Figs. 2.4 and 2.5), although disc swelling may occur as well.

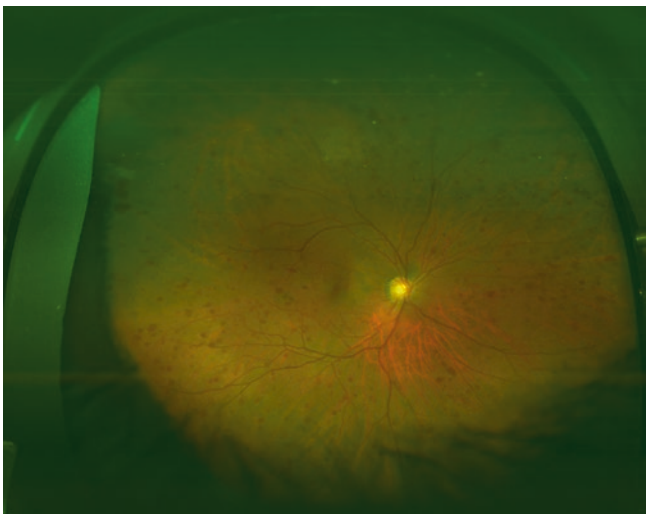

Fig. 2.2 Wide field fundus photograph illustrating retinal dot-blot hemorrhages predominantly in the mid-periphery in ocular ischemic syndrome

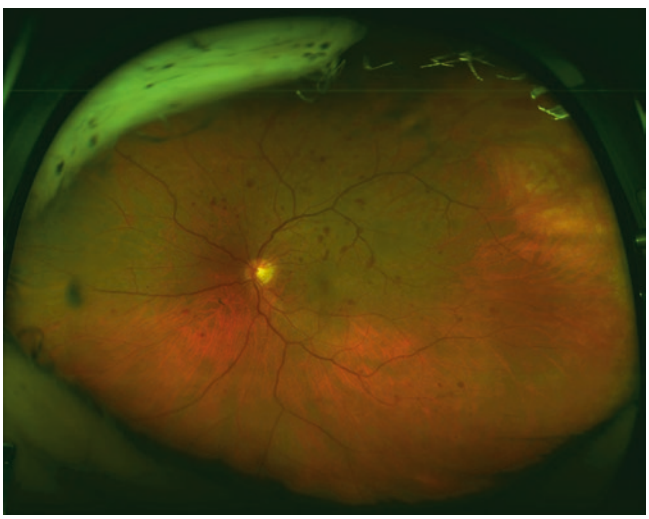

Fig. 2.3 Wide field fundus photograph illustrating dilated veins without tortuosity and dot-blot retinal hemorrhages in the posterior pole and mid-periphery in ocular ischemic syndrome

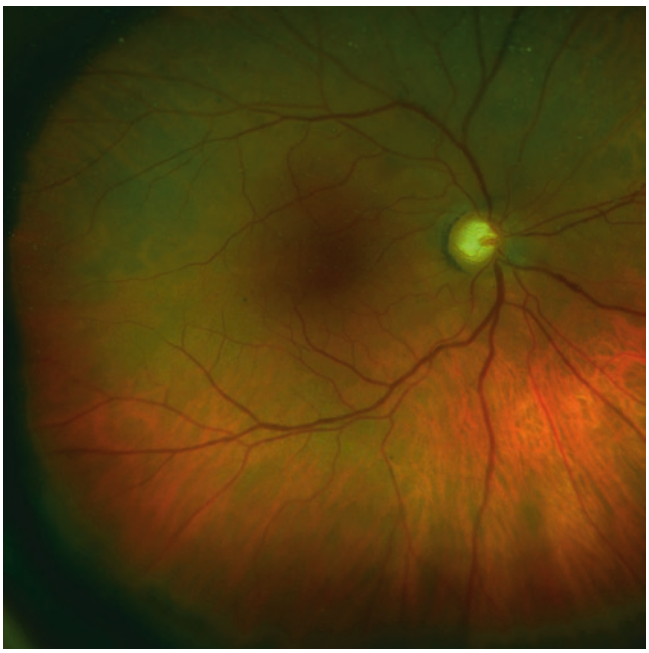

Fig. 2.4 Fundus photograph illustrating optic nerve cupping due to neovascular glaucoma and dilated retinal veins without tortuosity in ocular ischemic syndrome

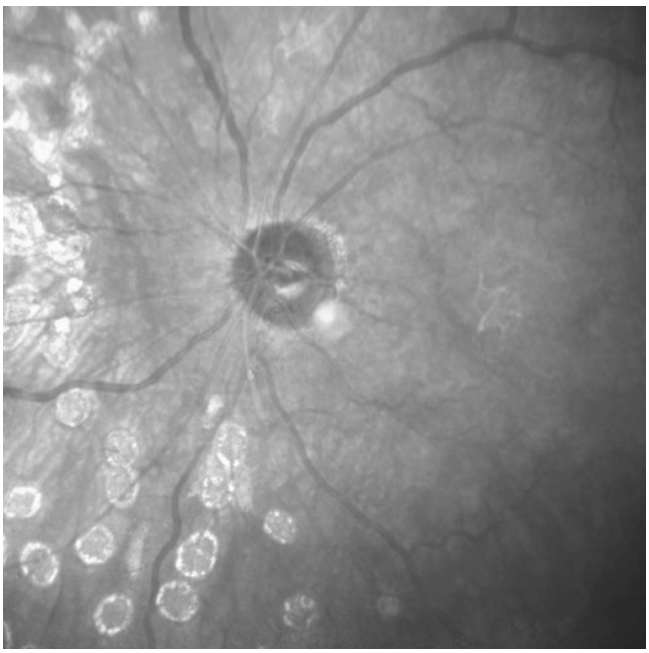

Fig. 2.6 Infrared image demonstrating an intra-arterial plaque inferior to the optic nerve in ocular ischemic syndrome. Laser scars are present from panretinal photocoagulation

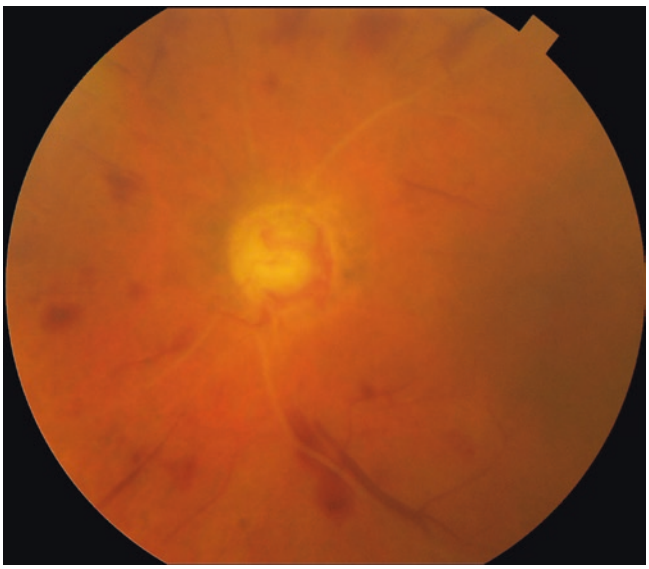

Fig. 2.5 Color fundus photograph demonstrating optic nerve cupping, neovascularization of the disc, sclerosed vessels, retinal hemorrhages, and preretinal hemorrhage secondary to ocular ischemic syndrome

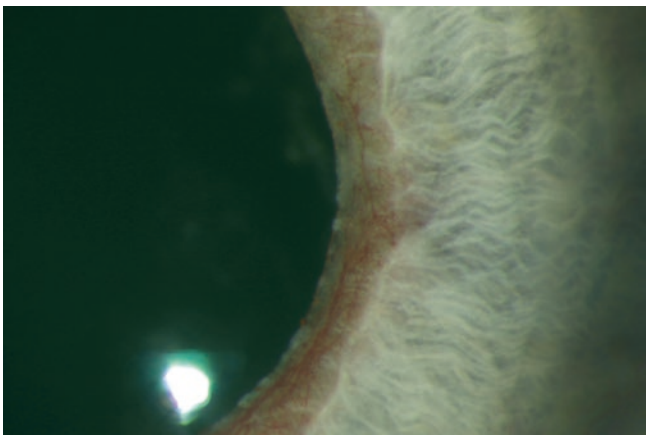

Fig. 2.7 Slit lamp photo of iris neovascularization in ocular ischemic syndrome

Anterior Segment Findings

In response to inadequate perfusion, iris neovascularization occurs in the majority of eyes with OIS (Fig. 2.7) (Brown and Magargal 1988; Mizener et al. 1997). Neovascularization of the angle is often present as well, and can lead to angle closure by peripheral anterior synechiae (Fig. 2.8). In some patients with OIS, angle closure causes elevated intraocular pressure, i.e., neovascular glaucoma. In other patients, the lack of ciliary body perfusion results in low aqueous humor production and normal or low intraocular pressure despite the lack of outflow. Anterior chamber cell and flare can be noted secondary to abnormal permeability of neovascular iris vessels. Thus, OIS should be considered on the differential diagnosis of uveitis. Other characteristic anterior segment findings in OIS include corneal edema and asymmetric cataract.

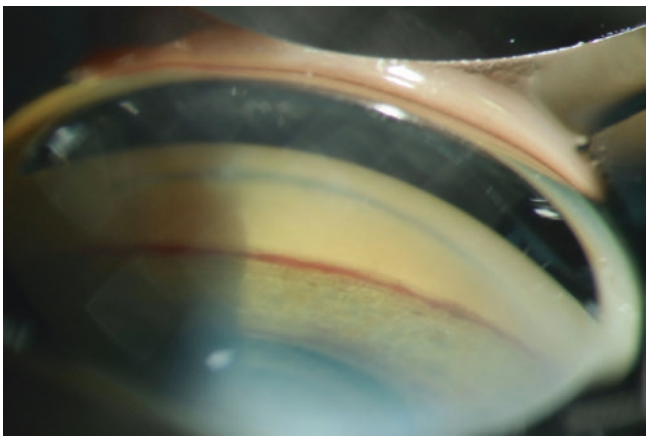

Fig. 2.8 Gonioscopy photo of angle neovascularization in ocular ischemic syndrome

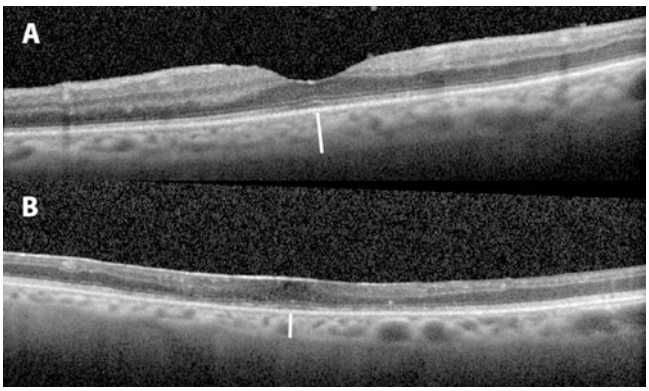

Fig. 2.9 Spectral domain optical coherence tomography demonstrating thinner submacular choroid (white line) in the eye affected with ocular ischemic syndrome (**b**) compared to the contralateral unaffected eye (**a**)

Ancillary Imaging

Optical Coherence Tomography

Eyes affected by OIS show decreased choroidal thickness compared to unaffected contralateral eyes, which may reflect choroidal ischemia (Fig. 2.9) (Kang et al. 2014). Enhanced depth imaging by spectral domain optical coherence tomography enables routine measurement of choroidal thickness. Optical coherence tomography may also demonstrate cystoid macular edema and retinal thinning (Fig. 2.10).

Optical coherence tomography angiography of one eye affected by OIS revealed peripapillary neovascularization that radiated into the vitreous (Lupidi et al. 2017).

Fluorescein Angiography

Fluorescein angiography can help establish the diagnosis of ocular ischemic syndrome when the view to the posterior segment permits. Patchy, delayed choroidal filling is a characteristic finding (Fig. 2.11), although this can be found in age-related macular degeneration and giant cell arteritis (Brown and Magargal 1988; Mack et al. 1991; Mizener et al. 1997; Gewaily et al. 2014). Delayed arm-to-retina times and delayed retinal arteriovenous circulation times are also commonly found (Fig. 2.12), but these findings are less specific to OIS. When present, late staining of retinal arteries greater than the veins (Figs. 2.13 and Fig. 2.14) distinguishes OIS from vein occlusions, in which the veins are predominately stained. However, vessel staining is not always present in OIS and may sometimes occur equally in arteries and veins, or only in veins. Vessel staining is thought to be due to hypoxic damage to the vascular endothelium (Brown and Magargal 1988).

Indocyanine Green Angiography

In OIS, indocyanine green angiography demonstrates slow filling of the choroidal arteries, delayed filling of the posterior watershed zone, and delayed filling or patchy occlusion of the choriocapillaris (Utsugi et al. 2004). This test is not commonly performed, but can be useful when the diagnosis is in doubt.

Electroretinography

Electroretinography of patients with OIS displays diminished or absent a-waves and b-waves (Brown and Magargal 1988). In OIS, choroidal and retinal vascular circulation are both decreased, affecting both the inner retina (measured in the b-wave) and the outer retina (measured in the a-wave). This contrasts with electroretinography in patients with retinal artery occlusions, in which only the b-wave is affected due to inner retinal ischemia without outer retinal ischemia.

Differential Diagnosis

Diabetic Retinopathy and Central Retinal Vein Occlusion

Diabetic retinopathy and central retinal vein occlusion (CRVO) share similar clinical features with OIS. All three diseases are characterized by retinal hemorrhages and dilated retinal veins, and can lead to neovascularization of the iris, angle, disc, and retina. The presence of unilateral or bilateral disease can help to distinguish the diseases, since diabetic retinopathy is usually bilateral and OIS is unilateral in 81% of cases (Brown and Magargal 1988). Therefore, in a diabetic patient with unilateral or highly asymmetric retinopathy, OIS should always be considered. The spatial distribution of retinal hemorrhages (posterior pole in diabetic retinopathy and mid-peripheral in OIS) can suggest a diagnosis, but should not be the sole basis of the diagnosis since hemorrhage locations can vary.

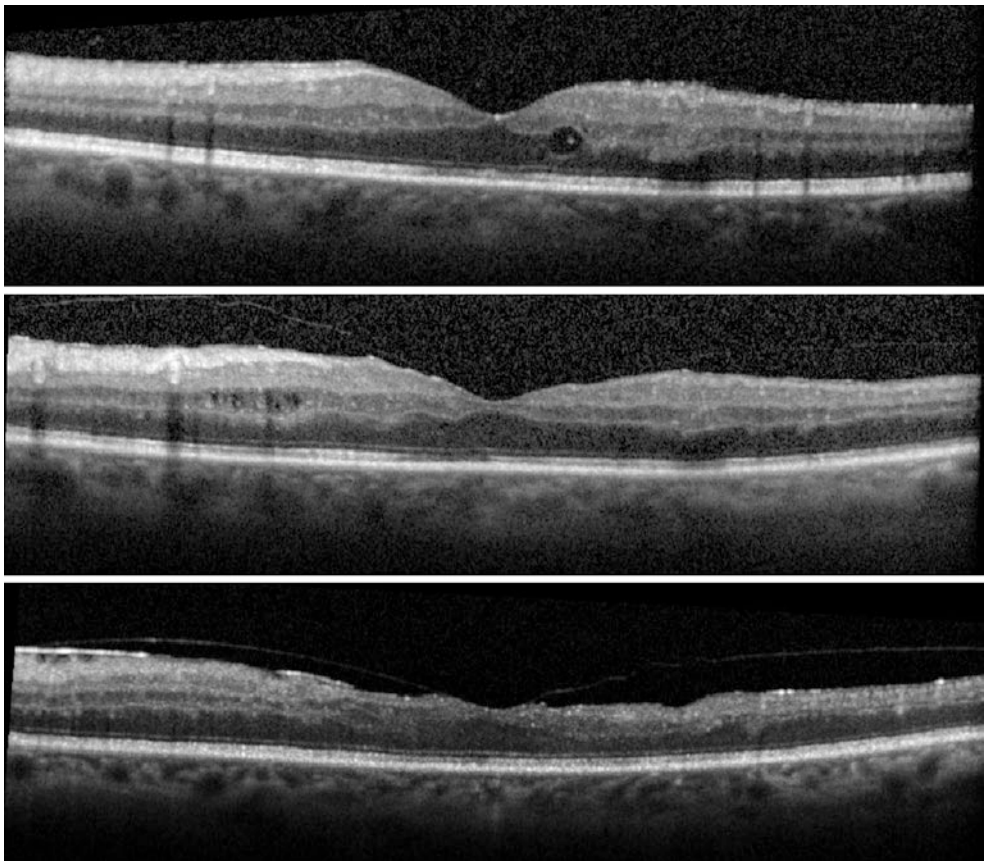

Fig. 2.10 Spectral domain optical coherence tomography demonstrating a single foveal cyst at presentation (top), macular edema at 5 months (center), and atrophy at 1 year (bottom) in ocular ischemic syndrome

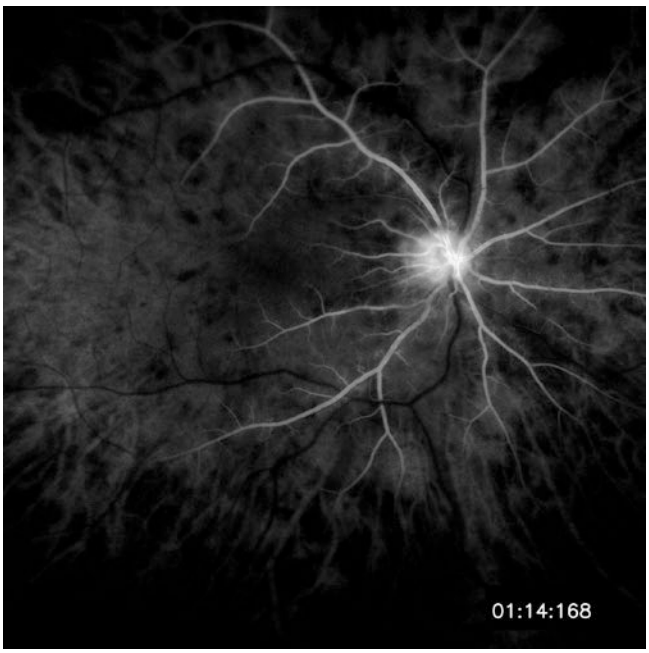

Fig. 2.11 Mid-phase fluorescein angiogram demonstrating delayed choroidal filling in ocular ischemic syndrome. Despite filling of some arteries and veins at 1 min and 14 s, minimal choroidal filling is observed

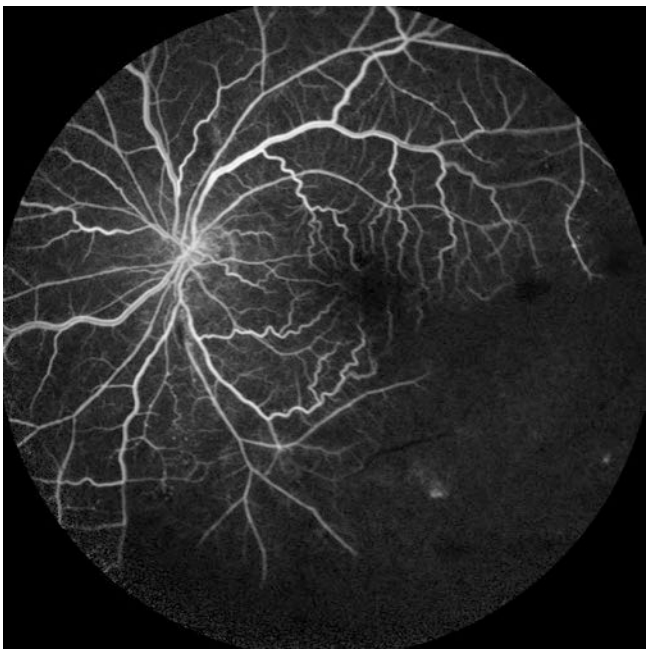

Fig. 2.12 Mid-phase fluorescein angiogram at 1 min and 12 s illustrating delayed arteriovenous transit in ocular ischemic syndrome. Forty-one seconds after arterial filling began, the veins are still demonstrating laminar flow and are not completely filled

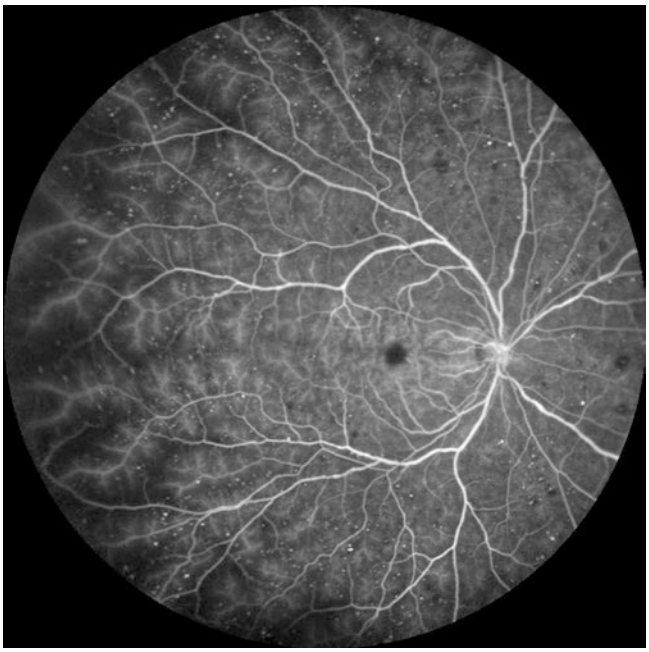

Fig. 2.13 Late phase wide field fluorescein angiogram demonstrating microaneurysms, retinal capillary nonperfusion, and retinal artery staining in ocular ischemic syndrome

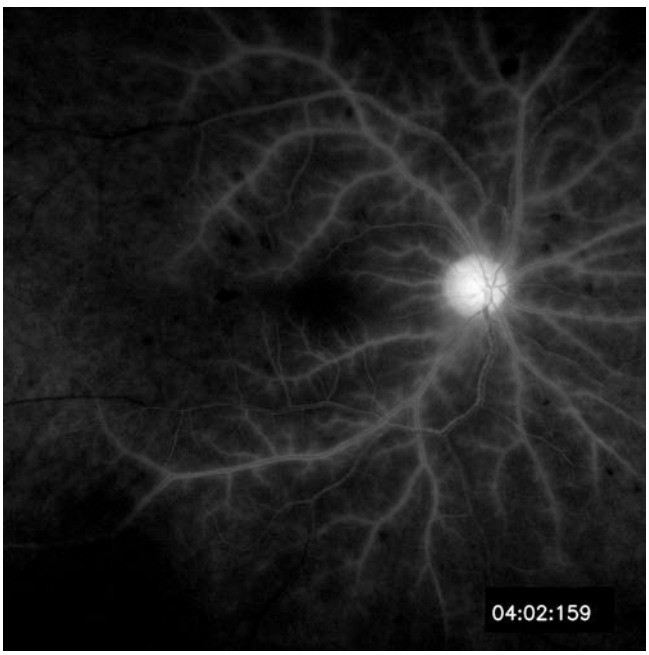

Fig. 2.14 Late phase fluorescein angiogram illustrating late arterial staining in ocular ischemic syndrome

The type of retinal hemorrhage can be used to identify cases of CRVO, in which nerve fiber layer hemorrhages are common. In contrast, OIS and diabetic retinopathy are characterized by dot-blot hemorrhages and microaneurysms. Dilated retinal veins are found in both CRVO and OIS, but a lack of venous tortuosity is indicative of OIS rather than CRVO. On fluorescein angiogram, late staining of arteries in OIS contrasts with late staining of veins in CRVO (Brown et al. 2018). Another helpful finding on fluorescein angiogram is patchy delayed choroidal filling, which is characteristic of OIS but not CRVO or diabetic retinopathy.

When evaluating a patient with a clinical picture consistent with CRVO or OIS, hyperviscosity due to a blood cell dyscrasia should be considered, although it is usually bilateral. For patients diagnosed with uveitis, OIS should be included on the differential diagnosis, although anterior chamber cell and flare in OIS are usually accompanied by neovascularization of the iris (Mizener et al. 1997).

Giant Cell Arteritis

Rarely, giant cell arteritis causes ophthalmic artery occlusion and results in a phenotype consisting of the typical features of OIS along with ischemic optic neuropathy. Corneal edema is also a prominent feature of OIS secondary to giant cell arteritis (Hamed et al. 1992; Hwang et al. 1999).

Takayasu Arteritis

Takayasu arteritis is an inflammatory disease of the aorta and its major branches. When it causes renal artery stenosis, it can lead to hypertension and hypertensive retinopathy. When it involves the carotid arteries, Takayasu retinopathy can be observed (Chun et al. 2001). Takayasu retinopathy is characterized by dilated retinal vessels, numerous microaneurysms, and arteriovenous shunting. Unlike OIS, Takayasu arteritis usually occurs in patients under the age of 40 years (Arend et al. 1990).

Recommended Workup/Ancillary Testing

Whenever OIS is suspected, a carotid duplex ultrasound should be ordered. Carotid duplex is the first-line test because it is noninvasive and has high sensitivity and specificity for severe carotid stenosis (Wardlaw et al. 2006). Magnetic resonance angiography (with and without contrast) and contrast-enhanced computed tomographic angiography have good sensitivity and specificity, although contrast carries risks of anaphylactoid reactions and renal injury. Carotid imaging in OIS usually demonstrates severe stenosis or occlusion, but may rarely show no stenosis or mild stenosis (Mizener et al. 1997). If a patient with high-grade carotid stenosis has experienced a recent transient ischemic attack, episode of amaurosis, or stroke, they should be evaluated for possible

carotid endarterectomy surgery to prevent future strokes (Barnett et al. 1991).

Color Doppler imaging of the retrobulbar vessels may correlate with the degree of stenosis found on ultrasonography and may identify signs of intracranial carotid stenosis, which cannot be detected by carotid duplex (Hu et al. 1993). Magnetic resonance and computed tomographic angiography can also detect intracranial carotid stenosis. Currently, there are no effective interventions for intracranial carotid stenosis, so additional imaging beyond carotid duplex is unlikely to impact management for a patient with a classic picture of OIS. However, if the diagnosis is in question, imaging of the intracranial carotid artery may help to determine whether the patient has OIS or another condition.

All patients diagnosed with OIS should be referred to an internist for optimization of systemic risk factors for atherosclerosis (Malhotra and Gregory-Evans 2000).

Systemic Associations

High rates of hypertension, diabetes, coronary artery disease, peripheral vascular disease, and cerebrovascular disease were noted in a series of 52 patients with OIS. Five-year follow up revealed a mortality rate of 40%, with most cases caused by ischemic heart disease, followed by stroke (Sivalingam et al. 1989).

Treatment and Prognosis

Most patients with OIS end up with vision at the finger counting level or worse despite treatment (Sivalingam et al. 1991). Therefore, the primary goals of treatment are to reduce pain and minimize neovascular glaucoma. Pain from anterior segment inflammation can be treated with topical corticosteroids and cycloplegia, but oral pain medications may be necessary.

Neovascular glaucoma can lead to pain and additional compromise of poor ocular perfusion in OIS. Fortunately, many patients have low or normal IOP despite significant angle neovascularization because low ciliary body perfusion decreases aqueous production. For patients with elevated intraocular pressure, topical aqueous suppressants, and oral carbonic anhydrase inhibitors can be helpful in the short term, but trabeculectomy, tube-shunting procedures, or diode laser ciliary ablation may become necessary (Malhotra and Gregory-Evans 2000).

To reduce the drive for neovascularization, panretinal photocoagulation (PRP) of ischemic retina can be performed if the view permits (Fig. 2.15). However, PRP only leads to regression of iris neovascularization in 36% of eyes (Sivalingam et al. 1991). Hayreh argues that PRP should only be used when there is evidence of retinal ischemia on fluorescein angiography (i.e., capillary drop out), since choroidal or ciliary body ischemia may be the driving factor for neovascularization rather than retinal ischemia (Mizener et al. 1997).

Neovascularization may also be treated with intravitreal anti-VEGF injection. Intravitreal bevacizumab administration caused rapid resolution of iris neovascularization and pain in two patients with OIS (Amselem et al. 2007). Neovascularization recurred in one case and was treated with another injection.

The standard treatment for symptomatic severe carotid stenosis is carotid endarterectomy, which significantly decreases the rate of future strokes. In the landmark North

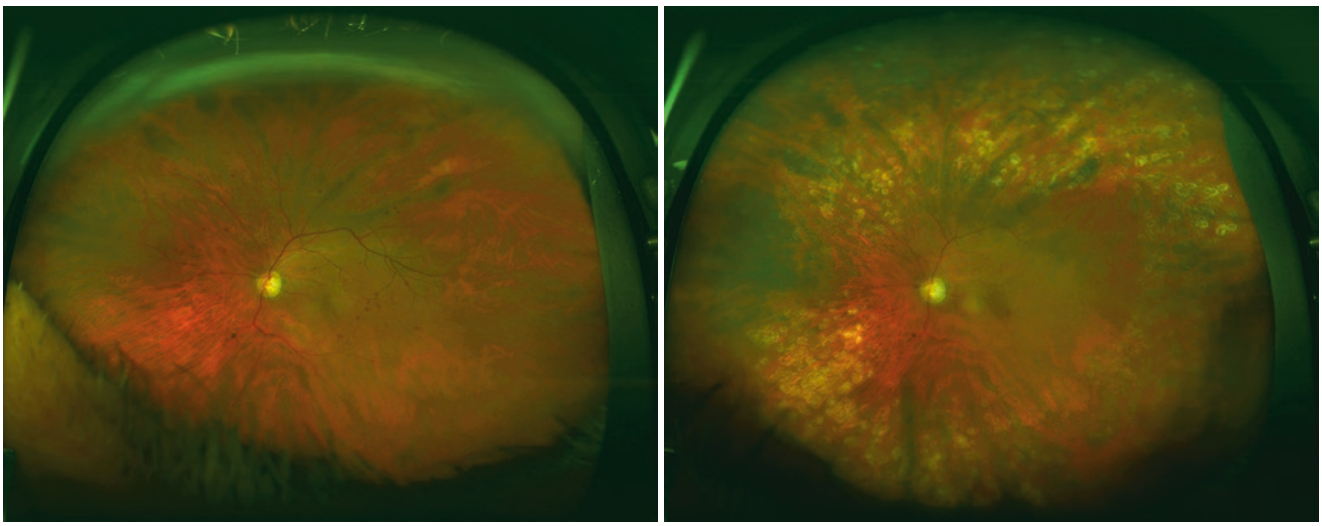

Fig. 2.15 Fundus photographs of ocular ischemic syndrome before (top) and after (bottom) treatment with scatter laser photocoagulation

American Symptomatic Carotid Endarterectomy Trial, symptomatic stenosis was defined as stroke, transient ischemic attack, or amaurosis within 120 days (Barnett et al. 1991). In clinical practice, the vascular surgeon may consider OIS to be evidence for symptomatic carotid stenosis when deciding whether to offer surgery. It is unclear whether carotid endarterectomy improves visual outcomes in OIS since comparative studies have not been performed. One case series reported that most patients experienced worse vision despite surgery (Sivalingam et al. 1991). Notably, most of the patients in this series had neovascularization of the iris, a poor prognostic sign. Another series found that most patients had stable or improved vision after carotid endarterectomy. However, patients with iris neovascularization were excluded from this series, so the studied population had a relatively good prognosis even without surgery (Kawaguchi et al. 2001).

Summary

Ocular ischemic syndrome is an ocular manifestation of severe carotid stenosis or occlusion and can be the first indication of carotid disease. While the visual prognosis is poor, the diagnosis may provide a critical opportunity to prevent a major stroke in close communication with the patient's internist and cardiovascular specialist. Ocular findings include retinal hemorrhages in the mid-periphery and dilated retinal veins without tortuosity. Ocular ischemic syndrome should be distinguished from other vascular diseases, and optical coherence tomography and fluorescein angiography may aid in establishing the diagnosis. Patients should be closely monitored for late complications such as neovascular glaucoma.

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Medical Management of Diabetic Retinopathy

3

Sean W. Tsao and Mitul Mehta

Pathophysiology and Clinical Features

Diabetic retinopathy is one of the few and useful circumstances where the examining physician can directly monitor the pathologic sequelae of an otherwise silent systemic disease on the microcirculation of the retina. The end-stage manifestations of diabetic retinopathy culminate from the eye's own regenerative responses to persistent ischemia. Dysregulated fibrovascular proliferation stemming from damaged retinal vessels leads to retinal detachment; or, proliferation of fibrovascular tissue in the anterior chamber can lead to neovascular glaucoma—both manifestations tend to portend a poor prognosis in the absence of prompt medical and surgical intervention.

The earliest microscopic evidences of damage in diabetic retinopathy are (1) the loss of pericytes from retinal capillaries and (2) the thickening of the capillary basement membrane (Cogan et al. 1961; Robison Jr et al. 1983, 1986; Kuwabara and Cogan 1963). The aldose reductase pathway and nonenzymatic glycation have both been implicated in the etiology of these microvascular changes (Robison Jr et al. 1983, 1986; Nishio et al. 1995).

The continued cycle of injury to the capillary endothelium leads to the first clinically visible sign of diabetic retinopathy, the microaneurysm. Histologically, these areas correspond to clusters of endothelial cell proliferation, which may be tied to the loss of pericytes (Cogan et al. 1961; Lindahl et al. 1997). On clinical examination, microaneurysms appear as tiny red dots visible within the retinal parenchyma (Fig. 3.1).

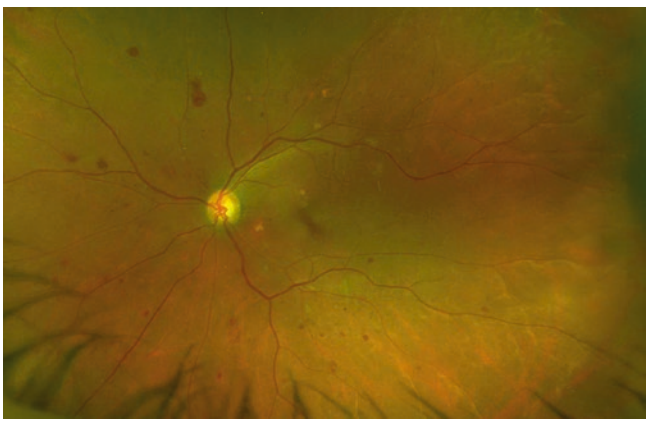

Fig. 3.1 Microaneurysms. The small red intraretinal specks that are characteristic of diabetic retinal microaneurysms just inferior to the macula

As endothelial damage accrues, the endothelial intercellular tight junctions degrade, and lead to vascular permeability and attendant retinal edema (Wallow and Engerman 1977). This is clinically manifested as diabetic macular edema, characterized by a thickening of the macula due to accumulation of extracellular fluid and/or hard protein exudates due to excess vascular permeability (Fig. 3.2). Vascular endothelial growth factor (VEGF), released by the retina as a response to ischemic injury, further promotes vascular permeability and exacerbates leakage in diabetic macular edema (Keck et al. 1989; Antonetti et al. 1999; Lakshminarayanan et al. 2000).

The extent of vascular leakage can vary greatly, and milder cases of macular edema may escape fundoscopic examination altogether. Prior to the advent of optical coherence tomography (OCT), the detection of diabetic macular edema was instead described as "clinically significant macular edema" (CSME), a term coined by the investigators of the Early Treatment of Diabetic Retinopathy Study (ETDRS) to a combination of fundoscopic criteria that warranted focal macular laser therapy, discussed in detail later in section "Early Treatment of Diabetic Retinopathy Study and Classification of Diabetic Retinopathy" (Early Treatment Diabetic Retinopathy Study Research Group 1991a). After the widespread adoption of OCT in the management of diabetic retinopathy, clinical trials, and medical management are

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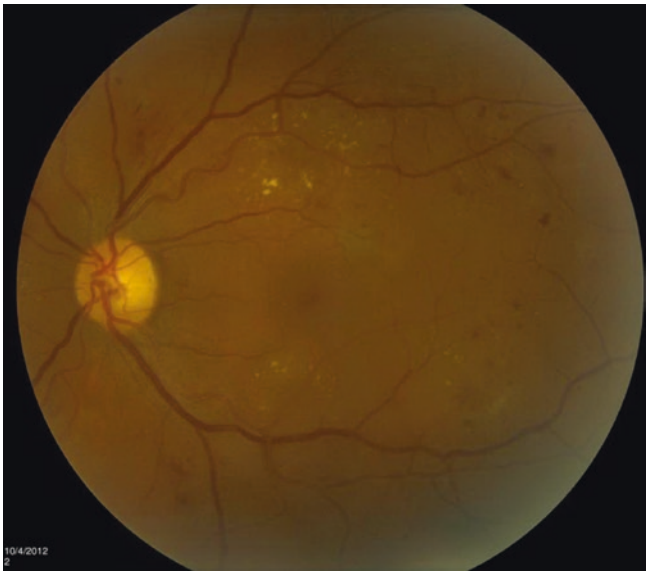

Fig. 3.2 Hard Exudates. Yellowish refractile deposits, typical of hard exudates, are seen scattered in clustered around the macula with mild thickening, imperceptible without stereopsis. (Image courtesy of Stephanie Lu)

now preferentially guided by a standardized quantitative measure of the foveal and macular thickness (Fig. 3.3a and b).

Capillary loss and acellularity marks the final stage of microvascular injury in diabetic retinopathy (Cogan et al. 1961; Kohner and Henkind 1970). These capillaries appear devoid of nuclei on histology and fail to convey circulation to the retina. When gathered in sufficiently confluent regions, acellular capillaries appear as "capillary drop out" on fluorescein angiography, an ominously dark territory of retina that tends to invade centripetally. The pattern resembles that of a view of earth from space at night: the lit areas still powered and perfused, the dark areas now in blackout and ischemic (Fig. 3.4a and b). Non-perfusion is typically difficult to detect on fundoscopic examination, though more severe cases of ischemic non-perfused retina may appear to have a dulled and thin retinal reflex as opposed to the healthy sheen of normal retina (Fig. 3.5a and b).

The hypoxia experienced by the regions of non-perfused retina is believed to be the trigger for VEGF production, stimulating dysregulated angiogenesis from existing retinal vessels in a desperate and disorganized attempt to revascularize oxygen-starved retina. This manifests as retinal neovascularization, often growing in weed-like bouquets sprouting off of existing retinal vessels, such as the vessels at the optic disc, vascular arcades, or at the margins of perfused and non-perfused retina.

If retinal neovascularization is seen growing flat along the plane of the retina, it is described as "intra-retinal microvascular abnormalities" (IRMA) (Fig. 3.6a and b). If the retinal neovascularization, unfortunately, elects to grow inward into the posterior hyaloid and enter the collagenous scaffold of the vitreous body, it is termed "neovascularization elsewhere" (NVE), or if present at the optic disc, "neovascularization of the disc" (NVD) (Fig. 3.7). In some cases, the degree of retinal ischemia and VEGF production is so robust that the demand for neovascularization affects the anterior chamber, causing neovascularization of the angle (NVA) leading to glaucoma due to zippering and occlusion of the trabecular meshwork.

A number of untoward consequences may occur after neovascularization takes root within the vitreous body. The continued proliferation of neovascularization occurs in a chaotic fashion, further increasing the adhesion between the retinal vessel and its neovascular tendrils which are freely thrown about with the stochastic movement of the vitreous humor. This may lead to:

1. Tractional Retinal Detachment. Retinal neovascularization sprouts as fronds into the vitreous cavity, invested within a very fine white-gray colored membrane, which is composed of fibro-contractile tissue (Kampik et al. 1981). Akin to the contractile tissue found in wound healing, the fibrovascular membranes accompanying neovascular fronds can also contract and lift the underlying retina, causing a tractional retinal detachment (Fig. 3.8).
2. Combined Rhegmatogenous Tractional Retinal Detachment. In some cases, the integrity of the retina is insufficient to withstand the anterior–posterior tractional force caused by the fibrovascular membrane, and a retinal tear develops, leading to a combined tractional-rhegmatogenous retinal detachment.
3. Vitreous Hemorrhage. Alternatively, the contractile forces may shred the bridging vessels between retinal circulation and the neovascular tufts, leading to vitreous hemorrhage (Fig. 3.9).

Epidemiology

Diabetes retinopathy is considered the leading cause of visual morbidity among individuals of working age worldwide (Resnikoff et al. 2004). The Centers for Disease Control and Prevention reported that 30.3 million individuals in the United States have diabetes mellitus, which constitutes approximately 10% of the entire population (Centers for Disease 2017). Among those aged 40 years or older in the United States, an estimated 4.1 million individuals (1 in 29 people) have signs of diabetic retinopathy and nearly 900,000 (1 in 132 people) have vision-threatening diabetic retinopathy (Kempen et al. 2004).

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) showed that nearly all of the patients

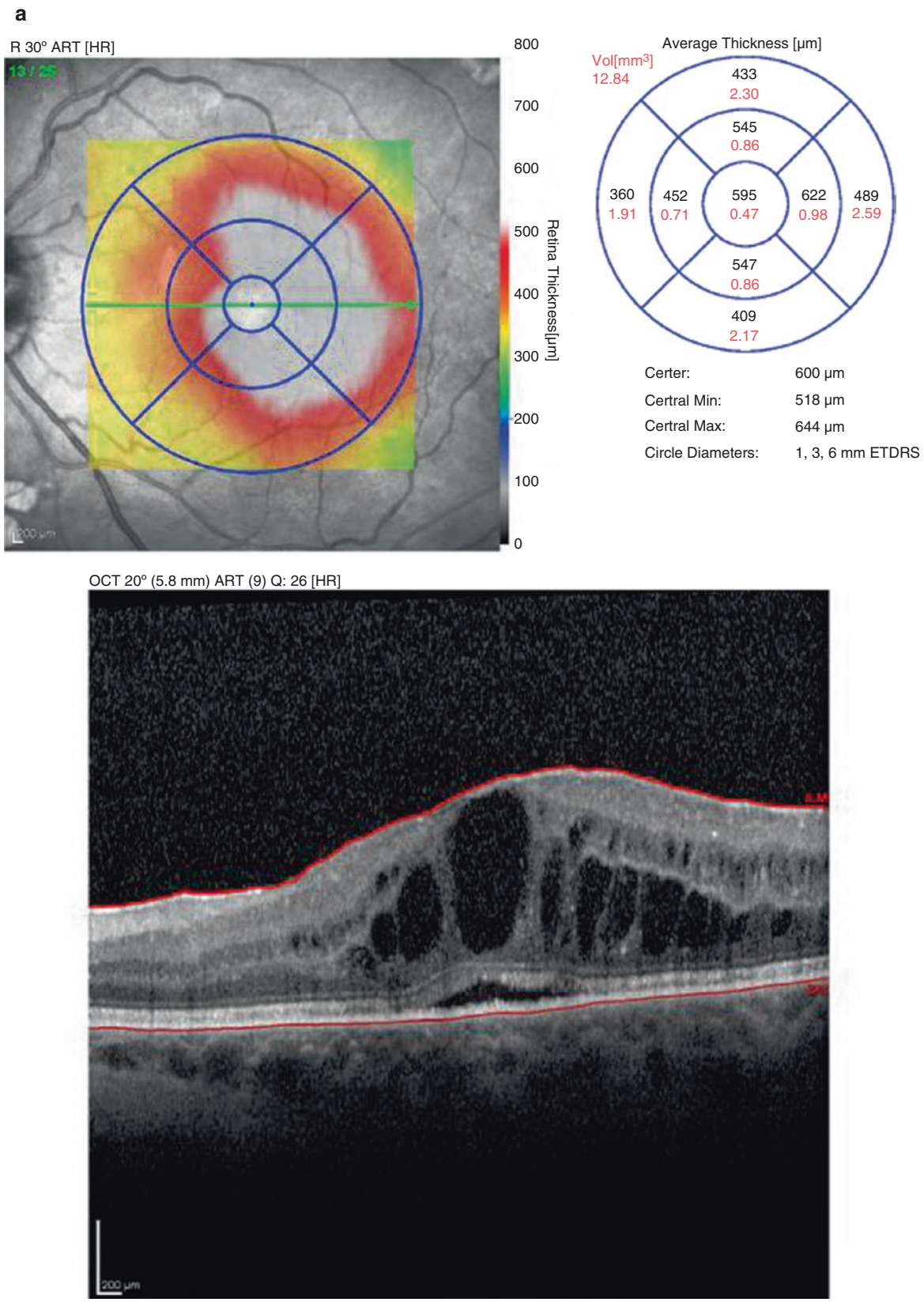

Fig. 3.3 (**a**) Clinically significant macular edema on optical coherence tomography. This optical section demonstrates significant retinal thickening due to intraretinal fluid as well as subretinal fluid. Prior to optical coherence tomography, clinical examination would not be able to distinguish between the presence of intraretinal versus subretinal fluid. (**b**) Clinically significant macular edema after treatment. This optical coherence tomography image was taken approximately 2 months following a single treatment with anti-vascular endothelial growth factor in the same patient presented previously (Fig. 3.3a). There is resolution of subretinal fluid, marked improvement of intraretinal fluid but still some residual perimacular thickening

b

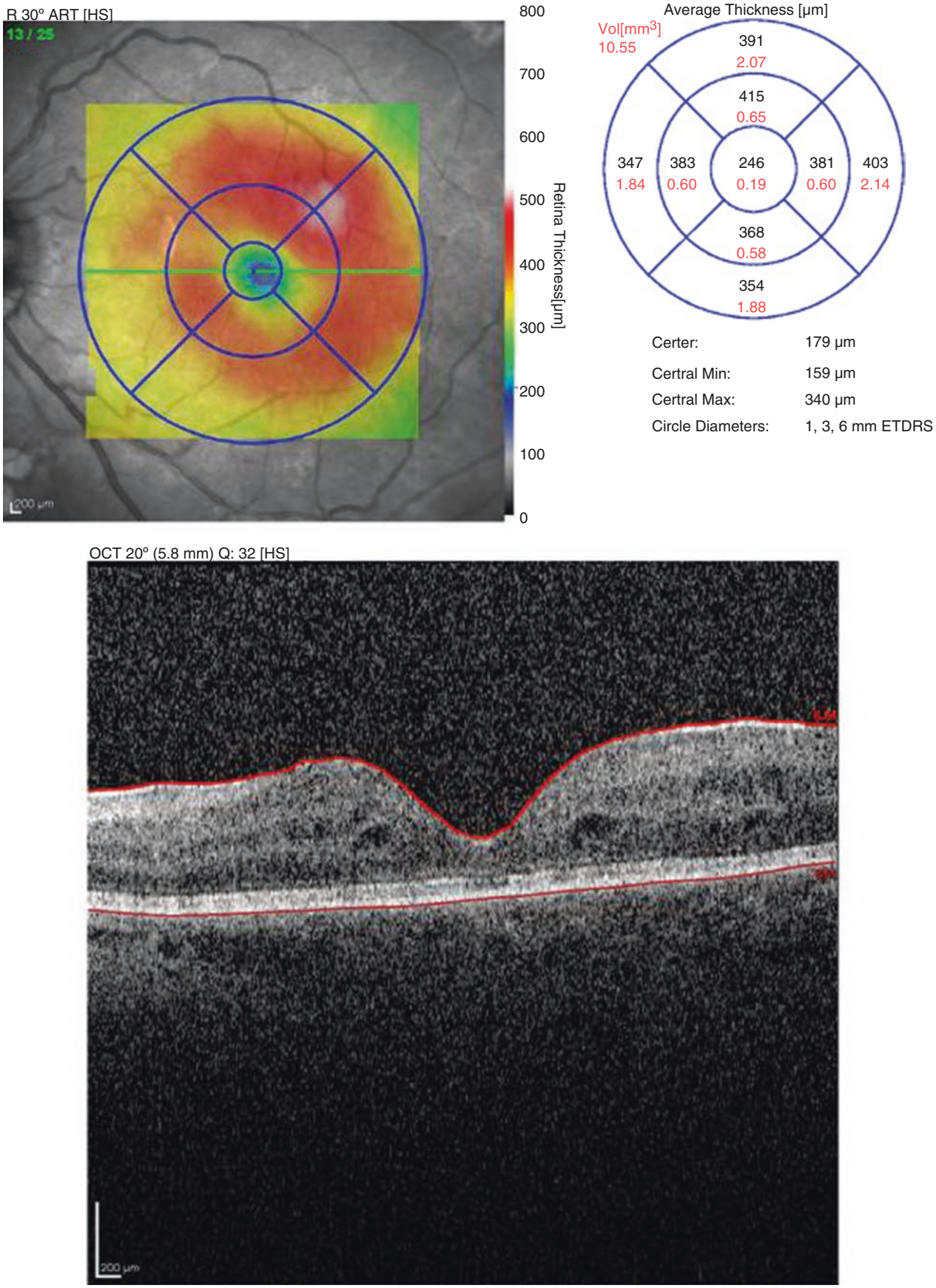

Fig. 3.3 (continued)

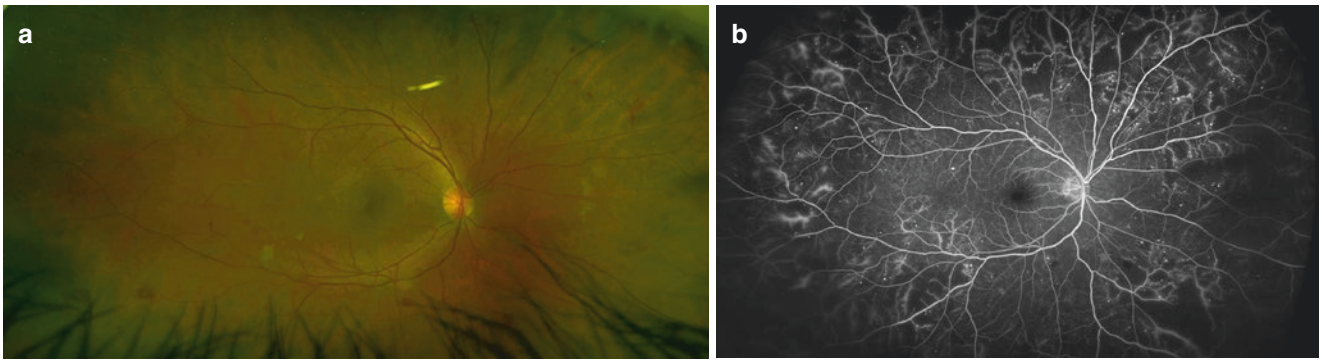

Fig. 3.4 (**a**) Wide-angle fundus photograph of capillary non-perfusion. This photograph reveals what appears to be innocuous non-proliferative diabetic retinopathy with scattered retinal microaneurysms and the absence of retinal neovascularization. (**b**) Fluorescein angiography of capillary non-perfusion. An angiogram performed on the same day of the fundus photograph discloses widespread capillary non-perfusion in the mid-peripheral retina, a finding that threatens to progress to proliferative diabetic retinopathy

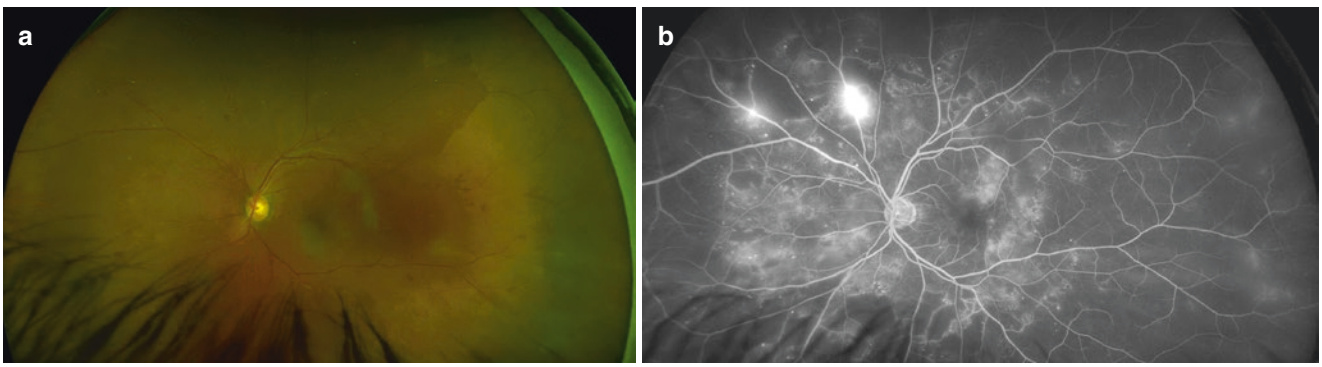

Fig. 3.5 (**a**) Wide-angle fundus photography of dulled atypical retinal sheen. This color photograph detects an atypical dulled whitening of the normal healthy retinal sheen in the temporal midperiphery, suggestive of retinal thinning due to peripheral ischemia. This clinical finding prompted a fluorescein angiogram to be performed, shown in **b**. (**b**) Fluorescein angiography confirming diffuse retinal ischemia. The capillary non-perfusion in the temporal midperiphery is confirmed on angiography, albeit not as dramatic as the patient from the previous Fig. 3.4a and b. The retinal ischemia is severe enough to stimulate retinal neovascularization, demonstrated by the intense hyperfluorescent areas just nasal to the optic nerve. Notably absent is retinal neovascularization in the temporal midperiphery, where the occlusion of circulation is severe enough to even prevent neovascularization

who began insulin therapy prior to age 30 years had signs of diabetic retinopathy at 10 years; whereas, approximately two-thirds of patients who did not require insulin therapy had signs of diabetic retinopathy at the same timepoint (Klein et al. 1994) (Table 3.1). The authors of WESDR also reported that CSME was present in 8.2% of the subgroup approximating type 1 diabetes, while it was 2.9% in the subgroup approximating type 2 diabetics not on insulin (Klein et al. 1989).

Systemic Risk Factors

The earliest interventions for diabetic retinopathy involved mitigation of hyperglycemia to reduce progression to blinding disease.

In 1977, the United Kingdom Prospective Diabetes Study (UKPDS) began enrolling patients in a longitudinal interventional study which compared the effect of intensive glycemic control with an oral sulfonylurea versus diet alone on diabetic retinopathy. The 12-year results showed that intensive glycemic control reduced the progression of diabetic retinopathy by 21% and the need for laser photocoagulation by 29% (UK Prospective Diabetes Study (UKPDS) Group 1998). The study also emphasized the importance of controlling hemoglobin A1C: for every 1.0% decrement in the hemoglobin A1C there was a 31% decrease in risk for developing diabetic retinopathy.

The Diabetic Control and Complications Trial (DCCT) was initiated in 1983, and randomized insulin-dependent diabetic patients to either intensive or conventional glycemic control. After a mean follow-up of 6.5 years, intensive glycemic

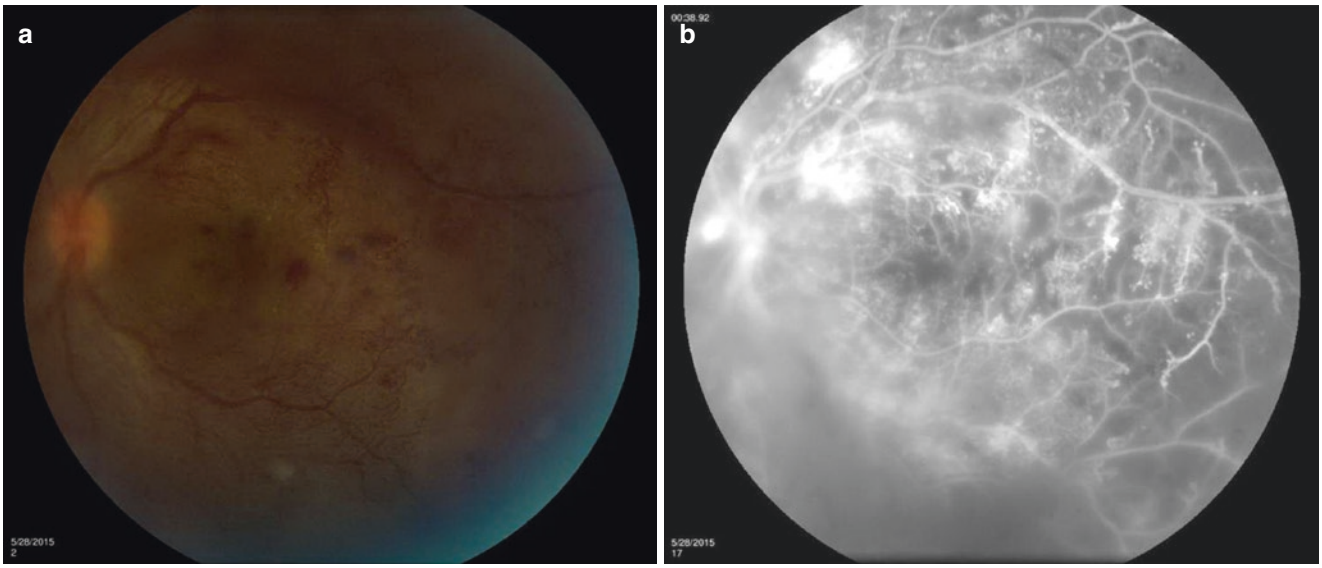

Fig. 3.6 (**a**) Intraretinal microvascular abnormalities. The thin and wiry vessels sprouting off the inferotemporal arcade in this fundus photograph are typical of intraretinal microvascular abnormalities. They represent neovascular growth that follows the contour of the retina, and do not grow upwards into the vitreous body. The moderate vitreous haze is due to the presence of a concomitant vitreous hemorrhage that obscures the media. (**b**) Fluorescein angiography of intraretinal microvascular abnormalities. This fluorescein angiogram performed on the same patient from the previous figure demonstrates the leakage of the dye through the immature vascular endothelium of the newly sprouted vessels. The intense late hyperfluorescence from fluorescein leakage is a hallmark of retinal neovascularization in all retinal vasculopathies. Note: while IRMA itself is not classically labeled "neovascularization" in the nomenclature of diabetic retinopathy (neovascularization of the disc and neovascularization elsewhere is considered separate clinical findings), the underlying pathophysiology of IRMA and neovascularization are indistinguishable

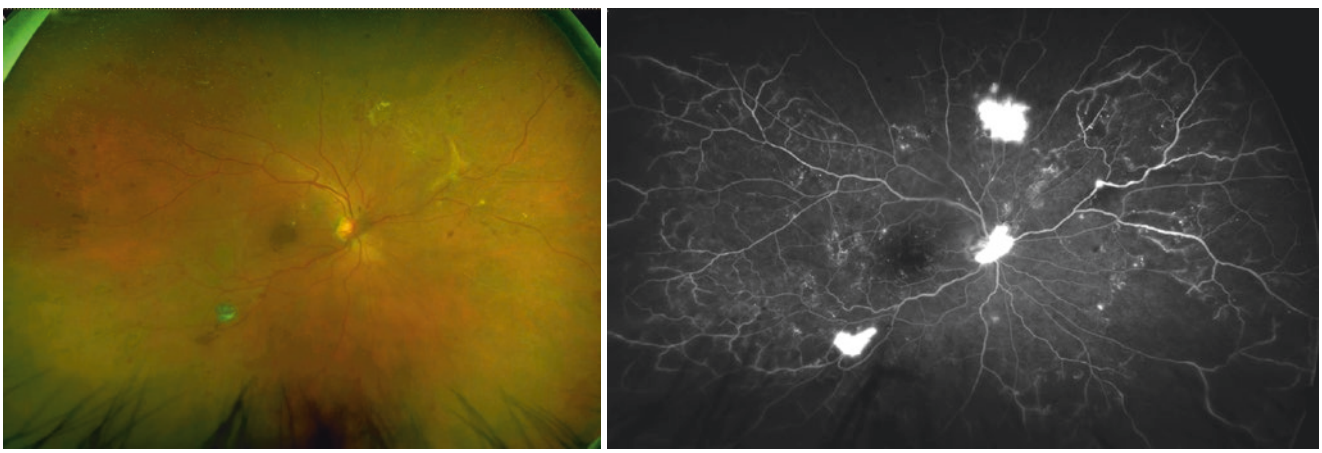

Fig. 3.7 Neovascularization of the disc and neovascularization elsewhere. This series of photographs demonstrates findings typical of neovascularization of the disc (NVD) and neovascularization elsewhere (NVE). On the fundus photograph, there is an obscure tuft of fine vessels that emerge from the peripapillary arterioles. In the superonasal and inferotemporal quadrant, there are gray-white fibrovascular membrane containing NVE. On examination, NVD and NVE are represented by fine wispy membranous fronds of fibrovascular tissue that emerge from the trunk of the retinal arterioles. The mid-phase fluorescein angiography photograph confirms the presence of NVD and NVE in these locations due to the intense fluorescein leakage into the extravascular space

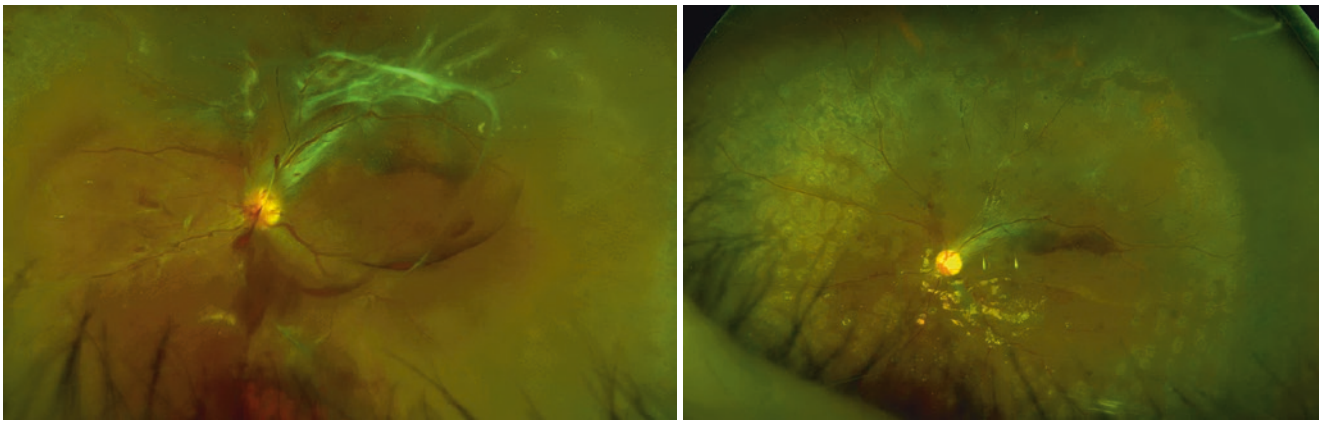

Fig. 3.8 Tractional retinal detachment. The unopposed proliferation of neovascular membranes begins to contract upon the retina, causing it to wrinkle upwards into the vitreous cavity, described as a diabetic tractional retinal detachment. The preretinal bands are visible overlying the vessels of the superotemporal arcade, pulling the retina into pleats and folds which are seen fanning out in the upper right-hand corner of the photograph. The slight greenish discoloration within the substance of the retinal folds is due to the presence of subretinal fluid. The second image is taken 1 month following surgical repair of the tractional retinal detachment. There is diffuse scatter endolaser burns applied to the retinal periphery to ablate ischemic retina and to fasten the retina against the retinal pigment epithelium. The sheen of silicone oil upon the inner retinal surface can also be seen

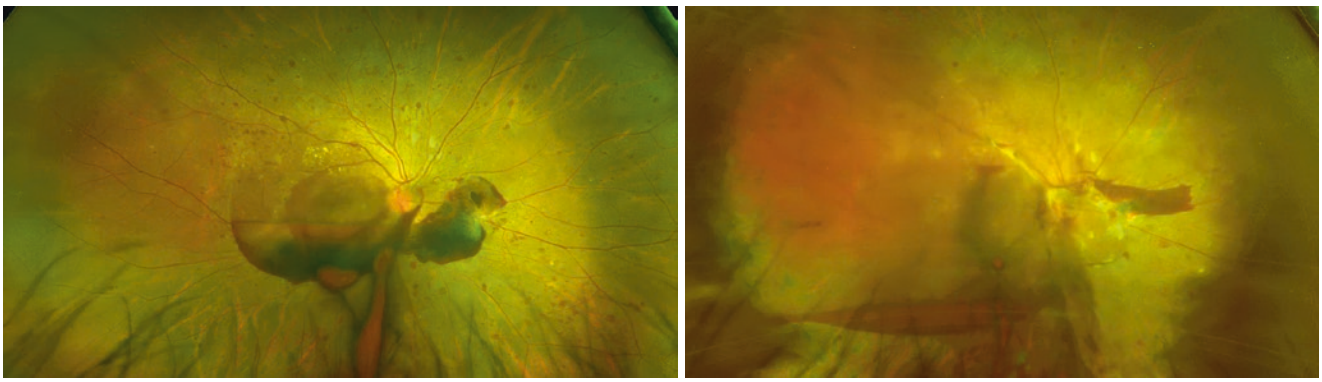

Fig. 3.9 Progression of vitreous hemorrhage in a young individual. This pair of images, taken 1 month apart, show evolution of a subhyaloid hemorrhage into a vitreous hemorrhage. The subhyaloid hemorrhage, at first confined to the pre-macular bursa, has only begun to break through the posterior hyaloid face and stream into the vitreous cavity, as illustrated by the finger of lighter red blood traversing the inferior hemifield. The posterior hyaloid, still turgid and firmly attached to the midperipheral retina in this 33-year-old diabetic male, prevented the progression of hemorrhage along the preretinal plane. This permitted laser photocoagulation to be performed, which then led to contraction of the posterior hyaloid and dispersion of the subhyaloid blood, as seen in the second photograph which is more typical of that found in vitreous hemorrhage

Table 3.1 Wisconsin epidemiologic study of diabetic retinopathy—10 year data summary

Demographics at baseline	Number of subjects	Any retinopathy (%)	Proliferative retinopathy (%)	Clinically significant macular edema (%)
Group 1: Age 30 years or younger on insulin	765	89	30	8.2
Group 2: Age 30 years or older on insulin	251	79	24	8.4
Group 3: Age 30 years or older not on insulin	282	67	10	2.9

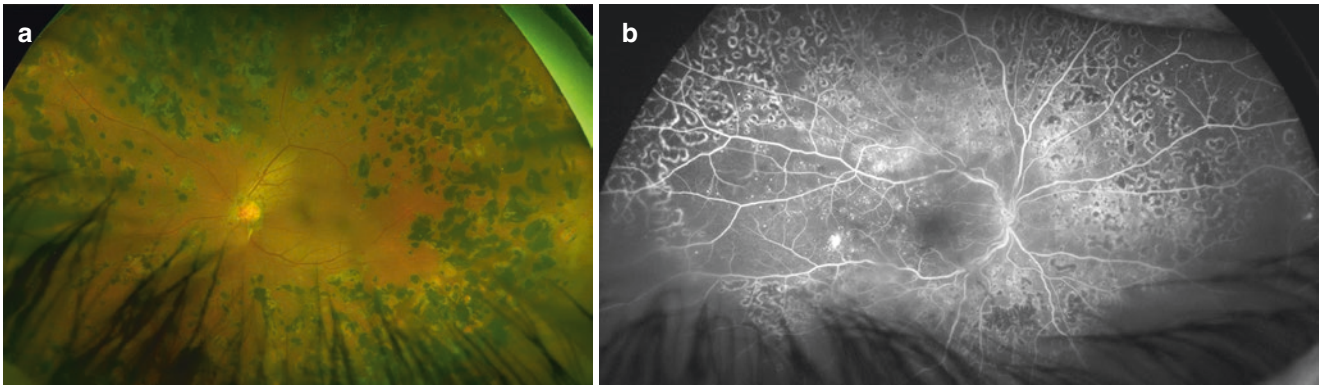

Fig. 3.10 (**a**) Treatment of proliferative diabetic retinopathy with panretinal photocoagulation. This fundus photograph was taken of a patient who had received in-office treatment with argon panretinal photocoagulation several years earlier. The laser scars have expanded over time and there is retinal pigment epithelial proliferation in response to the trauma of the thermal burn. There are a few very fine fibrovascular tufts at the optic disc, which represents regressed neovascularization of the disc. (**b**) Fluorescein angiogram of diabetic retinopathy following panretinal photocoagulation. This fluorescein angiogram demonstrates regression of all neovascularization several months after panretinal photocoagulation. The laser scars have a scalloped appearance with hyperfluorescence of the margins and hypofluoresence centrally due to retinal pigment epithelial proliferation. Note the absence of intensely leaking vessels that would indicate persistent active proliferative diabetic retinopathy (compared to Fig. 3.7) (Image courtesy of Stephanie Lu)

control reduced the overall risk of diabetic retinopathy by 76% and cut the risk of developing severe non-proliferative diabetic retinopathy by half (Diabetes Control and Complications Trial Research Group et al. 1993). The DCCT also validated the clinical observation of "early worsening" (Dahl-Jørgensen et al. 1985), a transient worsening of retinopathy for nearly 2 years after glycemic control is established.

Photocoagulation

Diabetic Retinopathy Study

The clinical observation that chorioretinal scars in myopic patients appeared to be protective against proliferative diabetic retinopathy gave rise to the concept that inducing chorioretinal scars with laser burns could bring about this same protection in patients who had proliferative diabetic retinopathy (Beetham et al. 1969). The mechanism by which the laser scar reduces neovascularization is not precisely known. One theory suggests that the ablation of ischemic retina reduces the release of pro-angiogenic factors; alternatively, it is also thought that laser scars allow for better penetration of oxygen from the choroidal circulation (Glaser et al. 1987; Stefánsson et al. 1986).

The need for a large controlled randomized trial to assess the anecdotal benefits of laser photocoagulation spurred the design of the Diabetic Retinopathy Study (DRS). 1758 patients were enrolled from 15 centers across the United States between 1972 and 1975. The study examined whether scatter laser photocoagulation could reduce progression to the primary endpoint, severe vision loss, defined as a visual acuity worse than 20/800 on two consecutive visits 4 months apart.

Table 3.2 Classification of high-risk proliferative diabetic retinopathy (from the Diabetic Retinopathy Study)

Mild NVD (<1/3) with vitreous hemorrhage
Moderate-to-severe NVD (>1/3) without vitreous hemorrhage
Moderate NVE (1/2 disc area) with vitreous hemorrhage

By 1975, only 2 years after enrollment began in the DRS, data strongly supported the benefit of scatter laser photocoagulation, reducing the risk of severe vision loss by 60% (Fig. 3.10). This prompted the authors to alter the protocol in order to offer therapy to untreated fellow eyes if they met the criteria for high-risk proliferative diabetic retinopathy, which were the eyes deemed at the highest risk for progression to severe vision loss (Table 3.2) (Royle and Mistry 2015; The Diabetic Retinopathy Study Research Group 1981, 1987). With the new protocol in place, the risk of severe vision loss was still reduced by 58% at 5 years follow-up (33.0 vs. 13.9% in untreated eyes and treated eyes, respectively) (The Diabetic Retinopathy Study Research Group 1981).

While the DRS established that scatter laser photocoagulation was exceptionally useful in reducing the risk of severe vision loss, it did not address the timing of laser therapy. The question of timing was the founding motivation for the ETDRS. The ETDRS recruited 3711 patients from 22 clinical centers across the United States between 1979 and 1985 (Royle and Mistry 2015).

Early Treatment of Diabetic Retinopathy Study and Classification of Diabetic Retinopathy

The ETDRS protocol established the hallmark non-proliferative diabetic retinopathy grades (Table 3.3) and CSME (Table 3.4). Eyes were randomized to immediate ver-

Table 3.3 Classification of non-proliferative diabetic retinopathy (from the Early Treatment Diabetic Retinopathy Study)

Mild non-proliferative	At least one microaneurysm
Moderate non-proliferative	Hemorrhages, microaneurysms, or venous beading or mild intraretinal microvascular abnormalities present
Severe non-proliferative	Hemorrhages and microaneurysms in 4 quadrants, or venous beading present in 2 quadrants or moderate intraretinal microvascular abnormalities in 1 quadrant
Very severe non-proliferative	Two or more combined features of severe non-proliferative diabetic retinopathy

Table 3.4 Classification of clinically significant macular edema (from the Early Treatment Diabetic Retinopathy Study)

Retinal edema located at or within 500 μm of the center of the fovea
Hard exudates at or within 500 μm of the center of the macula if associated with adjacent thickening
Zone of thickening larger than one disc area if located within 1 disc diameter of the fovea

sus delayed therapy for CSME; and immediate versus deferred "rescue" therapy if high-risk proliferative diabetic retinopathy developed. Because of this, very few eyes in the ETDRS progressed to severe vision loss in both the early scatter laser (2.6%) and the delayed scatter laser (3.7%) groups at 5 years follow-up (Early Treatment Diabetic Retinopathy Study Research Group 1991a).

The major conclusions from ETDRS were that:

1. Focal laser photocoagulation for CSME reduced the risk of moderate visual loss by up to 50% at 3 years, although this difference became diluted by the presence of severe diabetic retinopathy (Early Treatment Diabetic Retinopathy Study Research Group 1991a) (Table 3.5).
2. Scatter laser photocoagulation should be offered promptly in patients with very severe non-proliferative diabetic retinopathy or worse because the 1-year risk of progression to high-risk proliferative diabetic retinopathy is nearly 50% at this stage (Early Treatment Diabetic Retinopathy Study Research Group 1991a) (Table 3.6).
3. Aspirin 650 mg daily had no effect on progression of retinopathy, visual acuity, or risk of vitreous hemorrhage (Table 3.7) (Early Treatment Diabetic Retinopathy Study Research Group 1991b).

The ETDRS demonstrated that focal laser photocoagulation was beneficial in preventing vision loss when CSME was present. However, there was still limited evidence to inform which technique should be employed in treating CSME since the ETDRS protocol permitted investigators to use their discretion in choosing whether to use a grid pattern or focal photocoagulation of leaking microaneurysms.

Table 3.5 Effect of focal laser on moderate vision loss (Loss of 15 letters or more) in CSME when combined with early full scatter laser photocoagulation (from the Early Treatment Diabetic Retinopathy Study)

	Early focal laser (%)	Delayed focal laser (4 months) (%)	
With mild or moderate non-proliferative retinopathy and clinically significant macular edema			
At 1 year	5.3	15.9	$p < 0.001$
At 2 years	7.6	19.1	$p < 0.001$
At 3 years	11.2	23.1	$p < 0.001$
At 5 years	22.4	29.8	
With severe non proliferative or early proliferative retinopathy and clinically significant macular edema			
At 1 year	16.2	16.9	
At 2 years	21.1	20.0	
At 3 years	23.6	20.9	
At 5 years	26.2	24.1	

Table adapted from early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):766–785. Table 9
Abbreviations: *CSME* Clinically significant macular edema

Table 3.6 Cumulative risk of progression to high-risk proliferative diabetic retinopathy (from the Early Treatment of Diabetic Retinopathy Study)

	1 year (%)	3 years (%)	5 years (%)
With mild non-proliferative retinopathy	0.8	6.7	15.5
With moderate non-proliferative retinopathy	3.3	14.2	26.5
With severe non-proliferative retinopathy	14.6	39.5	56.0
With very severe non-proliferative retinopathy	45.0	64.9	71.3

Table adapted from early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):766–785. Table 6

Table 3.7 Moderate vision loss by visit (loss of 15 letters or more) in all eyes assigned to deferred laser treatment

	Aspirin (%)	Placebo
At 1 year	8.9	9.1
At 2 years	14.1	15.5
At 3 years	18.0	20.3
At 5 years	26.0	27.4

Table adapted from effects of aspirin treatment on diabetic retinopathy. ETDRS report number 8. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):757–765. Table 9

Peribulbar and Intravitreal Corticosteroids for Macular Edema

DRCR.net Protocol B sought to compare intravitreal triamcinolone against focal macular laser photocoagulation (Diabetic Retinopathy Clinical Research Network 2008). A total of 690 patients were randomized to either receive focal macular laser photocoagulation, intravitreal triamcinolone 1 mg or 4 mg and followed for 2 years. There was better visual acuity at 4 months follow-up in the 4 mg triamcinolone group, but at 12 months the visual acuity equalized between all three groups. At 16 and 24 months, visual acuity was better in the laser groups (Table 3.8). The study concluded that laser was superior to intravitreal triamcinolone in terms of visual acuity and side effect profile at 2 years, and reconfirmed the same findings at 3-years follow-up (Diabetic Retinopathy Clinical Research Network (DRCR.net) et al. 2009).

DRCR.net Protocol E compared the effect of peribulbar steroids (posterior and anterior subtenon kenalog injection) against focal macular laser photocoagulation (Diabetic Retinopathy Clinical Research Network et al. 2007). Data from 12-month endpoint led authors to conclude that there was minimal to no benefit of peribulbar steroids over focal macular laser.

Anti-Vascular Endothelial Growth Factor for Diabetic Macular Edema

Rise/Ride: The Landmark Trials

RISE (377 patients) and RIDE (382 patients) were parallel phase 3 clinical trials for Lucentis® (Genentech, San Francisco, CA, ranibizumab) in diabetic macular edema (Nguyen et al. 2012). Patients were randomized to ranibizumab 0.3 mg, 0.5 mg, or sham injections administered every month for 24 months. Focal laser was available beginning at month 3 and onwards if they met strict treatment criteria.

At the primary endpoint after 24 months of follow-up, the ranibizumab groups performed significantly better in mean visual gain and reduction of central macular thickness (Table 3.9 and Fig. 3.11).

Table 3.8 DRCR.net Protocol B visual acuity outcomes

		4 months	12 months	24 months	36 months
Laser	Proportion gaining 3 lines	7%	14%	20%	26%
	Proportion losing 3 lines	9%	14%	13%	8%
	Mean letters gained	0	0	4[a]	5
Triamcinolone 1 mg	Proportion gaining 3 lines	5%	10%	15%	20%
	Proportion losing 3 lines	10%	10%	21%	17%
	Mean letters gained	1	0	0	0
Triamcinolone 4 mg	Proportion gaining 3 lines	12%	12%	16%	21%
	Proportion losing 3 lines	4%	12%	21%	16%
	Mean letters gained	2[b]	−2	−4	0

[a]Laser was superior to both Triamcinolone 1 mg and 4 mg Groups ($p = 0.02$ against Triamcinolone 1 mg and $p = 0.002$ against Triamcinolone 4 mg)
[b]Triamcinolone 4 mg was statistically superior to both Triamcinolone 1 mg and Laser Groups ($p < 0.001$ for each pairwise comparison)

Table 3.9 RISE and RIDE visual and anatomic outcomes at 24 months

	Mean letters gained	Proportion gaining 3 lines (%)	Proportion losing 3 lines (%)	Proportion achieving CMT < 250 μm (%)	Mean number of injections	Mean number of laser rescue treatments
RISE						
Sham	2.6	18.1	10.3	43.0	0	1.8
Ranibizumab 0.3 mg	12.5[a]	44.8	2.4	74[a]	21.5	0.8
Ranibizumab 0.5 mg	11.9[a]	39.2	2.4	76[a]	20.9	0.8
RIDE						
Sham	2.3	12.3	8.4	46.0	0	1.6
Ranibizumab 0.3 mg	10.9[a]	33.6	1.6	76[a]	20.5	0.7
Ranibizumab 0.5 mg	12[a]	45.7	4.0	81[a]	21.9	0.3

[a]$p < 0.001$ against sham
Abbreviations: *CMT* central macular thickness

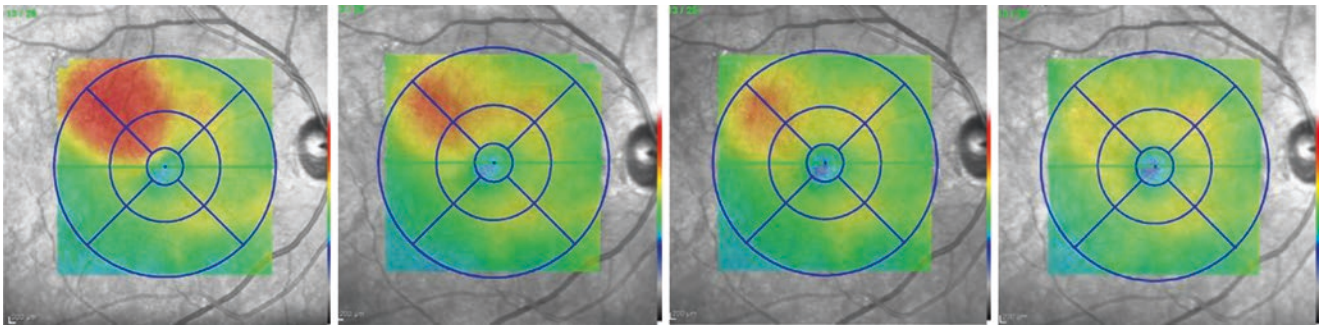

Fig. 3.11 Response of diabetic macular edema to sequential anti-vascular endothelial growth factor injections. This series of macular thickness maps are taken sequentially each month after an anti-VEGF injection was administered for the treatment of non-central diabetic macular edema. Each month saw a gradual reduction and eventual elimination of retinal thickening due to macular edema. This clinical course typifies the ideal outcome with anti-VEGF therapy

Table 3.10 RISE and RIDE visual outcomes at month 36

		Mean letters gained	Proportion gaining 3 lines (%)
RISE	Sham	4.3	22.0
	Ranibizumab 0.3 mg	14.2	51[a]
	Ranibizumab 0.5 mg	11	41.6[a]
RIDE	Sham	4.7	19.2
	Ranibizumab 0.3 mg	10.6	36.8[a]
	Ranibizumab 0.5 mg	11.4	40.2[a]

[a]$p < 0.01$ compared to sham
After Sham arm crossover to Ranibizumab 0.5 mg

The 36-month results of the RISE and RIDE trials crossed patients in the sham arm to receive monthly ranibizumab 0.5 mg injections (Brown et al. 2013). The investigators found that the sham arm failed to catch up to the visual gains experienced by patients who were initially in the treatment arms of the study (Table 3.10). This was an important concept in anti-VEGF therapy: that vision was being (in retina parlance) "left on the table" and irreversibly lost due to late initiation of therapy.

The robust analyses of RISE and RIDE contributed several key points to the growing body of literature on anti-VEGF therapy in diabetic macular edema:

1. Ranibizumab is highly effective at treatment of diabetic macular edema.
2. Visual outcomes are suboptimal when treatment of diabetic macular edema with ranibizumab is delayed. This would become the impetus for practitioners to offer anti-VEGF therapy before the previously stalwart standard of care, focal macular laser.
3. The visual gains achieved by a strict monthly injection schedule continue to be durable when switching to a PRN treatment schedule.

Bevacizumab for Diabetic Macular Edema

Bevacizumab, an earlier version of anti-VEGF therapy first utilized in the treatment of colon cancer, was widely understood to have a similar efficacy to ranibizumab, though no trial had yet validated its use in diabetic macular edema. This spurred the design of BOLT, an investigator initiated a randomized control trial that sought to compare the outcomes of bevacizumab against focal laser therapy in diabetic macular edema (Rajendram et al. 2012). There was no commercial backing for this trial since the use of bevacizumab was off-label, thus the study was relatively small compared to the industrial-sized RISE/RIDE trials, with only 80 subjects total. The authors of BOLT were able to demonstrate that bevacizumab was superior to laser for the treatment of diabetic macular edema, +8.6 letters for the bevacizumab arm and −0.5 letters in the laser arm at 2 years follow-up ($p = 0.005$). Interestingly, the investigators in BOLT used a 6-week interval for injections, achieving a median of four injections annually for patients in the study, showing that a reduced frequency of injections can still maintain an acceptable visual outcome.

Aflibercept for Diabetic Macular Edema

In 2012, results from a phase-2 trial of a new anti-VEGF agent, Eyelea® (Regeneron Pharmaceuticals, Tarrytown, NY, aflibercept 2.0 mg), aflibercept, was released in the DAVINCI trial (Do et al. 2012). Aflibercept was reported to higher binding affinity than ranibizumab and bevacizumab against the VEGF-A isoform, leading to the postulation that aflibercept would have a longer duration of therapy in the eye (Stewart and Rosenfeld 2008).

DAVINCI was designed with this presumed longer biologic half-life in mind. Impressively, the PRN and bimonthly treatment arms in DAVINCI performed equally as well as the

subjects assigned to the monthly aflibercept treatment arm at 12 months follow-up.

VISTA and VIVID were two parallel phase 3 clinical trials for aflibercept (Korobelnik et al. 2014). Between both trials, 872 patients were randomized to three treatment arms, (1) 2 mg aflibercept every 4 weeks (2) 2 mg aflibercept every 8 weeks after 5 monthly initial doses, and (3) focal laser photocoagulation. The primary endpoint was the mean gain in visual acuity at 52 weeks: +12.5 letters in the monthly aflibercept group, +10.7 letters in the bimonthly group, and +0.2 letters in the laser only group.

At nearly 3 years of follow-up, data from the VISTA and VIVID trials demonstrated the durability of results with continued adherence to treatment protocol (Heier et al. 2016a; Brown et al. 2015). The laser treatment arms were eligible for aflibercept injections starting at month 6 if they met stringent criteria for visual loss, and starting at month 25 they were eligible for injections on a pro re nata (PRN) basis with even less stringent set of criteria. Despite the rescue therapy, the eyes in the laser arms did not make up the difference in visual gains experienced by the aflibercept treatment arms.

Paradigm Shift: From Laser to Anti-vascular Endothelial Growth Factor Therapy in Diabetic Retinopathy

Ranibizumab Versus Pan-retinal Photocoagulation: Protocol S

DRCR.net's Protocol S sought to determine if anti-vascular endothelial growth factor therapy was non-inferior to pan-retinal laser photocoagulation for preventing loss of visual acuity in the management of proliferative diabetic retinopathy (Writing Committee for the Diabetic Retinopathy Clinical Research Network et al. 2015). Anti-vascular endothelial growth factor therapy was already known to have a beneficial effect on reducing the diabetic retinopathy severity score from RISE/RIDE, VISTA/VIVID, and DRCR.net's Protocol I; however, pitting pan-retinal laser photocoagulation directly against anti-vascular endothelial growth factors had not yet been studied up to this point in the narrative of retinal clinical science.

Protocol S enrolled a total of 305 patients (394 eyes) across 55 clinical sites, and the initial report was released in 2015 with a total of 2 years of follow-up. Patients were randomized to either pan-retinal laser photocoagulation or ranibizumab 0.3 mg monthly for three loading doses, followed by a step-down period through month 6 (ranibizumab monthly unless neovascularization absent), then a PRN period through the remainder of the study (ranibizumab monthly unless neovascularization was stable or absent).

The 2-year outcomes showed that visual acuity was non-inferior in ranibizumab-treated eyes (+2.8 letters) when compared to eyes treated with laser photocoagulation (+0.2 letters, $p < 0.001$). In the ranibizumab arm, only 6% ($n = 12$) of eyes required supplemental pan-retinal laser photocoagulation, which was typically performed at the time of vitrectomy. In the laser arm, 45% of eyes ($n = 92$) received supplemental pan-retinal photocoagulation at a median of 7 months after enrollment.

One of the widely voiced concerns related to the logistics of real-world medicine: diabetics are often too sick or busy to maintain the religious follow-up schedules seen in clinical trials, and laser therapy as first-line treatment may be safer in the long term for patients (Mein 2016). Furthermore, the durability of results from Protocol S over a 5-year follow-up period is still under investigation at the time of this writing.

Anti-VEGF Monotherapy for Diabetic Macular Edema

DRCR.net's Protocol T compared the effectiveness of bevacizumab, ranibizumab, and aflibercept in the management of diabetic macular edema (Wells et al. 2016). Six hundred sixty eyes were enrolled and randomized to three treatment arms: (1) bevacizumab 1.25 mg, (2) ranibizumab 0.3 mg, or (3) aflibercept 2.0 mg.

Protocol T found that the visual gains were very similar between all groups at 2 years, +12.8 letters, +12.3 letters, and + 10.0 letters with aflibercept, ranibizumab, and bevacizumab, respectively (Table 3.11). In the subgroup analysis,

Table 3.11 DRCR.net protocol T 2-year outcomes

	Mean ETDRS letter gain	Proportion gaining 3 lines or more (%)	Proportion losing 3 lines or more (%)	Mean CMT reduction (μm)	Proportion achieving CMT <250 (%)	Median number of injections
Aflibercept 2.0 mg	12.8	39	2	−171[b]	71	15
Bevacizumab 1.25 mg	10[a]	35	3	−126	41	16
Ranibizumab 0.3 mg	12.3	37	2	−146[b]	65	15

[a] $p = 0.02$ bevacizumab inferior to aflibercept
[b] $p < 0.001$ bevacizumab inferior to both aflibercept and ranibizumab
Abbreviations: *CMT* central macular thickness

aflibercept was superior to bevacizumab in achieving better visual outcomes (+18.1 letters with aflibercept versus +13.1 letters with bevacizumab, $p = 0.02$) with patients who began with a visual acuity 20/50 or worse at baseline. 20/50 was chosen since it was the median baseline visual acuity (69 ETDRS letters) for all of the treatment arms because it divided the cohort into roughly equal halves for analysis.

After many open-forum discussions on Protocol T in the retina community, the general consensus reached is that all three anti-VEGF agents are beneficial in the treatment of diabetic macular edema. In patients who have visual acuity worse than 20/50, aflibercept should be considered earlier as it seems to be more effective in drying the macula as a consequence of its putative increased affinity for VEGF receptors. The results from Protocol T are not reflective of "real-life" practice as it isolates and commits patients to anti-VEGF monotherapy, which does not factor in corticosteroid supplementation or switching between anti-VEGF agents (Heier et al. 2016b).

Corticosteroid Implants

Fluocinolone Acetonide Implant

In 2011, the FAME (Fluocinolone Acetonide for Diabetic Macular Edema) study group released their 2-year findings from a phase 3 randomized clinical trial of Iluvien® (Alimera Sciences, Alpharetta, GA, fluocinolone acetonide implant) (Campochiaro et al. 2011). The fluocinolone implant was constructed of nonbiodegradable polyamide, a material similar to the haptics on implanted intraocular lenses.

A total of 953 patients were randomized 1:2:2 to the sham, fluocinolone 0.2 μg/day or 0.5 μg/day treatment arms. The study preferentially enrolled patients with chronic diabetic macular edema as it was required that patients had failed one treatment with focal macular laser before enrolling in this study. At 2 years, the proportion of patients achieving a three-line gain in vision was 26.1%, 26.7%, and 13.0% ($p < 0.001$ compared to sham) in the 0.2 μg/day, 0.5 μg/day, and sham treatment groups, respectively. About 20% of each treatment group received two or more fluocinolone acetonide implants during the study period.

The results from the FAME study were hailed as a landmark moment as it became the first implantable steroid agent to be approved for use in diabetic macular edema. The study was a proof-of-concept showing that implantable steroids had an acceptable safety profile and could demonstrate some benefit beyond focal laser, which was the standard of care at the time. Results from this study eventually led to the approval of the fluocinolone acetonide implant 0.2 μg/day dose for treatment of diabetic macular edema.

Dexamethasone Intravitreal Implant

In 2014, the MEAD study group released their findings from a phase 3 randomized control trial of Ozurdex® (dexamethasone intravitreal implant, Allergan, Inc., Irvine, CA) for the treatment of diabetic macular edema (Boyer et al. 2014). A total of 1048 patients were randomized 1:1:1 to either receive 0.7 mg of the intravitreal dexamethasone implant, 0.35 mg intravitreal dexamethasone implant or sham injection.

At 3 years follow-up, the proportion of patients gaining three lines of vision or more was 22.2%, 18.4%, and 12% ($p = 0.018$) for the 0.7 mg dexamethasone implant, 0.35 mg dexamethasone implant, and sham groups, respectively. The mean number of injections over 3 years was 4.1, 4.4, and 3.3 for the respective groups. Roughly two-thirds of patients developed cataracts in the treatment groups (compared to 20% in the sham group) and about one-quarter of patients had a 10 mm Hg or higher rise in intraocular pressure relative to baseline.

The findings from the MEAD study eventually led to the FDA approval of dexamethasone implant 0.7 mg dosing for the treatment of diabetic macular edema (Fig. 3.12).

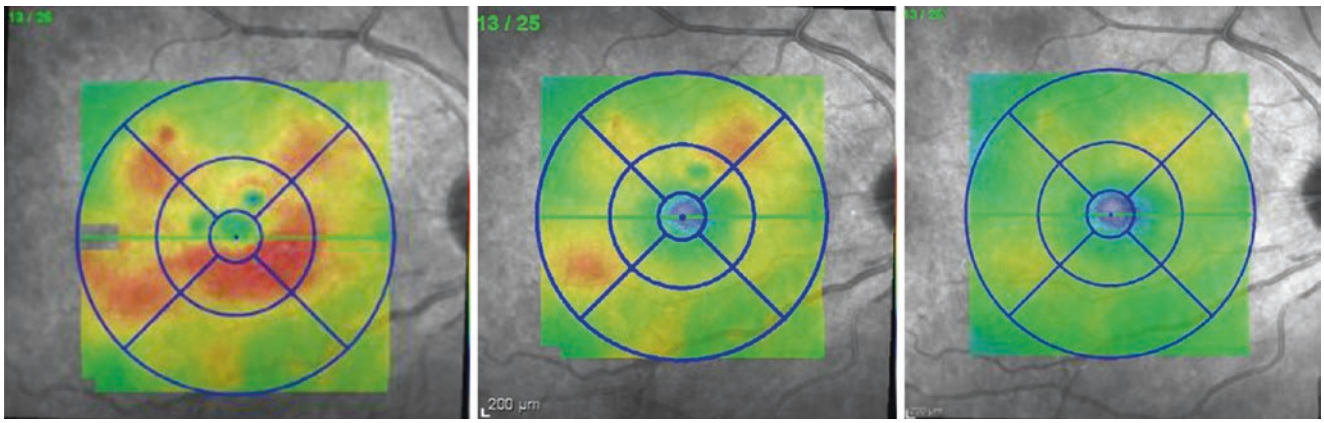

Fig. 3.12 Sustained response of diabetic macular edema to dexamethasone steroid implant. This pair of optical coherence tomography macular thickness maps are each taken 1 month apart from a 51-year-old diabetic patient who already had underwent cataract surgery in both eyes. He received a dexamethasone implant for the perimacular thickening seen in the first image, with continued and sustained resolution through the following 2 months without the need for any supplemental treatment

FDA approval of the dexamethasone intravitreal implant was an invaluable addition to the armamentarium of therapies available for diabetic macular edema. When paired with anti-VEGF therapy, the dexamethasone intravitreal implant makes for a formidable companion and has the anecdotal advantage of reducing injection frequency. While the MEAD study only allowed for injections every 6 months, real-world utilization of the dexamethasone implant is much more frequent (3 month intervals), which adds to the effectiveness of the medication.

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Central Retinal Vein Occlusion

4

Andrew M. Hendrick and Michael S. Ip

Introduction

As descriptively named as it is, central retinal vein occlusions (CRVO) are often misunderstood. In a CRVO, return of the venous circulation is relatively reduced by an obstruction. The obstruction itself is poorly understood due to our lack of ability to adequately visualize it, but is potentially compressive, inflammatory, thrombotic, or vasospastic. Histopathologic studies have demonstrated a thrombus at or proximal to the lamina cribrosa (Green et al. 1981), suggesting anatomic variations may be important.

It is important to recognize that a CRVO occurs in a *spectrum*, rather than as discretely ischemic or non-ischemic, perfused or nonperfused, complete or incomplete. The variability in severity belies the difficulty in studying and defining characteristics in central vein occlusions. In general, the larger the interruption in venous return, the more profound its effect, and the more likely the patient will consequently lose vision. Furthermore, although a CRVO can *manifest* acutely, it will commonly become a chronic condition that even with treatment has the potential for rebound and recrudescence requiring ongoing surveillance under appropriate expertise.

Epidemiology and Risk Factors

Worldwide prevalence of CRVO is estimated between 0.4 and 0.8% (Rogers et al. 2010; Mitchell et al. 1996) with little variation by ethnicity and geography. Data from the US reports the 5-year incidence of CRVO at 0.8% and the 15-year incidence was 2.3% in adults over 40 years old (Hayreh et al. 1994). Five-year incidence in the Beaver Dam Study was 0.2% which increased to 0.5% at 15 years (Klein et al. 2000; Klein et al. 2008). The Japanese 9-year incidence of CRVO was estimated at 0.3% (Arakawa et al. 2011), whereas adults over the age of 40 years in China 10 year incidence is 0.3% (Zhou et al. 2013).

The presence of a vein occlusion increases the likelihood of contralateral involvement with an estimated risk of around 1% per year up to 7% after 5 years (Hayreh et al. 1994; CVOS 1997). CRVO most commonly occurs as a primary disease process but can occur less commonly as a result of systemic causes, such as rheumatologic and hematologic conditions. However, local factors are also clearly important given the robust association of CRVO with open-angle glaucoma and possibility that some CRVO may derive from variances in anatomy (Hayreh et al. 2004).

Cardiovascular health plays an important role; substantiated by the increased risk with systemic hypertension and carotid artery disease (Eye Disease Case-Control Study 1996). Obstructive sleep apnea is likely an important risk factor for CRVO, with increased risk of venous thromboembolic events (Glacet-Bernard et al. 2010; Chou et al. 2012). As a result, an internist should be involved in the care of patients with CRVO (O'Mahoney et al. 2008) although specific workup is generally not necessary if the patient has typical risk factors.

Although a CRVO can affect individuals at any age, it is unusual under the age of 40 years and more common with increasing age (Rogers et al. 2010). Controversy exists regarding the necessity of diagnostic testing in young patients with vein occlusions (Gutman 1983; Fong and Schatz 1993), but 27% of patients with CRVO will demonstrate thrombophilia on laboratory testing (Lahey et al. 2002). In particular, homocystinuria has the most robust evidence suggesting increased risk, is correctable, and may affect cardiovascular health as well (Fong and Schatz 1993; Lahey et al. 2002). Clinical judgment is important in deciding whom to pursue additional diagnostic workup. In particular, special consideration should be applied for people with a strong family

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history of coagulopathy, personal history of prior thromboembolic events, or features suggestive of systemic etiology.

Clinical Features

Patients with CRVO are at risk of vision loss from several complications of the interrupted blood flow including macular edema, macular ischemia, optic neuropathy, or vitreous hemorrhage. However, patients with a mild CRVO may not have any symptoms (Image 4.1). Visual field abnormalities are common, but not frequently symptomatic (Hayreh et al. 2011). The elevated intravenous pressure leads to the characteristic venous tortuosity, intraretinal hemorrhages, cotton wool spots, and optic nerve edema (Arevalo et al. 2008). So called "blood and thunder" intraretinal hemorrhages can become so profound and diffuse to obscure visibility of deeper structures—even obviating fluorescein angiography due to difficulty in interpretation from blocking (Image 4.2). Macular edema can result in loss of visual acuity and metamorphopsia. Vitreous hemorrhage can occur as a breakthrough in venous congestion or a result of neovascularization (Image 4.3). Ocular neovascularization is an important visually threatening complication that requires substantial attention due to risks of vision loss and glaucoma. Eyes with more capillary nonperfusion (Image 4.4) have a greater risk of ocular neovascularization—most commonly the iris (NVI), angle (NVA), and optic nerve (NVD) (CVOS 1995a).

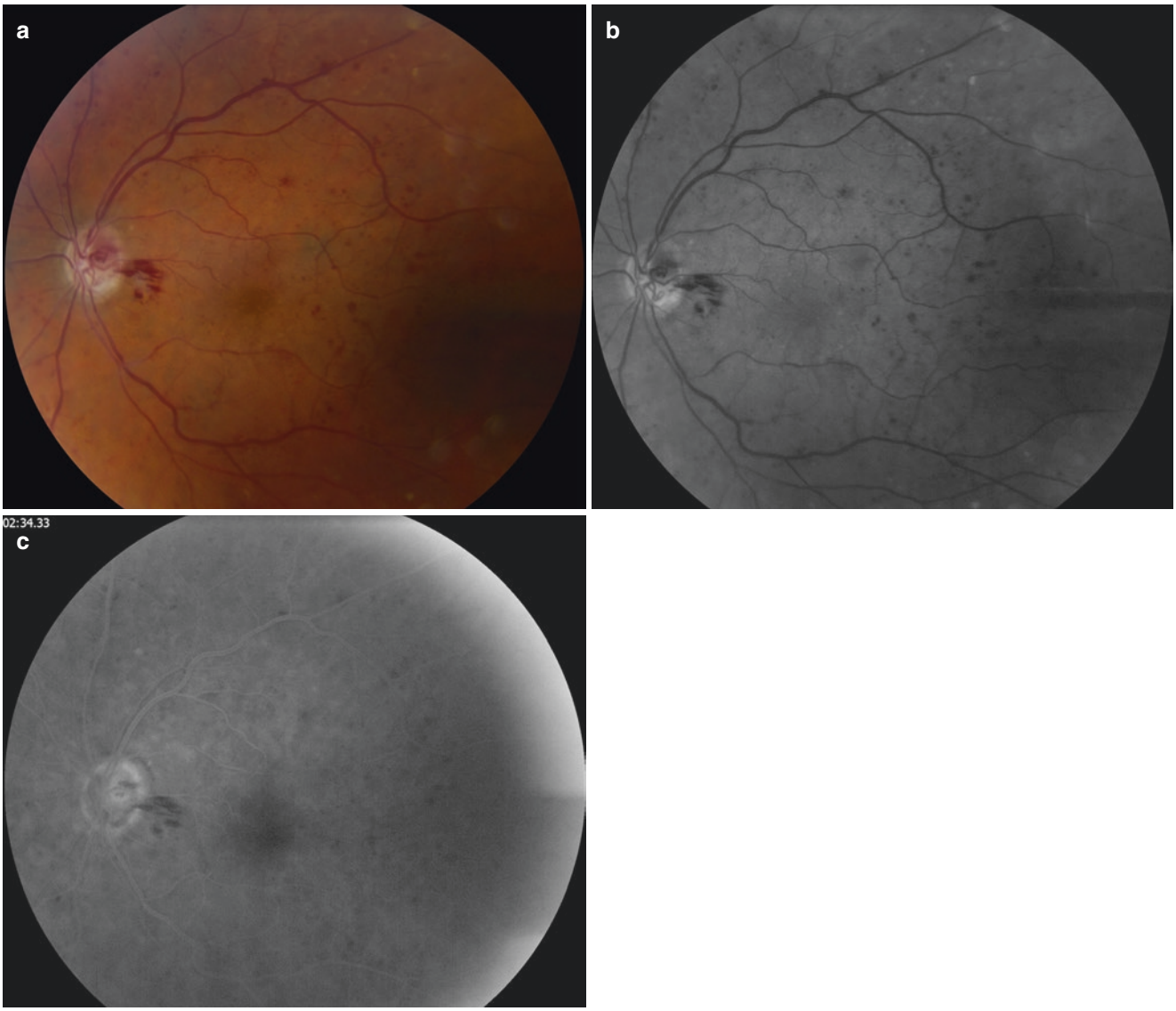

Image 4.1 (**a**) Color fundus photograph, left eye. Focal peripapillary hemorrhages and diffuse intraretinal hemorrhages are scattered in the fundus. (**b**) Red-free fundus photograph, left eye. Same eye as Image 4.1, presence of retinal hemorrhages are more easily visible under red-free conditions. (**c**) Fluorescein angiogram, left eye, recirculation phase. Note the absence of petalloid leakage and neovascularization

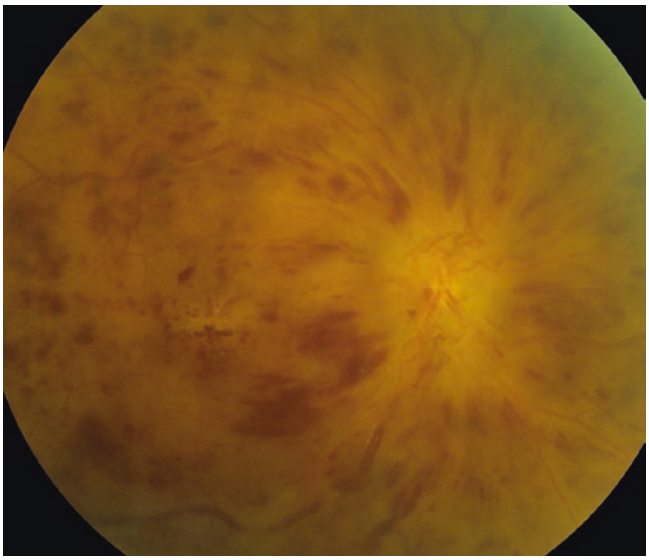

Image 4.2 Fundus photograph right eye. Severe congestion of the optic nerve and retinal veins result in a diffuse intraretinal and nerve fiber layer hemorrhages

Invasion of these vessels into the anterior segment can lead to neovascular glaucoma that portends a highly unfavorable prognosis. Central retinal artery occlusions are a rare complication of severe CRVO and may result from backup of perfusion across the capillary bed (Brown et al. 1993). In some patients, clinical findings will diminish, perhaps from development of venous collateralization (retina–retina and retina–choroid anastomoses) bypassing the obstruction (Image 4.5).

Diagnostic Tests

Central retinal vein occlusion is a clinical diagnosis, and requires a thorough examination to evaluate the patient for indications for potential treatment. Routine examination should include assessment of intraocular pressure, slit lamp examination with undilated gonioscopy, and dilated funduscopy to detect the presence of glaucoma, ocular neovascularization, and/or macular edema. Optical coherence tomography

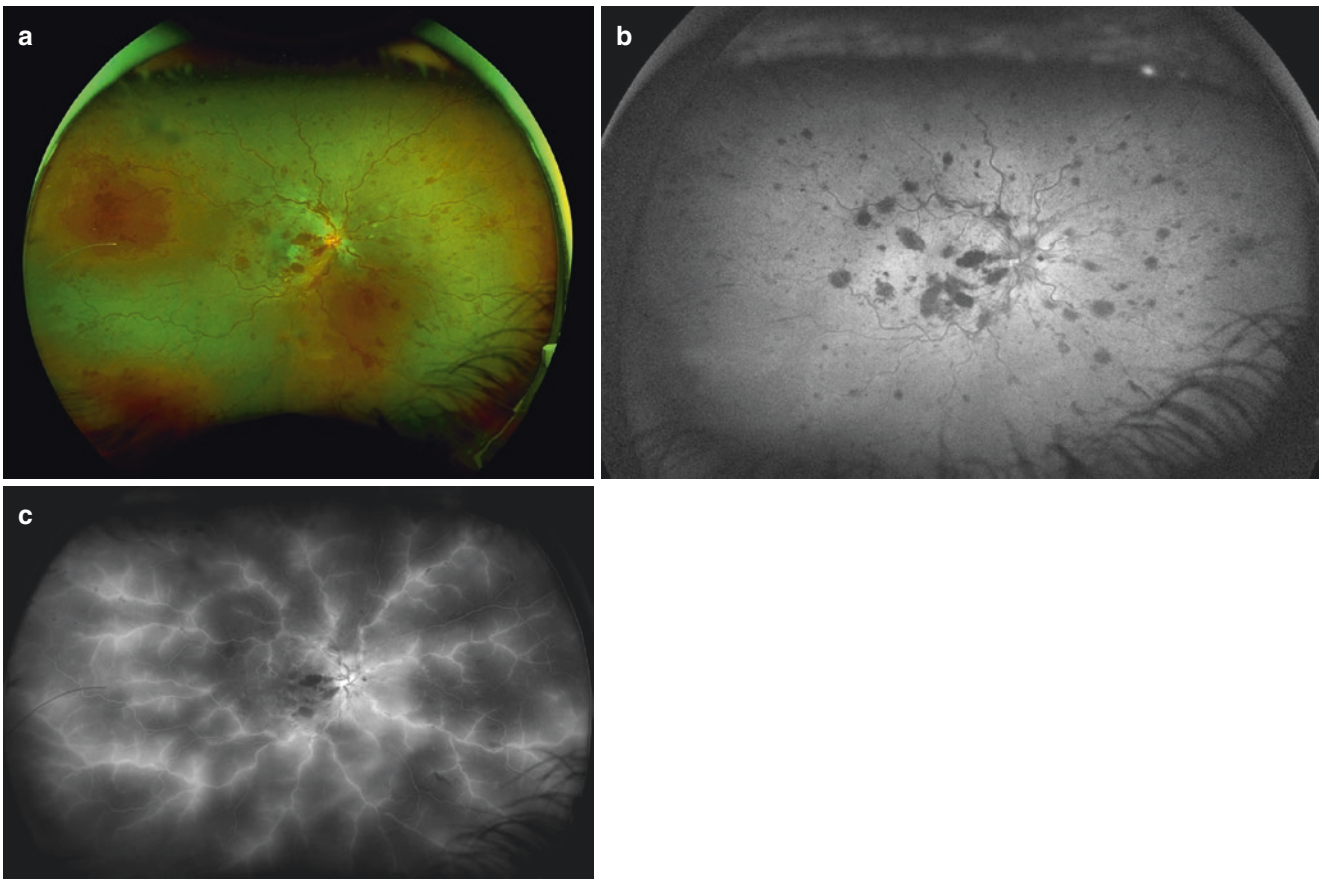

Image 4.3 (**a**) Ultra-widefield color image, right eye. Severe vascular congestion and tortuosity are visible with diffuse intraretinal hemorrhages. Lobular preretinal hemorrhages are visible temporal to the disc. Macular edema is present with a yellow discoloration in the fovea, and fine linear radial streaks. Inner retinal edema is visible as placoid yellow/white lesions adjacent to the fovea. (**b**) Ultra-widefield red-free image, right eye. Retinal hemorrhages of varying location, preretinal and intraretinal are more readily visible on red-free imaging. (**c**) Ultra-widefield angiogram, right eye. Diffuse hyperfluorescence of the retinal veins due to leakage demonstrates breakdown of the blood–retinal barrier

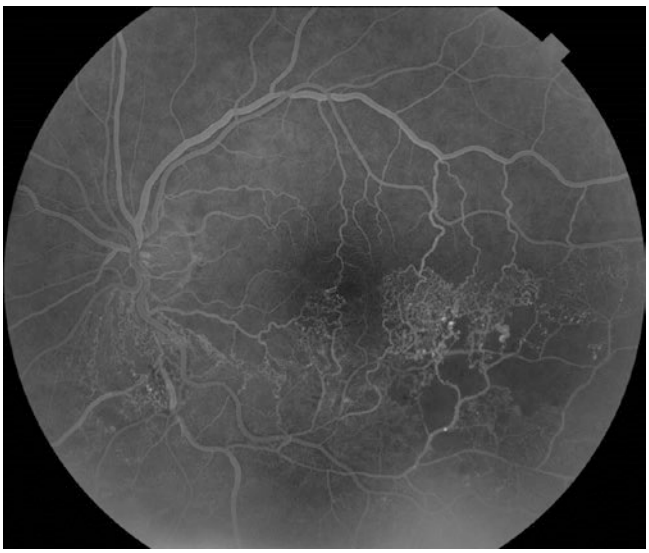

Image 4.4 Fluorescein angiogram, left eye. Hemiretinal vein occlusion with patches of capillary nonperfusion seen as hypofluorescence, and vascular collateralization within the retina that cross the horizontal raphe. Focal aneurysmal dilation can be seen as intense circular hyperfluorescence within the abnormal capillary beds

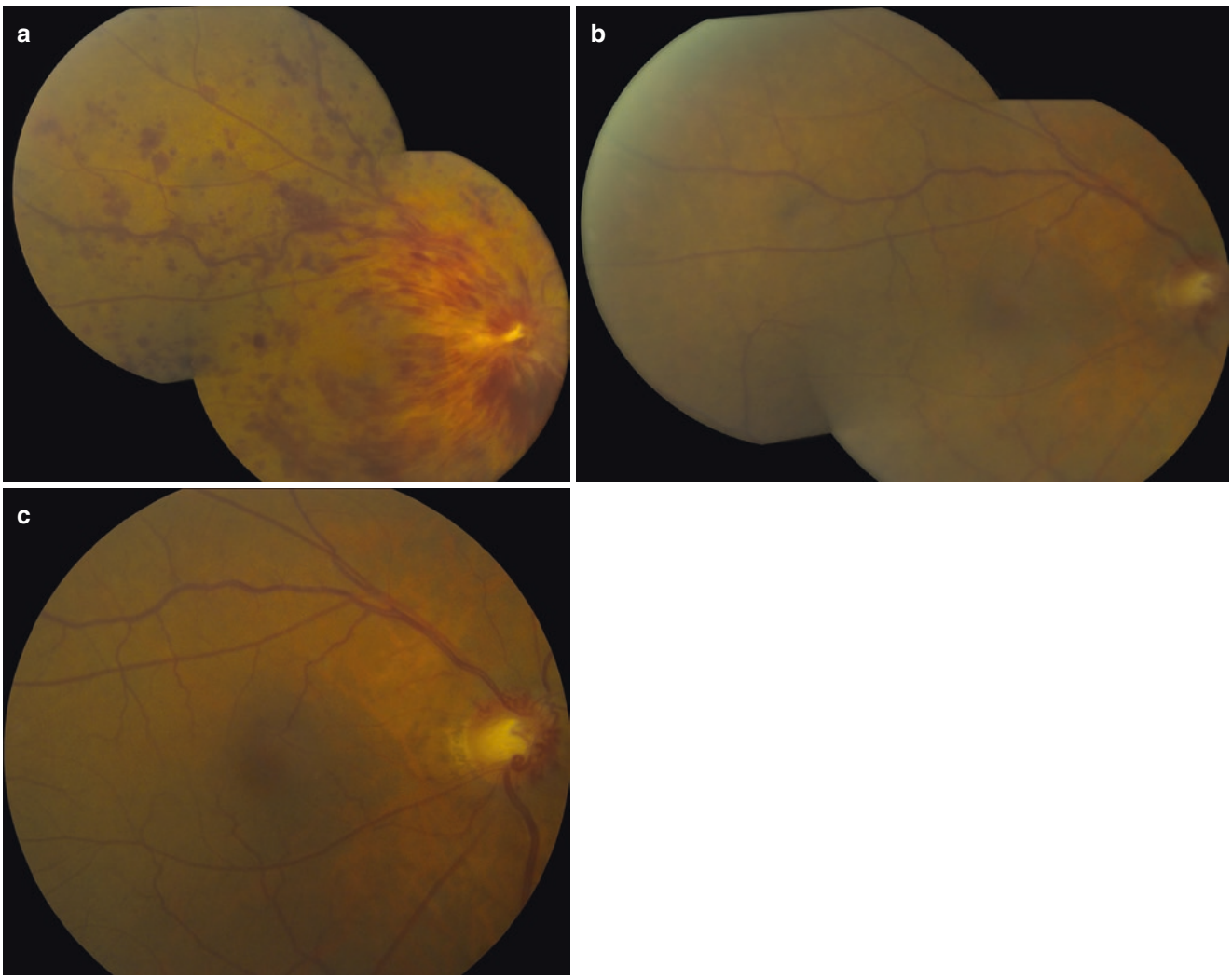

Image 4.5 (**a**) Montage color fundus photograph, right eye. Venous engorgement, and typical "blood and thunder" appearance due to dense intraretinal hemorrhages. Macular edema is present, although not readily visible. (**b**) Montage color fundus photograph, right eye. With 6 months of serial anti-VEGF injections, macular edema and clinical features of vein occlusion resolve. Collateralization of the optic disc is present. (**c**) Color fundus photograph, right eye. Collateralization of the optic nerve is readily visible with normalization of fundus appearance

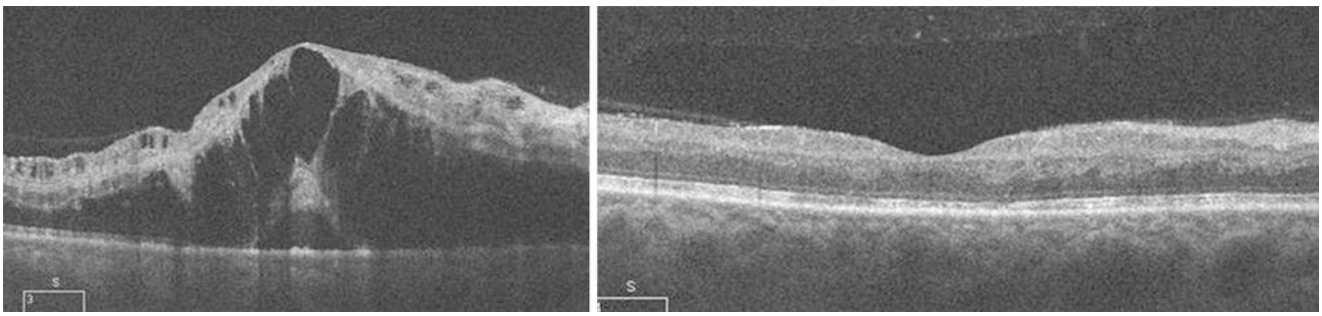

Image 4.6 Optical coherence tomography right eye, pre- and post-treatment. Left image demonstrates cystoid macular edema and subretinal fluid typical for a CRVO. Right image demonstrates complete resolution after a single intravitreal injection of anti-VEGF medication

(OCT) is extremely useful to confirm the presence of macular edema and provides a quantitative assessment of the thickening. High-resolution images from the OCT provide further information including presence of vitreoretinal interface abnormalities, neurosensory detachments, and/or loss of outer retinal integrity from chronic or undertreated CME that may further limit vision and guide therapy (Image 4.6).

Fluorescein angiography (FA) permits visualization of the capillary nonperfusion, macular ischemia, and detection of subtle neovascularization that may not be clinically apparent. Historically, 10 or more disc areas (DA) of nonperfusion on the FA was used in the Central Vein Occlusion Study to dichotomize CRVO into perfused, non-perfused, or indeterminate (CVOS 1995a). This framework was useful for study purposes, but is largely outdated with the advent of ultra-widefield testing (Image 4.7) (Tsui et al. 2011; Spaide 2011) and more predictive testing to assess perfusion statuses such as afferent pupillary defect, electroretinography, and visual field testing (Hayreh 2005). Fluorescein angiography is also useful to distinguish collateralization from neovascularization if there is uncertainty on examination—the former does not leak angiographically, whereas the latter does (Image 4.8).

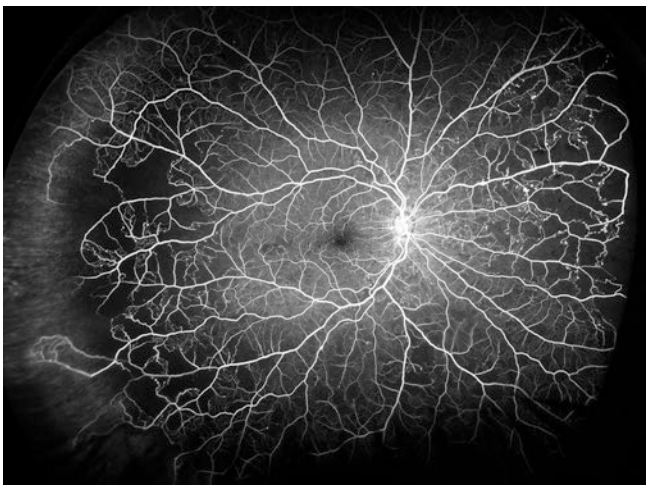

Image 4.7 Ultra-widefield fluorescein angiogram right eye. Despite the treatment of macular edema with serial anti-VEGF injections, vascular remodeling, aneurysmal dilations, and peripheral capillary nonperfusion remains

Treatment

Management of systemic associations and concurrent glaucoma, if present, are fundamental but do not immediately influence outcomes. Theoretically, if venous return could be diverted around the obstruction, signs, and symptoms of disease should improve. Unfortunately, therapies directly targeting resolution of the vein occlusion itself have not historically proven beneficial or cannot be reproduced effectively. Attempts have been made to create anastomoses through surgery (Fekrat and de Juan 1999) and laser (McAllister et al. 2010), relieve the obstruction through thrombolytic administration (Feltgen et al. 2007), and bypassing the congestion via optic nerve sheathotomy (Arevalo et al. 2008). Rather, mainstays of CRVO treatment are directed at improving the consequences that result from the venous obstruction.

Macular Edema

The most common visually threatening complication of a CRVO is cystoid macular edema (CME). Several landmark trials provide guidance in improving visual outcomes compared to the natural history. In general, presenting visual acuity is predictive of outcomes when no therapy is delivered. The presence of an afferent pupillary defect and extent of capillary nonperfusion further influence likelihood of vision loss in the Central Vein Occlusion Study (CVOS) (CVOS 1995a), but patients with an APD were excluded from landmark anti-vascular endothelial growth factor (VEGF) trials, making this prediction less certain with intravitreal therapy.

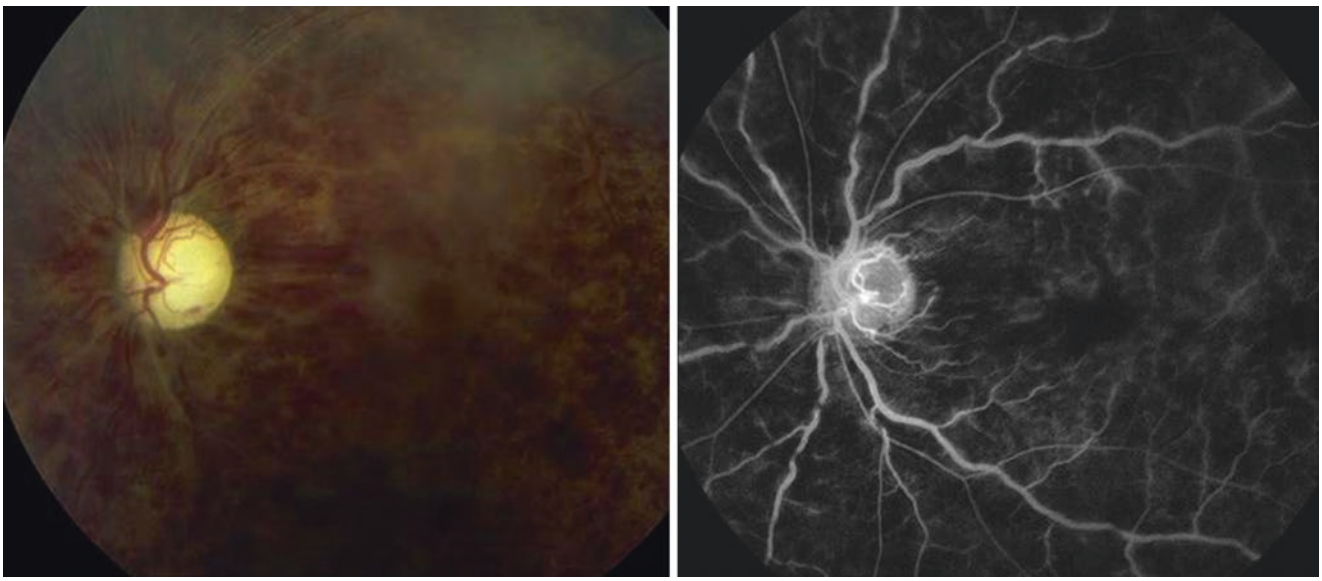

Image 4.8 Fundus photograph and fluorescein angiogram left eye. Abnormal vessels around the optic nerve demonstrate collateral vessels, with a lack of hyperfluorescence confirming absence of neovascularization

- *Laser for macular edema*

  The CVOS was designed to answer several questions regarding the use of laser for CRVO. With respect to its use for macular edema, the CVOS demonstrated a lack of benefit across the trial population. However, post hoc analysis revealed a reduced likelihood of vision worsening in the younger subgroup (CVOS 1995b). In general, laser is not used to treat CRVO-associated macular edema due to more effective options.

  More recently, several reports explored the use of peripheral "targeted" laser photocoagulation to angiographically nonperfused retina in an attempt to reduce the burden of treatment associated with intravitreal anti-VEGF therapy. Theoretically, if the peripheral ischemic retina is driving VEGF production, turning off that source could potentially be accomplished with laser ablation of the affected retina. However, at this time, no study has demonstrated a benefit in using peripheral laser for macular edema (Spaide 2011; Campochiaro et al. 2015; Wykoff et al. 2017).
- *Steroids for macular edema*

  Inflammation plays an important role in the pathogenesis of CRVO, promoting vascular permeability driving macular edema. Off-label preservative-free intravitreal triamcinolone acetate for CRVO-associated macular edema was explored in the Standard Care vs. COrticosteroid for REtinal Vein Occlusion (SCORE) trial. This study compared observation to 1 mg and 4 mg doses over 2 years. Both active arms experienced a higher proportion of subjects with 3 line improvement compared to observation (26–27% vs. 7%). However, subjects in the 1-mg cohort had a lower rate of cataract, cataract surgery, and intraocular pressure increases than individuals in the 4-mg arm (Scott et al. 2009). Triamcinolone is off-label for CRVO-associated macular edema and infrequently used in clinical practice due to the side effect profile.

  The Global Evaluation of implantable dExamethasone in retinal VEIN occlusion (GENEVA) trial compared 2 doses of intravitreal dexamethasone implantation compared to sham for individuals with both branch retinal vein occlusion and CRVO (Haller et al. 2010). Pooled data reflected a breakdown of 66% with BRVO and 34% with CRVO. All subjects had visual acuity 20/50 or worse and central thickness greater than 299 um on optical coherence tomography (OCT). Both arms reported 6-month outcomes after a single intravitreal injection of both doses (0.7 mg vs. 0.35 mg) of the implant randomized 1:1:1 versus sham. The percentage of eyes that achieved a 3-line gain of visual acuity was higher at 30 days than 90 days, suggesting a waning of treatment effect. However, at the primary endpoint (6 months), no differences in visual nor anatomic outcomes were detectable. Ocular hypertension was more common with the implant group in 4% of eyes compared to 0.7% in the sham group. The dexamethasone implant was approved by the Food and Drug Administration for RVO associated CME in 2009. Due to the side effect profile, it is less commonly used than anti-VEGF therapy, and optimal dosing strategies (timing and use in combination with anti-VEGF) are still uncertain.
- *Anti-VEGF for macular edema*

  VEGF is a cytokine that promotes vascular permeability and is highly upregulated in eyes with vein occlusions (Aiello et al. 1994; Funk et al. 2009). Three different anti-VEGF agents are routinely given via intravitreal injection

in clinical practice; both ranibizumab and aflibercept are FDA approved for this purpose. Although bevacizumab is off-label for CRVO-associated macular edema, it is far less expensive than the alternatives, and is utilized by a majority of retina specialists in the United States as favored initial therapy (Elman et al. 2010). Both ranibizumab and bevacizumab are humanized monoclonal antibodies with activity against the VEGF-A molecule.

The Central Retinal Vein OcclUsIon (CRUISE) trial compared the effectiveness of 6 consecutive months of intravitreal ranibizumab to observation for adults with CRVO with macular edema. It demonstrated visual- and OCT-based anatomic improvement in the ranibizumab group (Brown et al. 2010). Importantly, the individuals who were initially randomized to the observation arm were permitted to cross over to active treatment after 6 months. Unfortunately, the visual outcomes in that group never rivaled the cohort randomized to serial anti-VEGF (Campochiaro et al. 2011). The HORIZON trial is the open-label extension of this study, which demonstrated modest improvement in the control arm, but persistent differences are maintained between these groups (Heier et al. 2012). This indicates that although not an emergency, prompt treatment of the macular edema is important in determining visual outcomes, at least for initiation of treatment within 6 months of onset. It is likely that the inflection point for treatment is much earlier and treatment should be provided as soon as reasonable for the patient.

Aflibercept is a competitive receptor decoy of the VEGF molecule. In the GALILEO/COPERNICUS trial, aflibercept was compared to sham injection monthly over 1 and 2 years. Benefit was shown with monthly treatment, robust visual improvement is much more likely than in sham controlled eyes (Heier et al. 2014; Korobelnik et al. 2014).

Similar efficacy is demonstrated using bevacizumab serial intravitreal injections for BRVO- and CRVO-associated CME, but these reports are often limited due to small size (Ehlers et al. 2011; Russo et al. 2009; Epstein et al. 2012). Multicentered prospective data on bevacizumab for RVO associated CME is being generated in the Standard Care Of Retinal vein occlusion 2 trial (SCORE2) (Scott et al. 2017). In SCORE2, monthly aflibercept is being compared to monthly bevacizumab for the 6 consecutive months. At the primary endpoint, visual acuity and anatomic endpoints were similar in both groups, demonstrating non-inferiority of bevacizumab to aflibercept with this strategy (Scott et al. 2017). The SCORE2 is ongoing with plans to examine outcomes for nonresponders and alternate dosing paradigms.

Clinical trials help provide guidance over a limited duration. In clinical practice, CRVO-associated macular edema is a chronic condition requiring a large burden of care. Deciding to provide treatment when the retina is swollen is fairly straightforward. However, nuance is teased out with combination treatments, use of supplemental laser, when patients miss visits, and in the de-escalation of treatment. For these circumstances, meaningful guidance is not extrapolated from multicenter trials and clinical judgment is required.

In eyes that are actively receiving treatment with resolution of even microscopic macular edema on the OCT, reducing the burden of treatment can be explored. In general, eyes should have little to no clinical signs of disease activity such as minimal hemorrhages, cotton wool spots, disc edema to be considered for reduced treatment strategies. Different strategies to accomplish de-escalation include providing "as needed" treatment (pro re nata, *PRN)* and treat and extend. In a PRN paradigm, the patient is monitored at a fixed interval and intravitreal therapy is given if edema recurs. Rebound edema is an undesirable setback that can occur with this strategy (Matsumoto et al. 2007). In a treat and extend paradigm, intravitreal injections are given every visit, regardless of the presence of edema, with the intent to increase the interval between injections, and increasing the interval between injections if no edema has recurred.

Ocular Neovascularization

The other major visually threatening consequence of CRVO is the development and consequences of ocular neovascularization. Hypoxia and capillary nonperfusion upregulate VEGF which promotes increased vascular permeability and angiogenesis. The CVOS study also examined the risk of ocular neovascularization with and without preemptive scatter laser photocoagulation, as determined by initial perfusion status. Ocular neovascularization is more likely in eyes with more nonperfusion—such that 35% of ischemic or indeterminate eyes developed neovascularization compared to 10% of eyes that were nonischemic (CVOS 1995a). Prophylactic scatter laser photocoagulation was found to reduce likelihood of ocular neovascularization, but prompt resolution of ocular neovascularization occurred more frequently when laser treatment is deferred. Due to this, the laser treatment is often deferred until ocular neovascularization develops.

Neovascular glaucoma carries a grim visual prognosis without treatment, and scatter laser photocoagulation can be difficult when the patient is uncomfortable, the cornea is cloudy, and/or the intraocular pressure is elevated. The use of anti-VEGF medications acutely for neovascular glaucoma patients can temporarily aid in the resolution of the neovascularization until laser can be applied when waiting for the cornea to clear, or pressure to decrease to a reasonably safe level (Iliev et al. 2006).

Summary

Central retinal vein occlusion is a chronic condition that threatens eyesight within a spectrum of severity. They are common and highly associated with cardiovascular comorbidities. To date, treatment has not demonstrated reliable methods for directly improving perfusion. Instead, current strategies focus on the consequences of RVO to minimize vision loss from macular edema and neovascularization. Although serial anti-VEGF therapy is the current standard of care for treatment of macular edema, scatter laser photocoagulation and intravitreal steroids are reasonable to consider in certain circumstances.

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Branch Retinal Vein Occlusion

5

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Introduction

Branch retinal vein occlusion (BRVO) was first described in 1855 as a "retinal apoplexy" by Liebreich (Liebreich 1855) and as thrombotic in nature by von Michel in 1878 (von Michel 1878).

After diabetic retinopathy, BRVO is the most common retinal vascular disease (Hayreh 2005). It is estimated that over 16.4 million people worldwide (aged 30 years or over) are affected. It is over 6 times more common than CRVO with a reported prevalence of 4.42 per 1000 (Mitchell et al. 1996; Klein et al. 2008; Rogers et al. 2010a, b). It is more common in Asians and Hispanics than Caucasians. In 65% of cases, the superotemporal vein is the most commonly affected followed by the inferotemporal vein (Feist et al. 1992). However, the prevalence of nasal BRVOs may be reduced by their relatively asymptomatic manifestation.

BRVOs typically occur more frequently in males compared to females and are unilateral in 90% of cases. While most BRVOs occur in patients over 65 years of age, some occur in younger patients. However, the frequency of underlying risk factors differs between these two subgroups, which may warrant different approaches to medical work-ups. BRVOs may be asymptomatic, or they may produce reduced vision through associated cystoid macular edema (CME), macular ischemia, vitreous hemorrhage, and neovascular glaucoma.

Etiopathogenesis

BRVOs typically arise at arteriovenous crossings or near the optic disc edge as a hemiretinal vein occlusion (HRVO) and is more likely to occur if the artery crosses over the vein (Weinberg et al. 1990; Feist et al. 1992). The underlying pathogenesis relates back to Virchow's triad encompassing the three risk factors for thrombosis: endothelial damage, hypercoagulable state, and abnormal blood flow. Deviation of the retinal vein at crossing sites may cause hemodynamic turbulence and endothelial damage, thus increasing thrombotic risk (Christoffersen and Larsen 1999). Vein compression by an atherosclerotic retinal artery at the arteriovenous (A-V) crossing within the common adventitial sheath can also contribute to thrombosis (Zhao et al. 1993). Abnormal hematological factors such as hyperviscosity can also contribute (Trope et al. 1983).

Age is an important risk factor for BRVO, likely related to its association with increasing incidence of hypertension, atherosclerosis, and ocular risk factors such as glaucoma (Hayreh et al. 1994; Cheung et al. 2008; Rogers et al. 2010a, b). Other known risk factors for BRVO include hypercholesterolemia, increased creatinine, and ischemic heart disease (Rogers et al. 2010a, b). The higher incidence of systemic hypertension and poorly controlled hypertension in Hispanics and Asians compared to Caucasians may be reflected in the relatively higher prevalence of BRVO in these ethnic groups.

In younger patients who are less likely to have sufficient atherosclerotic changes to induce venous thrombosis at A-V crossings, an investigation into an underlying hypercoagulable state is pursued. However, similar risk factors have been found with an older cohort (Lam et al. 2010).

Clinical and Imaging Features

BRVOs can be divided into major and macular subtypes. Major BRVOs (Fig. 5.2) involve a large vein close to the optic disc with effects on over one-quarter of the retina.

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Macular BRVOs (Fig. 5.1) involve venular branches draining the macula with effects on only a proportion of this region. Both large and small BRVOs can occur outside of the macula, where they often remain asymptomatic unless retinal neovascularization with vitreous hemorrhage occurs.

Early features (Figs. 5.1 and 5.2) of BRVOs include dilated and tortuous retinal veins, intraretinal hemorrhages, cotton wool spots, retinal exudates, and macular edema. Varying degrees of ischemia are often present, representing an important risk factor for the subsequent occurrence of neovascular complications including vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma. As two-thirds of major BRVOs are ischemic, these eyes are at higher risk for developing these secondary complications (Fig. 5.3).

Fluorescein angiography performed in eyes with BRVO typically demonstrates a delayed A-V transit time within the involved vasculature and often shows hyperfluorescent areas secondary to vascular leakage. Late petaloid hyperfluorescence may occur related to cystoid macular edema (CME). It is important to look at early angiographic images both centrally and in the periphery to assess the extent of ischemia, an important risk factor for secondary neovascularization. Confluent intraretinal hemorrhages in acute BRVOs may interfere with this assessment. In eyes with more long-standing BRVOs, non-leaking collateral vessels and retinal neovascularization showing hyperfluorescent leakage may be detected (Figs. 5.4 and 5.5).

Optical coherence tomography (OCT) is an important diagnostic and management tool that can detect the presence of cystoid macular edema (Figs. 5.6 and 5.7), epiretinal membrane, and intraretinal exudates in eyes with BRVO. Visual prognosis may correlate with the integrity of the outer retinal bands, in particular the ellipsoid and interdigitation zones. Ischemic retinal areas will show thinning of the inner retinal layers.

The time course for BRVO evolution from acute to chronic can vary from weeks to many months. During this period, hemorrhages begin to resolve and late features appear which may include retinal thinning, sclerotic vessels, and collateral vessels (Figs. 5.8, 5.9, and 5.10).

Potential complications of ischemic major BRVOs include retinal neovascularization, vitreous hemorrhage, and neovascular glaucoma (Fig. 5.11). Other sequelae include epiretinal membrane and tractional retinal detachment.

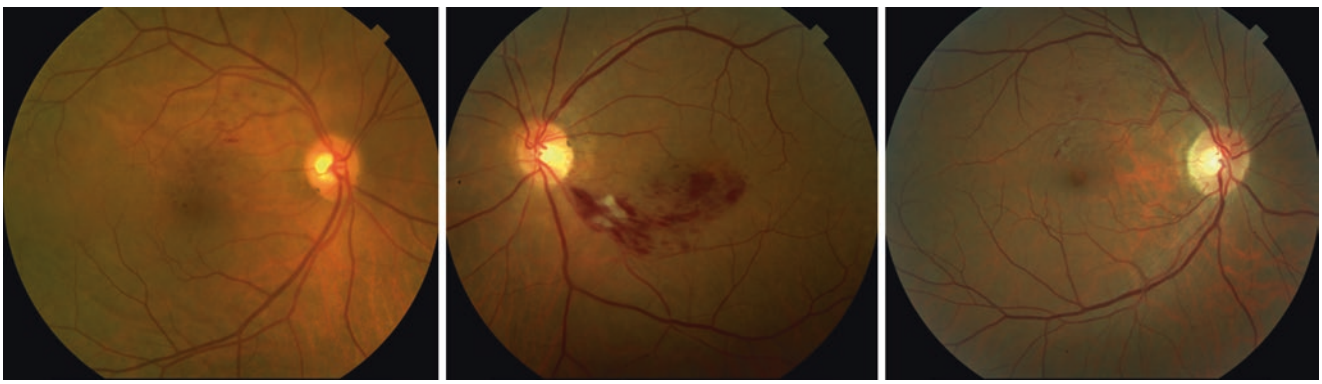


Fig. 5.1 Examples of acute macular BRVOs

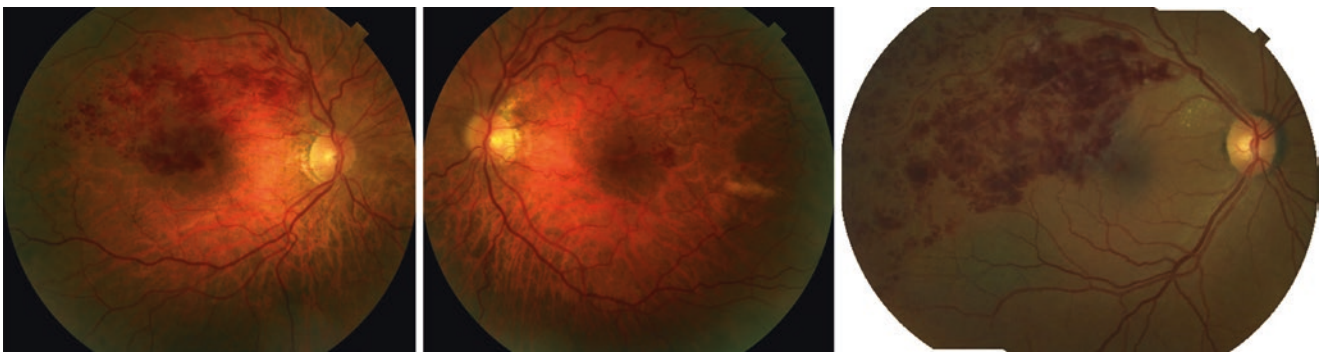


Fig. 5.2 Examples of acute major BRVOs

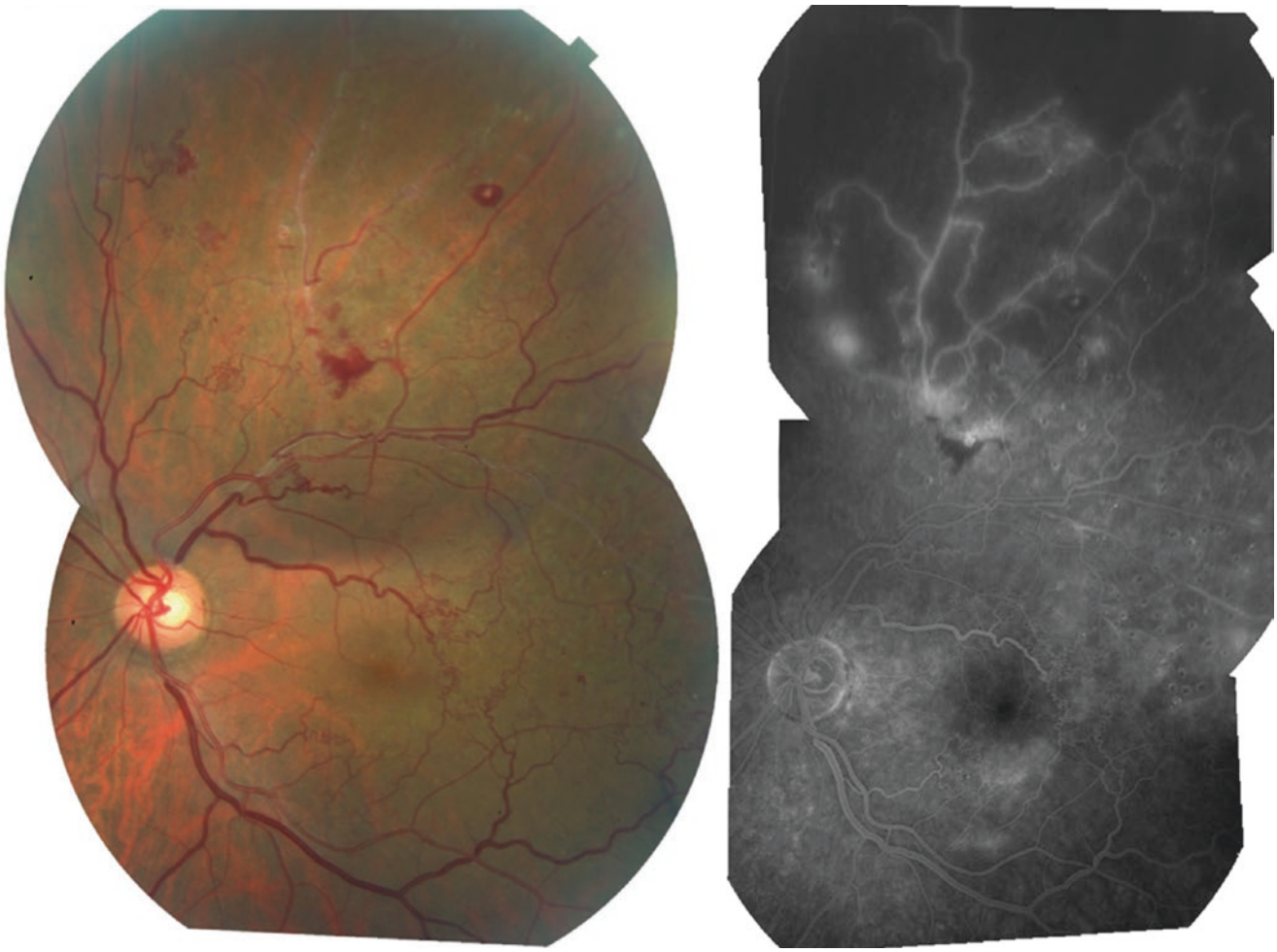


Fig. 5.3 Retinal neovascularization (yellow arrows) related to ischemia in the superior fundus in an eye with a left major superotemporal BRVO. Scatter thermal laser was performed in this case

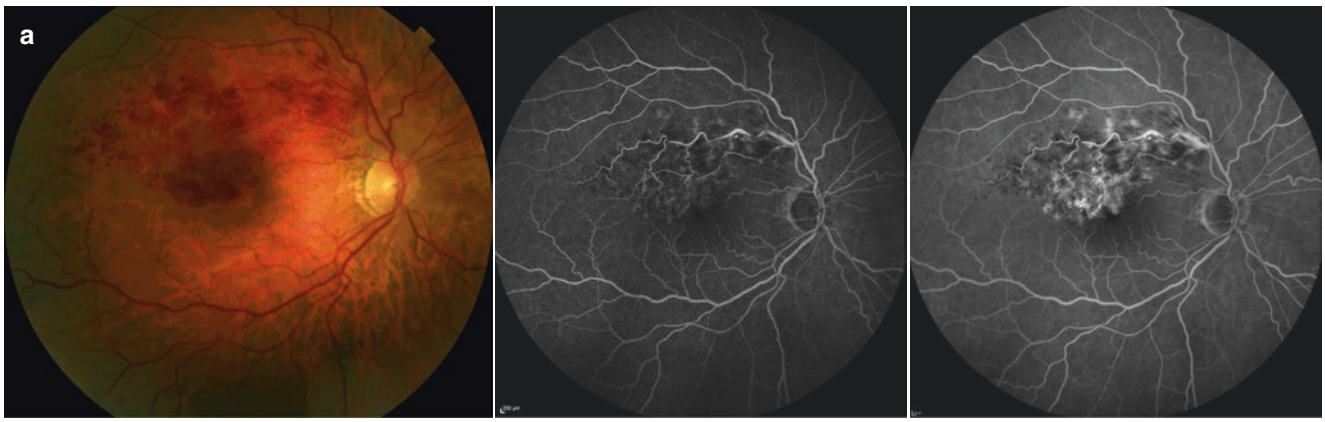


Fig. 5.4 Fluorescein angiography in a patient with right macular and subsequent left major BRVOs (**a**, **b**). In another patient, fluorescein angiography shows how the blocking effect of hemorrhage may obscure ischemia in a major left BRVO (**c**)

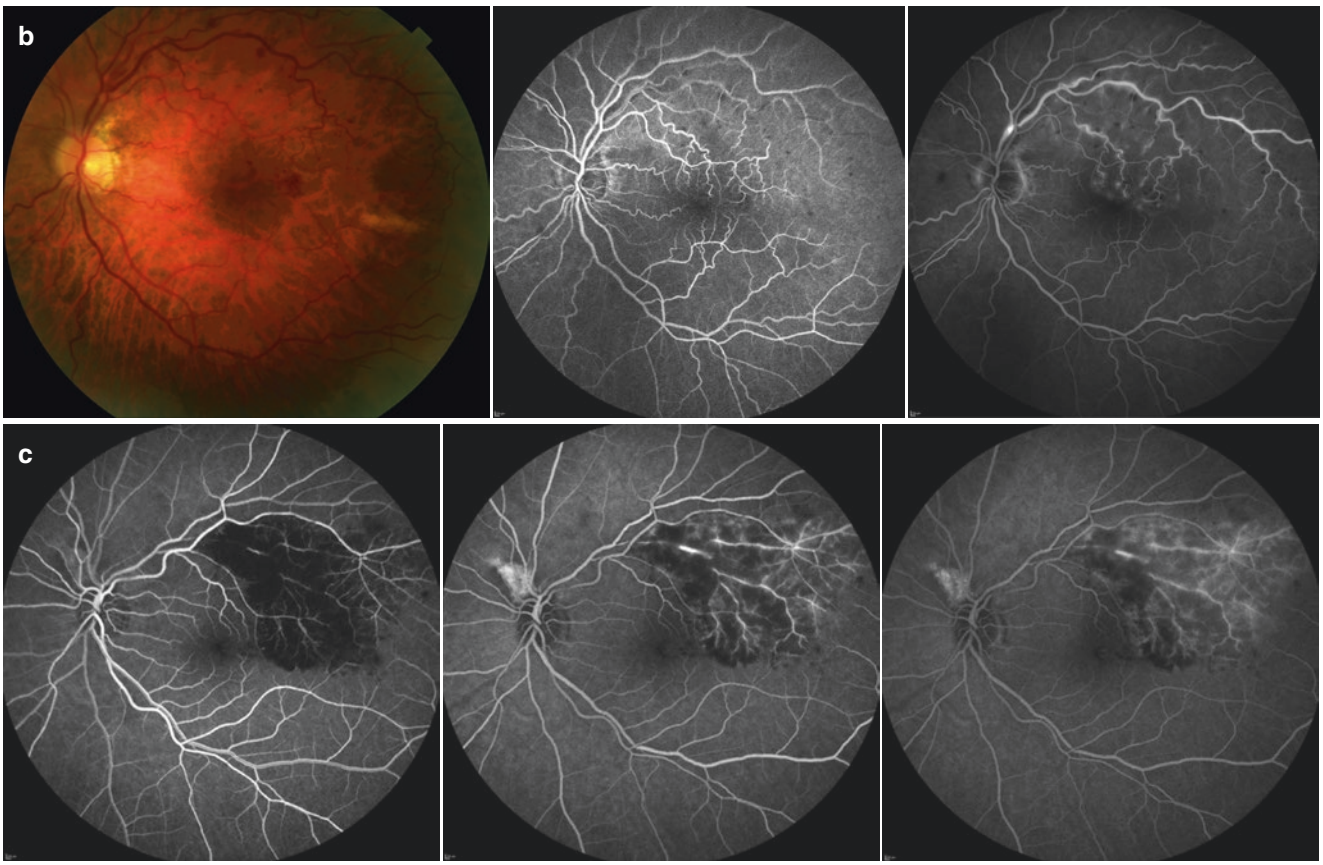


Fig. 5.4 (continued)

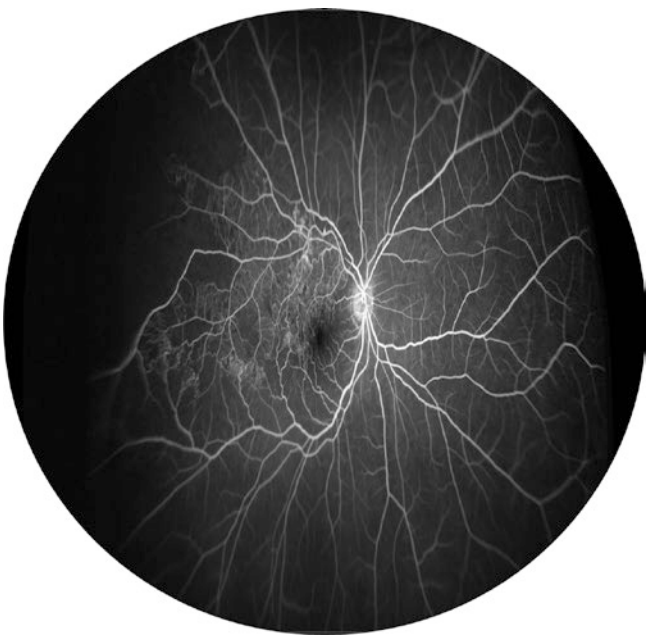


Fig. 5.5 Ultra-widefield fluorescein angiogram shows peripheral ischemia due to the right major BRVO. The patient subsequently underwent sectoral scatter thermal laser treatment

Management

It is important to distinguish major BRVOs from macular BRVOs for management and prognostic purposes. Complications from major BRVOs depend on the specific vein occluded. A macular BRVO would neither be expected to result in vitreous hemorrhage nor neovascular glaucoma due to the smaller proportion of retina involved. Initial visual acuity has a prognostic bearing on the final visual outcome.

Observation

Fifty to sixty percent of eyes with BRVO retain a vision of 20/40 or better without treatment (Rogers et al. 2010a, b). However, it is important to ensure that systemic risk factors are identified and managed appropriately as the recurrence of either a BRVO or a central retinal vein occlusion (CRVO) in the same eye is 2.5% over 4 years. In addition, the risk of a BRVO in the fellow eye within the following 3.3 years is 4.0% for macular BRVO and 6.6% within the

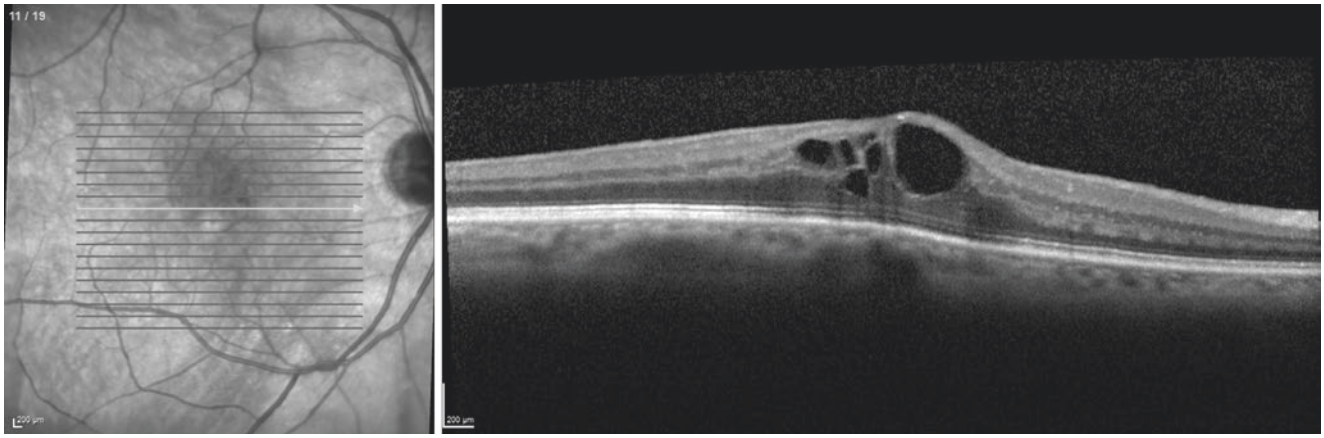


Fig. 5.6 Optical coherence tomography (OCT) demonstrates CME in an eye with a right macular BRVO. The green arrow indicates the location and direction of the OCT B-scan

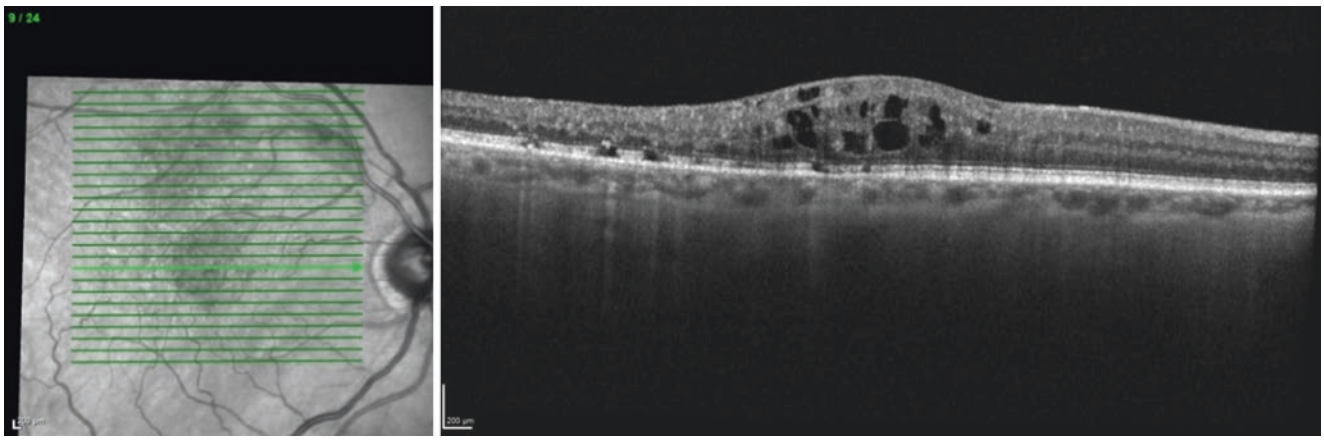


Fig. 5.7 Optical coherence tomography (OCT) in an eye with CME secondary to a right major BRVO. There are focal areas of outer retinal disruption resulting from a prior thermal grid laser treatment. The green arrow indicates the location and direction of the OCT B-scan

following 4 years for major BRVO (Hayreh et al. 1983,1994).

In eyes presenting with pronounced vision reduction from macular edema due to BRVO, visual acuity may often improve with observation alone, but it is uncommon for untreated eyes to improve beyond 20/40 (Rogers et al. 2010a, b). Up to 25% of untreated eyes with ischemic major BRVOs will develop neovascularization (Hayreh et al. 1983).

Thermal Laser

The role of thermal laser for the treatment of macular edema associated with BRVO has diminished with the advent of intravitreal anti-vascular endothelial growth factor (VEGF) therapy (BVOS Group 1984). While the prior standard of care for treating persistent macular edema secondary to BRVO was thermal laser (Fig. 5.12), studies evaluating visual outcomes for intravitreal anti-VEGF therapy have reported that there is no benefit in performing early or late focal/grid laser for BRVO-related CME (Tadayoni et al. 2017). However, focal laser may remain a potential adjunctive treatment option in select cases with persistent leakage originating from focal aneurysms (which can occur in eyes with longstanding BRVOs) or as a means to reduce the burden of frequent intravitreal injections. Figure 5.13 demonstrates a case in which thermal focal/grid laser resulted in CME resolution that eliminated the need for additional anti-VEGF injections. Figure 5.14 shows a case that required laser treatment only.

In one study, the adjunctive thermal laser was not found to improve long-term visual acuity outcomes, promote macular

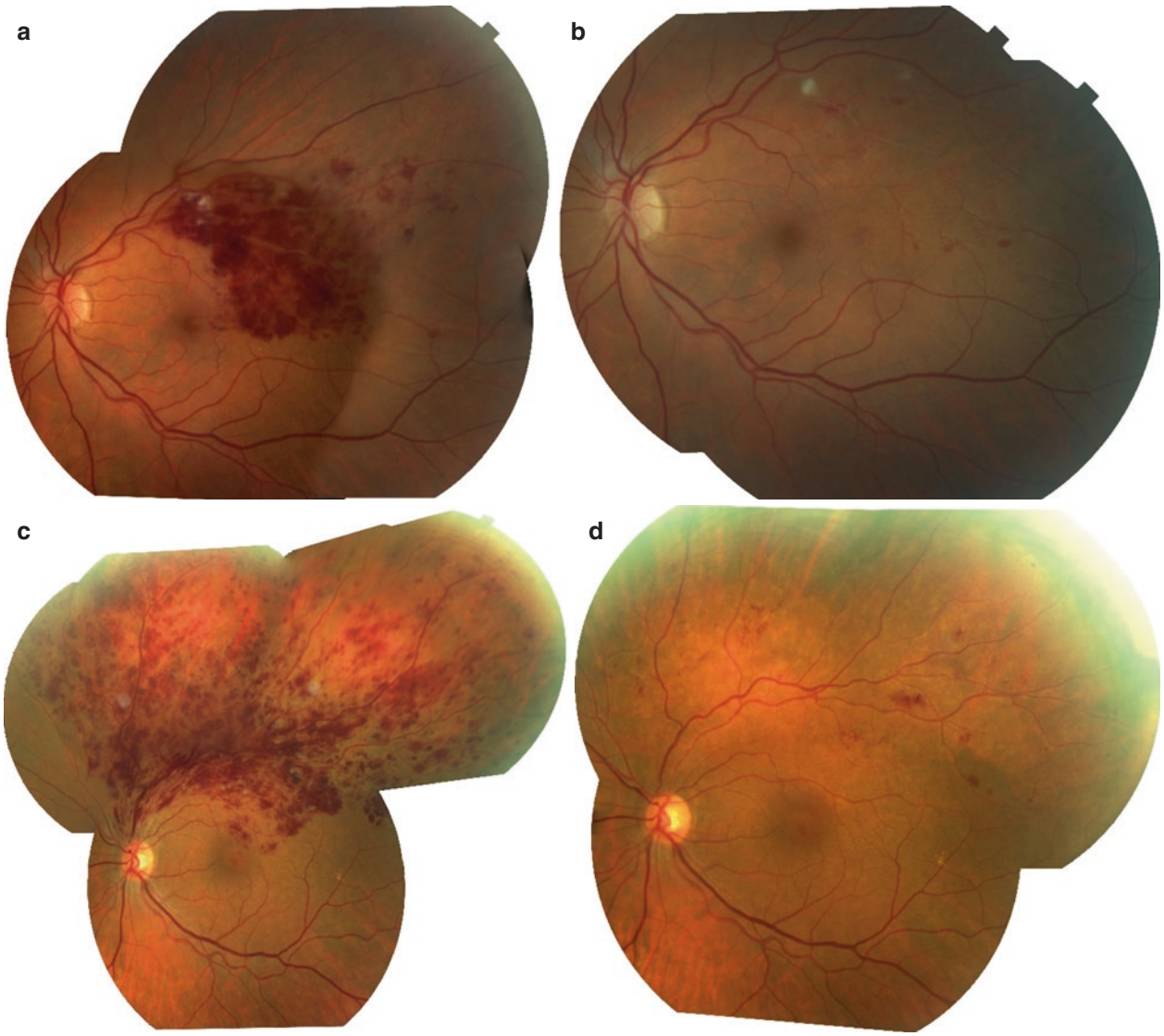


Fig. 5.8 Color montage images demonstrate the acute (**a**, **c**) and chronic (**b**, **c**) findings in 2 cases of left superotemporal major BRVOs. Most of the hemorrhagic changes have resolved by 11 months in one patient (**a**, **b**) and by 23 months (**c**, **d**) in the second patient

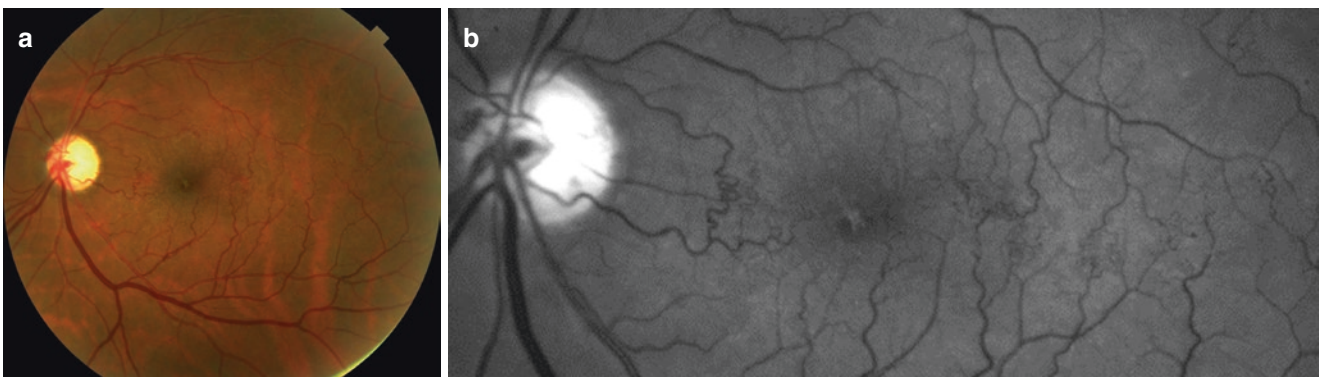
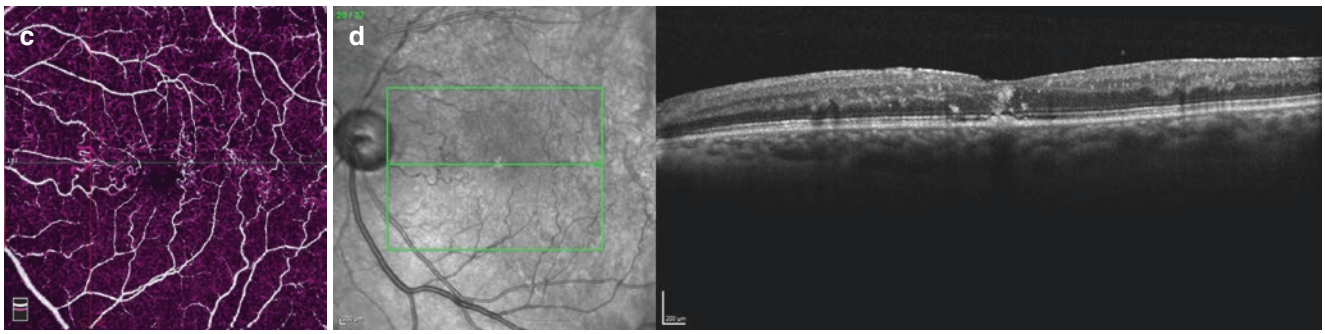


Fig. 5.9 Collateral vessels can be easier to discern on red-free images (**b**) compared to color fundus photographs (**a**). The collateral vessels in this eye with a left superotemporal major BRVO were well-visualized with optical coherence tomography (OCT) angiography imaging. (**c**) Visualization of flow in the superficial vascular plexus is shown in white, while the deep vascular complex (DVC) flow is shown in purple. Structural OCT shows intraretinal hyperreflective foci, some representing the dilated collateral vessels within the DVC and a mild epiretinal membrane (**d**). The green arrow indicates the location and direction of the OCT B-scan



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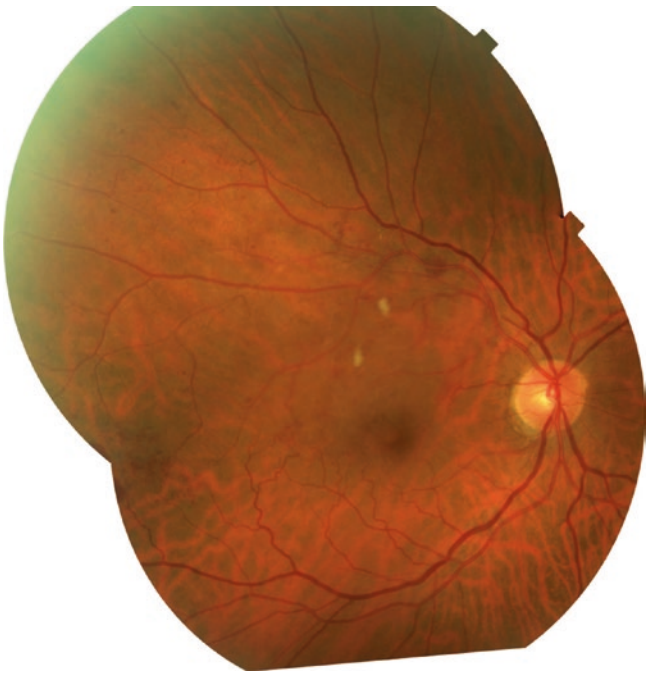


Fig. 5.10 Color montage photograph shows collaterals connecting a second-order superotemporal retinal vein to its accompanying second-order branching vein and to veins inferior to the horizontal raphe

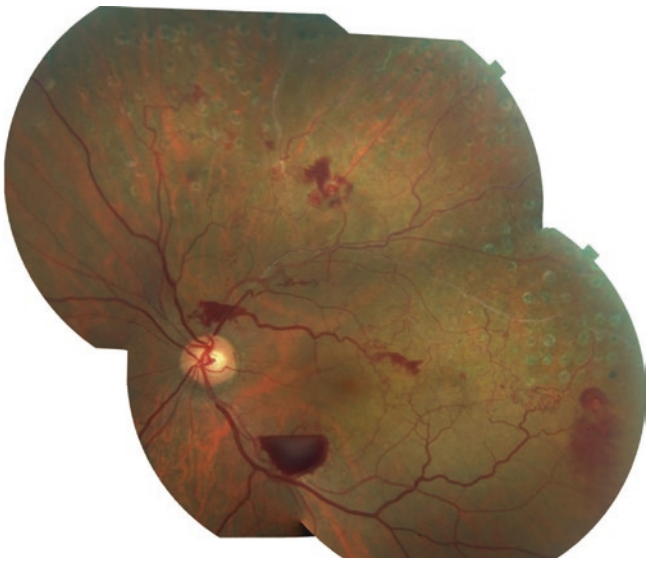


Fig. 5.11 Color montage photograph demonstrates a left chronic major BRVO with subsequent sclerosis of the occluded vein. There is prominent collateralization of vessels both proximal to the occlusion and inferior to the horizontal raphe. Retinal neovascularization is present in multiple locations associated with preretinal and intraretinal hemorrhage

edema resolution, or reduce anti-VEGF treatment burden of general BRVO cases (Campochiaro et al. 2015). However, the investigators acknowledged that they could not rule out a benefit for more timely treatment in a less step-wise fashion.

Scatter thermal laser to the involved quadrant should be considered in eyes with ischemic major BRVOs associated with preretinal neovascularization, as approximately 50% of these eyes will develop vitreous hemorrhage (Fig. 5.15) (BVOS Group 1986). Scatter thermal laser should be performed in eyes with neovascular glaucoma due to ischemic BRVO.

Intravitreal Anti-Vascular Endothelial Growth Factor (Anti-VEGF) Therapy

The advent of intravitreal anti-VEGF therapy has revolutionized the management of macular edema secondary to BRVO. Clinical trials have demonstrated the superiority of this treatment over macular focal/grid thermal laser (Campochiaro et al. 2010; Tan et al. 2014; Clark et al. 2016). Figures 5.16 and 5.17 demonstrate resolution of macular edema 1 month after a single intravitreal anti-VEGF intravitreal injection.

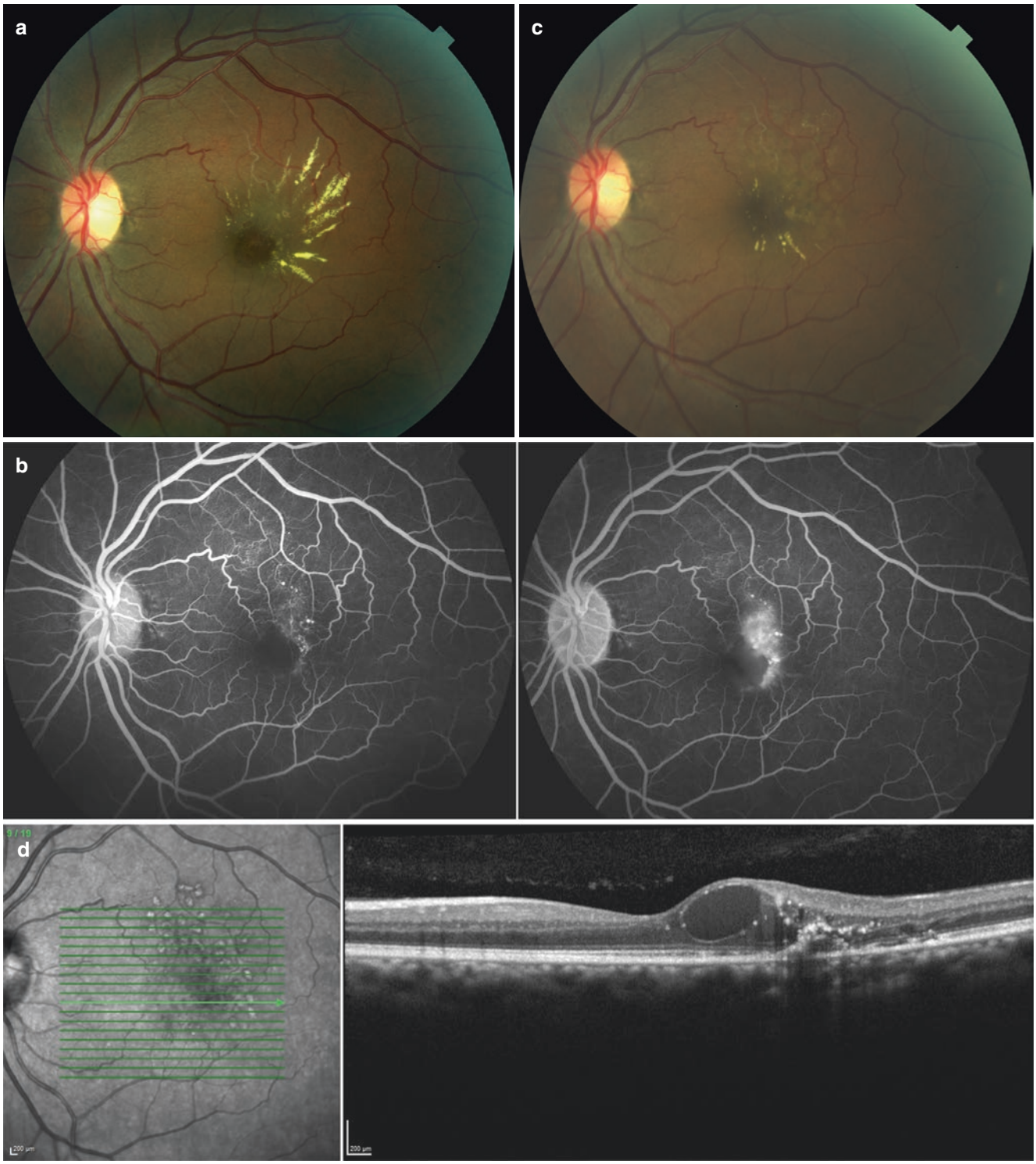
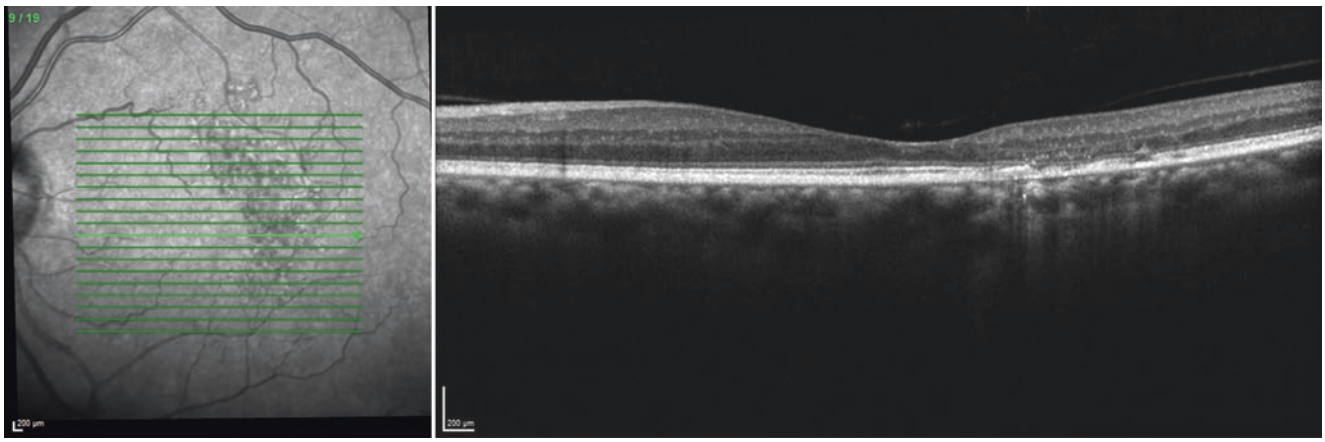


Fig. 5.12 A chronic left superotemporal macular BRVO with macular edema. Color fundus photograph shows macular edema and intraretinal lipid. (**a**) Fluorescein angiogram shows focal hyperfluorescent microaneurysms and late leakage (**b**). Color fundus photograph (**c**) shows a marked reduction in intraretinal lipid several months following focal/grid thermal laser. Optical coherence tomography showing CME prior to thermal laser (**d**) with a resolution of edema several months after treatment. The green arrows indicate the location and direction of the OCT B-scans



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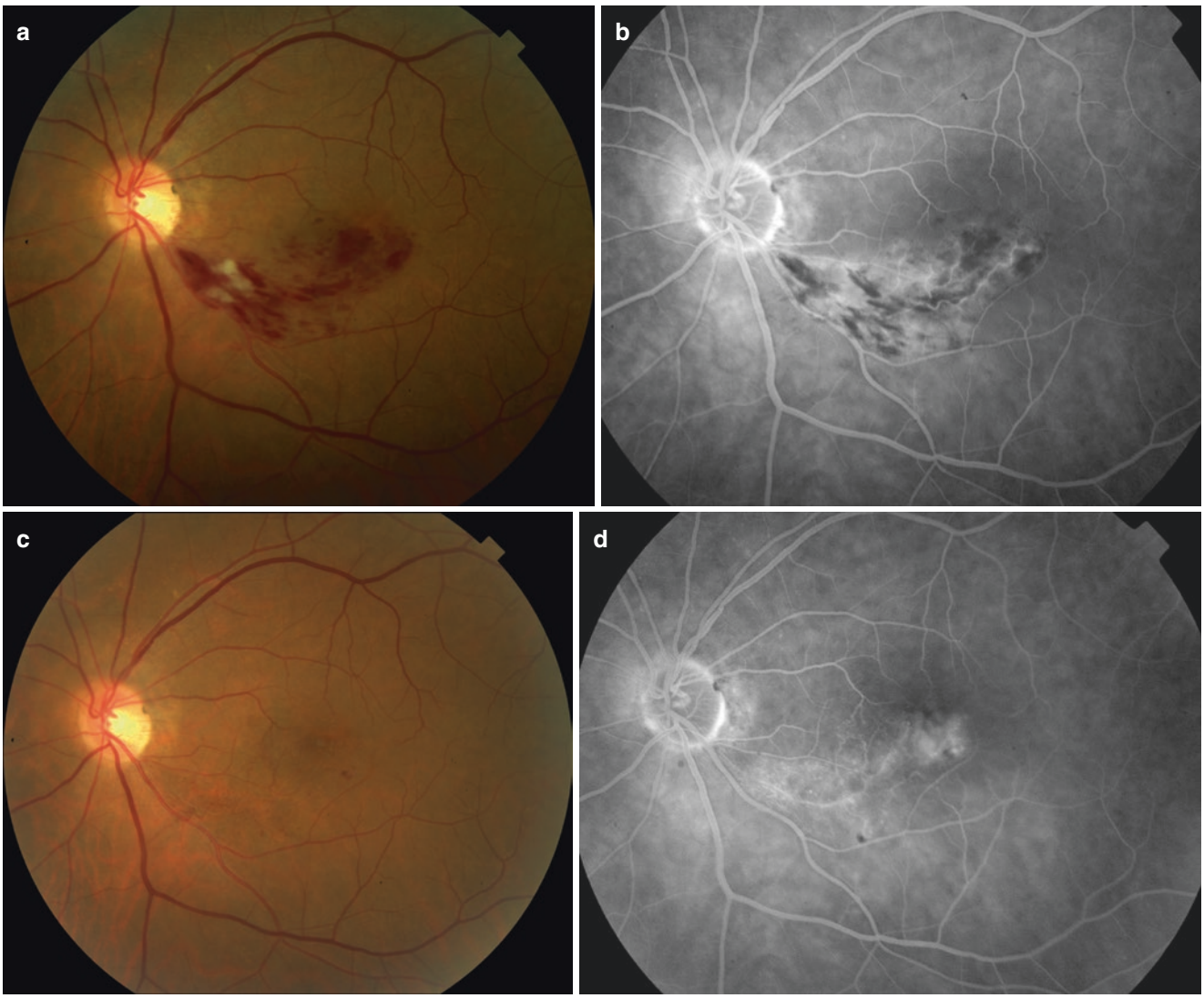
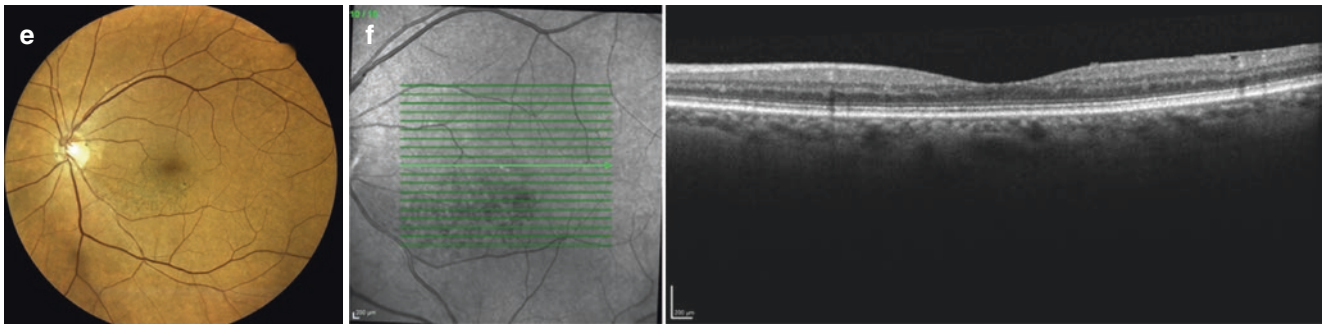


Fig. 5.13 This patient with macular edema secondary to a right macular BRVO (**a**, **b**) responded well to intravitreal anti-VEGF therapy (**c**, **d**) but required ongoing maintenance injections to prevent recurrence. Subsequent focal laser alleviated the need for ongoing intravitreal therapy (**e**, **f**). The green arrow in (**f**) indicates the location and direction of the OCT B-scan



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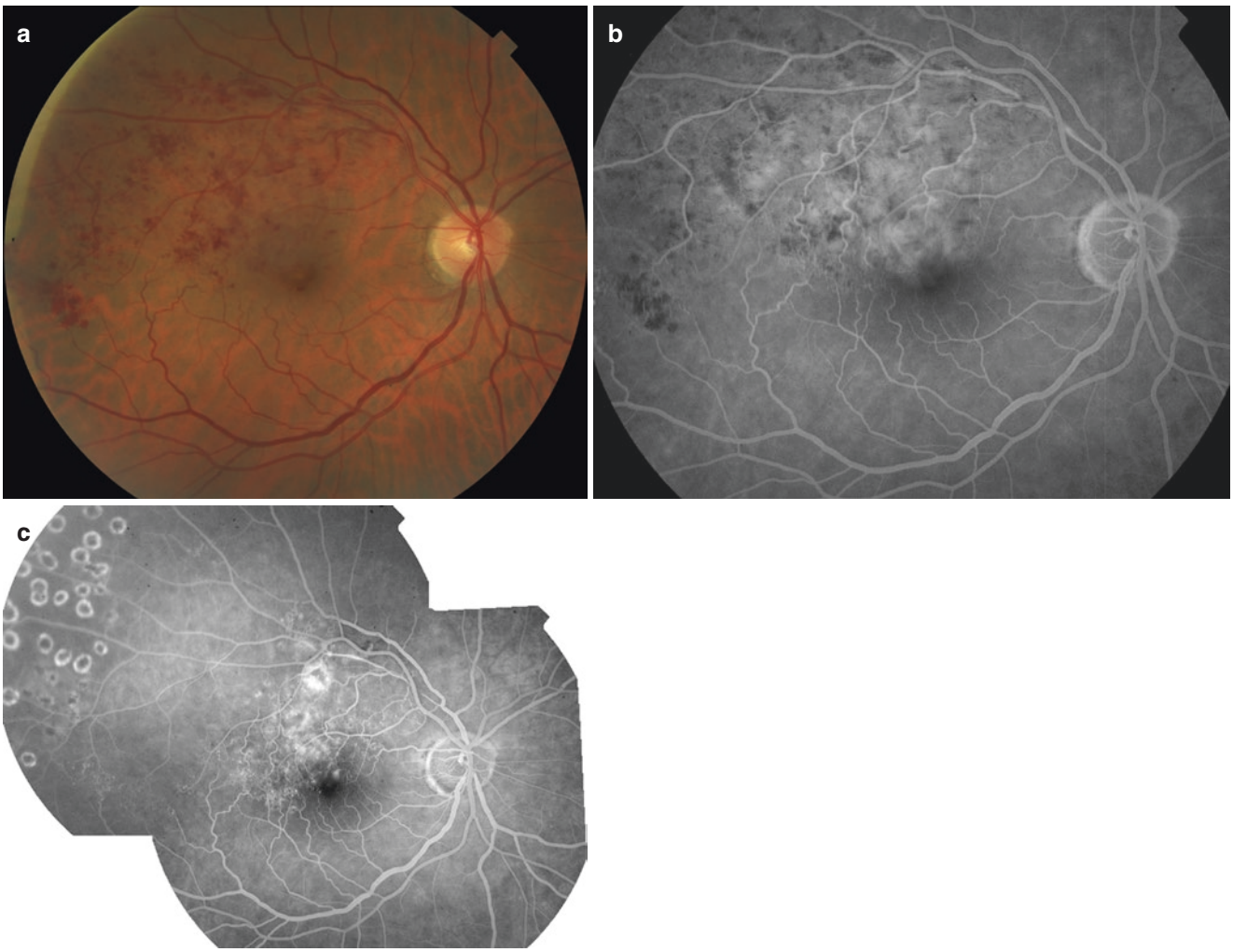


Fig. 5.14 Pre-thermal laser color photograph and fluorescein angiogram (FA) at initial presentation (**a**, **b**) and post-thermal laser FA (**c**) in an eye with the right major superotemporal BRVO treated with both focal/grid and scatter thermal laser

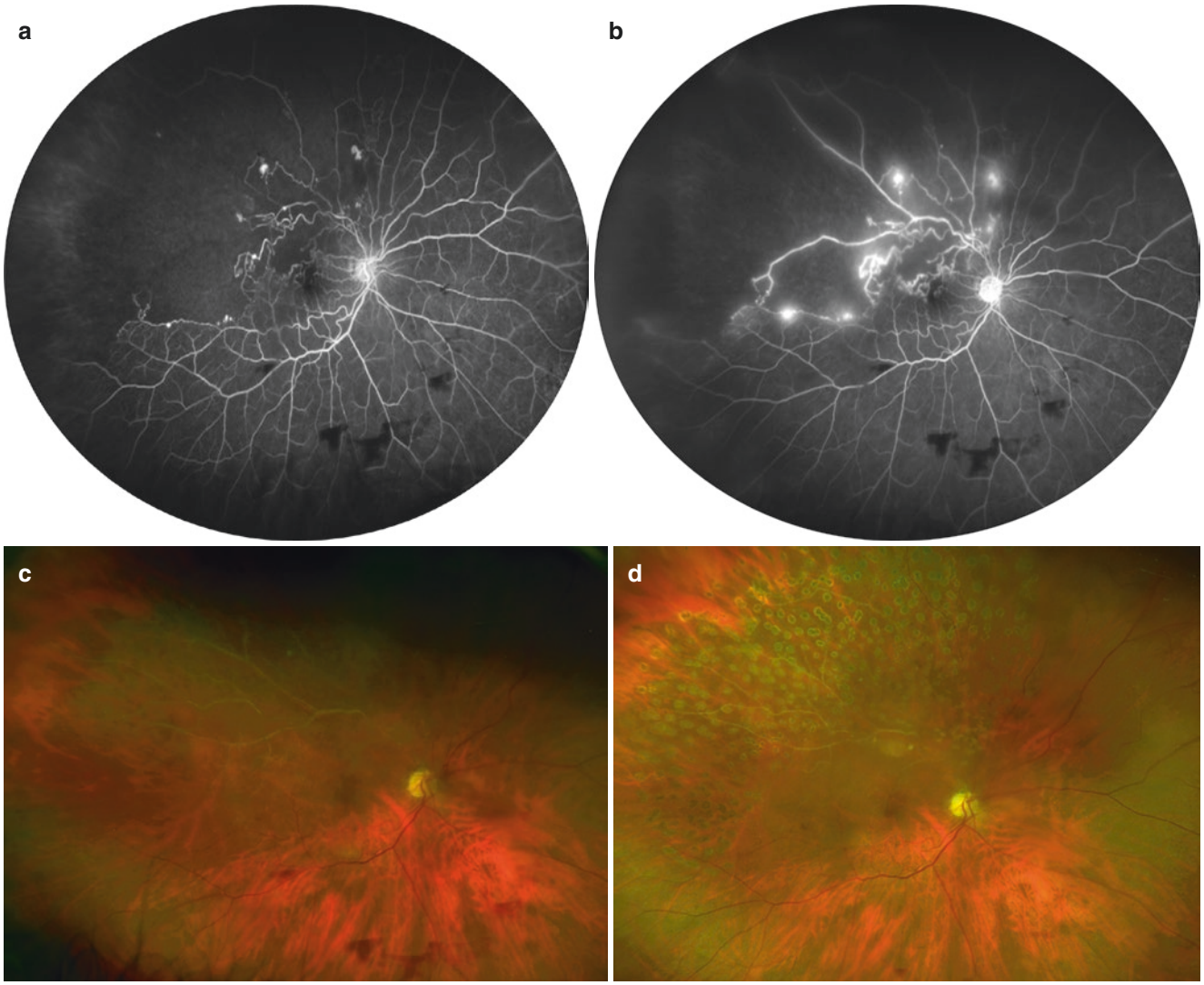


Fig. 5.15 Early phase (**a**) and late phase (**b**) ultra-widefield fluorescein angiographic images show ischemia, retinal macroaneurysms, collateral vessels, and preretinal hemorrhage in an eye with a right major superotemporal BRVO. Ultra-widefield color image (**c**) shows inferior preretinal hemorrhage which has nearly resolved one-month following scatter thermal laser targeting the non-perfused retina (**d**)

Long-term visual gains with intravitreal anti-VEGF therapy appear to be sustainable with both OCT-guided pro re nata *(PRN)* and "treat-and-extend" (TER) regimens (Fig. 5.18) (Heier et al. 2012; Campochiaro et al. 2014; Rush et al. 2014; Tadayoni et al. 2017). Ongoing studies are exploring if the intravitreal anti-VEGF treatment burden can be reduced with concurrent thermal laser and/or intravitreal corticosteroid treatment (Tadayoni et al. 2017) (Fig. 5.19).

Intravitreal Corticosteroid Therapy

Intravitreal and periocular corticosteroids such as triamcinolone acetonide have been used as an off-label treatment for macular edema secondary to BRVO. Although anatomic and visual outcomes of corticosteroids may be similar to focal/grid thermal laser, cataract progression, and elevated intraocular pressure (IOP) are common side effects with this treatment (Scott et al. 2009). More recently, a slow release intravitreal dexamethasone implant (Ozurdex®, Allergan Inc., Irvine CA, USA) became available as an on-label treatment for macular edema secondary to BRVO. This treatment appears to be associated with a lower risk of increased IOP than alternative intravitreal steroids (Haller et al. 2011).

Vitreoretinal Surgery

Vitreoretinal surgery is not typically employed in BRVO cases unless a non-remitting vitreous hemorrhage and/or tractional retinal detachment ensues from retinal neovascularization.

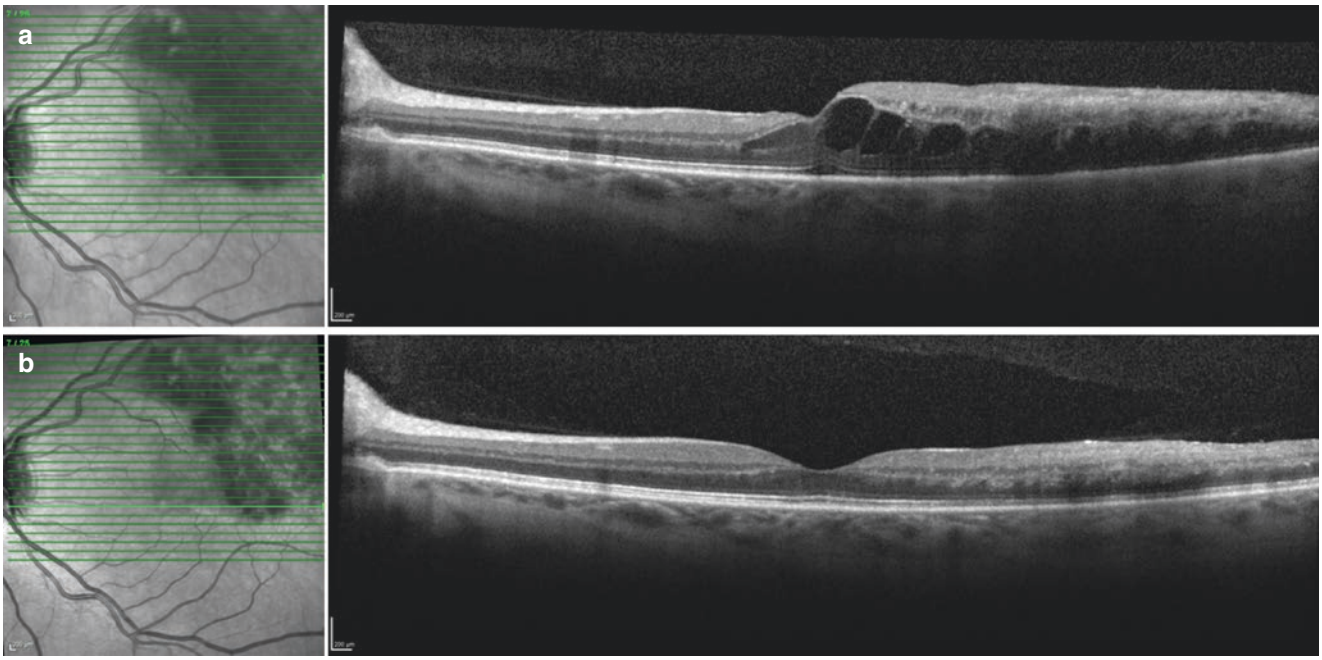


Fig. 5.16 Optical coherence tomography B-scans show macular edema (**a**) which resolves (**b**) 1 month following a single intravitreal anti-VEGF injection in an eye with a left superotemporal major BRVO. The green arrows indicate the location and direction of the OCT B-scans

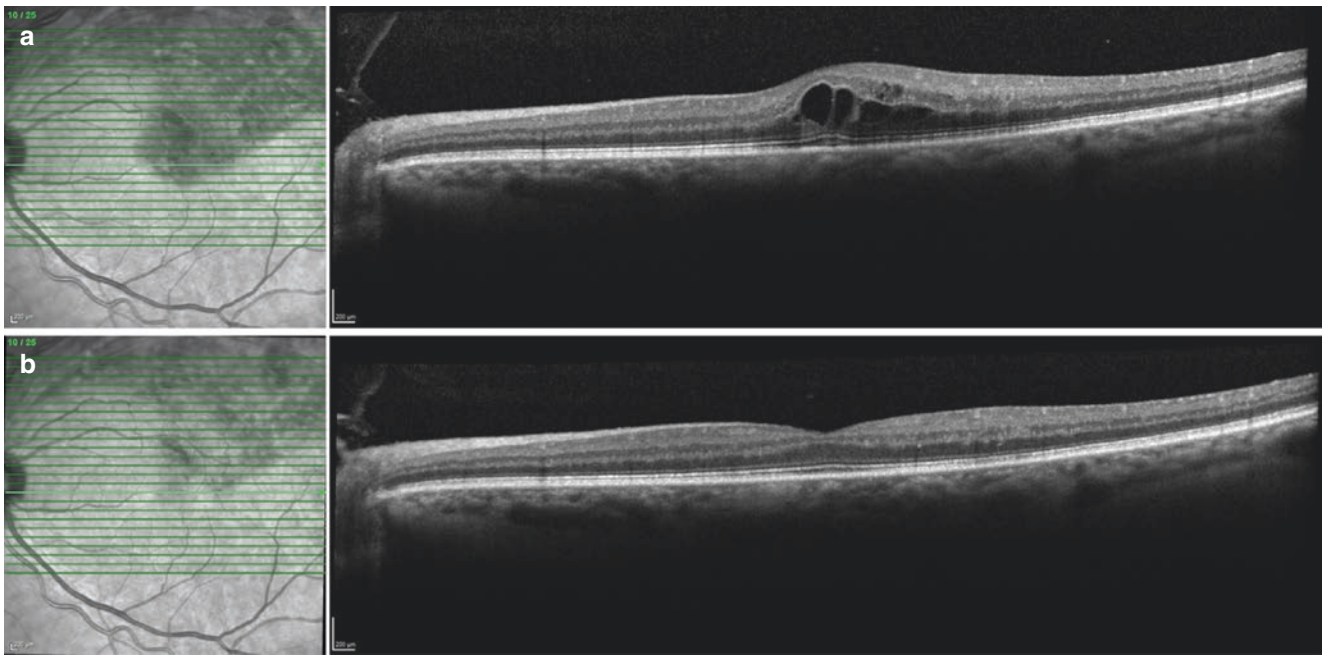
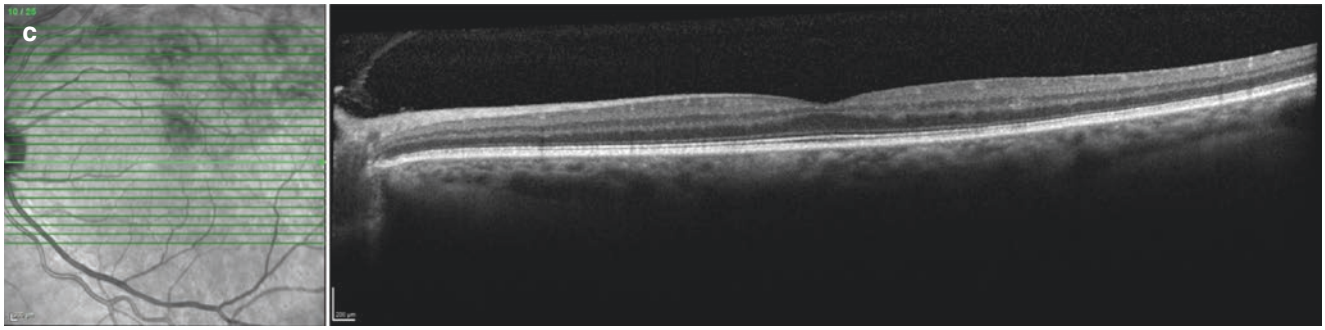


Fig. 5.17 Optical coherence tomography B-scans of an eye with an acute left superotemporal major BRVO show macular edema (**a**) that has resolved at 1 week (**b**) and 1 month (**c**) after an initial intravitreal anti-VEGF injection. The green arrows indicate the location and direction of the OCT B-scans



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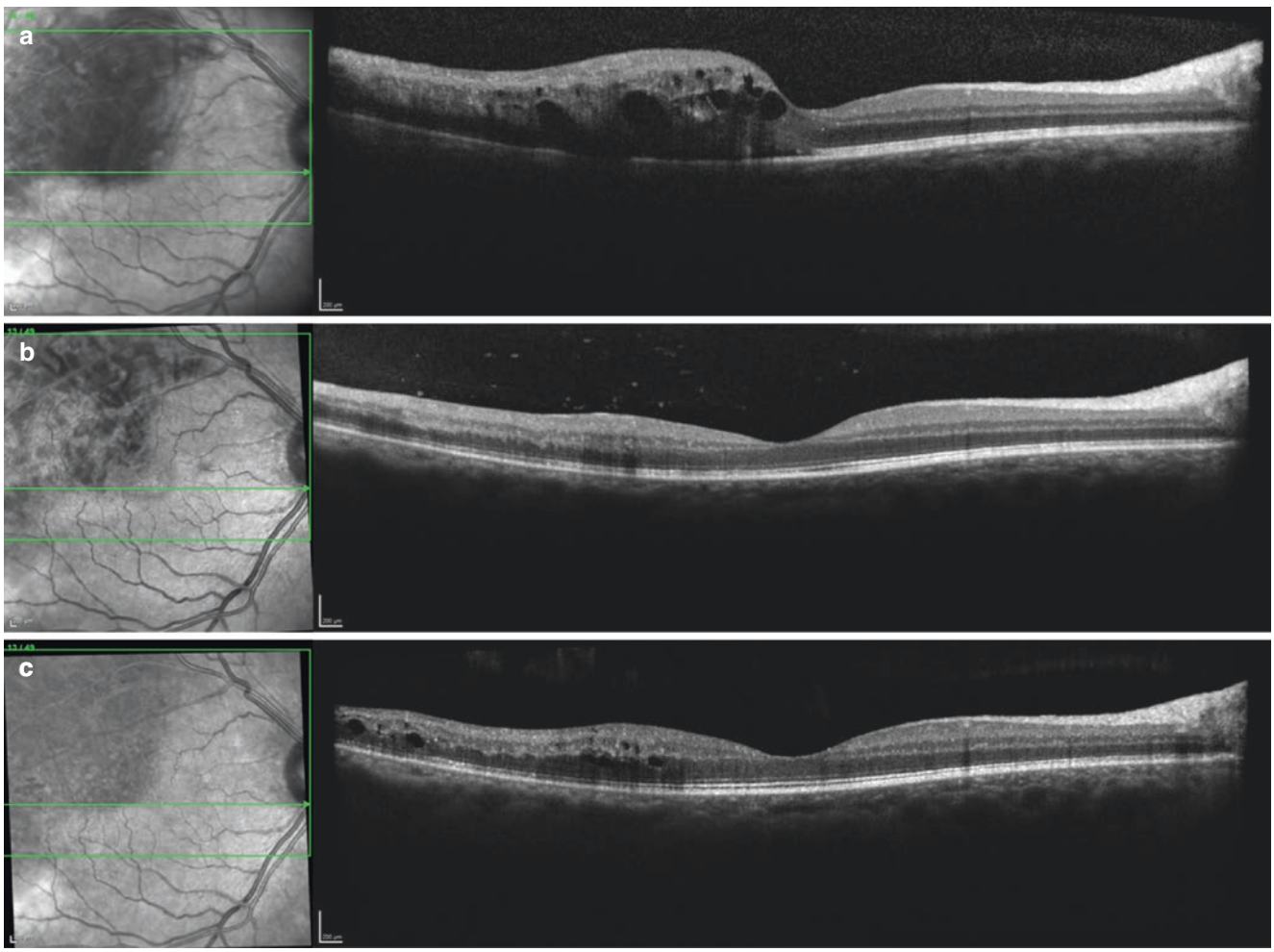

Fig. 5.18 Optical coherence tomography B-scans of an eye with an acute right superotemporal major BRVO showing macular edema (**a**) that resolves 1 month after intravitreal anti-VEGF therapy (**b**) but recurs when the injection interval is extended to more than 6 weeks (**c**). The green arrows indicate the location and direction of the OCT B-scans

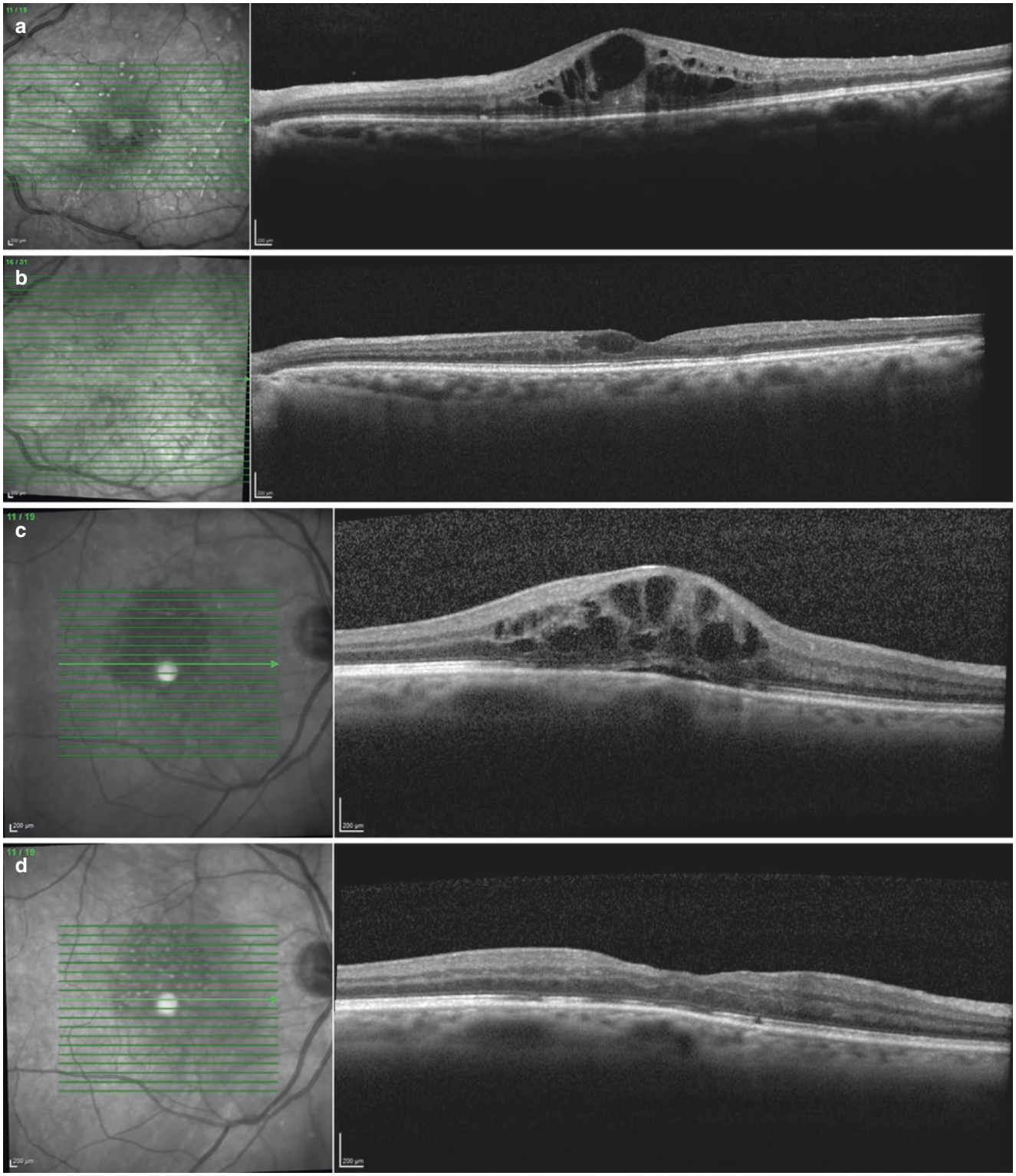

Fig. 5.19 Two eyes with macular edema secondary to BRVO showing an inadequate response to focal/grid laser (**a, c**). Monthly intravitreal anti-VEGF therapy was subsequently used to control the edema (**b, d**)

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Retinal Arterial Macroaneurysm

6

Kim Jiramongkolchai and J. Fernando Arevalo

Introduction

Retinal arterial macroaneurysm (RAM) was first published in a report by Loring in 1880 in which he described a bulging ectasia of the inferotemporal retinal artery in an asymptomatic healthy 25-year-old man (Loring 1880). Fernandez made the first association of retinal artery macroaneurysm with systemic hypertension in 1920 (Fernandez 1920). Robertson was the first to define retinal artery macroaneurysm as a distinct clinical entity and its natural history in 1973 (Robertson 1973). RAM most commonly affects women in their 60s and 70s and is associated with hypertension and atherosclerotic vessel disease. RAM is usually unilateral but may be bilateral in 10% of cases (Rabb et al. 1988). They are usually single but may be multiple in 20% of cases (Rabb et al. 1988).

Retinal arterial macroaneurysms are characterized by an acquired, round, fusiform dilation of the retinal arteriole wall. They occur within the first three orders of arterial bifurcation and often occur at a branch point or arteriovenous crossing (Fig. 6.1). The superotemporal artery is the most frequently reported site.

Although patients may be asymptomatic, the most common presenting symptom is acute vision loss that may arise from exudation, edema, or hemorrhage in the macula (Fig. 6.2) or vitreous cavity. Hemorrhage surrounding the macroaneurysm can be seen in up to 50% of eyes (Rabb et al. 1988). The retinal hemorrhage can be described as preretinal, intraretinal, or subretinal. Hourglass hemorrhage is a term used to describe hemorrhage that affects all retinal layers. Breakthrough vitreous hemorrhage can occur in about 10% of cases (Nadel and Gupta 1976). Circinate hard exudates surrounding the macroaneurysm or distal to the macroaneurysm are common. Rarely, a serous retinal detachment may be seen surrounding the macroaneurysm.

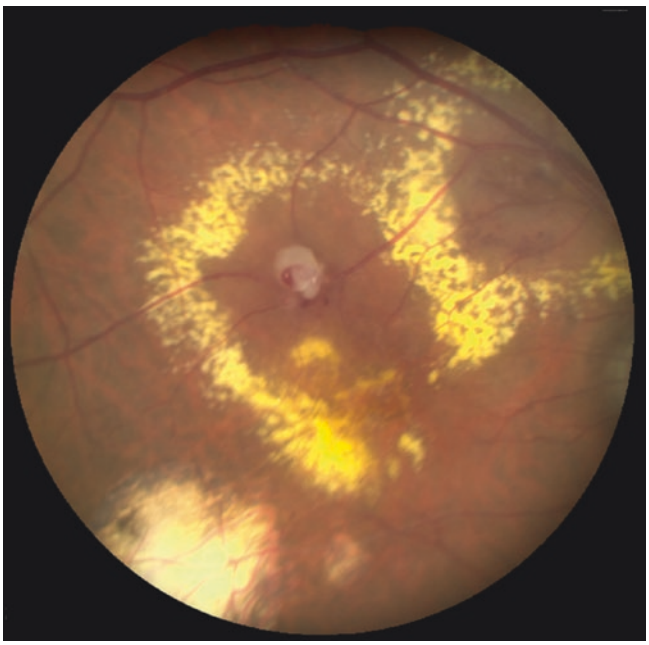

Fig. 6.1 Color fundus photograph showing retinal macroaneurysm with surrounding circinate intraretinal lipid hard exudates

Etiopathogenesis

Histological examination of RAM shows abnormal clot formation within the vessel wall consisting of hyaline, fibrin, and foamy macrophages (Fichte et al. 1978). The focal thrombus formation within the vessel wall leads to localized ischemia and further collagen remodeling which predisposes to vessel dilation and formation of RAM.

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A. Sheyman, A. A. Fawzi (eds.), *Retinal Vascular Disease*, Retina Atlas, https://doi.org/10.1007/978-981-15-4075-2_6

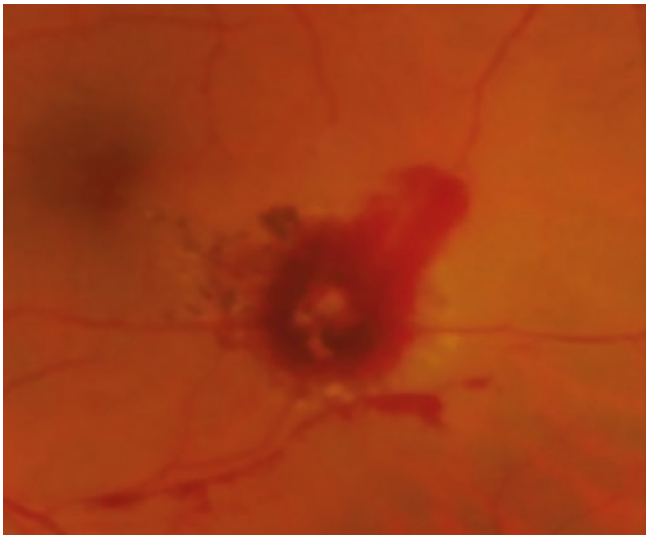

Fig. 6.2 Although patients may be asymptomatic, the most common presenting symptom is acute vision loss which may arise from exudation, edema, or hemorrhage in the macula

Clinical Features

Early phase fluorescein angiography shows a uniform filling of the macroaneurysm (Fig. 6.3a, b) (Amalric et al. 1979). Late phase fluorescein angiography may show mild or no staining of the vessel wall or marked leakage depending on vessel damage (Fig. 6.3c). Delayed or incomplete filling may indicate involution of the macroaneurysm. Massive amounts of lipid exudation surrounding the macroaneurysm may block fluorescein. The macroaneurysm may be surrounded by small areas of capillary non-perfusion or microaneurysms (Fig. 6.4). The artery or arteriole proximal to the macroaneurysm is usually narrowed. In the presence of dense hemorrhage, the macroaneurysm may not be seen in fluorescein angiography due to the blockage from the hemorrhage (Fig. 6.5). Indocyanine green angiography, which uses an absorption and emission spectra in the near-infrared range may allow better penetration through hemorrhage than fluorescein angiography and improve visualization of the macroaneurysm (Townsend-Pico et al. 2000). Round focal hot spots on indocyanine green angiography next to retinal arterioles are characteristic of retinal arterial macroaneurysm. A small case series demonstrated that A pulsatile lesion contiguous with the arterial wall on indocyanine green videoangiography is indicative of a RAM (Schneider et al. 1997).

Management

Observation

The natural history of RAM has been described and most lesions undergo spontaneous thrombosis and involution with resolution over a few months (Rabb et al. 1988). Observation, therefore, has been advocated by some as visual acuity can be excellent in these cases in which there is spontaneous resolution (Robertson 1973). However, moderate-to-severe loss of vision can occur in RAM associated with exudation and hemorrhage. Severe vision loss can occur from subretinal hemorrhage and its toxicity to the photoreceptors. Macular edema is the most common sequelae of RAM and permanent macular structural damage can occur from chronic lipid exudation.

Laser Photocoagulation

Laser photocoagulation with yellow dye laser surrounding the RAM and treating directly the RAM itself has been considered due to its theoretical advantage of causing less damage to the retinal pigment epithelium (Fig. 6.6) (Mainster and Whitacre 1988). Nd:Yag laser photodisruption has also been described for premacular hemorrhage with good visual outcomes (Dahreddine et al. 2011). Yag laser photodisruption disrupts the inner limiting membrane of the retina allowing evacuation of the hemorrhage into the vitreous for quicker clearance. Complications of Yag laser photodisruption include secondary non-clearing vitreous hemorrhage, macular hole, and retinal detachment (Wu et al. 2011; Ulbig et al. 1998).

Anti-Vascular Endothelial Growth Factor Treatment

Variable visual outcomes have been reported for vitrectomy to clear non-clearing vitreous hemorrhage from a ruptured macroaneurysm and were influenced by the location of the RAM. Poorer visual outcomes were associated with dense submacular hemorrhage (Nakamura et al. 2008). Intravitreal anti-vascular endothelial growth factor has been used to treat symptomatic macular edema and vitreous hemorrhage from macroaneurysm and has been shown to lead to faster resolution of retinal hemorrhage (Cho et al. 2013). However, visual acuity improvement is variable. In one retrospective study, there was no significant difference in final visual acuity or central macular thickness (Cho et al. 2013). In a prospective

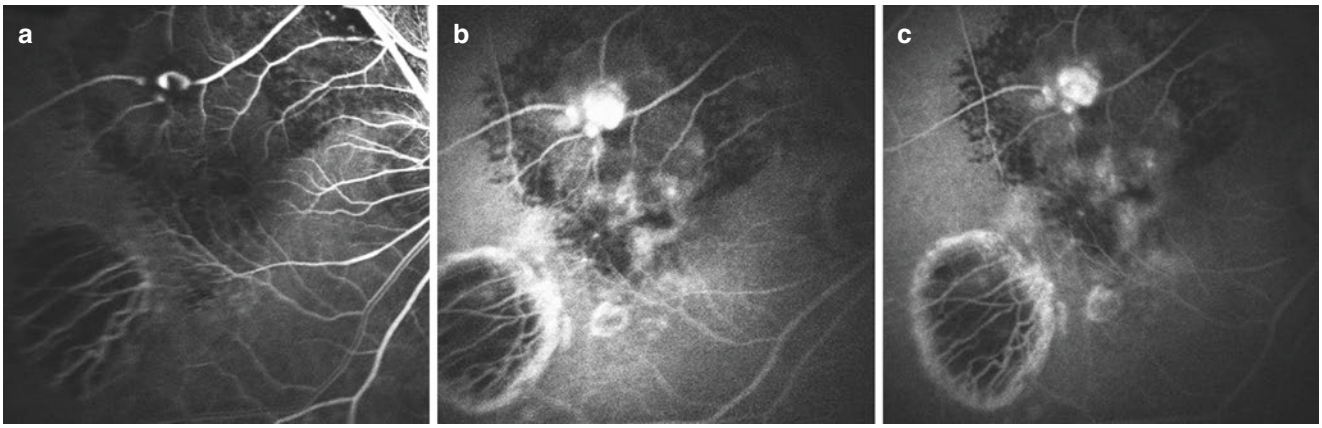

Fig. 6.3 Fluorescein angiography showing progressive uniform filling of the retinal macroaneurysm during the early (**a**), middle (**b**), and late phase (**c**)

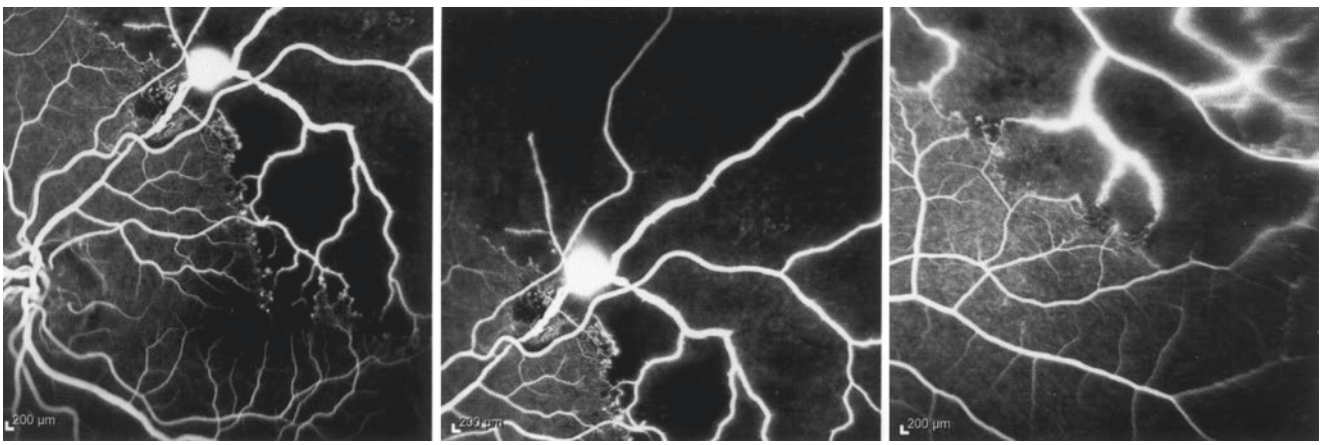

Fig. 6.4 Fluorescein angiography showing a macroaneurysm surrounded by areas of capillary non-perfusion and microaneurysms

study, monthly injections of intravitreal bevacizumab resulted in the closure of the RAM in 94% of patients at 6 weeks (after 2 injections) and 100% of patients had complete resolution of macular edema 4 weeks after the third injection of bevacizumab with corresponding significant improvement in visual acuity (Pichi et al. 2013). Anti-VEGF may reduce macular edema by stimulating the production of endothelial nitric oxide and activating the coagulation cascade and vasoconstriction (Cho et al. 2013).

Surgery

Pneumatic displacement with tissue plasminogen activator and SF6 gas has been tried and is not recommended due to a higher incidence of vitreous hemorrhage (Mizutani et al. 2011). Surgical excision of the RAM with scissors and diathermy has also been described in two patients with good visual outcomes (Dahreddine et al. 2011).

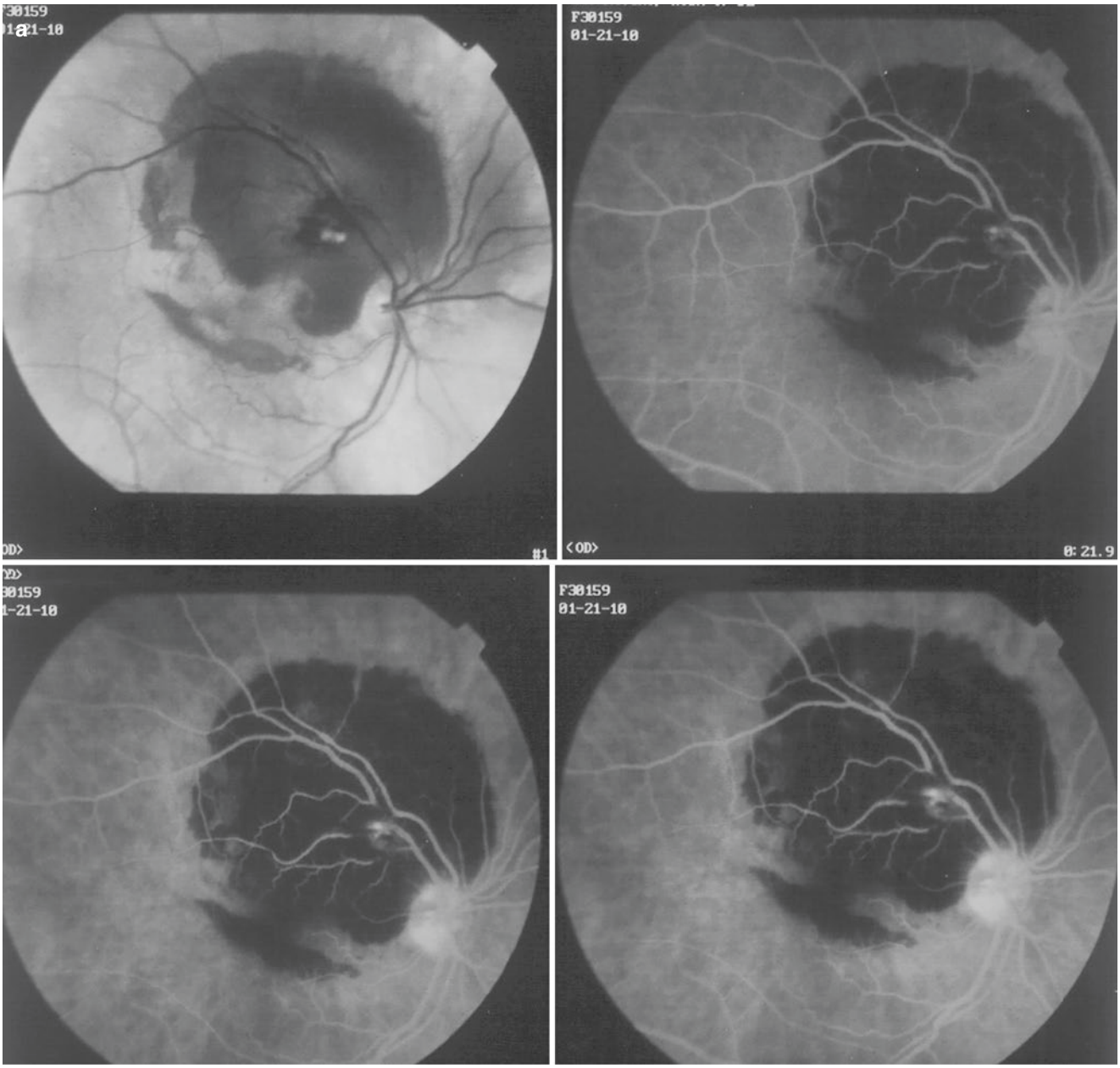

Fig. 6.5 In the presence of dense hemorrhage, the macroaneurysm may not be seen in fluorescein angiography due to the blockage from the hemorrhage. Fluorescein angiography showing a macroaneurysm that is barely visible due to blockage from the hemorrhage (**a**). Optical coherence tomography (OCT) demonstrates a large subretinal hemorrhage (**b**)

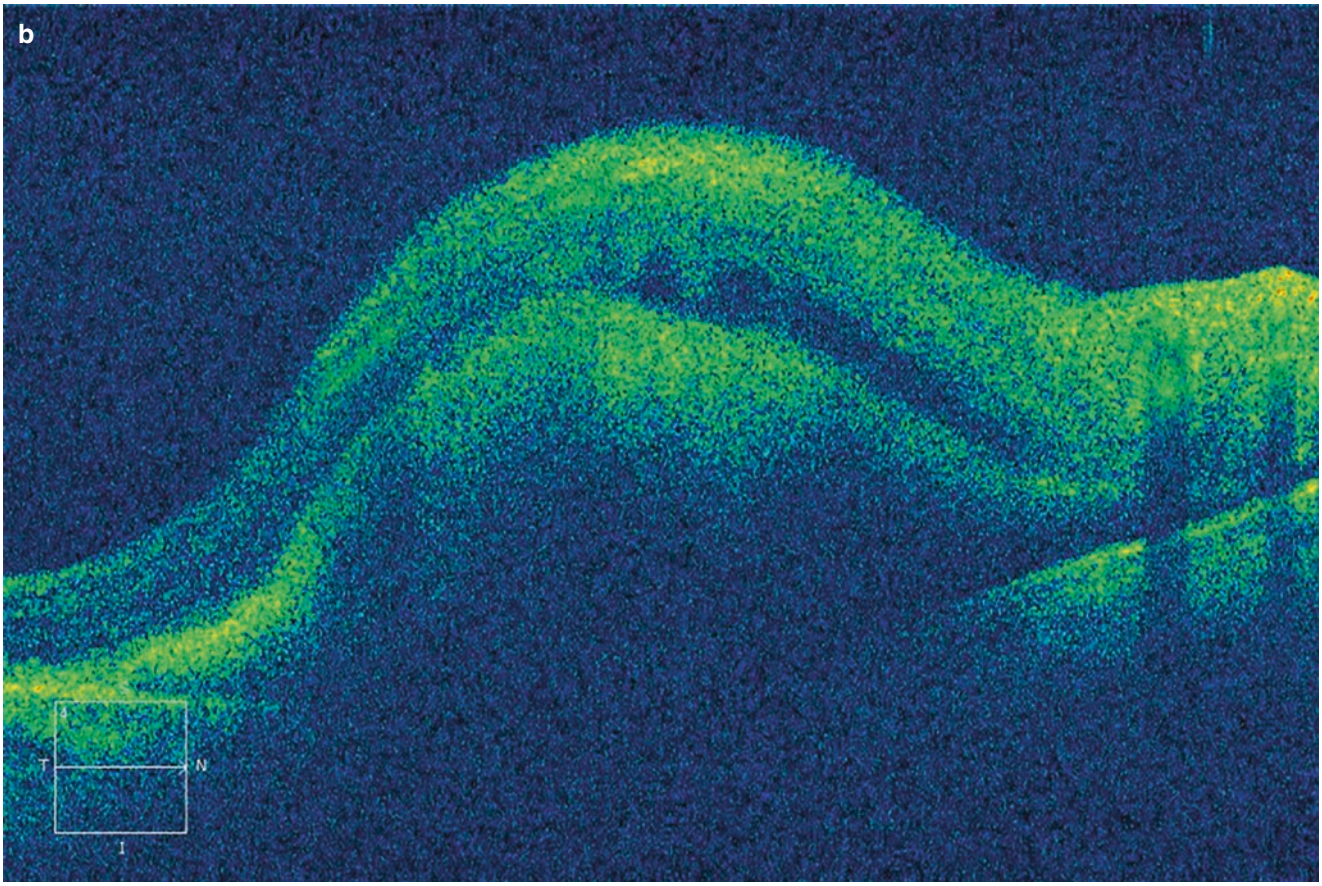

Fig. 6.5 (continued)

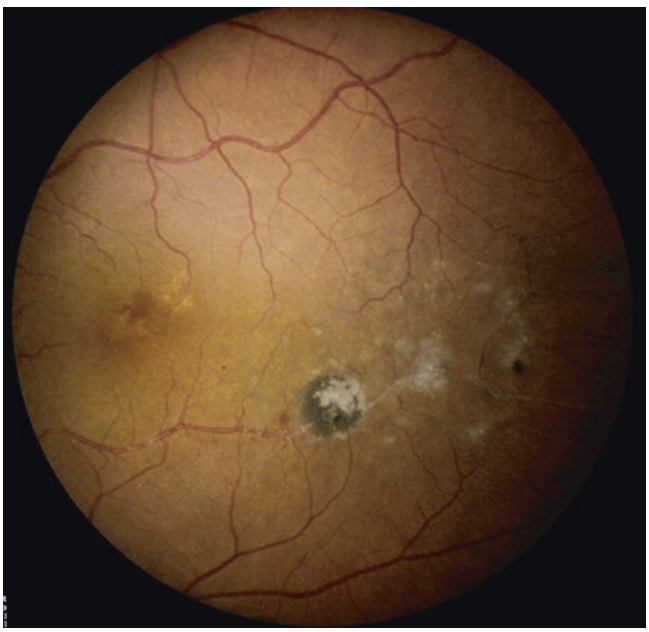

Fig. 6.6 Color fundus photograph showing laser photocoagulation of the retinal macroaneurysm

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Coats' Disease

7

Sally S. Ong and Lejla Vajzovic

Introduction

Coats' disease is a pediatric vitreoretinopathy that is characterized by the presence of idiopathic retinal vascular telangiectasias with possible retinal exudation and exudative retinal detachments (Shields and Shields 2001). It was first described by George Coats in 1908 as a disease entity with retinal exudation and vascular anomalies (Coats 1908). In 1912, a similar condition characterized by multiple retinal aneurysms and retinal degeneration was reported by Theodor Leber and was named Leber's miliary aneurysm (Leber 1912). In 1956, Reese observed that patients with the condition described by Leber eventually progressed to the clinical appearance reported by Coats. He then further pointed out the similarities between both conditions and suggested that the term Coats' disease was used to describe both entities (Reese 1956).

Coats' disease is a sporadic and nonhereditary condition that more commonly affects males in the first two decades of life (Shields and Shields 2001; Gomez Morales 1965; Harris 1970; Tarkkanen and Laatikainen 1983; Ong et al. 2017). An adult form of the disease, which is usually milder, can be found in older patients. The majority of cases are unilateral, but when bilateral, the disease is usually asymmetric between the two eyes (Shields et al. 2001). Coats' disease is rare—the reported incidence is 0.09 per 100,000 people (Morris et al. 2010).

Pathognomonic findings in Coats' disease include aneurysmal dilatations, telangiectatic vessels, and nonperfusion in the periphery (Fig. 7.1). When aneurysmal telangiectatic vessels are only found in the macula, this is considered a variant of Coats' disease and thought to be the type 1 form of idiopathic macular telangiectasia (Yannuzzi et al. 2006) (Fig. 7.2). Other characteristic findings in Coats' disease include retinal exudation (Fig. 7.3) and exudative retinal detachments (Fig. 7.4).

Etiopathogenesis

Early on, Coats' disease was thought to be caused by infectious and inflammatory etiologies but various attempts to treat the disease with antibiotics and anti-inflammatory agents were unsuccessful and thus these theories have been discredited (Imre 1967). More recently, immunohistochemistry and electron microscopy studies have demonstrated a decrease in the number of endothelial cells and pericytes in telangiectatic retinal vessels in Coats' disease (Fernandes et al. 2006; Tripathi and Ashton 1971). Dilated, aneurysmal, and telangiectatic vessels were also shown to have an irregular wall infiltrated with plasmoid and fibrinous material and in some places this fibrous wall was extremely thin or absent (Tripathi and Ashton 1971). Abnormal permeability of the retinal vasculature is therefore thought to be important in the etiology of Coats' disease and could be the result of a functional or structural breakdown of the blood–retinal barrier. To date, however, the exact etiology of these vessel changes in Coats' disease remains unknown.

Clinical Features

Untreated Coats' disease can progress to secondary glaucoma or phthisis bulbi. In 2001, Shields et al. proposed a classification system to help guide therapeutic decisions. Stage 1 is defined as retinal telangiectasias only (Fig. 7.5), stage 2 by telangiectasias and exudation (Figs. 7.6 and 7.7), stage 3 by retinal detachment without glaucoma (Figs. 7.8, 7.9, and 7.10), stage 4 by total retinal detachment with glaucoma and stage 5 by advanced end-stage disease (Shields

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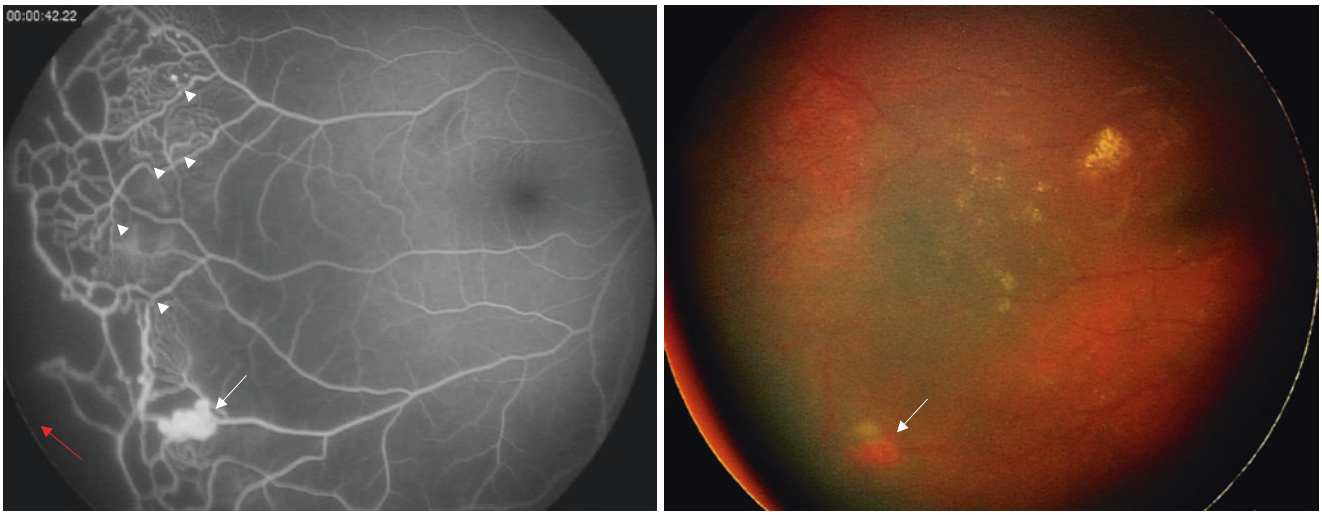

Fig. 7.1 Fluorescein angiography demonstrates tortuous and telangiectatic vessels (arrowheads), aneurysmal dilatation (white arrow), and nonperfusion (red arrow) in the periphery. These vascular changes are difficult to appreciate on the corresponding color photograph although the aneurysmal dilatation can be seen as an orange saccular structure in the periphery (white arrow)

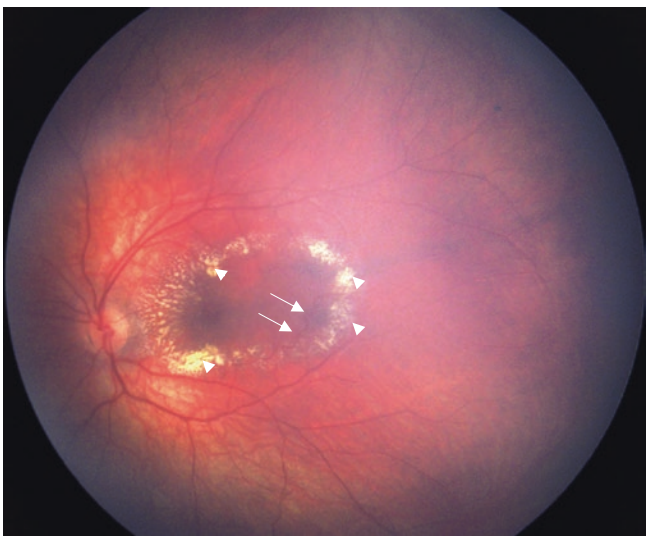

Fig. 7.2 Color photography shows aneurysmal dilatation (arrow) and exudation (arrowheads) in the macula only

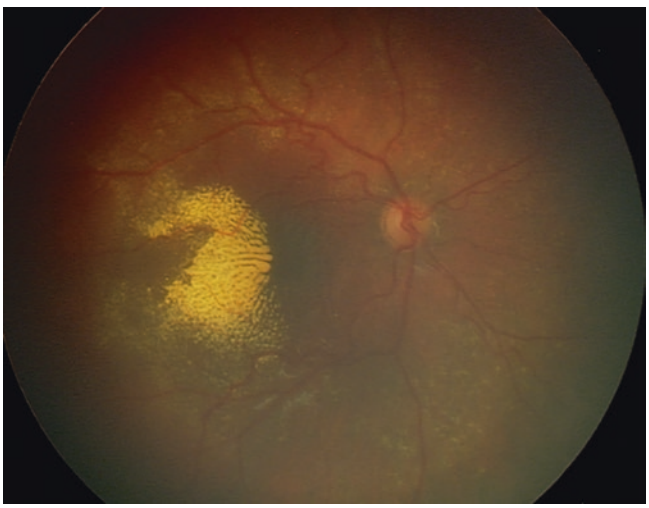

Fig. 7.3 Retinal exudates involving the fovea, in the macula and scattered in the midperiphery and periphery

et al. 2001). The authors recommended a multimethod approach to treatment based on stage of disease (Table 7.1). Updates to the classification system to incorporate the presence of subfoveal fibrotic nodule have also been suggested (Daruich et al. 2016).

Fluorescein Angiography

Fluorescein angiography (FA) is important in demonstrating pathognomonic peripheral vascular changes in Coats' disease including telangiectasias, aneurysms, and areas of abnormal perfusion that can be difficult to visualize on color photography alone (Blair et al. 2013). Capillary dropout is seen in the areas of telangiectasia in the periphery but retinal neovascularization is not commonly observed (Shields et al. 2001). FA can also show hypofluorescence of exudates, mild hyperfluorescence of subretinal fluid and hyperfluorescence of macular edema in the late frames (Shields et al. 2001) (Fig. 7.11).

Ultrasonography

Ophthalmic B-scan ultrasonography can be particularly useful when indirect ophthalmoscopy is limited by media opacities, severe pathology, or patient cooperation. Ultrasonography can detect exudative retinal detachments with hyperechoic crystalline deposits or exudates in Coats' disease (Fig. 7.12). Ultrasonography is also helpful to exclude

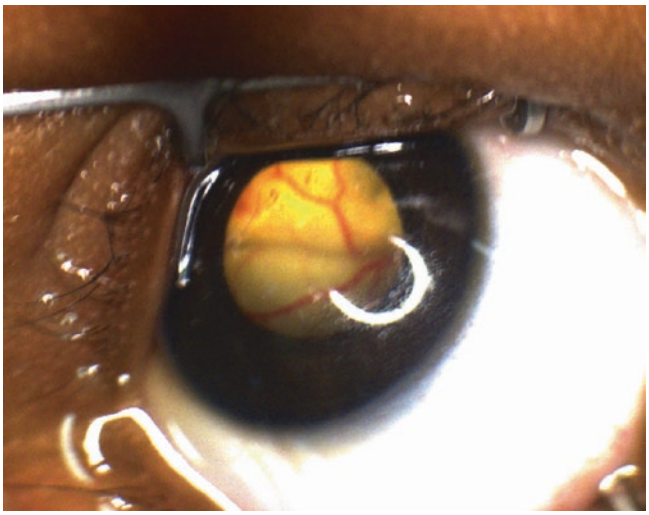

Fig. 7.4 Color photography shows retrolental total retinal detachment in a patient with Coats' disease

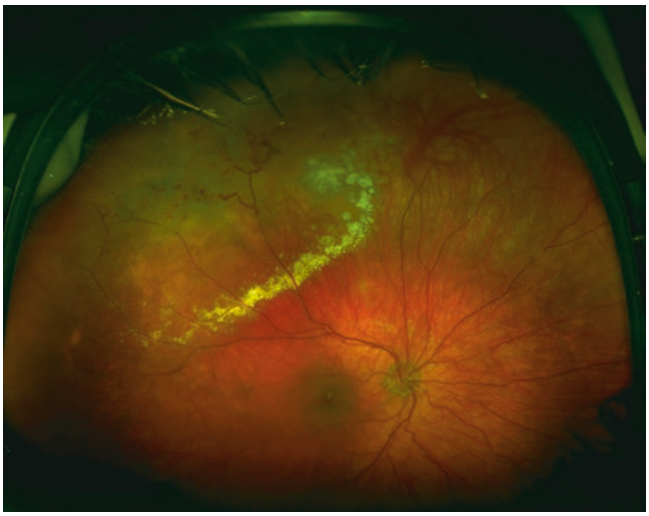

Fig. 7.6 Wide-field photography in a stage 2A patient shows the rim of extrafoveal exudates with telangiectatic vessels in the periphery

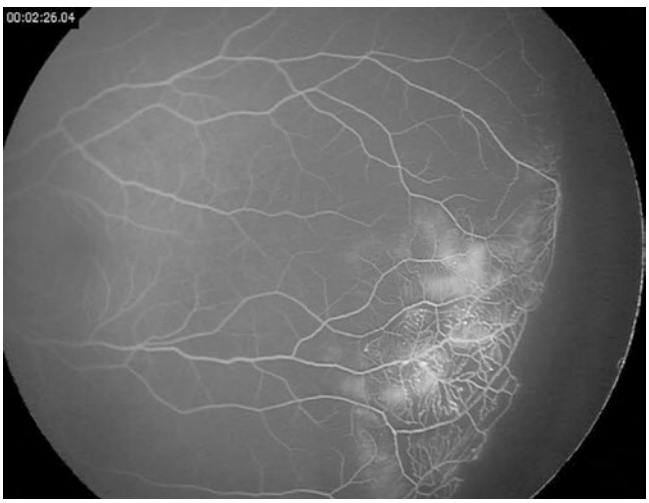

Fig. 7.5 Fluorescein angiography in a patient with stage 1 Coats' disease demonstrates telangiectatic vessels and nonperfusion in the periphery

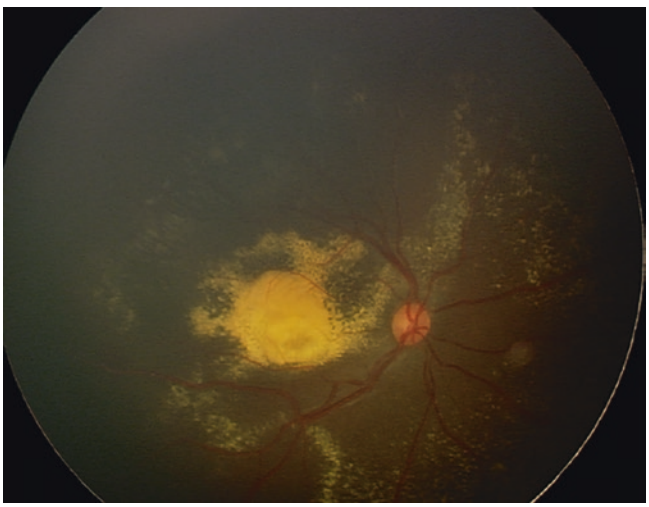

Fig. 7.7 Retcam photograph taken during examination under anesthesia for a stage 2B patient reveals widespread exudation that involves the fovea

the presence of calcification or mass lesions that would suggest a potential malignancy like retinoblastoma (Sigler et al. 2014).

Optical Coherence Tomography

Optical coherence tomography (OCT) is useful in the visualization and localization of exudates, fluid, fibrotic scar, epiretinal membrane, and retinal atrophy (Figs. 7.13, 7.14, 7.15, and 7.16). OCT can also be used to monitor response to treatment as it provides high-resolution cross-sectional images of the retina. Our group had previously shown that OCT demonstrates transient and permanent effects of Coats' disease on the retina that are comparable to histopathological findings (Ong et al. 2019). With the advent of portable OCTs, OCT can be performed during examination under anesthesia.

Management

Laser Photocoagulation and Cryotherapy

Conventionally, the goal of treatment is to eliminate exudation by destruction of anomalous retinal vessels. Laser photocoagulation is applied to telangiectatic vessels when there is less severe exudation and no subretinal fluid. When severe exudation or subretinal fluid prevents laser uptake, cryotherapy is used to ablate abnormal blood vessels

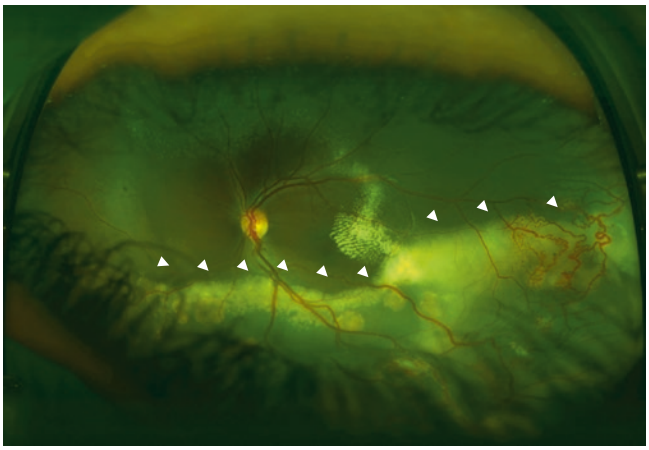

Fig. 7.8 Wide-field photography in a stage 3A1 patient demonstrates telangiectatic vessels in the temporal periphery with retinal exudates and partial extrafoveal retinal detachment (denoted by arrowheads)

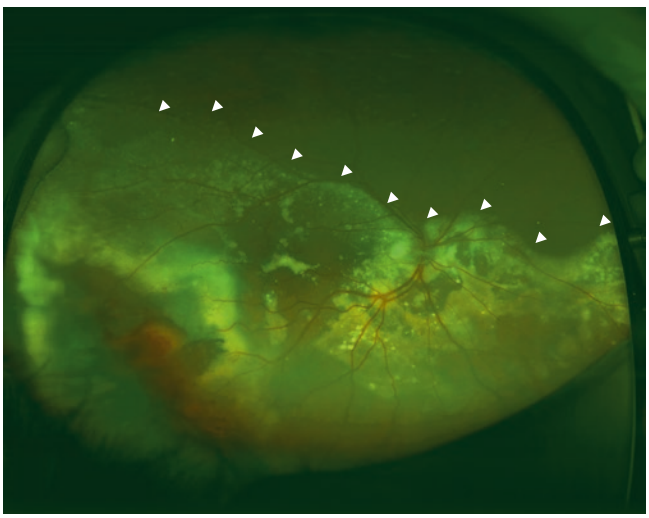

Fig. 7.9 Wide-field photography in a stage 3A2 patient shows retinal exudation, partial retinal detachment involving the fovea (denoted by arrowheads) and intraretinal hemorrhage inferotemporally

(Tarkkanen and Laatikainen 1983; Shields et al. 2001; Ridley et al. 1982). In the biggest case series of Coats' disease involving 124 eyes, Shields et al. found that laser photocoagulation was most successful in stage 2 disease while cryotherapy was employed when there were peripheral telangiectasias associated with extensive exudation and subtotal retinal detachment (stage 3A disease) (Shields et al. 2001). In our center, periocular steroids are injected along with cryotherapy to decrease the incidence of inflammation posttreatment.

However, a few recent reports have advocated the use of laser photocoagulation even in advanced disease when there is exudative retinal detachment. One study found that repetitive 810 nm infrared laser ablation (median of 4.8 sessions)

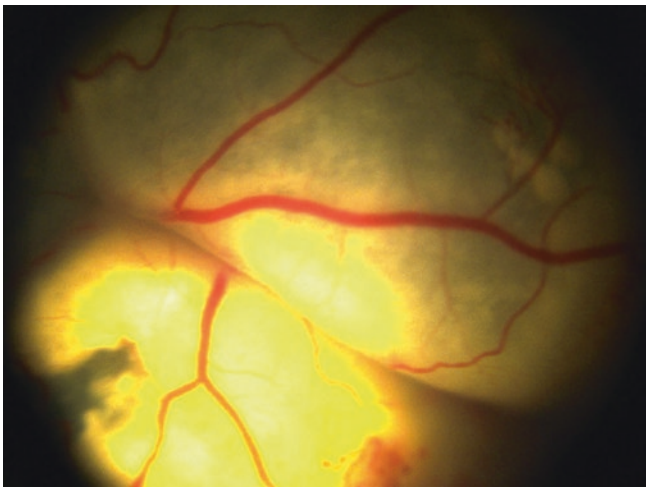

Fig. 7.10 Retcam photography during examination under anesthesia for a stage 3B patient demonstrates total retinal detachment

Table 7.1 Classification system for Coats' disease

Stages	Features
A. Coats' disease	
Stage 1	Retinal telangiectasias only
Stage 2A	Telangiectasias and extrafoveal exudation
Stage 2B	Telangiectasias and foveal exudation
Stage 3A1	Telangiectasias with extrafoveal partial retinal detachment
Stage 3A2	Telangiectasias with foveal partial retinal detachment
Stage 3B	Telangiectasias with total retinal detachment
Stage 4	Total retinal detachment with secondary glaucoma
Stage 5	Advanced end-stage disease

applied to areas of retinal telangiectasias and/or exudative retinal detachment in stages 2A to 4 disease resulted in anatomic success in 82% of patients and globe salvage in 64% of patients (Schefler et al. 2008). Another study similarly reported that 532 nm green laser applied to areas of retinal telangiectasias (median of 2 sessions) in stages 2 to 4 disease resulted in no active exudation in 93% of eyes (Shapiro et al. 2011). More recently, Levinson and Hubbard studied the use of 577 nm yellow laser on eyes that ranged from stages 2 to 3B. Eyes received a median of 3 sessions and 94% of eyes were fully treated defined as complete ablation of all visible telangiectasias and resolution of subretinal fluid (Levinson and Hubbard 3rd. 2016).

Vitreoretinal Surgery

In advanced disease in the presence of extensive retinal detachment, cryotherapy may not be able to ablate retinal vascular lesions. In these cases, vitreoretinal surgical approaches like external subretinal fluid drainage or vitrec-

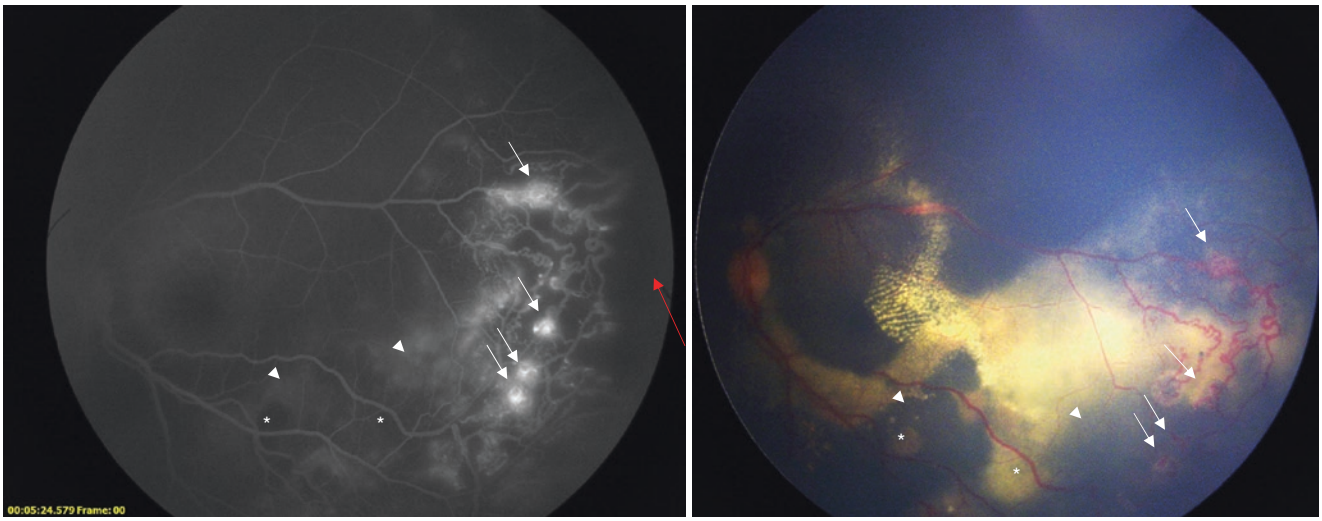

Fig. 7.11 Fluorescein angiography demonstrates hyperfluorescence of aneurysms (arrow), mild hyperfluorescence of subretinal fluid (arrowheads), and hypofluorescence of exudates (asterisks). Capillary dropout and retinal nonperfusion are also visualized on FA (red arrow). Color photography with corresponding markers is included for comparison

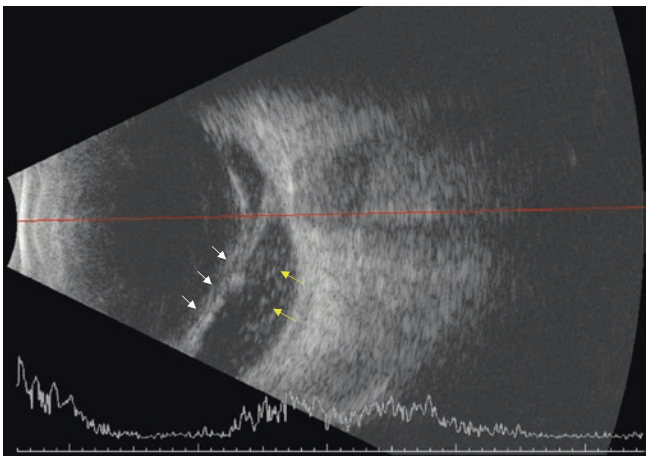

Fig. 7.12 Ophthalmic B-scan ultrasonography shows an exudative retinal detachment (white arrows) with hyperreflective crystalline deposits or exudates (yellow arrows)

tomy have been utilized to allow the treatment of retinal telangiectasias. Although visual prognosis is poor, failure to treat these patients may result in progression to secondary angle closure or neovascular glaucoma resulting in a blind and painful eye requiring enucleation (Shields et al. 2001).

Silodor et al. found that for patients with total retinal detachment (stage 3B), 4 of 6 patients (66.7%) who were observed developed painful neovascular glaucoma requiring enucleation while none of the other 7 patients who underwent vitreoretinal surgery had progressed to neovascular glaucoma. The surgical procedure performed entailed the following—intraocular infusion into the anterior chamber or vitreous, external drainage of subretinal fluid and double-freeze cryotherapy to telangiectatic retinal vessels with optional xenon arc photocoagulation of more posterior affected vessels (Silodor et al. 1988). Yoshizumi et al. suggested a different approach with vitrectomy, internal drainage of subretinal fluid, and cholesterol and diathermy to retinal telangiectasias with intravitreal gas or silicone oil injection to similarly prevent progression to secondary angle closure glaucoma in these eyes (Yoshizumi et al. 1995).

For Coats' patients with advanced disease and combined exudative and tractional retinal detachments, Schmidt-Erfurth and Lucke applied an encircling buckle followed by vitrectomy, removal of preretinal membranes and retinectomies to remove subretinal lipid exudates (Schmidt-Erfurth and Lucke 1995). None of the three patients in the study had progression of disease at follow up 13 months to 6 years after surgery. Meanwhile, in Mrejen and colleagues' series, initial or second treatment with vitrectomy with or without gas or silicone oil tamponade was performed in seven eyes, while scleral buckling was applied in one eye (Mrejen et al. 2008). All eyes also received laser or cryotherapy. Six eyes had anatomic improvement while two eyes developed phthisis bulbi but none had developed neovascular glaucoma.

Intravitreal Triamcinolone

In recent years, given the successful use of intravitreal triamcinolone in other exudative retinal diseases like diabetic macular edema and cystoid macular edema from retinal vein occlusion or cataract surgery, this therapeutic modality has also been studied as an adjunct to reduce exudation and fluid in Coats' disease. Bergstrom and Hubbard (Bergstrom and Hubbard 3rd. 2008) treated four pediatric stage 3B and one

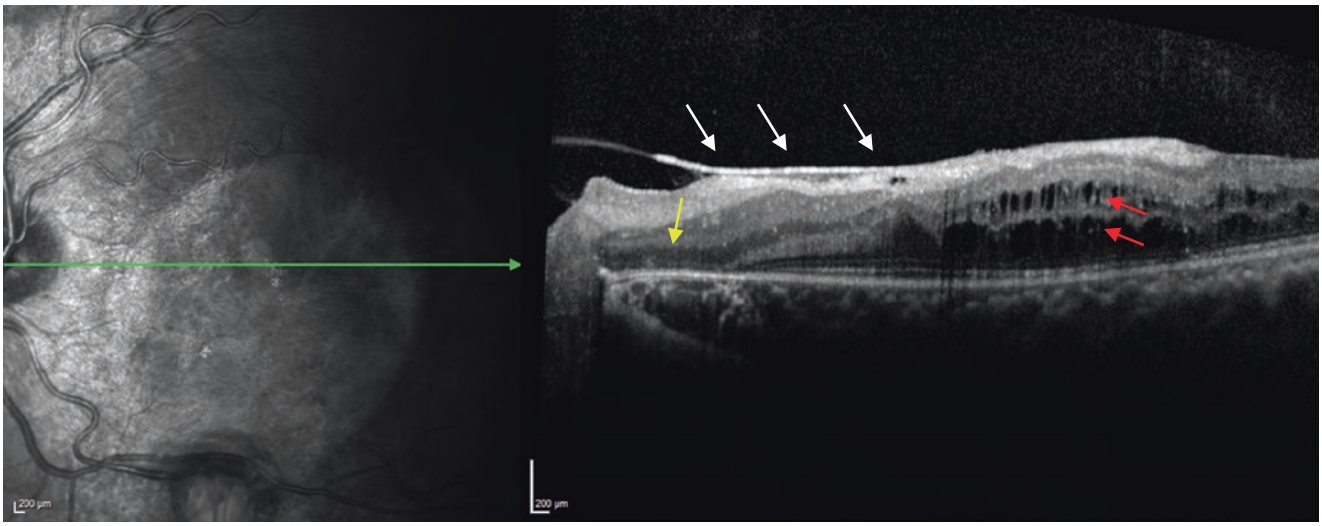

Fig. 7.13 Optical coherence tomography shows the presence of epiretinal membrane (white arrows), cystoid intraretinal fluid (red arrows), and outer retinal atrophy (yellow arrow)

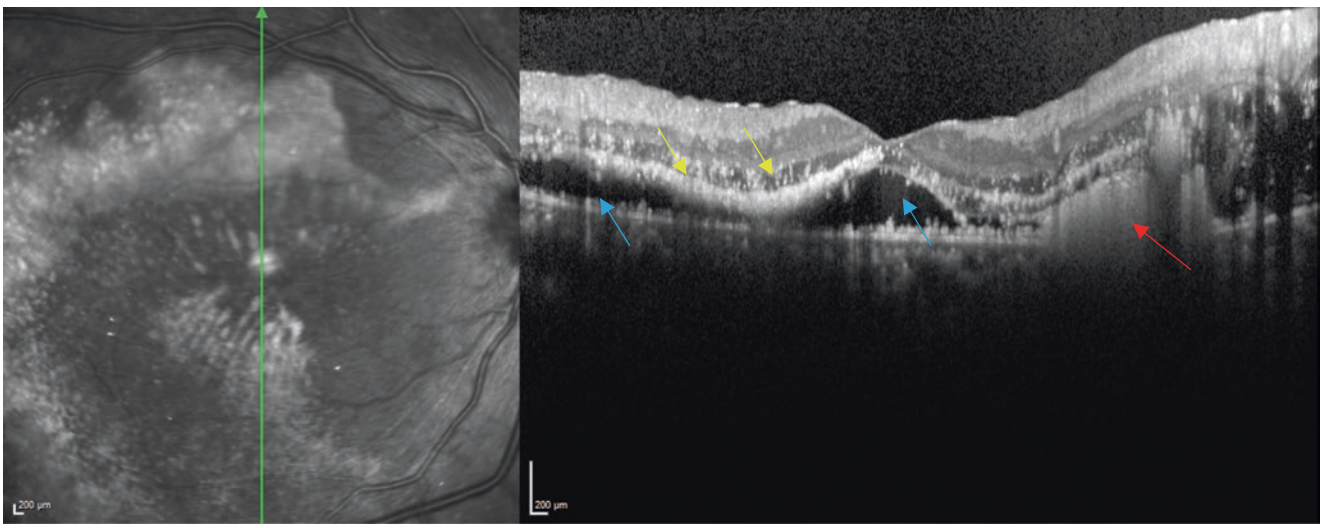

Fig. 7.14 Optical coherence tomography demonstrates the intraretinal (yellow arrows) versus subretinal location of exudates (red arrow) and the presence of subretinal fluid (blue arrows)

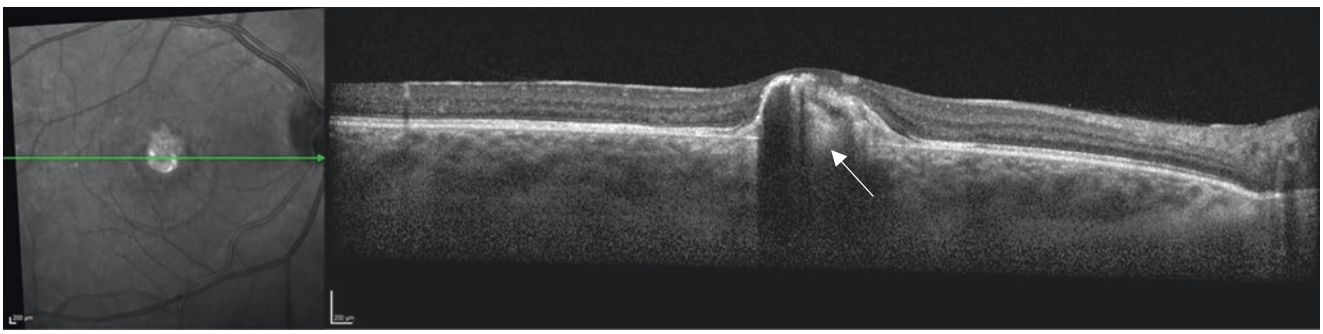

Fig. 7.15 Optical coherence tomography shows a fibrotic nodule (arrow) that formed at the fovea and remained stable after completion of treatment over many follow-up visits

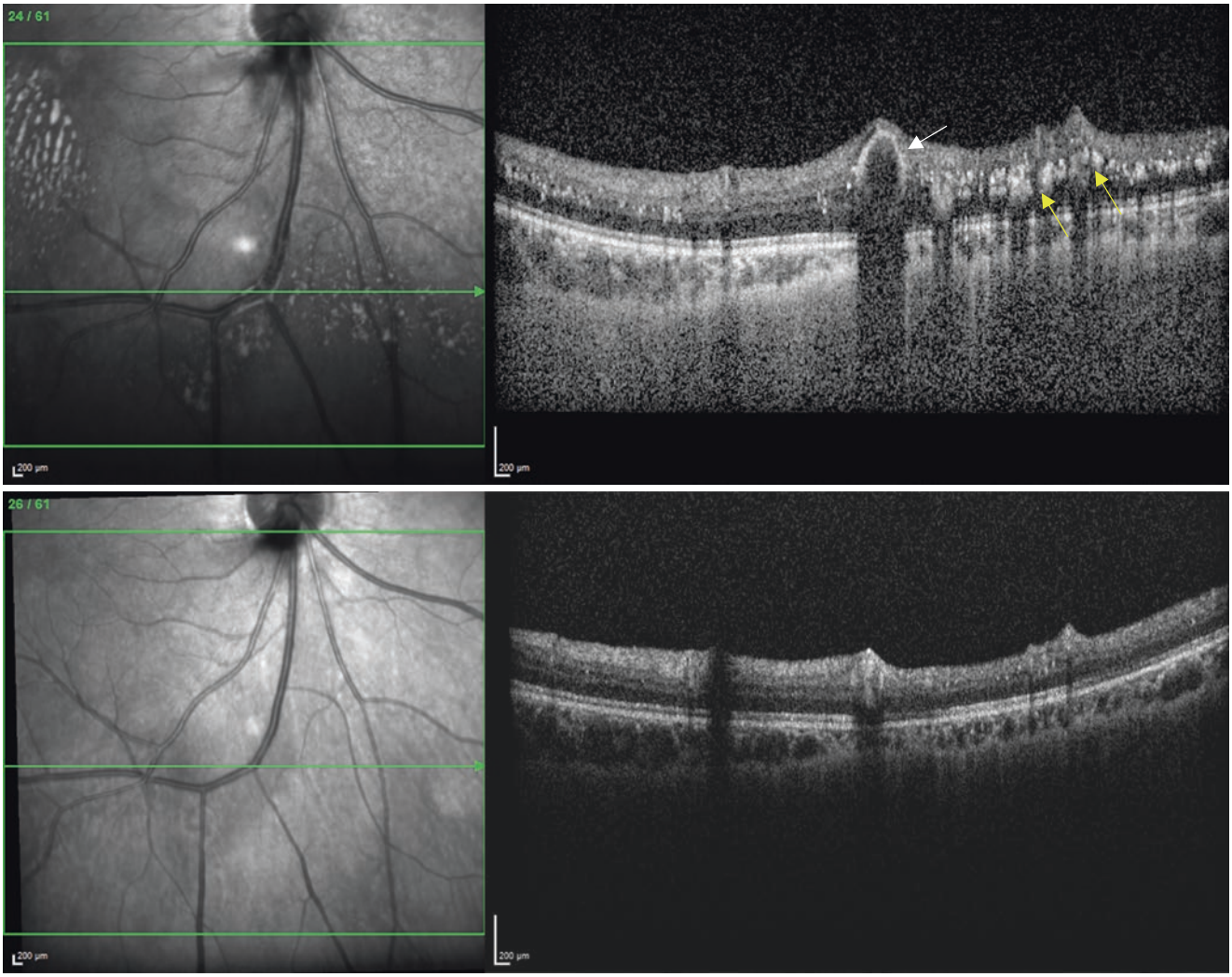

Fig. 7.16 Optical coherence tomography demonstrates a dilated vessel with a hyperreflective rim (white arrow) as well as intraretinal exudates (yellow arrows), which resolved after treatment with laser photocoagulation

stage 3A patients with intravitreal triamcinolone and cryotherapy. Although intravitreal triamcinolone successfully reduced subretinal fluid to allow cryotherapy, three patients developed inoperable rhegmatogenous retinal detachment with proliferative vitreoretinopathy. Additionally, four patients had elevated intraocular pressure requiring topical medications and three patients developed severe cataracts. The authors postulated that the combination of intravitreal triamcinolone and cryotherapy had promoted contraction of the vitreous or preexisting subretinal fibrosis, therefore, leading to retinal breaks (Bergstrom and Hubbard 3rd. 2008). Meanwhile, Ghazi and coauthors injected intravitreal triamcinolone in three stage 3B eyes and one stage 4 eye and observed that subretinal fluid improved within 4 weeks allowing application of laser photocoagulation (Ghazi et al. 2012). However, follow-up for these patients ranged from 1 to 18 months, which is insufficient to determine long-term outcomes for these patients. Separately, Othman et al. studied seven stage 3A and eight stage 3B eyes and demonstrated that intravitreal triamcinolone caused resorption of subretinal fluid to allow laser and/or cryotherapy in stage 3A disease. However, the authors added vitreoretinal surgery to most of the stage 3B eyes, making it difficult to determine if fluid resolution was a result of intravitreal triamcinolone or subretinal fluid drainage (Othman et al. 2010).

Intravitreal Anti-Vascular Endothelial Growth Factor (VEGF)

In 2007, Sun et al. injected intravitreal pegaptanib sodium therapy in a 2-year-old boy with stage 4 Coats' disease refractive to scleral buckle with subretinal fluid drainage and cryotherapy. After anti-VEGF therapy, there was a dramatic decrease in VEGF levels (908 to 167 pg/ml) from a vitreous tap and marked improvement of exudation, hemorrhage, and

near-complete retinal reattachment (Sun et al. 2007). This was followed by two studies that demonstrated higher intraocular VEGF levels in patients with Coats' disease compared to controls (He et al. 2010; Zhang and Liu 2012). Another study also showed higher levels of aqueous VEGF in Coats' patients compared to controls and higher concentrations of VEGF with increasing severity of Coats' disease (Zhao et al. 2014). Kase and coauthors examined enucleated eyes and demonstrated that VEGF was expressed in infiltrating macrophages in the subretinal space and vascular endothelial growth factor receptor (VEGFR)-2 in the endothelium of abnormal vessels in eyes with Coats' disease (Kase et al. 2012).

Multiple case reports and larger studies have been published on the use of anti-VEGF therapy in Coats' disease. One study demonstrated anatomic improvement after treatment with ablation and intravitreal anti-VEGF therapy for five patients with stages 2B and 3A disease but not for one patient with stage 3B disease (Lin et al. 2013). Another study compared two groups of patients (n = 10 in each group) matched by macular appearance, quadrants of subretinal fluid, and quadrants of telangiectasia (stages ranged from 2B to 3B). One group was treated with ablation only while the other group was treated with both ablation and intravitreal anti-VEGF therapy. While two of ten patients in the group treated with ablation only failed treatment (one patient required enucleation of the affected eye for a blind painful eye while the other patient had persistent retinal detachment with no light perception in the affected eye), all ten patients in the group treated with ablation and intravitreal anti-VEGF achieved treatment success defined as disease quiescence with fully treated telangiectasias and if present, resolved exudative retinal detachment at the last follow-up (Ray et al. 2013). Similarly, other studies have shown successful anatomic outcomes in patients treated with laser and anti-VEGF (Villegas et al. 2014; Sein et al. 2016).

However, Ramasubramanian and Shields cautioned that anti-VEGF therapy can cause vitreoretinal fibrosis and tractional retinal detachment (Ramasubramanian and Shields 2012). Other studies have also noticed this possible association (Zheng and Jiang 2014; Gaillard et al. 2014; Bhat et al. 2016) although one study reported that vitreoretinal fibrosis was already present in 2 of 3 patients prior to treatment (Zheng and Jiang 2014). Interestingly, Daruich and colleagues recently reported that tractional retinal detachment and macular fibrosis developed at a higher rate in patients with extramacular fibrosis and questioned whether the higher rate of tractional retinal detachment found in Ramasburamaniam and Shields' paper could be due to the fact that the eyes studied had stage 3B disease (Daruich et al. 2016). Our group has noted no relationship between anti-VEGF use and the development of tractional retinal detachment (Ong et al. 2017).

Enucleation

Enucleation is reserved for eyes with poor visual potential that are painful and interfere with patients' activities of daily living. The rate of progression to painful neovascular glaucoma in patients with total retinal detachment who are observed without treatment have been found to range from 17% to 67% (Ong et al. 2017; Shields et al. 2001; Silodor et al. 1988). For this reason, even though visual outcomes may be limited for eyes with advanced Coats' disease, observation is not recommended for these patients given the likelihood of progression to stage 4 disease with secondary glaucoma causing a painful blind eye.

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Eales' Disease

8

Sandeep Saxena

Introduction

Eales' disease is an idiopathic retinal periphlebitis that primarily affects the peripheral retina in young adults. Eales' disease was first described by Henry Eales, a British ophthalmologist, in 1880 and 1882 (Eales 1880; Eales 1882). He found it in seven young, male patients in age ranging from 14 to 29 years with recurrent vitreous hemorrhage. In addition, these patients had a history of headaches, variations in peripheral circulation, chronic constipation, and epistaxis. In the next century, the disease was redefined by several investigators (Cross 1963; Duke-Elder and Dobree 1967; Elliot 1975; Kimura et al. 1956). Elliot first recognized the inflammation of retinal vein and described it as periphlebitis retinae (Elliot 1975). Subsequently, several investigators documented both venular and arteriolar inflammation (Keith-Lyle and Wybark 1961; Kimura et al. 1956).

Eales' disease most commonly affects healthy young adult males and is an important cause of preventable blindness in young adults. The predominant age of onset of symptoms is 20–30 years. The disease is more commonly seen in the Indian subcontinent. However, it has been reported from the United Kingdom, United States, Canada, Germany, Greece, and Turkey.

Eales' disease is characterized by retinal periphlebitis (Fig. 8.1), peripheral retinal ischemia (Fig. 8.2), and neovascularization (Fig. 8.3). Visual loss is characteristically caused by recurrent vitreous hemorrhage (Gilbert 1935). Vascular involvement in Eales' disease may be peripheral or central. Central Eales' disease is markedly uncommon (Fig. 8.4) (Atmaca et al. 1993; Das et al. 1994; Kumar et al. 1995).

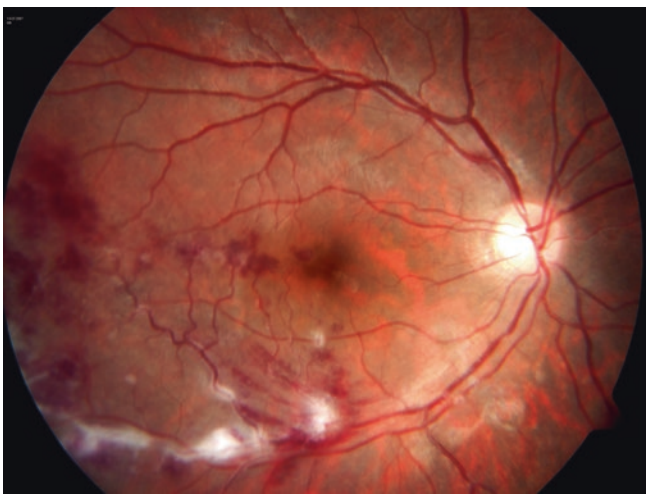

Fig. 8.1 Color fundus photograph shows retinal periphlebitis along with superficial retinal hemorrhages

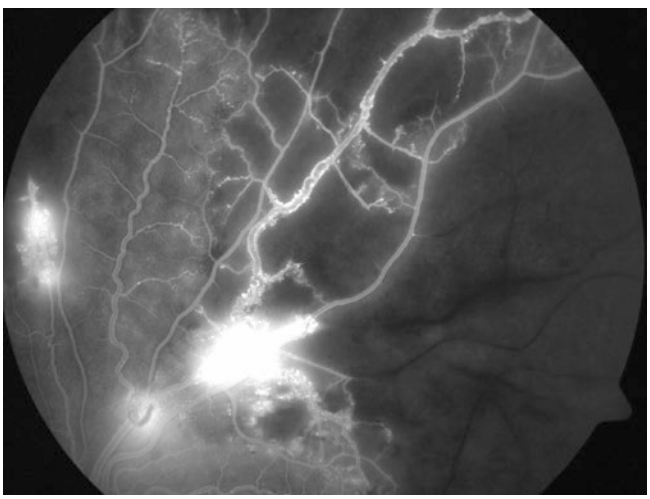

Fig. 8.2 Fundus fluorescein angiography shows capillary nonperfusion, microaneurysms, and leakage of fluorescein dye from retinal neovascularization

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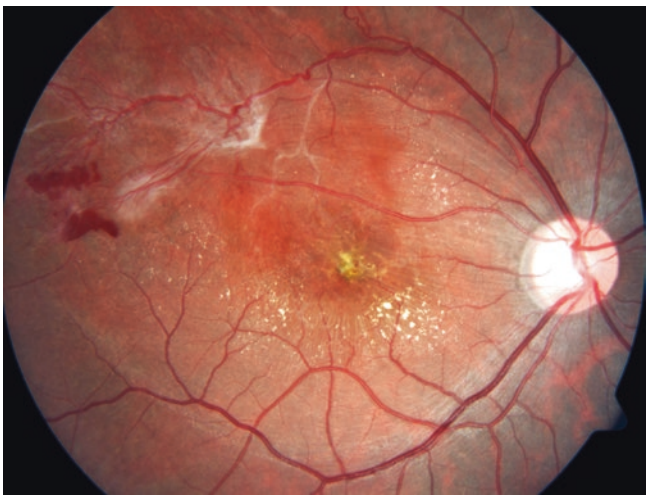

Fig. 8.3 Color fundus photographs show neovascularization elsewhere, sheathing of retinal vessels and hard exudates at macula

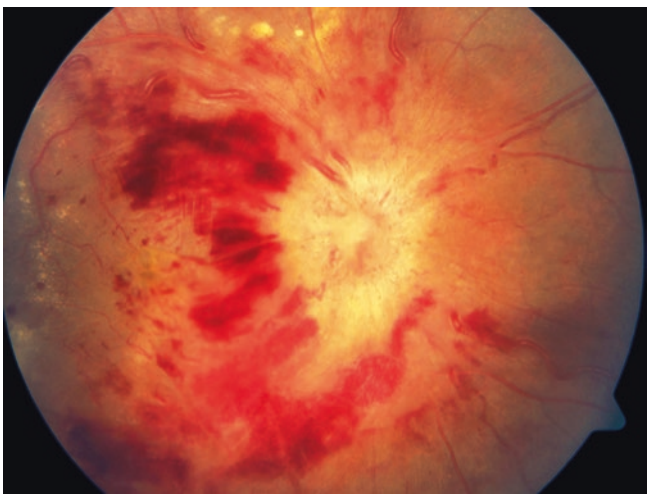

Fig. 8.4 Central Eales' disease

Etiopathogenesis

Eales' disease appears to be an immunologic reaction that may be triggered by an exogenous exposure. Retinal S-antigen and Interphotoreceptor Retinoid-Binding Protein play a role in the etiopathogenesis of this condition. An extraneous agent results in the exposure of normally sequestered uveitopathogenic antigens of the immune system, leading to an immune response in the eye that initiates the disease process (Saxena et al. 1999).

Oxidative stress has been found to play an important role in the etiopathogenesis (Bhooma et al. 1997; Saxena et al. 1999; Saxena et al. 2001; Saxena et al. 2004; Saxena et al. 2006; Srivastava et al. 2000; Sulochana et al. 1999; Swamy-Mruthinti et al. 2002). Lowered levels of antioxidant vitamins E and C and consequent accumulation of oxygen and lipid-free radicals, or vice versa, could explain the inflammation, neovascularization, and retinal pathology in patients with Eales' disease. Also, vitamin A deficiency could aggravate retinal illness. Elevated lipid peroxides have been found in the proliferative stage, which induces synthesis of cytokines and growth factors in the retina during neovascularization (Srivastava et al. 2000).

Eales' disease is distinctively characterized both by stage of inflammation as well as stage of proliferation (Keith-Lyle and Wybark 1961). Cytokines play an important role in intraocular inflammation (Gilbert 1935; Kumar et al. 1995). The cascade of multiple angiogenic cytokines induced by oxidative damage, associated with tissue hypoxia, may interact to promote sustained retinal neovascularization (Atmaca et al. 1993). During the inflammatory and proliferative stages of the disease statistically significant increase in IL-1β, IL-6, IL-10, and TNF-α expressions were observed as compared to controls, highlighting the role of pro- and anti-inflammatory cytokines in the pathogenesis (Saxena et al. 2009).

Markedly raised levels of IL-1β and TNF-α have been observed in the inflammatory stage that persisted in the proliferative stage (Saxena et al. 2011). Raised levels of IL-1β, in the inflammatory stage, decreased significantly in the proliferative stage. Elevated TNF-α levels, observed in the inflammatory stage, increased significantly in the proliferative stage where clinically, inflammation (periphlebitis) had subsided but retinal neovascularization and vitreous hemorrhage had developed with the occurrence of retina hypoxia and ischemia. This data suggests that despite clinical absence of periphlebitis in the proliferative stage of the disease, IL-1β and TNF-α levels remain raised significantly as compared to controls. The synergism of IL-1 and TNF is a commonly reported phenomenon. IL-1 and TNF initiate the cascade of inflammatory mediators by targeting the endothelium. Although the receptors for TNF and IL-1 are clearly different, the post-receptor events are similar. IL-1 often synergizes with TNF for nitric oxide induction, which mediates cell death (Das et al. 1994). Nitrosoactive stress has been found to promote retinal vasculitis in Eales' disease (Saxena et al. 1999). Significant TNF-α expression was observed during the proliferative stage. These findings indicate that angiogenesis during the proliferative stage is induced by TNF-α. Angiogenesis induced by TNF-α, during postischemic inflammation, may be modulated through induction of potent angiogenic factors (Saxena et al. 1999). Hypoxia-induced expression of vascular endothelial growth factor is only one aspect of the complicated processes in intraocular neovascularization (Srivastava et al. 2000). Chemokines have also been found to be involved in the recruitment of neutrophils and monocytes into the vitre-

ous and play a role in the intraocular neovascularization (Saxena et al. 2004). Thus, the IL-1 system represents a novel target for controlling inflammatory activity and/or the associated long-term sequelae related to angiogenesis in Eales' disease. Role of TNF-α in the inflammatory, as well as proliferative stage of the disease, has implications for anti-TNF-α therapy in Eales' disease. Reducing the biological activities of IL-1 and TNF may be accomplished by several different, but highly specific strategies, which involve neutralizing antibodies, soluble receptors, receptor antagonists, and inhibitors of proteases that convert inactive precursors to active, mature molecules. Anticytokine therapeutic agents such as TNF-neutralizing antibodies, soluble TNF receptors, and IL-1 receptor antagonists may prove beneficial. Infliximab (anti-TNF-α) may prove to be beneficial in patients of Eales'disease (Saxena et al. 2010).

A close relationship between the prominent neovascular proliferation in Eales' disease and the intense expression of VEGF has been found. The increased expression of VEGF, when compared to other conditions inducing neovascularization, might explain the severity of neovascular growth and the propensity of repeated vitreous hemorrhage in Eales' disease (Perentes et al. 2002).

Retinal photoreceptors and platelets have been shown to be an easy target of oxidants because of high proportion of polyunsaturated fatty acids. The decreased membrane fluidity in platelets suggests alterations in the physiological events, which may result in alterations in the functioning of retinal photoreceptors (Saxena et al. 2006).

Mycobacterium tuberculosis DNA has also been detected by polymerase chain reaction, in the vitreous of such patients (Biswas et al. 1999; Madhavan et al. 2000; Madhavan et al. 2002). However, the role of *Mycobacterium* genome in the pathogenesis is yet to be ascertained.

Clinical Features

Eales' disease with a characteristic clinical picture, fluorescein angiographic findings, and natural course is considered a specific disease entity. Recurrent vitreous hemorrhage is the hallmark of this disease. A new classification system has been proposed recently by the author (Saxena and Kumar 2004). This staging system, based on standard terminology and features, provides a simple method to categorize, according to the severity of the disease. This staging system takes into consideration the fundoscopic and fluorescein angiographic variables that have been shown to be prognostic of visual outcome (Table 8.1). Macular involvement is uncommon. Macular ischemia and traction macular detachment are associated with poor visual outcome (Fig. 8.5) (Saxena and Kumar 2000).

Table 8.1 Classification system for Eales' disease

Stages	Features
Eales' disease	
Stage 1a	Periphlebitis of small caliber vessels with superficial retinal hemorrhages
Stage 1b	Periphlebitis of large caliber vessels with superficial retinal hemorrhages
Stage 2a	Peripheral capillary non-perfusion
Stage 2b	Neovascularization elsewhere/ neovascularization of the disc
Stage 3a	Fibrovascular proliferation
Stage 3b	Vitreous hemorrhage
Stage 4a	Traction/combined rhegmatogenous detachment
Stage 4b	Rubeosis iridis, neovascular glaucoma, complicated cataract, and optic atrophy
Central Eales' disease	

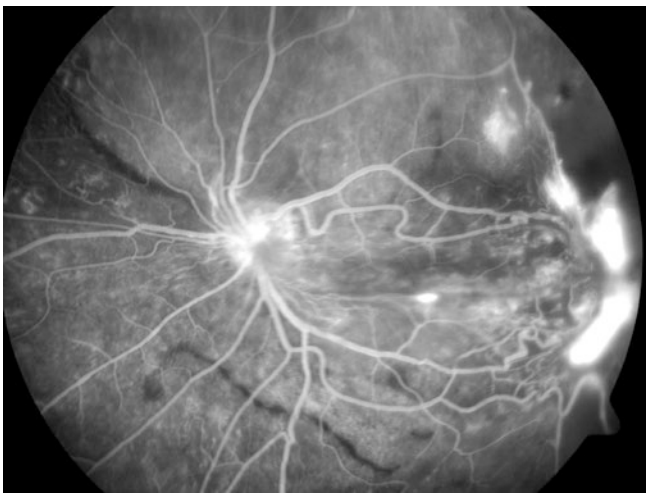

Fig. 8.5 Fundus fluorescein angiography shows traction macular detachment, neovascularization elsewhere associated with capillary non-perfusion and early neovascularization at the disc

The new classification system is consistent, simple, and easy to recall. It can also be used to monitor the effect of medical, laser, and/or surgical treatment.

Fluorescein Angiography

In cases of active retinal periphlebitis, staining of the veins can be seen in the early venous phase with extravasation of dye in the late phase (Fig. 8.6). In the healed stage, only staining of the vessel wall occurs without any leak in the late venous phase. Areas of capillary non-perfusion and retinal neovascularization can be easily delineated by fluorescein angiography (Fig. 8.7). Capillary non-perfusion of more than 20 disc area and 60 disc area are associated with neovascularization elsewhere (NVE) and neovascularization of the disc (NVD) (Fig. 8.8) (Saxena et al. 2003). Retinal neovascularization sites have been found to cluster around specific anatomic foci. The quadrantic distri-

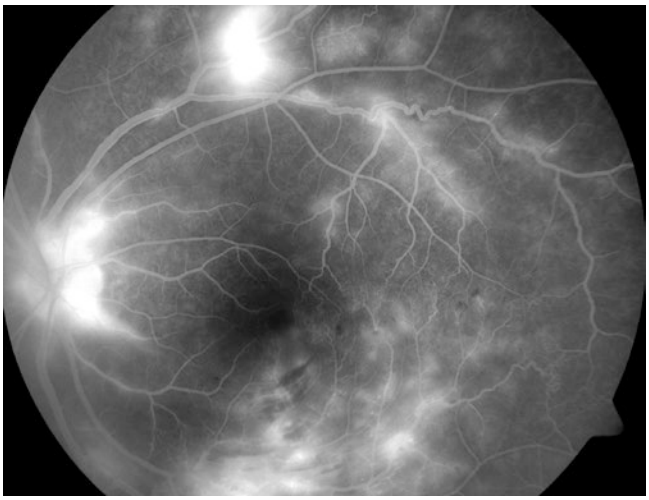

Fig. 8.6 Fundus fluorescein angiography shows leakage of fluorescein dye from neovascularization at the disc, neovascularization elsewhere, and areas of retinal periphlebitis

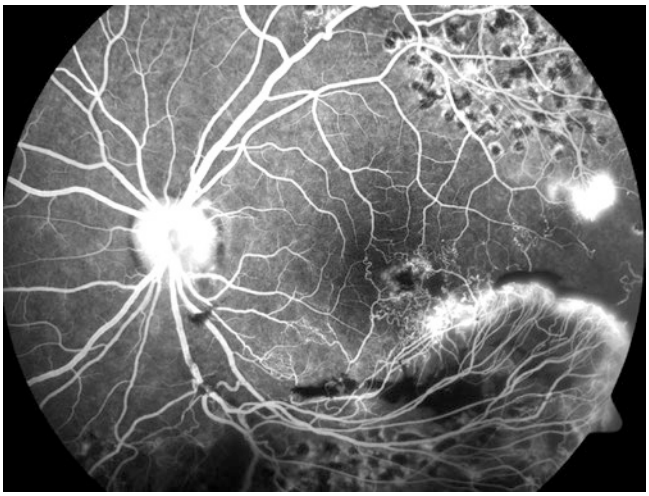

Fig. 8.8 Fundus fluorescein angiography shows neovascularization at the disc, neovascularization elsewhere, multiple laser spots, collateral vessel formation, and ischemia at macula

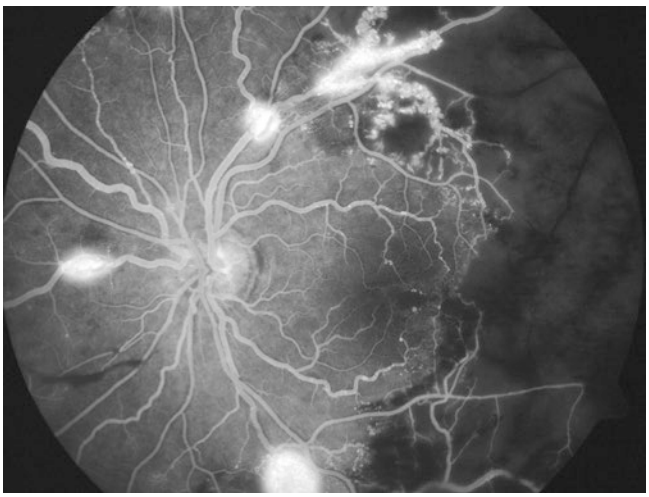

Fig. 8.7 Fundus fluorescein angiography shows multiple neovascularizations elsewhere, area of capillary non-perfusion, and macular ischemia along with numerous microaneurysms

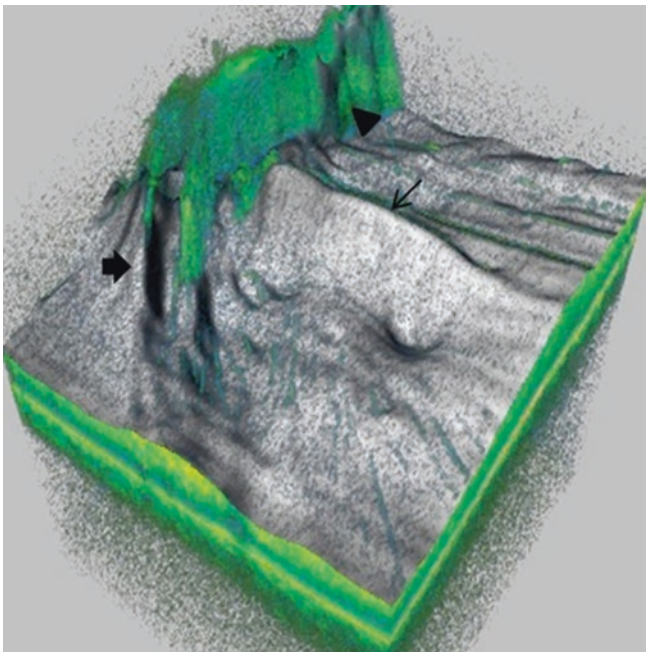

Fig. 8.9 Three dimensional spectral domain optical coherence tomography shows macular and vitreopapillary interface abnormalities

bution of the sites of NVE in Eales' disease is: superotemporal, 45.95%; inferotemporal, 24.32%; superonasal, 16.22%; and inferonasal, 13.51% (Saxena and Kumar 2005).

Optical Coherence Tomography

Imaging by spectral domain optical coherence tomography may highlight epiretinal membrane. Three-dimensional imaging documents vitreoretinal interface alterations exquisitely (Fig. 8.9).

Central Eales' disease is relatively uncommon. Such central retinal periphlebitis has a similar presentation as central retinal vein occlusion. Branch retinal vein occlusion with peripheral retinal periphlebitis (Fig. 8.10) and central Eales' disease have been found to be associated with favorable visual outcome (Saxena and Kumar 1999; Saxena and Kumar 2001).

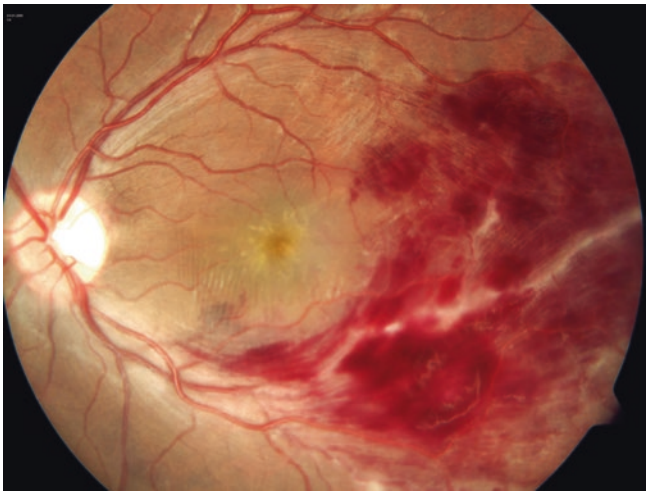

Fig. 8.10 Color fundus photograph shows inferotemporal retinal vein occlusion, retinal periphlebitis, and macular edema

Management

The management of Eales' disease depends on the severity of the disease. Management strategies can also be defined according to the stage of the disease. Stage 1, the stage of inflammation, is amenable to medical therapy. Stage 2, the stage of ischemia and neovascularization, requires observation/laser photocoagulation. Stage 3, the stage of proliferation, requires laser/pars plana vitrectomy and laser. Stage 4, the stage of complications, requires sophisticated surgical management strategies (Saxena and Kumar 2004).

Observation

Patients with inactive retinal periphlebitis can be observed periodically at a 6-month interval. Patients with fresh vitreous hemorrhage can also be observed at intervals of 4–6 weeks if the underlying retina is found to be attached by indirect ophthalmoscopy or by ultrasound.

Medical Therapy

Corticosteroids: Anti-inflammatory corticosteroid drugs are potent therapeutic agents for a wide range of ocular and systemic disorders and remain the mainstay of therapy in retinal periphlebitis in Eales' disease (1 mg/kg/day).

Methotrexate: Predominantly T-cell involvement has been demonstrated in the lymphocytic infiltration of epiretinal and subretinal membranes in Eales' disease. Hence, treatment should be directed to the downregulation of the activated T-cells. Search for safer and more specific forms of treatment have led to certain immunosuppressives, like methotrexate, which have found a role in patients with immunologically driven systemic diseases. As opposed to the more "cytostatic" effects of corticosteroids, the "cytotoxic" immunosuppressives exert their beneficial effects by actually killing the rapidly dividing clones of lymphocytes that are responsible for inflammation. Methotrexate, a folic acid antagonist, has anti-inflammatory and immunomodulatory actions. The drug reduces the synthesis of DNA by acting on the enzyme dihydrofolate reductase. Methotrexate is used as a weekly "pulsed" therapy. A "pulse" differs from chronic moderate dose therapy in its ability to "reset" an aberrant immune response. Inhibition of the proliferating lymphocyte clones, the temporary removal of recirculating T-lymphocytes from the blood and eye, and the profound suppression of peripheral inflammation, all occur simultaneously. Antigens exposed by viral, bacterial, or autoimmune injury are normally perpetuated by the inflammatory response but in such a system a pulse may abolish the source of antigen at the same time as it suppresses the immune response. When memory T-cells recirculate, the disease falters in the absence of the antigen (Bali et al. 2005; Saxena et al. 2000). Anti-oxidant supplementation: Anti-oxidant supplementation decreases oxidative stress and prevents photoreceptor loss (Saxena et al. 2010).

Anti-vascular endothelial growth factor (VEGF) therapy: Intravitreal anti-VEGF therapy helps in clearing vitreous hemorrhage. Intravitreal anti-VEGF supplementation, few days before surgery, is helpful during vitreoretinal surgery.

Photocoagulation

Photocoagulation is the mainstay of therapy in proliferative stage of the disease (El-Asrar and Al-Kharashi 2002). Laser photocoagulation leads to the resolution of retinal neovascularization due to its anti-VEGF effect. In cases of gross capillary non-perfusion photocoagulation is suggested. For NVE and NVD, sectoral scatter photocoagulation and panretinal photocoagulation, respectively, is suggested (Figs. 8.11 and 8.12).

Vitreoretinal Surgery

Vitrectomy alone or combined with other vitreoretinal surgical procedures is often required. Vitrectomy for nonresolving vitreous hemorrhage done at 3–6 months has a

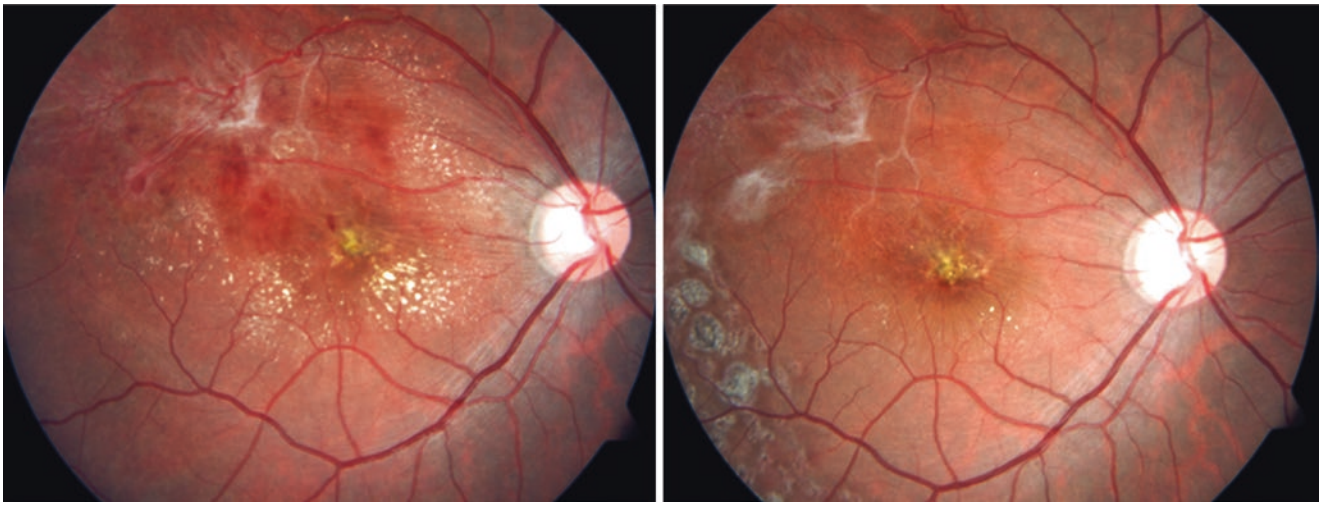

Fig. 8.11 Color fundus photograph shows the regression of retinal neovascularization following laser photocoagulation

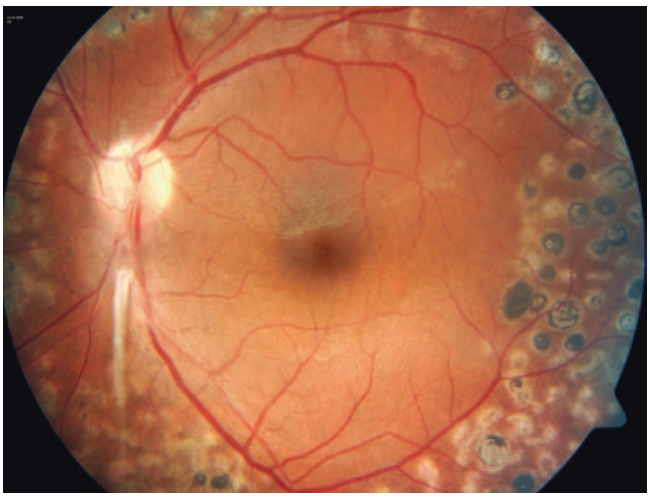

Fig. 8.12 Color fundus photograph after laser photocoagulation shows residual fibrous proliferation from the disc following resolution of neovascularization at the disc

better visual outcome than done after 6 months. Patients with fewer episodes of vitreous hemorrhage and preoperative laser have better visual prognosis (Kumar et al. 2000; Shanmugam et al. 1998).

Anterior Retinal Cryo Ablation

Anterior retinal cryo ablation is usually reserved as an adjunct to photocoagulation in Eales' disease for effect in peripheral retina.

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Hypertensive Fundus Changes

9

Jacqueline Chua, Carol Yim-Lui Cheung,
Leopold Schmetterer, and Tien Yin Wong

Introduction

Systemic hypertension, also known as high or raised blood pressure, remains the leading contributor to the global burden of disease and to global mortality, leading to 9·four million deaths every year (Lim et al. 2012). Its diagnosis is based on a blood pressure cutoff point (systolic blood pressure equal to or above 140 mmHg and/or a diastolic blood pressure equal to or above 90 mmHg, or both), where nearly 40% of adults aged 25 years and above globally may have hypertension (The World Health Organization 2017).

Hypertension may lead to multiple harmful consequences to the eye. Its effects on the retinal, choroidal, and optic nerve vasculature may result in hypertensive retinopathy, choroidopathy, and optic neuropathy, respectively (Wong and Mitchell 2007). Because the vascular damage in the eye develops in response to elevated blood pressure, ophthalmologists, or optometrists must become familiar with the variety of signs associated with hypertension retinopathy. Early detection of such changes is imperative for appropriate diagnosis and prompt intervention. There are numerous patients who are underdiagnosed or undertreated hypertension and are thus at risk for all the consequences associated with hypertension.

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Pathophysiology

Hypertensive retinopathy was first described by Marcus Gunn, a Scottish ophthalmologist (Gunn 1892). He found hypertensive retinopathy signs in patients with severely elevated blood pressure and chronic renal disease. In the next century, Keith, Wagener, and Barker provided the clinical significance for these retinal signs (Keith et al. 1939). They found that in patients with hypertension, the severity of retinopathy was an indicator of systemic morbidity.

The direct adverse consequences of hypertension on the retinal vasculature are related to the degree and duration to which it is exposed to the increased blood pressure. The pathophysiology of hypertensive retinopathy is described in four phases (Tso and Jampol 1982): vasoconstrictive, sclerotic, and exudative phases, followed by complications of the sclerotic phase, and "malignant hypertension."

(1) In the initial "vasoconstrictive" phase, there is vasospasm and an increased vasomotor tone in the retinal arterioles, with consequent narrowing of retinal arterioles to control for optimal blood volume. This phase is observed clinically as a generalized narrowing of the retinal arterioles. (2) Persistently elevated blood pressure leads to the development of more chronic arteriosclerotic changes, such as intimal thickening, media wall hyperplasia and hyaline degeneration of the retinal arterioles. This second phase is clinically visible as more severe generalized arteriolar narrowing coupled with localized (focal) arteriolar narrowing, arteriolar wall opacification (silver or copper wiring), and compression of the venules by structural changes in the arterioles at common adventitial locations (arterio–venous nicking or nipping or Gunn sign). (3) In the presence of chronically sustained blood pressure elevation, the blood–retinal barrier becomes disrupted. Pathological changes during this "exudative" phase include the necrosis of the smooth muscles and endothelial cells, exudation of blood and lipids, and retinal nerve fiber layer ischemia. These changes are manifested in the retina as microaneurysms, retinal hemorrhages, hard exudates, and cotton wool spots. (4) The

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"malignant hypertension" phase occurs at severely elevated blood pressure, where there may be variable degrees of optic disc swelling. Because of the availability of better antihypertensive medications for the general population, this last phase is rarely seen. These phases of hypertensive retinopathy, however, are not meant to be sequential (Tso and Jampol 1982). For example, the exudative phase, such as hemorrhage or microaneurysm, has been observed to occur before the sclerotic phase (i.e., arteriovenous nicking). In addition, the signs seen in the exudative phase are nonspecific clinical signs, since they are also seen in patients with diabetes mellitus.

Clinical Features

Hypertensive retinopathy is diagnosed based upon its clinical appearance on dilated fundus examination and coexistent hypertension (duration and severity of hypertension). A variety of grading systems have been proposed for hypertensive retinopathy in an attempt to classify its severity. The most widely used is the Keith–Wagener–Barker (KWB) system (Table 9.1), which defines four grades of retinal damage (Keith et al. 1939): grade 1 (arteriolar narrowing), grade 2 (arteriovenous crossings), grade 3 (hemorrhages and exudates), and grade 4 (optic disc swelling). Subsequently, several investigators redefined the KWB classification system and documented additional associations with severity of hypertension (Wong and Mitchell 2004). In the updated Wong–Mitchell grading of hypertensive retinopathy (Table 9.1), the two earlier grades of retinopathy have been combined because these two grades are not easily distinguished clinically (Downie et al. 2013).

The Wong–Mitchell system conferred a higher intraobserver and interobserver level of agreement than the KWB classification system (Aissopou et al. 2015). Thus, the simplified yet consistent Wong–Mitchell classification of hypertensive retinopathy is preferred to the KWB classification system for clinical practices. Furthermore, it has been shown to be prognostic of stroke, cardiovascular disease, and mortality outcome (Wong and Mitchell 2004): (1) Mild hypertensive retinopathy (arteriolar narrowing and arterio–venous nicking; Fig. 9.1). (2) Moderate hypertensive retinopathy (mild retinopathy signs together with hemorrhages, microaneurysms, cotton wool spots, and/or hard exudates; Figs. 9.2, 9.3, 9.4, 9.5, and 9.6). (3) Malignant hypertensive retinopathy (moderate retinopathy signs together with optic disc swelling in the presence of severely elevated blood pressures) is relatively uncommon. Symptoms are rare usually do not develop in patients with mild and moderate hypertensive retinopathy. However, some patients with malignant hypertensive retinopathy may report decreased or blurred vision.

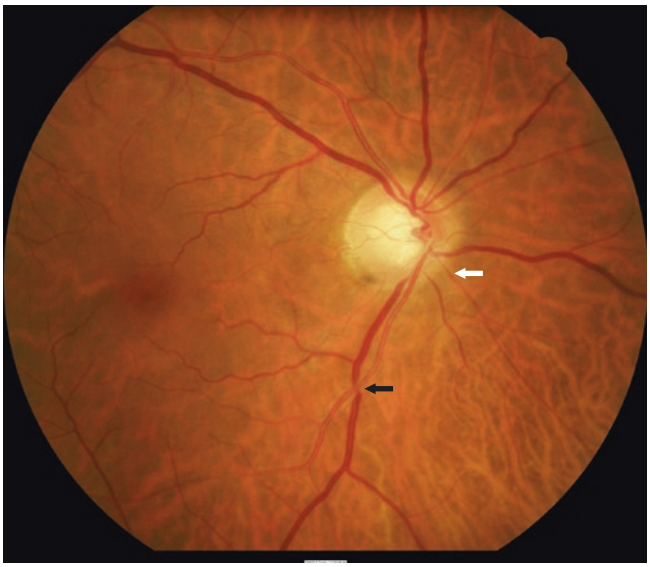

Fig. 9.1 Arterio–venous nicking (black arrow) with generalized and focal arteriolar (white arrow) narrowing: Mild Hypertensive Retinopathy

Table 9.1 Classification system for hypertensive retinopathy

	Keith–Wagener–Baker (1939)		Mitchell–Wong (2004)	
Grade	Clinical features of hypertensive retinopathy	Grade	Clinical features of hypertensive retinopathy	Systemic associations
1	Generalized arteriolar narrowing	Mild	Generalized or focal arteriolar narrowing, arteriovenous nicking/nipping, opacity of arteriolar wall (copper/silver wiring)	Modest association with risk of stroke, coronary heart disease, and death
2	Focal narrowing and arteriovenous nicking/nipping			
3	Grade 2 plus exudates, hemorrhages, and cotton wool spots	Moderate	Exudates, hemorrhages (flame, dot, blot), and cotton wool spots	Strong association with risk of stroke, cognitive decline, and death from cardiovascular causes
4	Grade 3 plus optic disc swelling	Malignant	Moderate grade plus optic disc swelling	Strong association with death

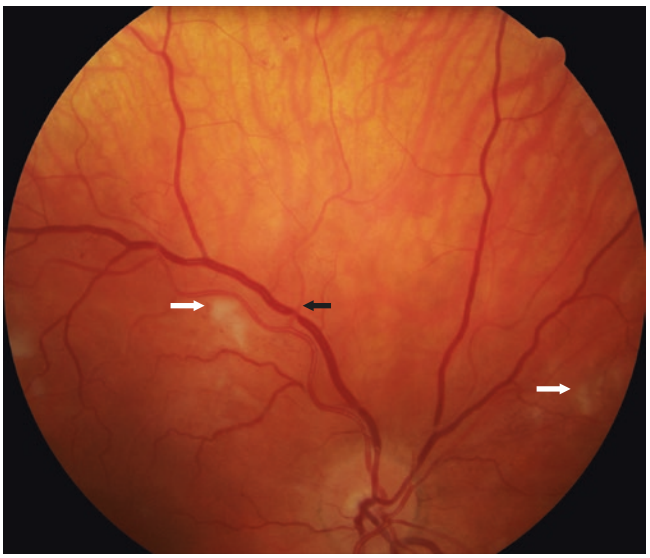

Fig. 9.2 Arterio–venous nicking (black arrow) and cotton wool spots (white arrows): Moderate Hypertensive Retinopathy

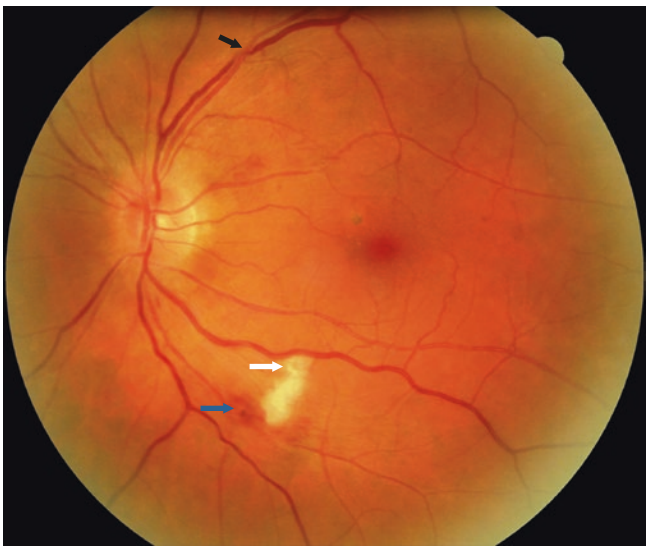

Fig. 9.4 Arterio–venous nicking (black arrow) and cotton wool spots (white arrow) with flame-shaped (blue arrow) hemorrhages: Moderate Hypertensive Retinopathy

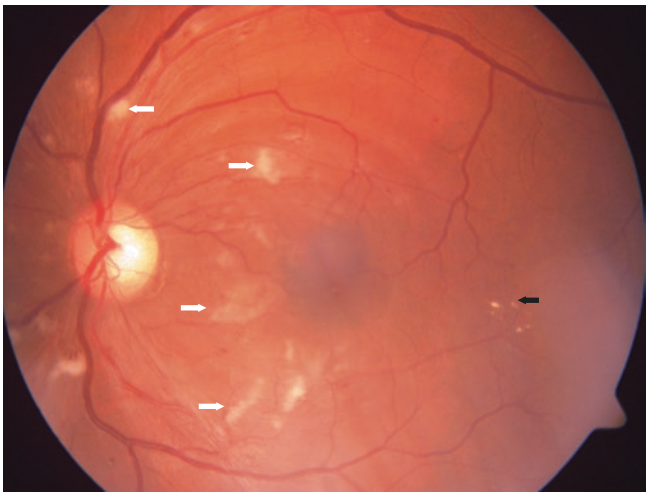

Fig. 9.3 Cotton wool spots (white arrows) with hard exudates (black arrow): Moderate Hypertensive Retinopathy

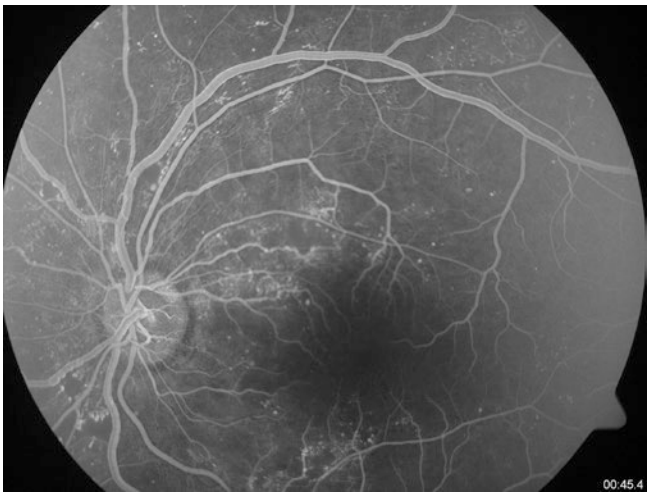

Fig. 9.5 Fluorescein angiogram demonstrates areas of hyperfluorescent cotton wool spots: Moderate Hypertensive Retinopathy

Epidemiology

Population-based studies from the United States (Chao et al. 2007; Klein 1992, 1994, 2000; Ojaimi et al. 2011; Sharrett et al. 1999; Wong et al. 2003a, b), United Kingdom (Sharp et al. 1995), Denmark (Munch et al. 2012), Holland (Stolk et al. 1995), Norway (Bertelsen et al. 2014), Australia (Cugati et al. 2006; Leung et al. 2004; Wang et al. 2003; Wong et al. 2003b; Yu et al. 1998), Japan (Fukushima et al. 2013), Singapore (Bhargava et al. 2014; Jeganathan et al. 2010), and China (Peng et al. 2010) have used standardized retinal photographs to identify and quantify various hypertensive retinopathy signs. These studies in different cohorts have consistently shown that hypertensive retinopathy signs are common in persons aged 40 years and older, even in the absence of diabetes mellitus, with prevalence ranges from 2 to 17%. Signs of hypertensive retinopathy also increased with age (Cugati et al. 2006; Klein 1992; Peng et al. 2010; Wong et al. 2003b) are predominantly prevalent in men (Bertelsen et al. 2014; Chao et al. 2007; Peng et al. 2010), varied by race/ethnicity (Persons of Chinese and African descent have a higher prevalence of hypertensive retinopathy than whites) (Ojaimi et al. 2011; Sharp et al. 1995; Wong et al. 2003a).

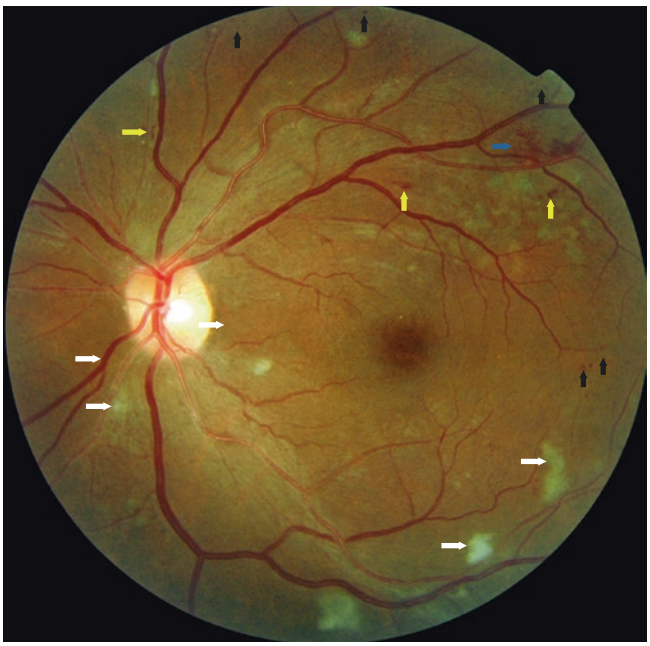

Fig. 9.6 Cotton wool spots (white arrows) with flame-shaped (blue arrow) and dot blot (yellow arrow) hemorrhages and microaneurysms (black arrows): Moderate Hypertensive Retinopathy

Hypertensive Retinopathy Correlates with Hypertension and Incident Hypertension

Hypertensive retinopathy is strongly related with the presence and severity of hypertension (Bertelsen et al. 2014; Chao et al. 2007; Klein 1992; Klein et al. 1994; Munch et al. 2012; Ojaimi et al. 2011; Wang et al. 2003; Wong et al. 2003a, d). People with uncontrolled hypertension, despite the use of medications, have a higher risk to develop hypertensive retinopathy than well-controlled hypertensive individuals (Wang et al. 2003). The retinopathy signs, while more frequent in persons with hypertension, have also been shown to occur in persons without hypertension (Ding et al. 2014; Ikram et al. 2006; Kawasaki et al. 2009; Klein et al. 2006; Smith et al. 2004; Tanabe et al. 2010; Wang et al. 2008; Wong et al. 2004b, c). In particular, "normotensive" persons with generalized retinal arteriolar narrowing were more likely to develop hypertension. Interestingly, persons with early stages of hypertension, masked hypertension, and white coat hypertension have noticeably narrower retinal arteriolar than normotensive individuals (Triantafyllou et al. 2013). Therefore, vascular damage to the eye, possibly preceding clinically measurable blood pressure elevation, may potentially identify patients who may be at risk of developing hypertension.

Hypertensive Retinopathy Correlates with Current and Past Blood Pressure Levels

Studies have consistently shown that hypertensive retinopathy is strongly correlated with blood pressure levels (Bhargava et al. 2014; Fukushima et al. 2013; Jeganathan et al. 2010; Klein 1992; Klein et al. 1994; Leung et al. 2004; Peng et al. 2010; Sharrett et al. 1999; Wong et al. 2003a, b). However, the presence of hypertensive retinopathy signs may differ between current and past blood pressure levels (Leung et al. 2004; Sharrett et al. 1999; Wong et al. 2002a). Focal arteriolar narrowing, microaneurysms, retinal hemorrhages, and cotton wool spots are related *only* to concurrently measured blood pressure, mirroring the effects of short-term blood pressure changes. In contrast, generalized retinal arteriolar narrowing and arteriovenous nicking are related not only to current blood pressure levels, but also to blood pressure levels measured in the past, suggesting it reflects persistent arteriolar damage from hypertension (Cheung et al. 2011; McGowan et al. 2015; Sun et al. 2008). This is consistent with histopathological data that show retinal arteriolar narrowing results from intimal thickening and medial hyperplasia, hyalinization, and sclerosis of arteriolar walls (Tso and Jampol 1982). It is likely that generalized retinal arteriolar narrowing reflects more widespread systemic peripheral vasoconstriction, thereby potentially reflecting those having long-term hypertension. Furthermore, the central blood pressure, directly reflecting the blood pressure load on end organs, is more closely associated with retinal arteriolar narrowing than brachial blood pressure (Kumagai et al. 2015).

Retinal Venular Diameter Correlates with Hypertension

Retinal venular diameter, previously not considered part of the spectrum of hypertensive retinopathy signs, may also convey information regarding the state of the retinal vasculature and systemic health. Interestingly, in the case of the retinal venular alterations, a significant inverse relationship was found to elevated blood pressure levels and incident hypertension (Cheung et al. 2011; Ding et al. 2014; Ikram et al. 2006; Wong et al. 2006). This finding suggests that venules may exhibit different optimal principles than arterioles, possibly due to their different physiological function, although this is not entirely clear (Patton et al. 2006). Therefore, the retinal venular diameter is not yet included as part of the classification of hypertensive retinopathy.

Clinical Significances

Clinical Significance with Cerebrovascular Diseases and Dementia

The retinal and cerebral small vessels share similar embryological origin, morphological, and physiological properties. Both vascular systems have a distinct blood–tissue barrier, undergo autoregulation through local myogenic and metabolic control, and are relatively low flow and high oxygen extraction systems (Patton et al. 2005). These overlaps in structure and function strongly suggest that microvascular changes in the brain in relation to vascular disease and aging can also be observed in the retina (Cheung et al. 2017; Heringa et al. 2013).

Numerous large-scale, population-based studies such as the Atherosclerosis Risk in Communities (ARIC) Study (Wong et al. 2001, 2002b; Yatsuya et al. 2010), the Beaver Dam Eye Study (BDES) (Wong et al. 2003c), the Blue Mountains Eye Study (BMES) (Mitchell et al. 2005), the Cardiovascular Health Study (CHS) (Longstreth et al. 2007; Wong et al. 2006), the Multi-Ethnic Study of Atherosclerosis (MESA) (Kawasaki et al. 2012) and Southall and Brent REvisited (SABRE) (Hughes et al. 2016) have examined community-based cohorts of middle-aged and elderly participants and showed that retinopathy signs are related with incident and prevalent clinical stroke. Retinopathy signs are also reported to be associated with subclinical MRI-defined markers of cerebrovascular disease, including cerebral infarction (Cheung et al. 2010; Cooper et al. 2006; Kwon et al. 2007), white matter lesions (Wong et al. 2002b) and cerebral atrophy (Kawasaki et al. 2010). Studies have produced consistent associations between arteriolar narrowing and venular widening with incidence of stroke (Longstreth et al. 2007; McGeechan et al. 2009; Wieberdink et al. 2010; Wong et al. 2006), incidence of lacunar stroke (Ikram et al. 2006; Yatsuya et al. 2010), white matter lesion progression (Qiu et al. 2009), and normal-appearing white matter microstructure (Mutlu et al. 2016).

Recent studies have shown that retinal microvascular changes are associated with specific subtypes of stroke. In particular, generalized arteriolar narrowing and venular widening were associated with lacunar stroke, while retinal hemorrhages were linked with cerebral hemorrhages (Baker et al. 2010a, b; Gobron et al. 2014; Liew et al. 2014; Lindley et al. 2009). These findings suggest that hypertensive signs reflect specific cerebral microvasculopathy and may further help to understand the underlying pathologic mechanisms. Studies on Asians also demonstrated that subjects having changes in retinal microvasculature were more likely to have cerebral microbleeds (Hilal et al. 2014), incident stroke (Cheung et al. 2013), and predicted the risk of recurrent vascular events after ischemic stroke (De Silva et al. 2011). These associations were also independent of blood pressure levels and other traditional cardiovascular risk factors, suggesting that these retinal signs may provide additional information for stroke risk stratification.

Hypertension is a risk factor for cognitive decline and dementia (Iadecola 2014). Population-based studies have demonstrated that hypertensive retinopathy signs and other retinal vascular measures, including retinal arteriolar narrowing, retinal venular widening, and sparser retinal vascular network, are associated with a decline in cognitive function, as assessed by various neuropsychological tests (Cheung et al. 2014a; Gatto et al. 2012; Haan et al. 2012; Kim et al. 2011; Lesage et al. 2009; Liew et al. 2009a; Ong et al. 2014; Patton et al. 2007; Taylor et al. 2015). Retinal microvascular changes such as retinopathy and venular widening have also been linked to prevalent dementia (Baker et al. 2007; Qiu et al. 2010), incident dementia (de Jong et al. 2011), and prevalent Alzheimer's disease (Cheung et al. 2014b), even controlling for age, blood pressure levels, and traditional risk factors. However, not all studies are consistent and in one, retinopathy was not associated with incident dementia (Schrijvers et al. 2012). These retinal studies might provide insight into the mechanism underlying the relationship between hypertension and cognitive impairment.

Clinical Significance with Cardiovascular Diseases

Population studies have reported on the associations of hypertensive retinopathy with various systemic cardiovascular diseases, including incident coronary heart disease (Duncan et al. 2002; Wong et al. 2002c), congestive heart failure (Wong et al. 2005), coronary heart disease mortality (Liew et al. 2009b), and cardiovascular mortality (Sairenchi et al. 2011; Wong et al. 2003c). The presence of hypertensive retinopathy signs is also associated with multiple markers of subclinical atherosclerotic diseases, including coronary artery calcification (Wong et al. 2008), aortic stiffness (Cheung et al. 2007b; Triantafyllou et al. 2014), and left ventricular hypertrophy (Cheung et al. 2007a; Cuspidi et al. 2005b; Kim et al. 2010; Tikellis et al. 2008), suggesting that its presence is an indicator of other end organ damage. Namely, narrower retinal arterioles and wider venules were associated with long-term risk of mortality and ischemic stroke in both sexes (Seidelmann et al. 2016) and coronary heart disease in women (Gopinath et al. 2014; Seidelmann et al. 2016).

However, not all reports support the concept that retinal arterial vascular alterations are correlated with markers of cardiac disease (Cuspidi et al. 2004) and severity of coronary heart disease (Phan et al. 2016). Instead, recent data suggested that the clinical value of the detection of early signs of hypertensive retinopathy might be potentially of value in younger individuals (Aissopou et al. 2015). In particular, mild retinopathy did not correlate with aortic stiffness and carotid hypertrophy in the whole-sample population. Rather, the association was significant in men than in women, and in younger persons than in older persons. It is possible that the search for mild hypertensive retinopathy in the elderly group of the hypertensive population has a limited value in refining cardiovascular risk stratification, because of the impact of age on retinal vessels.

Clinical Significance with Renal Impairment

The retinal and renal circulations share similarities in its anatomic and physiologic characteristics. The significance of hypertensive retinopathy signs as risk indicators has long been recognized in patients with renal disease (Gunn 1892). Retinal microvascular changes have also been associated with renal dysfunction (Edwards et al. 2005; Wong et al. 2004a), chronic kidney disease (Bao et al. 2015; Liew et al. 2012), and incident chronic kidney disease (Yau et al. 2011; Yip et al. 2015, 2017). Such association was independent of blood pressure, diabetes, and other risk factors, and was also seen in persons without diabetes or hypertension. However, not all reports the association between retinal microvascular abnormalities and chronic kidney disease (McGowan et al. 2015; Phan et al. 2016) and decline in renal function (Grunwald et al. 2014). Despite this, the presence of microvascular changes in the eye (presence of retinopathy and widened retinal venules) and kidney (microalbuminuria) was independently associated with incident cardiovascular disease (Yip et al. 2016). Notably, the risk of cardiovascular disease is significantly increased in people with coexistent retinal abnormalities and microalbuminuria.

Taken in totality, these data suggest hypertensive retinopathy signs and retinal vascular parameters are markers of systemic vascular alterations which may mirror preclinical structural changes in the cerebral, coronary, and renal microcirculation, and may be used as markers to better stratify high risk individuals for hypertension and its related end organ damage. Hence, the evaluation of retinal microvasculature could, in the near future, be performed in all hypertensive patients, to obtain a better stratification of cardiovascular risk, and, possibly, it might be considered as an intermediate endpoint in the evaluation of the effects of antihypertensive therapy.

Differential Diagnosis

Several diseases can result in retinopathy that can be difficult to distinguish from hypertensive retinopathy. Of noteworthy is nonproliferative diabetic retinopathy with regard to retinopathy signs such as microaneurysms, intraretinal retinal hemorrhages, hard exudates, and cotton wool spots. Apart from the evaluation of the patient's systemic disease status, certain retinopathy signs confer greater specificity (Grosso et al. 2011). In early stage of the disease, retinal arteriolar abnormalities, such as arteriolar narrowing and arterio–venous nicking, are commonly seen in people with hypertension, whereas clustering of microaneurysms point to more toward diabetes and has been shown to predict diabetic retinopathy progression (Kohner et al. 1999). As retinopathy worsens, additional distinctive signs may appear (Grosso et al. 2011). In hypertensive retinopathy, optic disc swelling is a specific sign of malignant hypertension, whereas in diabetic retinopathy, retinal swelling is observed almost invariably in the macula. Finally, the formation of new vessel, or neovascularization, is often associated with chronic diabetes and not of long-standing hypertension. Other conditions with hemorrhage that can resemble hypertensive retinopathy include radiation retinopathy, anemia, and other blood dyscrasias, ocular ischemic syndrome, and central retinal vein occlusion.

Management

The treatment for hypertensive retinopathy is primarily focused upon lowering blood pressure. Patients found to have hypertensive retinopathy signs may be referred to primary care physicians for blood pressure-lowering management strategies and cardiovascular risk assessment (i.e., assessment of cholesterol levels). However, no randomized controlled studies have evaluated whether treating the hypertension will reverse established hypertensive retinopathy changes. Patients with malignant retinopathy will need urgent antihypertensive management (Strachan and McKnight 2005). However, no recommendation for routine fundus examination of follow-up in known hypertensive patients can be made. Apart from identifying fundus-related changes, ophthalmologists, and optometrists can also help to promote antihypertensive medication adherence and emphasize lifestyle modifications for all patients, with and without hypertension.

Prognosis

Hypertensive retinopathy has long been proposed to mirror the underlying vascular dysfunction of the body. Presence of hypertensive retinopathy signs can provide important clues

to systemic hypertension, both clinically manifested and subclinical (Cheung et al. 2012a). Patients with hypertensive retinopathy signs have an increased risk for stroke (Wong et al. 2001; Yatsuya et al. 2010) and coronary heart disease (Cuspidi et al. 2005a; Kim et al. 2010; Wong et al. 2005). These data suggest that patients with hypertensive retinopathy signs may benefit from a careful cardiovascular evaluation, and appropriate risk reduction therapy, if indicated. Since the retinal arteriosclerotic changes (i.e., arterio–venous nicking) do not regress, patients with hypertensive retinopathy remain at a higher risk for retinal artery occlusions, retinal vein occlusions, and retinal macroaneurysms.

Complications

Hypertensive Choroidopathy

The choroidal circulation, derived from the long and short posterior ciliary arteries, supplies oxygen to the outer retina including the photoreceptors. The effects of hypertension on these vessels cause choroidopathy (Bourke et al. 2004). The underlying mechanism of hypertensive choroidopathy is related to poor perfusion of the choriocapillaris. Like the retinal vessels, the choriocapillaris may also undergo fibrinoid necrosis in the presence of elevated blood pressure. The changes seen in hypertension are correlated with the anatomy of the choroidal circulation: Areas of focal ischemia (Elschnig spots) appear as pale, yellow, well-demarcated lesions which may eventually become pigmented as a secondary consequence of tissue infarction and linear pigmented streaks (Siegrist streaks) may develop along the course of underlying choroidal arteries.

Hypertensive Optic Neuropathy

The main source of blood supply of the optic nerve head is the posterior ciliary artery circulation, with retinal branches supplying only the surface nerve fiber layer. Accelerated or malignant hypertension (i.e., diastolic blood pressure > 130, although there is no agreed definition) may lead to optic neuropathy bilateral optic disc swelling or papilledema. The pathogenesis of optic disc swelling secondary to accelerated hypertension remains unclear. Ischemia, raised intracranial pressure and hypertensive encephalopathy are all possible mechanisms that can result in papilledema (Chatterjee et al. 2002). At this level of blood pressure, it is sufficient to cause damage to multiple organ systems including the kidney, heart, and brain (Keith et al. 1939). Malignant hypertension should be treated as a medical emergency requiring urgent treatment to prevent irreversible complications such as hemorrhagic stroke (Cremer et al. 2016).

Other Types of Ocular Diseases

In addition to hypertensive retinopathy, hypertension predisposes patients to many ocular conditions, including diabetic retinopathy (Yau et al. 2012), central or branch retinal vein occlusion (Wong and Scott 2010), retinal arteriolar emboli (Wang et al. 2006), retinal arterial macroaneurysm (Panton et al. 1990), and possibly age-related macular degeneration (Age-Related Eye Disease Study Research 2000) and glaucoma (Wong and Mitchell 2007).

Future Directions

There are several novel advances in the field of hypertensive retinopathy. First, in addition to the use of digital fundus photography and objective measurement of retinal vascular caliber, new research has identified other retinal vascular features, such as bifurcation, fractal dimension, tortuosity, that may also be related to hypertension. Higher blood pressure levels were associated with a reduction in the complexity of retinal vasculature (Cheung et al. 2012b; Liew et al. 2008). In never-treated hypertensive patients, retinal vessels were more torturous than the normotensive subjects (Triantafyllou et al. 2015). Furthermore, retinal vascular geometric measures (e.g., sparser and more tortuous retinal vessels) were associated with stroke (Hughes et al. 2016; Ong et al. 2013), incident stroke (Kawasaki et al. 2011), Alzheimer's disease (Cheung et al. 2014b; Frost et al. 2013; Williams et al. 2015), coronary artery disease (Wang et al. 2018), and risk of mortality from ischemic heart disease and stroke (Witt et al. 2006).

This suggests that pathological changes that adversely affect perfusion and vessel wall function in the cerebral small vessels are likely to be reflected as similar changes in the retinal vessels. These newer, quantitatively measured vascular network changes across the retina may offer increasingly accurate and reliable parameters reflecting early and subtle retinal vascular abnormalities, which potentially provide additional predictive value of vascular disease outcomes.

Second, given the exponential rise of hypertension globally, the manpower needed for screenings of hypertensive retinopathy signs is likely to be outpaced. Recent study showed that artificial intelligence (AI) predicted cardiovascular risk factors (age, gender, and systolic blood pressure) from digital fundus photographs in 284,335 patients (Yip et al. 2016). Retinal image analysis based on AI employs machine learning methods to extract salient features from fundus photographs. Highly accurate artificial intelligence algorithms have been employed on fundus photographs to detect diabetic retinopathy (Gulshan et al. 2016) and other eye diseases (Ting et al. 2017) with comparable

accuracy to human experts. Hence, artificial intelligence system for detection of hypertensive retinopathy from fundus photographs can reduce the workload for manual grading considerably by identifying individuals with higher cardiovascular risks to aid in quicker diagnosis and reduce human error. Digital fundus photography using an automated artificial intelligence system may be a feasible and cost-effective public healthcare strategy for the surveillance and prevention of cardiovascular risks due to hypertension in primary health care settings in view of the lack of resources.

Third, newer ocular imaging technology, such as capillary-level non-dye-based mapping of retinal vasculature using optical coherence tomography angiography (OCT-A) and flicker light-induced vasodilation using dynamic retinal vessel analysis have been developed. The novel OCT-A technology enables the identification of impaired perfusion and capillary remodeling within the retinal, choroidal, and optic nerve vasculature (Kashani et al. 2017; Spaide et al. 2017). Technology such as the OCT-A can provide information about the architectural organization of capillaries, whose changes in structures may be the earliest markers of ischemia/hypoxia, before the arterioles (Chua et al. 2018; Fig. 9.7).

Much more work needs to be done, but OCT-A holds the promise for continuing advances in improvements in clinical care for patients with systemic hypertension by examining the hypertensive changes in the eye and systemic end organ damage. Using the dynamic retinal vessel analysis, others showed that in patients with chronic heart failure, there was a marked reduction of retinal arterioles dilatation in response to flicker light compared to controls (Nagele et al. 2018). These technologies hold promise for further examining hypertensive changes in the eye and systemic end organ damage.

Finally, there is some indication that antihypertensive medication can reverse hypertensive retinopathy signs. There is evidence that antihypertensive treatment may promote the reversal of arteriolar narrowing (Antonio et al. 2014; Hughes et al. 2008). Furthermore, some classes of antihypertensive drugs may exert favorable effects on retinal vessels as compared with others (Thom et al. 2009). This indicates that precise assessment of the retinal vascular network may be a useful approach to evaluating microvascular structural responses in clinical trials of antihypertensive therapy.

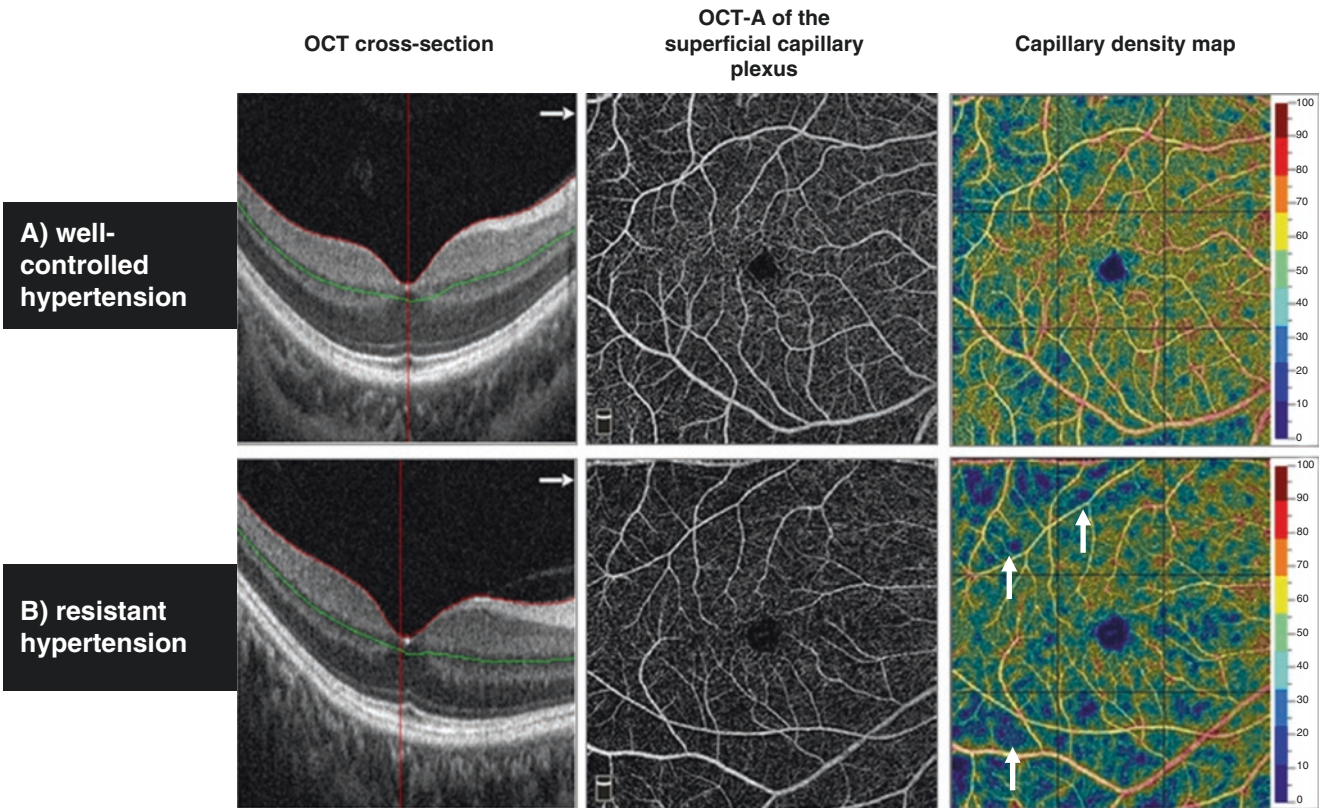

Fig. 9.7 Optical coherence tomographic angiograms demonstrate focal areas of peripheral capillary non-perfusion seen as dark blue areas (white arrows). Comparison of retinal superficial capillary plexus between persons with (**a**) well-controlled hypertension (BP 106/73; 49-year-old woman) with higher capillary density (51%) and (**b**) resistant hypertension (BP 142/95; 50-year-old woman) with lower capillary density (41%) (with permission from Chua et al. 2018)

Conclusion

Hypertension is usually asymptomatic and hypertensive retinopathy signs can be detected incidentally during eye examinations. It is not unusual for eye care specialists to be the first to diagnose hypertension because the clear media of the eye allows blood vessels to be observed directly. Patients found to have hypertensive retinopathy signs should be appropriately referred to their primary care physicians. The attending ophthalmologist or optometrist, who discovers hypertensive retinopathy in a previously undiagnosed hypertensive patient, is therefore in a fortuitous position to potentially reduce the patient's future risk of stroke, dementia, cardiovascular diseases, chronic kidney disease, and overall mortality.

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Takayasu Disease

10

Takeshi Iwase and Hiroko Terasaki

Introduction

Takayasu disease was first described by Dr. Mikito Takayasu, a Japanese ophthalmologist, in 1908 (Takayasu 1908). He described his findings in a 22-year-old woman with an absent radial artery pulse whose eyes had severe retinal vessel abnormalities; the retinal vessels branched 2–3 mm away from the disc, and the branches anastomosed to one another to create a wreath around the disc which was called wreath-like anastomosis (Fig. 10.1). Because the pulse of the radial artery was not palpable in patients with Takayasu disease, investigations have focused on the ischemic signs and symptoms of the upper body. In 1948, Shimizu and Sano investigated the etiology of Takayasu disease from clinical and pathological aspects, and called Takayasu disease a "pulseless disease" (Shimizu and Sano 1948, 1951). The arterial lumens, including that of the carotid and subclavian arteries, were either narrowed or obstructed due to inflammation at the aortic arch and at its branches, which caused the upper body to become ischemic (Fig. 10.2).

The ocular symptoms of Takayasu disease result from stenosis or occlusion of the aortic arch and carotid arteries, and the degree and rate of progression of the ocular vascular insufficiency depend on the adequacy of the collateral blood supply to the eye (Peter et al. 2010). Takayasu disease is characterized by vasculitis of the large vessels that often results in the pulselessness due to fibrotic stenosis, and it predominantly affects young women. The ocular syndrome is a hypoperfusive retinopathy that results from chronic hypoperfusion of the ophthalmic artery secondary to carotid artery stenosis (Koz et al. 2007; Peter et al. 2010, 2011; Malik et al. 2015).

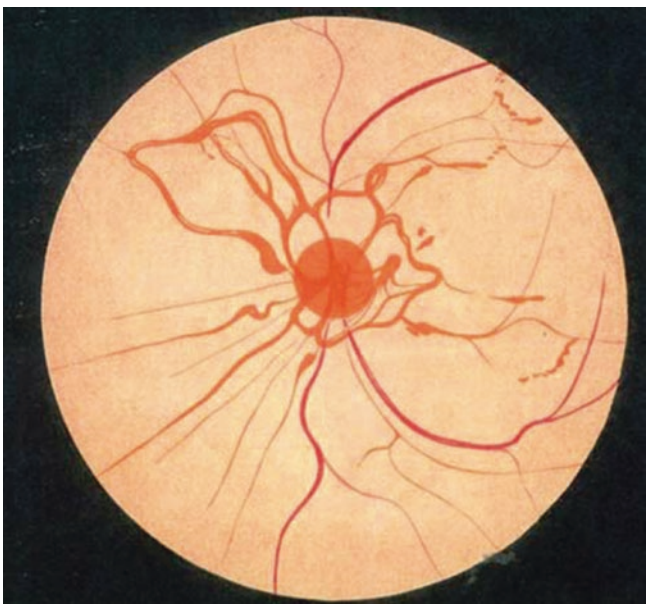

Fig. 10.1 Original schema: Inverted image of the fundus of the right eye from "A case with curious change in the central retinal vessel" described by Takayasu in 1908. The retinal vessels are branched 2–3 mm away from the disc, and the branches anastomose to one another to create a wreath around the disc, a wreath-like anastomosis

Epidemiology

The male:female ratio of patients with Takayasu disease is approximately 1:9, and the age of onset peaks in the 20s in women but has not been clearly determined in men. This suggests that the female hormones may be associated with the development of Takayasu disease.

The distribution of patients with Takayasu disease throughout the world differs from region to region. More cases are reported in Asia and the Middle and Near East, but

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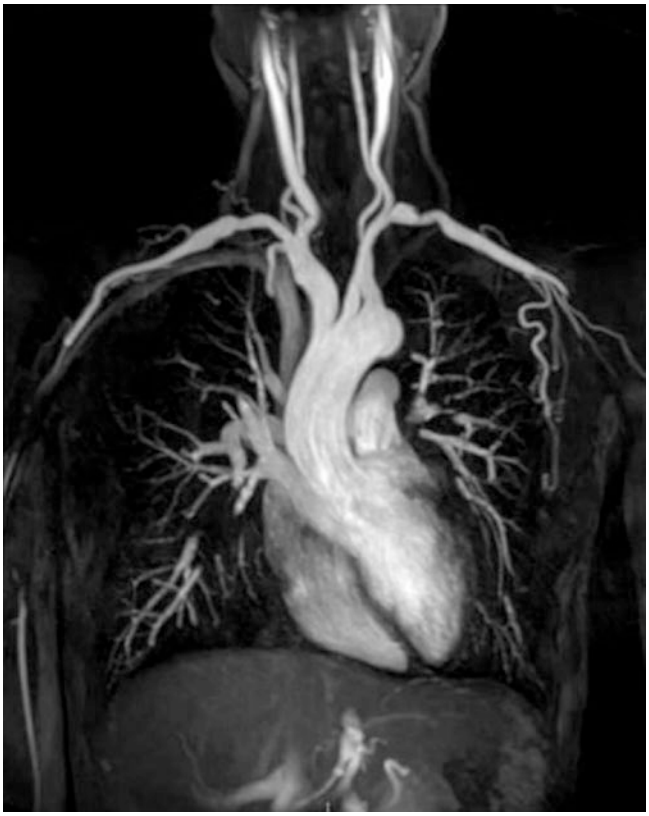

Fig. 10.2 Systemic angiography. Bilateral subclavian artery stenosis. Coronal reconstruction of magnetic resonance angiogram shows non-calcified stenosis of both subclavian arteries suggestive of Takayasu arteritis. Copyright J Vasc Surg Cases Innov Tech, 2016

the incidence of Takayasu disease is higher in women in all regions (Numano et al. 2000).

Early diagnosis and treatment of Takayasu disease by physicians and surgeons have resulted in a substantial reduction of advanced cases. In addition, the number of newly diagnosed patients has been decreasing according to data reported by the research team of the Ministry of Health, Labour, and Welfare of Japan (Isobe 2006).

Etiopathogenesis

Takayasu's disease is a chronic, inflammatory disease of the aortic arch and its main branches resulting in fibrosis of all layers of the arteries (Fig. 10.3). The inflammation of the arteries is detected, especially in the outer membrane and vasa vasorum causing panarteritis. These alterations lead to granulomatous changes. The arteritis in patients with Takayasu disease begins as a granuloma that grows diffusely and finally ends as fibrosis (Nasu 1963).

It has been postulated that the chain of pathologic events in the retinal vascular system in Takayasu disease is secondary to a gradual decrease of blood pressure in the central retinal artery. This decrease is due to vaso-occlusive lesions in

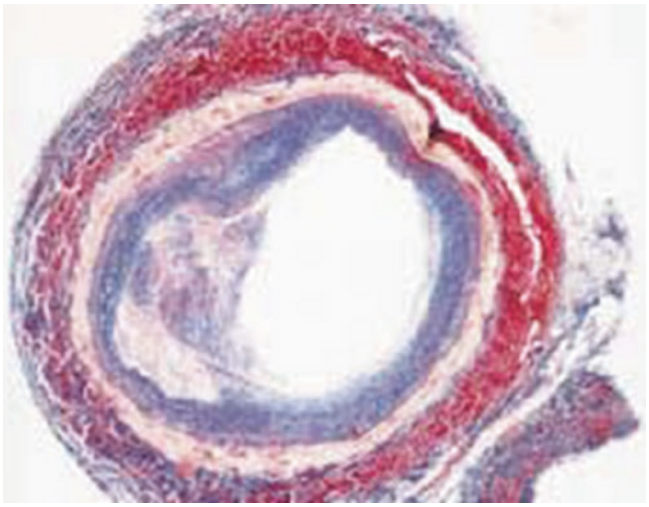

Fig. 10.3 Pathology. Subclavian artery of a patient with Takayasu's arteritis. Note atherosclerotic changes in the intima, damage of the medial layer, and thickened adventitia with cellular infiltration. Azan-Mallory staining; original magnification ×10. Copyright Lancet, 2000

the common carotid arteries. Retinal vascular lesions develop only after hypotension develops in the central retinal artery. When the blood pressure in the retina decreases below a critical level, the retinal vessels initially react with general vasodilation, followed by capillary microaneurysms, hyperpermeability of the vessel walls, capillary nonperfusion, and eventually neovascularization.

A reduction in the gap between the arterial pressure and the venous pressure is involved in the development of arteriovenous anastomosis in the preferential channel, and a weakening of the vascular wall is involved in the development of the anastomoses at arteriovenous crossing sites (Fig. 10.4) (Tanaka and Shimizu 1987).

Electron microscopic studies of the retina show irregularities in the laminar structure of the outer segments of the photoreceptors and degeneration in the nuclear layer of the photoreceptor cells and the vascular system. Histopathological examinations of eyes enucleated from patients with pulseless disease showed retinal atrophy and degeneration accompanied by a moderately reduced number of photoreceptor nuclei and fewer ganglion and bipolar cells (Font and Naumann 1969).

Clinical Features

Ocular symptoms are present in 30–45% of the patients with Takayasu disease (Kiyosawa and Baba 1998; Chun et al. 2001; Peter et al. 2011). The most common ocular symptom is a reduction in the visual acuity. Generally, ocular pain, irritation, and metamorphopsia are not common. The prevalence of amaurosis fugax varies from 1.6% (Peter et al. 2011) to 25.7% (Chun et al. 2001).

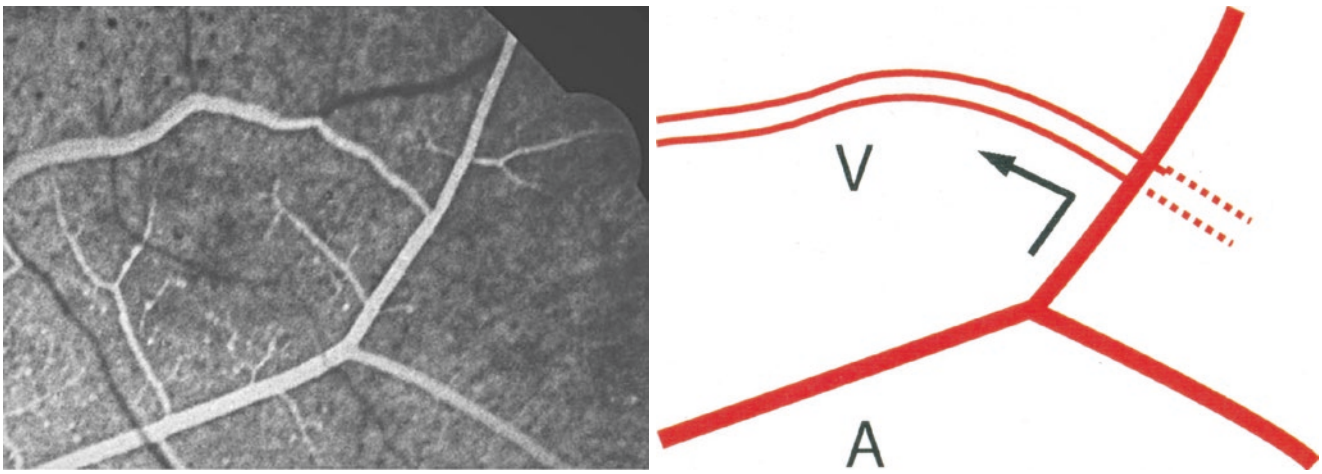

Fig. 10.4 Arteriovenous anastomosis. Fluorescein angiogram (left) and schema (right) at the anastomotic site. A discrete arteriovenous shunt forms at an arteriovenous crossing. The dye bolus flows into the vein through the shunt in an axial flow pattern. Black arrow, dye flow; *A* retinal artery, *V* retinal vein. Copyright American Academy of Ophthalmology, 1987

Table 10.1 Ocular classification for Takayasu disease

Stages	Characterization	Fundus findings
Stages 1	Dilatation of small vessels	Dilatation and dark color of retinal veins
Stages 2	Microaneurysm formation	Microaneurysms resembling a bunch of grapes or beads retinal hemorrhages and cotton wool spots
Stages 3	Arteriovenous anastomosis formation	Neovascularizations and anastomoses of retinal vessels dilatation of bulbar conjunctival vessels
Stages 4	Further ocular complications	Mydriasis, iris atrophy, iris rubeosis, cataract, proliferative retinitis, and retinal detachment

The incidence of eye manifestations in Takayasu disease varies from 8.1% to 68% (Sagar et al. 1994; Kiyosawa and Baba 1998; Baba et al. 1999; Chun et al. 2001). The ocular manifestations are categorized as disease or treatment related. Uyama classified Takayasu retinopathy into four stages (Table 10.1) (Uyama and Asayma 1976): Stage 1 is characterized by distension and dilation of the veins, caliber dissimilarities, and darkening of the retinal veins (Fig. 10.5).

Stage 2 is characterized by the formation of microaneurysms which resemble bunches of grapes that are located at the end of small branches of dilated retinal vessels. The red blood cells in the retinal veins flow slowly and form rouleaux-like structures. Retinal hemorrhages and cotton wool spots are occasionally observed (Fig. 10.6).

Stage 3 is characterized by the formation of arteriovenous anastomoses and neovascularization. Anastomoses of retinal vessels are observed, especially around the optic disc. Dilatation of bulbar conjunctival vessels is observed. The formation of arteriovenous shunts in the retina is a unique

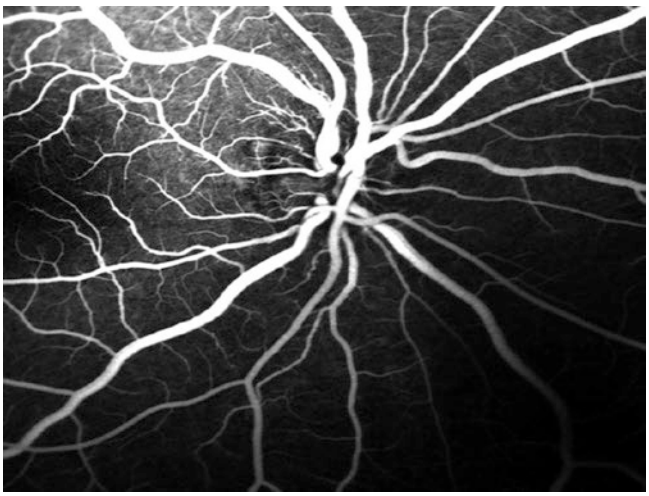

Fig. 10.5 Grade I Takayasu retinopathy. Fundus angiogram of the right eye showing venous dilatation. Copyright Retina, 2011

and an almost pathognomonic feature in both the moderate and advanced stages of Takayasu disease (Fig. 10.7). There are two types of shunts; arteriovenous shunts around the disc, and arteriovenous anastomoses over the entire retina.

Stage 4 is characterized by the presence of ocular complications such as cataract (Fig. 10.8), proliferative retinopathy (Fig. 10.9), vitreous hemorrhage, and retinal detachment. Kiyosawa and Baba classified 65 patients with Takayasu disease according to this classification and reported: stage 1, 27.7%; stage 2, 3.1%; stage 3, 4.6%; and stage 4, 0% (Kiyosawa and Baba 1998).

In Takayasu disease retinopathy, the fundi have characteristics of both hypotensive and hypertensive fundi (Uyama 1968; Peter et al. 2011).

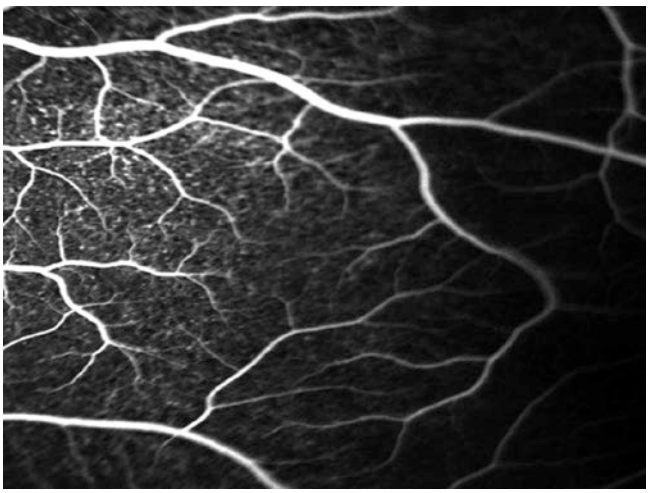

Fig. 10.6 Grade II Takayasu retinopathy. Fundus angiogram of the left eye showing microaneurysms. Copyright Retina, 2011

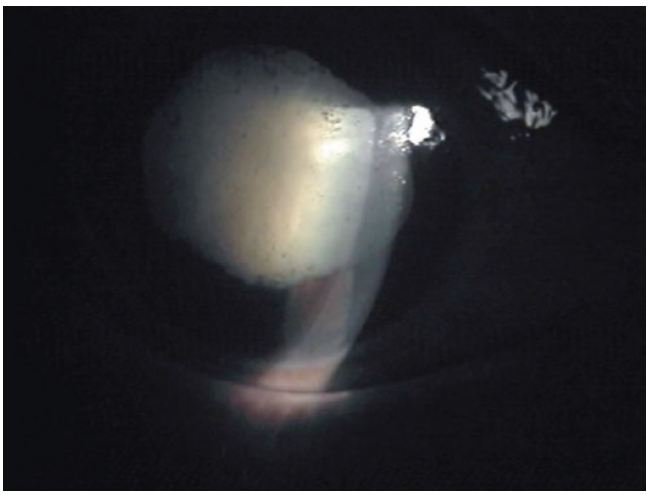

Fig. 10.8 Cataract in Takayasu disease. Ocular ischemic syndrome. Fundus photograph of the right eye of a patient showing nonreactive pupil, complicated cataract, and pigments suggesting earlier anterior uveitis secondary to ocular ischemic syndrome. Copyright Retina, 2011

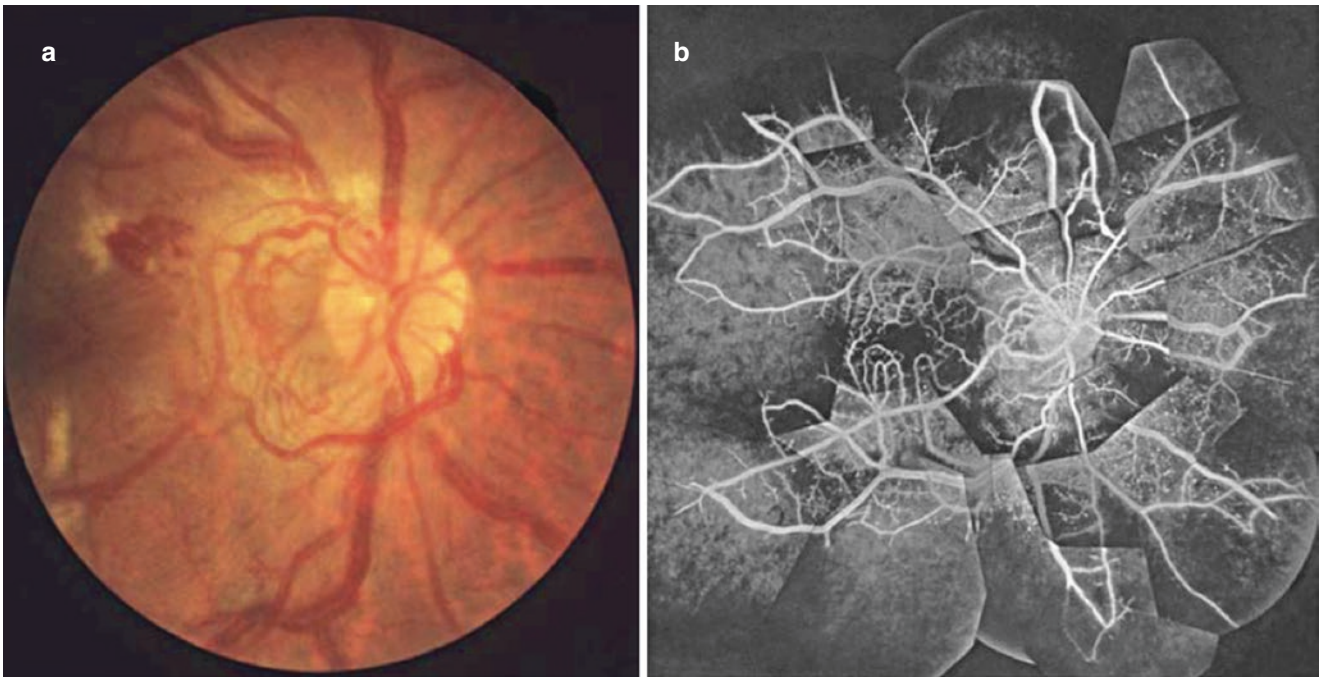

Fig. 10.7 Typical fundus. Color fundus photograph (**a**) and fluorescein angiogram (**b**) of an 42-year-old woman with Takayasu disease. Arteriovenous shunts form as vascular loops around the disc (**a**). Arteriovenous shunts form through dilatation of the capillaries inferior to the macula through the communication of major retinal vessels at an arteriovenous crossing and by formation of vascular loops around the optic disc. Copyright Japanese Journal of Ophthalmology, 2009

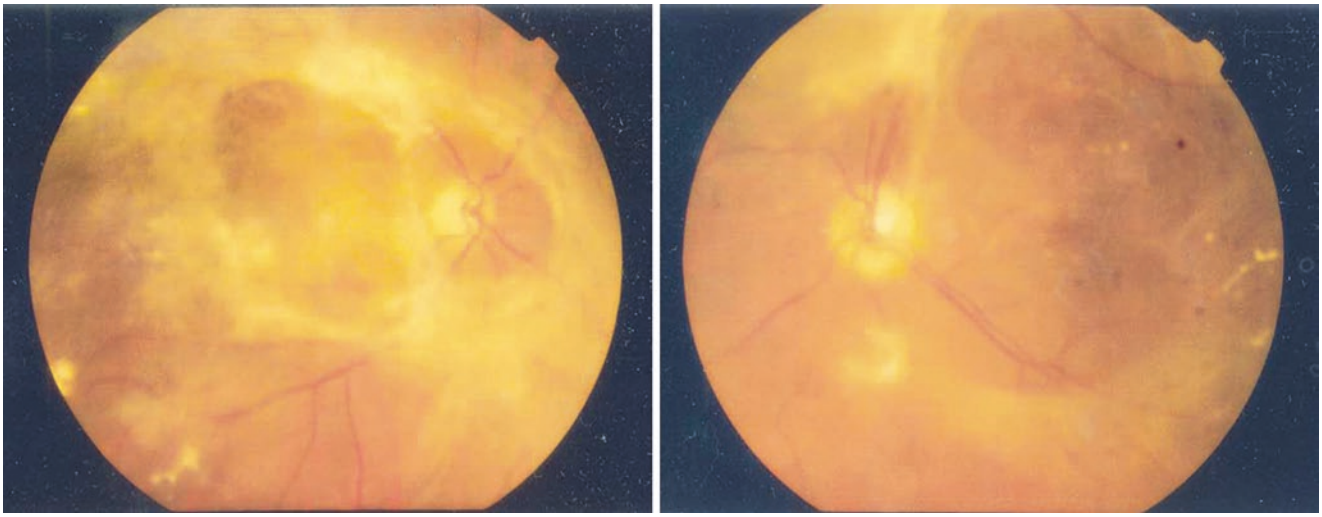

Fig. 10.9 Severe case of Takayasu disease. Fundus photographs of the right eye (left) and the left eye (right) showing tractional retinal detachments with extensive fibrovascular membranes. The visual acuity of the right eye was counting fingers and that of the left was 20/200. Copyright American Journal of Ophthalmology, 2003

Table 10.2 Systemic classification for Takayasu disease

Types	Characterization
Type I	Inflammatory process localized to the arch of the aorta and its branches
Type IIa	Lesions involving the ascending aorta, aortic arch, and its branches
Type IIb	Type IIa region plus thoracic descending aorta
Type III	Lesions involving thoracic descending aorta, abdominal aorta, renal arteries, or a combination
Type IV	Lesions involving abdominal aorta and renal arteries
Type V	Lesions involving entire aorta and branches

Systemic Features

Systemic Takayasu arteritis is classified into five types based on the American College of Rheumatology (Table 10.2). The systemic signs and symptoms include limb claudication, headaches, angina, visual disturbances, palpitations, syncope, and hemiplegia. It has been reported that the incidence of impalpable radial artery pulse is present in approximately 50% of the cases, and vascular bruit in the neck is 43.6–52.5% (Peter et al. 2011; Chun et al. 2001).

Fluorescein Angiography

Fluorescein Angiography (FA) show microaneurysms that are difficult to observe by ophthalmoscopy or color fundus photographs (Fig. 10.10). FA can also demonstrate the process of development of retinal vascular bed occlusions and arteriovenous anastomosis (Fig. 10.11). In addition, delayed arteriovenous circulation time, venous dilation, dye leakage around the macula, retinal neovascularization, and non-perfused areas

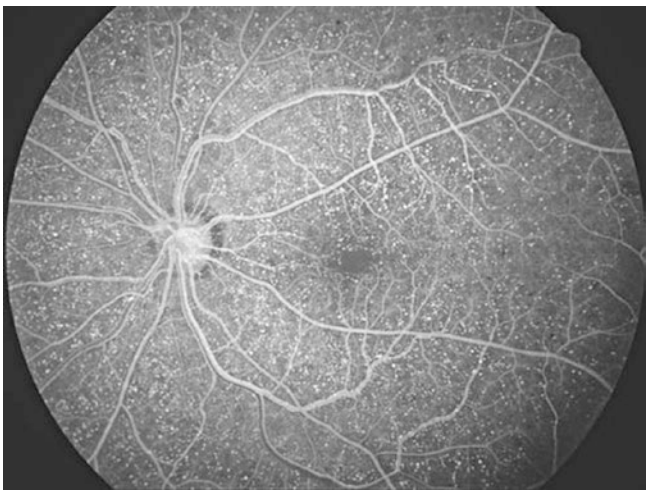

Fig. 10.10 Fluorescein angiogram of the left eye of a 32-year-old woman with Takayasu disease. Notice the numerous retinal microaneurysms. Copyright American Academy of Ophthalmology, 1987

can be observed in the fluorescein angiograms. In the capillary bed of the choroid, delayed inflow of fluorescent dye into the choriocapillaris can also be observed (Fig. 10.12).

Indocyanine Green Angiography

Indocyanine Green Angiography (ICGA) reveals patchy filling defects in the choriocapillaris in eyes at Stage 2 and severely delayed choroidal circulation at Stage 3. The brightness of the choriocapillaris is low in the entire fundus, and the choroidal veins are narrow in the ICG images. Delayed filling of the posterior pole choroid, narrowed choroidal veins, and patchy dark areas suggestive of occlusion of the choriocapillaris can be detected by ICGA.

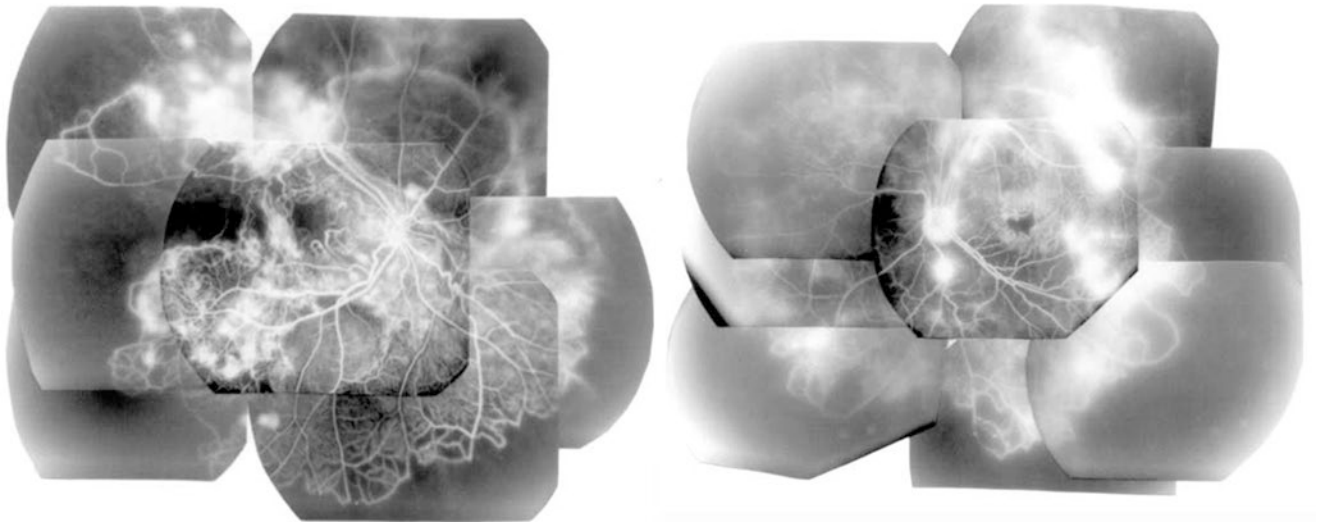

Fig. 10.11 Severe case Takayasu disease. Fluorescein angiograms of the right eye (left) and the left eye (right) demonstrating arteriovenous shunts, large nonperfused areas, and marked NEOVASCULARIZATION. Copyright American Journal of Ophthalmology, 2003

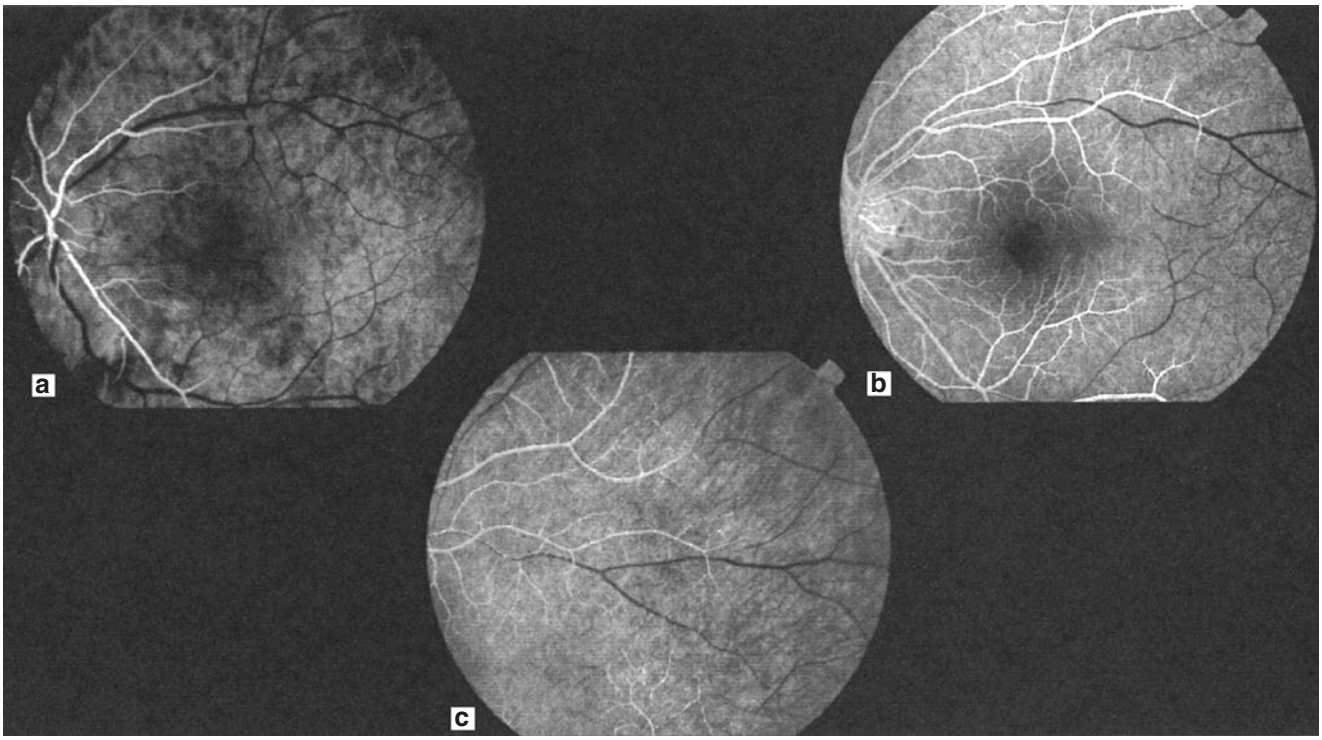

Fig. 10.12 Severe case of Takayasu disease. Fluorescein angiogram demonstrating a marked slowing of flow in the retinal arterioles with only partial arteriolar filling at 40 s (**a**), 1 min, 13 s (**b**), and at 3 min, 9 s (**c**). The multiple microaneurysms are much better seen here than by ophthalmoscopy. Copyright Archive Ophthalmology, 2000

Electroretinography

The electroretinographic (ERG) findings of Takayasu disease are reported to be similar to that of diabetic retinopathy suggesting that the retinopathy in Takayasu disease is associated with hypoxia. The typical ERG findings in Takayasu disease is a reduction or loss of the oscillatory potential reflecting retinal ischemia.

Management

Medical Therapy

Patients with Takayasu disease require systemic administration of corticosteroids to prevent the narrowing of vessels. The standard initial dose is 30 mg/day of prednisolone gradually tapered over time (Amer et al. 2007).

Immunosuppressants are effective in severe cases of Takayasu disease and in patients who cannot be withdrawn from corticosteroid therapy (Horigome et al. 1999; Ozen et al. 2007). Sixty percent of the patients reportedly achieve remission after corticosteroid monotherapy but about one-half of these have recurrences (Kerr et al. 1994). Of these, 40% achieve remission after the additional administration of immunosuppressants (methotrexate, cyclophosphamide, cyclosporin), although 23% fail to achieve remission even after the additional administration. Patients with severe Takayasu disease who are resistant to immunosuppressive therapy, can respond to antitumor necrosis factor therapy (Hoffman et al. 2004; Tanaka et al. 2006).

Photocoagulation

Patients with Takayasu disease with iris rubeosis and neovascular glaucoma respond to panretinal photocoagulation. (Yamaoka 1991) The intraocular pressure can be normalized by panretinal photocoagulation in patients with serious pulseless disease complicated by posterior ischemic optic neuropathy and neovascular glaucoma, although optic atrophy can lead to a reduced visual function.

Surgical Treatment

Surgical treatment is indicated for patients who have a narrowing or obstruction of the aorta and its main branches and aortic insufficiency resulting from aortic dilation (Miyata et al. 2003). The subjective and objective ophthalmologic findings improve after a reconstruction of the carotid artery to relieve the occluded common carotid in Takayasu disease. The typical retinal vascular lesions disappear within weeks after an increase in the rise in the blood pressure of the central retinal artery.

Vitrectomy is an option for eyes with severe complications, e.g., retinal detachment or proliferative vitreoretinopathy (Kuwahara et al. 2003).

Prognosis After Surgical Treatment

Surgical reconstruction of the major arteries can lead to an improved prognosis for patients with Takayasu disease (Miyata et al. 2003; Endo et al. 2003). In 120 patients with Takayasu disease, the 15-year survival rate was 67.9% in patients with major complications, e.g., hypertension, aortic regurgitation, aortic aneurysm, and Takayasu's retinopathy, and 96.4% in patients without major complications (Ishikawa and Maetani 1994). The overall survival rate was 82.9% in this cohort.

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Imaging of Retinal Vascular Disease

11

Alaa E. Fayed, Peter L. Nesper, and Amani A. Fawzi

Anatomy of the Retinal Vascular System

The retina is supplied by two circulations: the choroidal circulation via the choroidal vessels and the retinal circulation via the central retinal artery (Jakobiec 1982). In up to 32% of the eyes (Justice and Lehmann 1976), an additional branch, the cilioretinal artery, may extend from the choroidal circulation to supply a portion of the inner retina, mainly in the macular region.

The choroidal circulation is supplied by the ophthalmic artery via the medial and lateral posterior ciliary arteries, each of which gives rise to one long and multiple short posterior ciliary arteries. Apart from minor contributions from recurrent branches of the long posterior ciliary arteries, the choriocapillaris is supplied by the short posterior arteries, which penetrate the posterior globe near the optic nerve (Oyster 1999). Paula et al. demonstrated that there is a higher arteriolar supply from the posterior ciliary artery surrounding the macula than the rest of the retina, with approximately nine pairs of arterioles and venules distributed in the parafoveal regions (Paula et al. 2010).

It was previously thought that branches from the central retinal vessels form only two distinct capillary beds, one in the nerve fiber layer (superficial capillary plexus or SCP) and the other in the deep boundary between the inner nuclear layer and the outer plexiform player (deep capillary plexus or DCP) (Grant and Lutty 2012). Until recently, the visualization of these capillary systems remained inaccessible except via fluorescein angiography (FA). Weinhaus et al. reported that the SCP was visualized over four times more effectively than the DCP in FA, thereby limiting the understanding of the vascular pathology affecting these deeper layers (Weinhaus et al. 1995).

The development of optical coherence tomography angiography (OCTA) allowed visualization of the deeper capillaries with sufficient detail to evaluate the impact of various vascular disorders at this level. Park et al. utilized OCTA to distinguish a middle capillary plexus (MCP) from the SCP and DCP which lies at the inner boundary of the inner nuclear layer (Park et al. 2016) (Fig. 11.1). Around the optic nerve, an additional fourth, more superficial capillary network, the radial peripapillary capillaries, exists (Max Snodderly and Weinhaus 1990).

Fluorescein Angiography and Wide-Angle Imaging in Retinal Vascular Disease

Diabetic Retinopathy

Retinal capillary microaneurysms develop as a saccular outpouching from the capillary wall (Akram et al. 2013) and are readily detected in the early frames of FA where they appear as small hyperfluorescent dots. They may also show variable leakage which fades in the later frames. FA helps distinguish them from clinically similar tiny punctate dot hemorrhages that will generally block fluorescence (de Venecia et al. 1976) (Fig. 11.2).

Intraretinal microvascular abnormalities (IRMA) is a term used to describe clusters of abnormal hypercellular vascular structures that arise on the edges of areas of retinal capillary non-perfusion (Davis et al. 1968). Clinically, it can be difficult to distinguish IRMA from neovascularization (NV). On FA, IRMAs typically do not show leakage whereas NV does (Fig. 11.3).

In DR, distortion and enlargement of the foveal avascular zone (FAZ) result from occlusion of retinal capillaries and loss of precapillary arterioles near the fovea (Fig. 11.4). This was extensively documented by Conrath et al. (2005), Arend et al. (1995) and Bresnick et al. (1984). However, areas of

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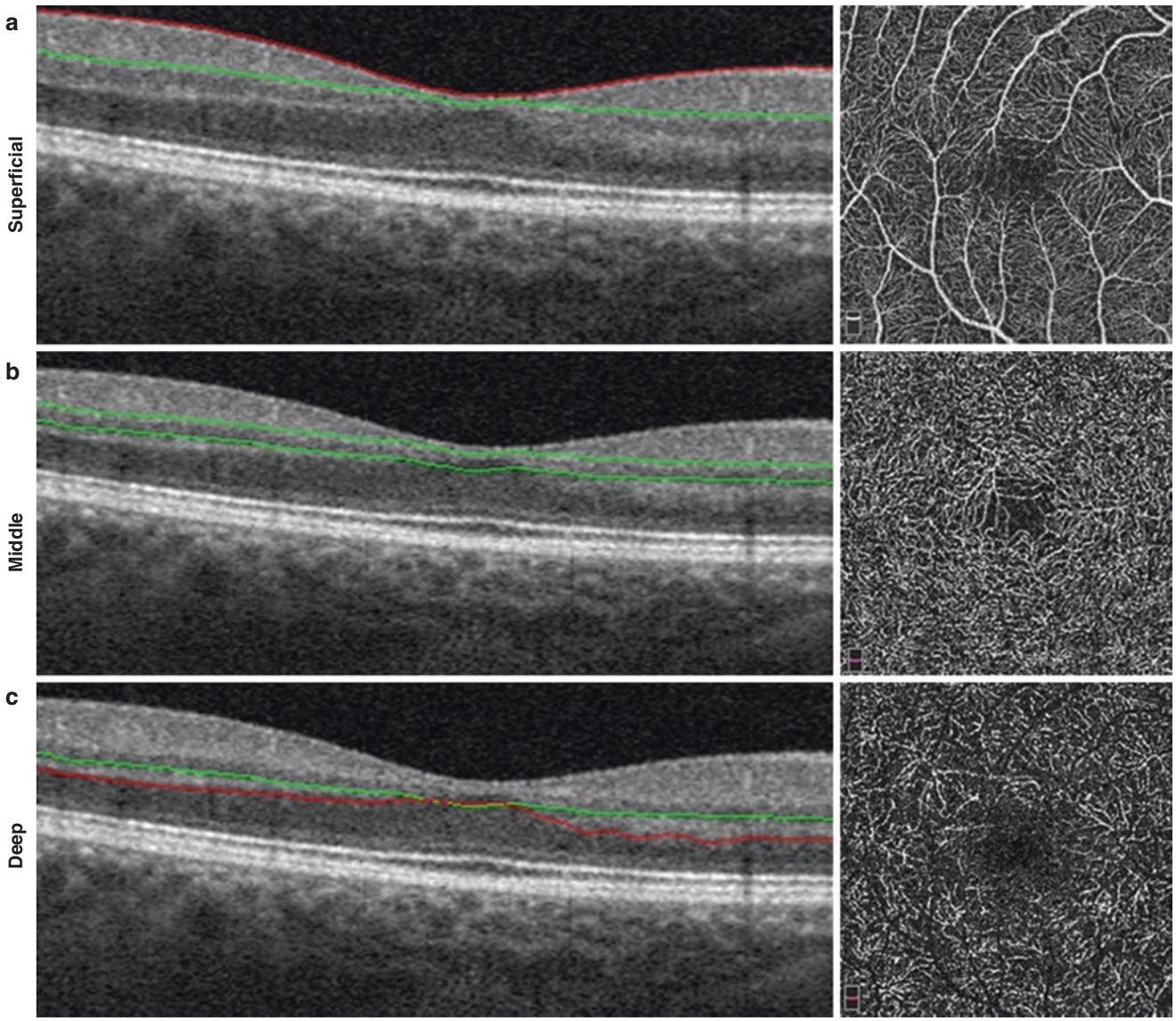

Fig. 11.1 The three retinal capillary plexuses. Optical coherence tomography angiography segmentation using 3D projection artifact resolution (3D PAR) to visualize the three capillary plexuses. (**a**) The SCP boundaries encompass the nerve fiber layer and the ganglion cell layer (GCL), with a lower boundary set at 10 μm above the IPL. (**b**) The MCP was captured with a 40-μm slab to encompass the inner boundary of the INL with an upper boundary set 10 μm above the IPL and a lower boundary set 30 μm below it. (**c**) The DCP was set to encompass the OPL and deep boundary of the INL, with an upper boundary set 30 μm below the IPL and a lower boundary at 10 μm below the OPL

non-perfusion may be underappreciated on FA because of the diffuse leakage from surrounding vessels, especially in later frames.

Proliferative diabetic retinopathy (PDR) is characterized by the development of neovascularization at or around the disc (NVD) or surrounding areas of ischemia in the periphery, referred to as neovascularization elsewhere (NVE). NVD and NVE appear hyperfluorescent and tend to exhibit leakage on FA and wide field imaging (Figs. 11.5 and 11.6).

Diabetic macular edema (DME) is characterized by macular thickening caused by leakage from hyperpermeable vasculature (Wilkinson et al. 2003). It can be appreciated by FA as leaking of the dye in early frames, typically in a petalloid or honeycomb pattern (Otani and Kishi 2007) (Fig. 11.7). Borders of edematous retinal tissue may show waxy yellowish deposits, known as hard exudates. They form as a result of leakage of lipoprotein and fluid from damaged capillaries into the extracellular space of the retina (Ferris and Patz 1984). Increased amounts of hard exudate within the 30° photographic field centered on the macula has been associated with a higher risk of visual impairment (Chew et al. 1996).

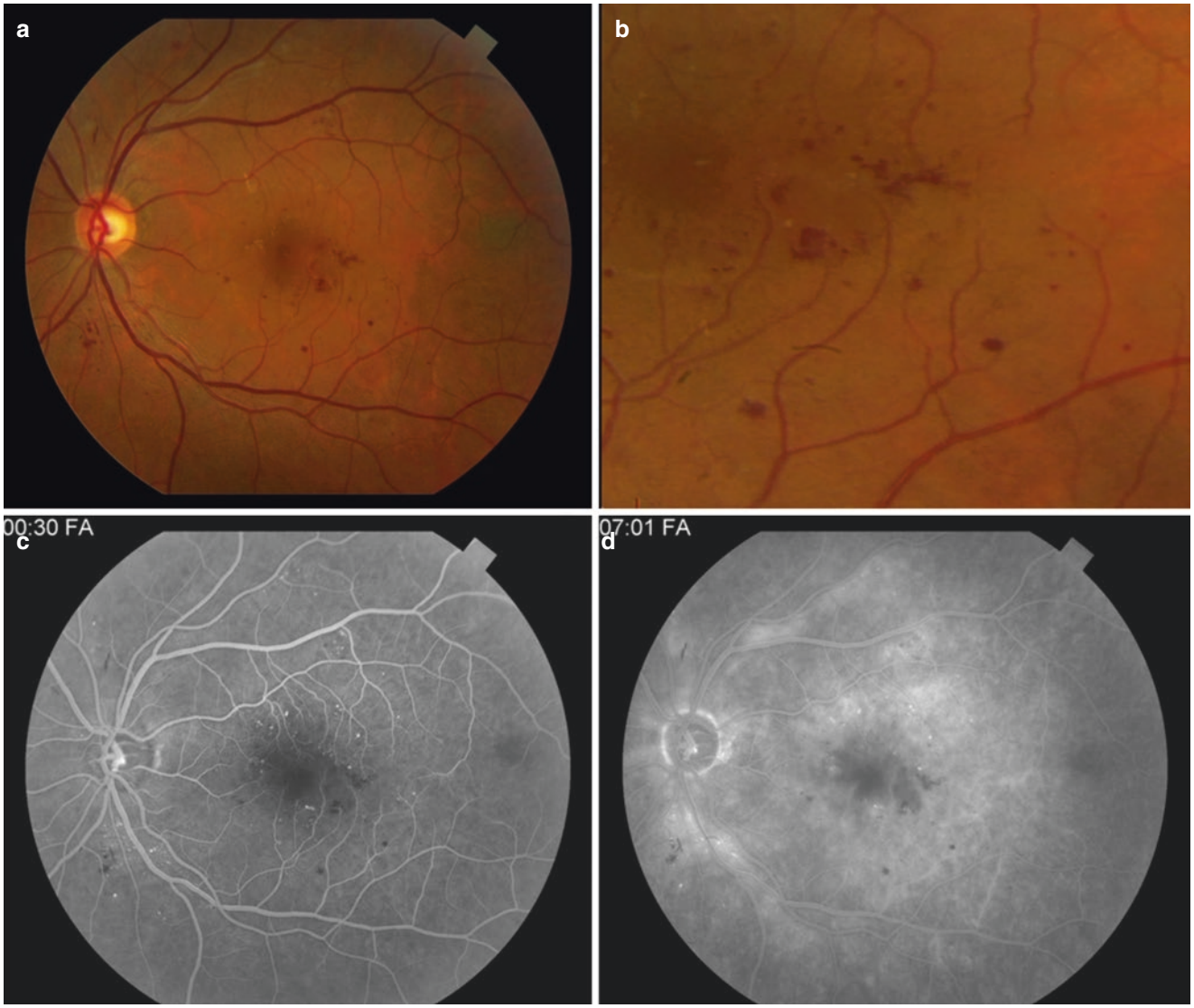

Fig. 11.2 Microaneurysms in NPDR. (**a**) Fundus photo of the left eye showing multiple scattered microaneurysms throughout the posterior pole. (**b**) Scattered microaneurysms inferior and temporal to the fovea. (**c**) Fluorescein angiogram of the left eye during the late venous phase showing multiple scattered hyperfluorescent dots (microaneurysms) surrounding the fovea with multiple tiny dots of blocked fluorescence representing retinal dot hemorrhages. (**d**) Fluorescein angiogram of the same eye during the late phase showing diffuse leakage (leaking microaneurysms) across the posterior pole involving the foveal avascular zone and distorting its outline

Retinal Vein Occlusion

The clinical presentation of retinal vein occlusion (RVO) may vary according to the site of the occlusion. A branch occlusion (BRVO) typically occurs at the site of an arteriovenous crossing, while central retinal vein occlusions (CRVO) occur at the level of the lamina cribrosa (Browning 2012).

Fundus photographs reveal extensive intraretinal hemorrhage and exudation in the area drained by the occluded vein which appears tortuous and dilated. The optic nerve head may also appear elevated, hyperemic and swollen, particularly in central vein involvement. Long standing cases may be associated with the development of optociliary collaterals, NV and the development of fibrous tissue (Hayreh et al. 1983; Murakami et al. 1983). On FA, acutely there is typically a delay in arteriovenous transit followed by staining of the walls of the affected veins. This is accompanied by capillary non-perfusion and extensive leakage distal to the site of the occlusion (Clemett 1974) (Figs. 11.8 and 11.9). In cases where the macular circulation is involved, extensive leakage of the fluorescein dye is seen in or around the fovea. In long standing ischemic cases, FA may demonstrate the development of NVD or NVE, which appear as hyperfluorescent leaking areas in the later frames (Hayreh et al. 1983).

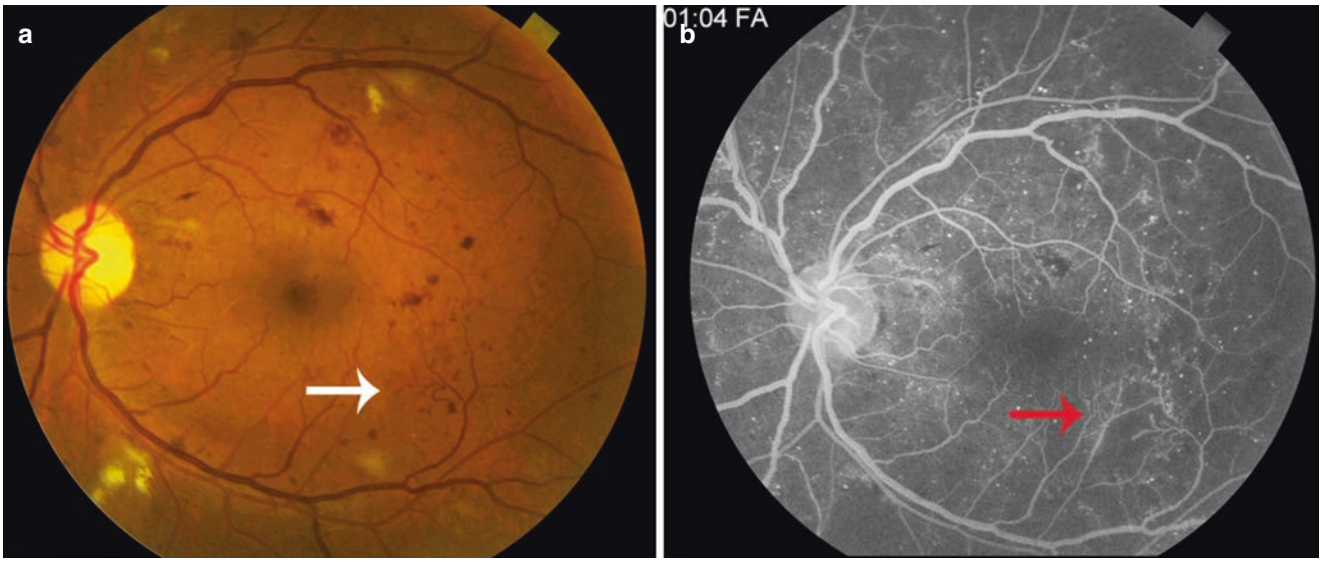

Fig. 11.3 IRMA in very severe NPDR. (**a**) Fundus photo of the left eye showing multiple scattered intraretinal dot and blot hemorrhages and hard exudates across the posterior pole and outside both temporal arcades. There is a large intraretinal microvascular abnormality (IRMA) arising from the inferotemporal branch (white arrow). (**b**) Fluorescein angiogram of the left eye during the late phases showing multiple scattered hyperfluorescent leaking microaneurysms with areas of blocked fluorescence (retinal hemorrhage), as well as areas of capillary non-perfusion, more obvious at the temporal and inferior periphery. The red arrow points to the hyperfluorescent IRMA, which shows no leakage

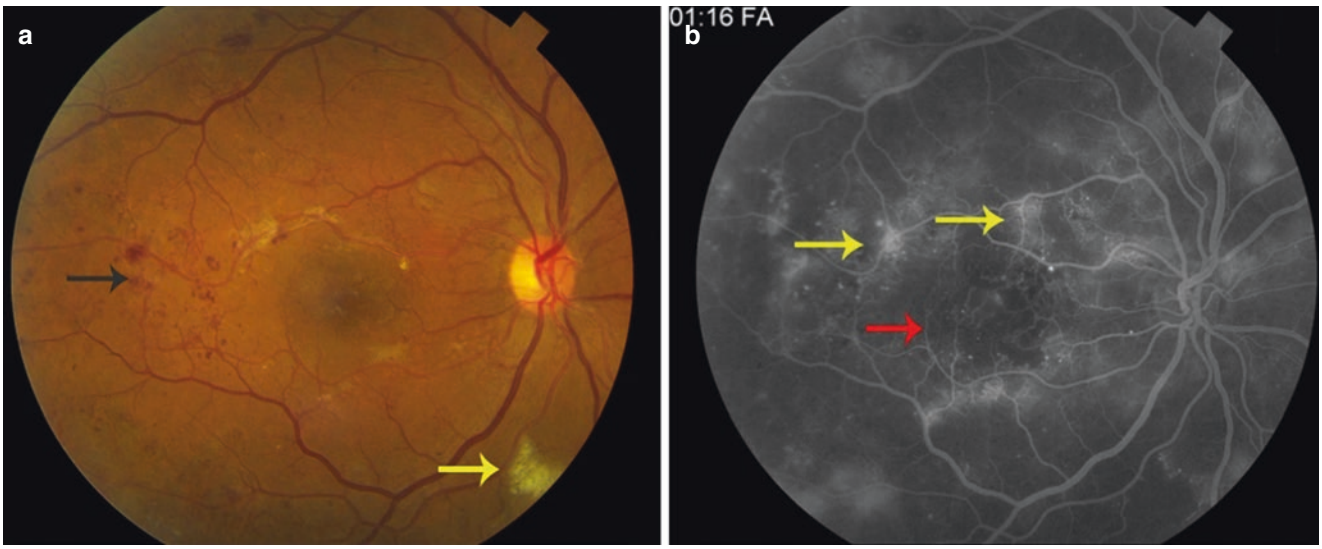

Fig. 11.4 Enlarged FAZ in PDR. (**a**) Fundus photo of the right eye showing a blunt foveal reflex with multiple scattered microaneurysms and dot and blot hemorrhages across the posterior pole and along the arcades, as well as multiple areas of neovascularization (black arrow), more obvious temporal to the macula. A large cotton wool spot is seen about 2 DD inferior to the optic disc. (**b**) Fluorescein angiogram of the right eye during the late phase showing multiple hyperfluorescent leaking microaneurysms and neovascularization (yellow arrows), as well as large areas of capillary non-perfusion including an enlarged foveal avascular zone (red arrow)

Retinal Artery Occlusion

Occlusion of the retinal arterial supply may occur at different levels, including the main trunk of the central retinal artery (CRAO), one of the terminal branches of the central artery (BRAO) or, in some cases, the cilioretinal branch of the short posterior ciliary arteries. Clinically, the diagnosis of retinal artery occlusion has commonly been based on clinical findings of retinal thickening and whitening in the area supplied by the occluded vessel. In case of CRAO, a cherry red spot

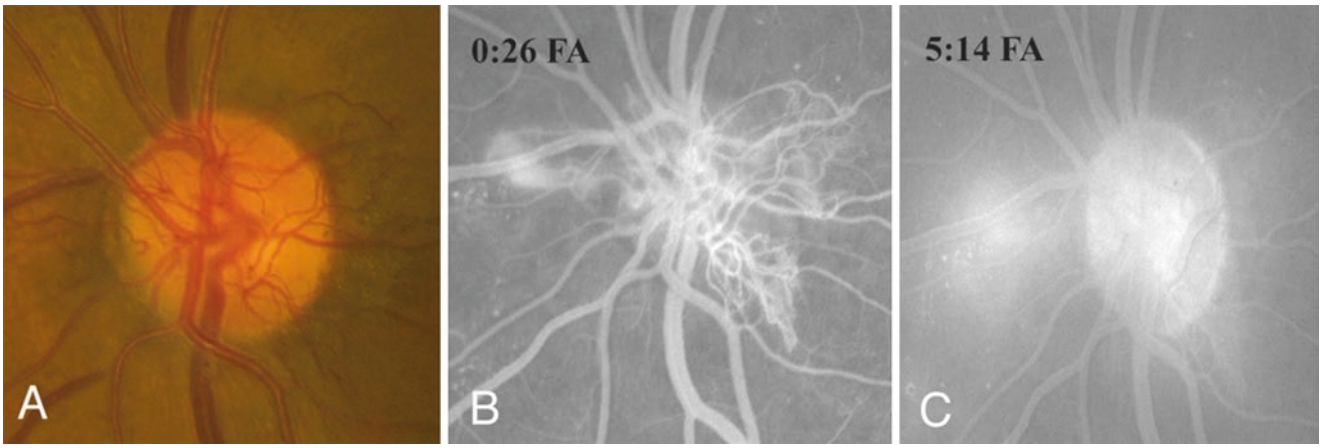

Fig. 11.5 NVD in high-risk PDR. (**a**) Fundus photo of the left eye showing high risk neovascularization on the surface and surrounding the optic disc. (**b**) Fluorescein angiogram of the left eye during the late venous phase showing extensive active neovascularization on the surface of the optic disc. (**c**) Fluorescein angiogram during the late phases showing leakage of the NVD

can be appreciated at the site of the fovea. In acute presentations, FA reveals a delay in retinal arterial filling, as well as arteriovenous transit time. FA also shows hypofluorescence of the affected area caused by thickening and swelling of the tissue and "cattle-trucking" of the blood column in the branch arteries (Beatty and Eong 2000) (Fig. 11.10).

Sickle Cell Retinopathy

Sickle cell retinopathy is characterized by an initial non-proliferative phase characterized by vascular tortuousity, salmon patch hemorrhages between the internal limiting membrane (ILM) and the retinal surface, intraretinal hemorrhages and dark areas of RPE hyperpigmentation known as black sunbursts. Eventually, prolonged retinal ischemia and peripheral capillary non-perfusion results in the development of the proliferative phase, characterized by NV, which acquires a "sea fan" configuration, subhyaloid and/or vitreous hemorrhage as well as tractional or combined tractional-rhegmatogenous retinal detachment (Goldberg 1971).

FA remains the most widely used tool in the assessment of patients with sickle cell retinopathy to evaluate peripheral capillary non-perfusion, particularly temporally, as well as hyperfluorescent leaking NV in the earlier frames of the angiogram (Rednam et al. 1982). Owing to the peripheral nature of the retinal pathology, wide-field FA is of particular importance in these cases where some areas, particularly those close to the ora serrata, may be missed by conventional FA (Cho and Kiss 2011) (Fig. 11.11). FA may also demonstrate an enlarged FAZ. Clinically, the optic disc may exhibit small dilated capillaries that are occluded on FA (Goldbaum et al. 1978; Condon and Serjeant 1972; Moriarty et al. 1988). Later stages of sickle cell retinopathy with development of fibroglial tissue may show staining of these membranes in the later frames of the angiogram.

Optical Coherence Tomography in Retinal Vascular Disease

Diabetic Macular Edema

Clinically significant macular edema (CSME) is defined as the clinical detection of any one of the following: thickening of the retina located 500 μm or less from the center of the macula, hard exudates with thickening of the adjacent retina 500 μm or less from the center of the macula, or a zone of retinal thickening one disc area or larger in size, located 1 disc diameter (DD) or less from the center of the macula. OCT DME is defined as thickening of the retina with or without partial loss of transparency within 1 DD from the center of the macula (Klein et al. 1995). OCT may also reveal distortion of the structural retinal anatomy caused by the accumulation of intraretinal and subretinal fluid (Hee et al. 1995) (Fig. 11.12).

OCT also provides a quantitative retinal thickness map, thus allowing easier and more thorough follow-up (Fig. 11.13). On the other hand, it is worth noting that there is no direct correlation between retinal thickness and visual acuity. Patients with higher retinal thickness may show paradoxical better visual acuity than those with lower retinal thickness, and vice versa (Network 2007) (Fig. 11.14).

Using SD-OCT, Sun et al. found a correlation between the detection of disorganization of the retinal inner layers (DRIL) in patients with DME and worsening of visual acuity (Sun et al. 2014). It may be attributed to the higher incidence of DCP affection and photoreceptor involvement associated with DRIL (Onishi et al. 2019) (Fig. 11.15).

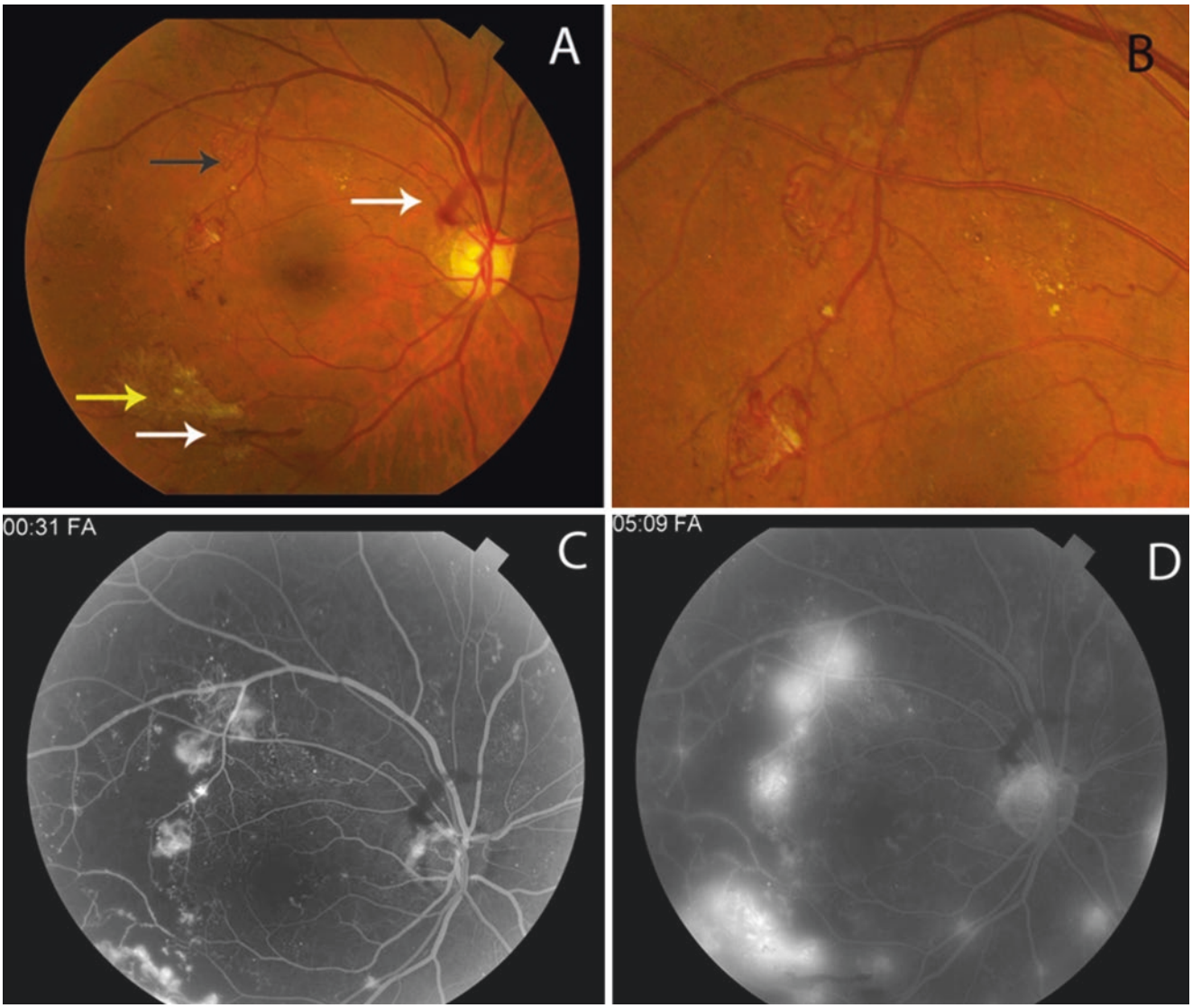

Fig. 11.6 NVE in high-risk PDR. (**a**) Fundus photo of the right eye showing extensive areas of neovascularization across the superotemporal and inferotemporal arcades (black arrow) with a fibrous membrane arising inferotemporally (yellow arrow). There are multiple scattered microaneurysms, as well as two fine areas of pre-retinal hemorrhage, one superior to the optic disc and the other superior to the inferotemporal arcade (white arrows). (**b**) Areas of extensive neovascularization elsewhere. (**c**) Fluorescein angiogram of the right eye during the late venous phase showing hyperfluorescent leakage of the temporal neovascularization and scattered microaneurysms. There is an area of blocked fluorescence caused by pre-retinal hemorrhage superior to the disc. (**d**) Fluorescein angiogram of the same eye during the late phases showing extensive hyperfluorescent leakage from the temporal neovascularization with the appearance of other areas of neovascularization in the inferonasal area

Retinal Vein Occlusion

SD-OCT is a helpful tool in the assessment of the macular involvement in cases of RVO. Macular edema is typically characterized by marked thickening and/or interruption of the retinal layers accompanied by the development of hypotranslucent cystic spaces (Hee et al. 1995). Long-standing cases show higher incidences of development of epiretinal membranes, which are can be readily monitored by OCT (Mitchell et al. 1997) (Fig. 11.16).

Retinal Artery Occlusion

SD-OCT has been used in retinal artery occlusion to visualize the effect of non-perfusion on the structural integrity of the retinal layers. Increased reflectivity and thickness of the inner retina in early presentations as a result of swelling and thickening has been documented on OCT. These findings are followed by a decrease in reflectivity and thickness of the inner retina, as well as an increase in reflectivity in the outer retina and RPE/choriocapillaris layer attributed to atrophy of

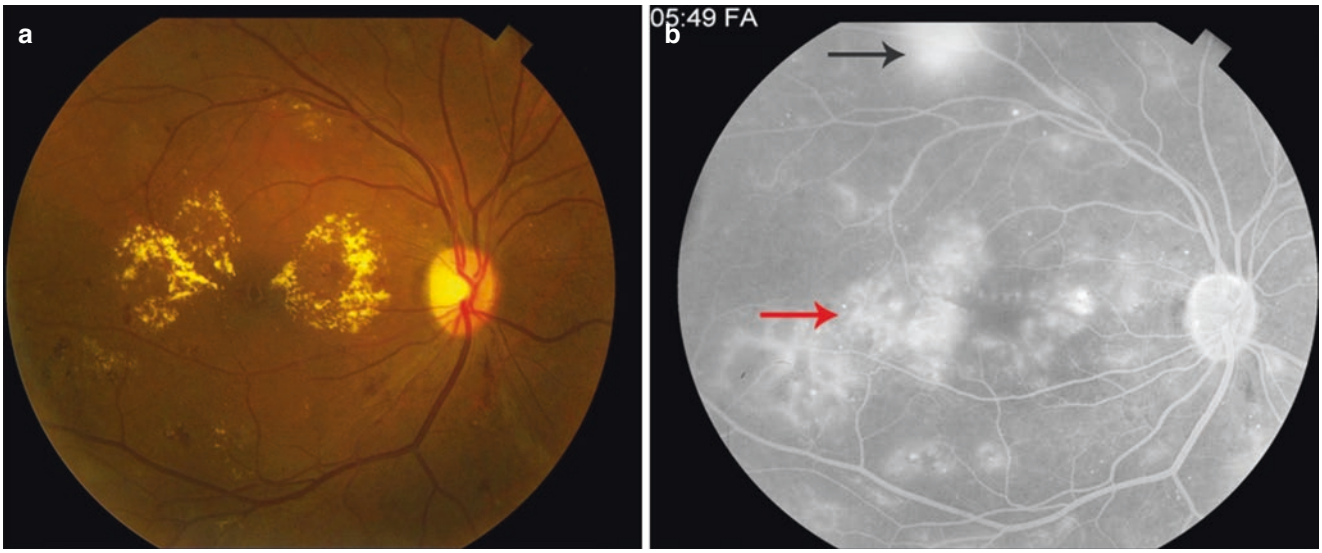

Fig. 11.7 DME in PDR. (**a**) Fundus photo of the right eye showing extensive exudation surrounding the fovea forming a circinate maculopathy, as well as multiple scattered microaneurysms and dot and blot hemorrhages across the posterior pole. (**b**) Fluorescein angiogram of the right eye during the late phases showing multiple scattered hyperfluorescent microaneurysms with extensive leakage surrounding the fovea and along the inferotemporal arcade (red arrow). There is an area of hyperfluorescent leaking neovascularization along the superotemporal arcade (black arrow)

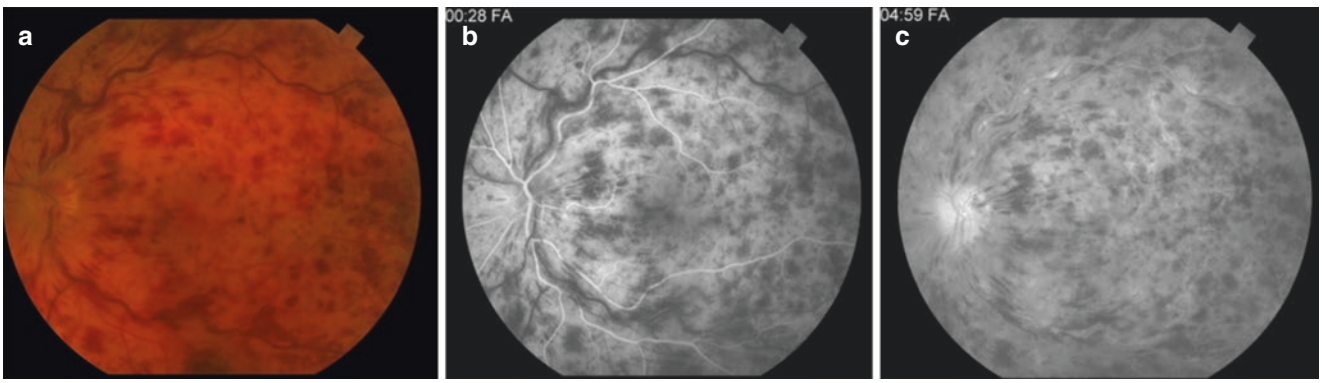

Fig. 11.8 Central retinal vein occlusion (CRVO). (**a**) Fundus photo of the left eye showing markedly dilated and tortuous veins, with extensive retinal hemorrhage and cotton wool spots. The optic disc is swollen and hyperemic and the macula appears edematous. (**b**) Fluorescein angiogram of the left eye during the late venous phase showing marked delay in arteriovenous transit with blocked fluorescence by extensive retinal hemorrhage and edema. (**c**) Fluorescein angiogram of the left eye during the late phases showing staining of the walls of the affected veins, as well as blocked fluorescence by extensive retinal hemorrhage and edema

the neurosensory retina (Ahn et al. 2015; Falkenberry et al. 2006; Yu et al. 2015).

Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy

SD-OCT, as well as OCTA, have allowed better characterization of distinct manifestations of retinal ischemia named acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM).

Clinically, AMN is characterized by the presence of intraretinal, reddish-brown, wedge-shaped lesions, commonly in the perifoveal area. A characteristic feature of these wedges is that their apices tend to point to the fovea (Bos and Deutman 1975; Bhavsar et al. 2016). They are commonly unimpressive on fundus photographs and are better appreciated on infrared imaging as parafoveal hyporeflective lesions.

FA does not add to the clinical findings and does not greatly help in the diagnosis of AMN (Priluck et al. 1978). During the acute phase of the lesion, SD-OCT shows a transient hyperreflectivity of the OPL and ONL. Within days,

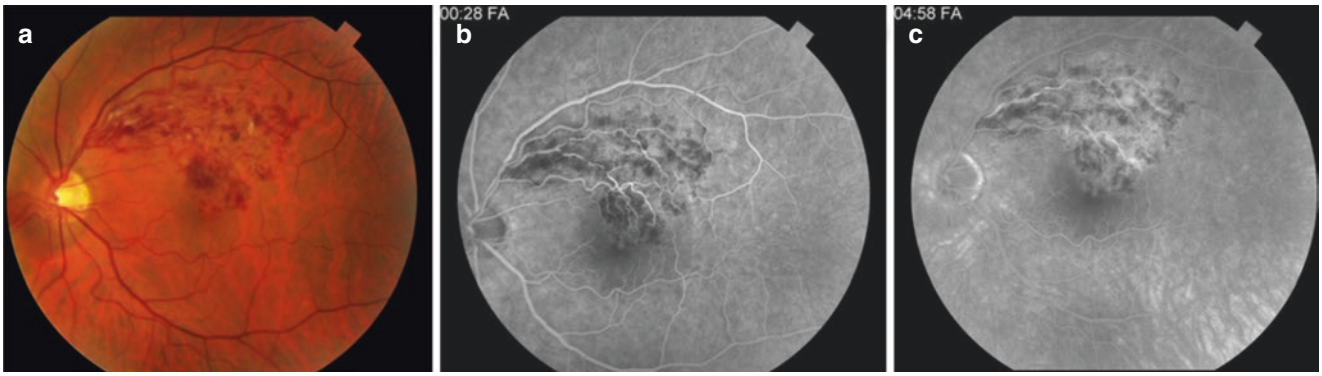

Fig. 11.9 Superotemporal branch retinal vein occlusion (BRVO). (**a**) Fundus photo of the left eye showing a blunt foveal reflex and extensive intraretinal hemorrhage and cotton wool spots along the superotemporal arcade extending to the macula. (**b**) Fluorescein angiogram of the left eye during the late venous phase showing a prolonged arteriovenous transit at the superotemporal branch of the central retinal vein. There is noted tortuousity of the affected vein as well as blocked fluorescence secondary to the hemorrhage and edema. The leakage is seen encroaching on the foveal avascular zone. (**c**) Fluorescein angiogram of the left eye during the late phases showing delayed filling of the affected veins and staining of their walls with extensive exudation and hemorrhage

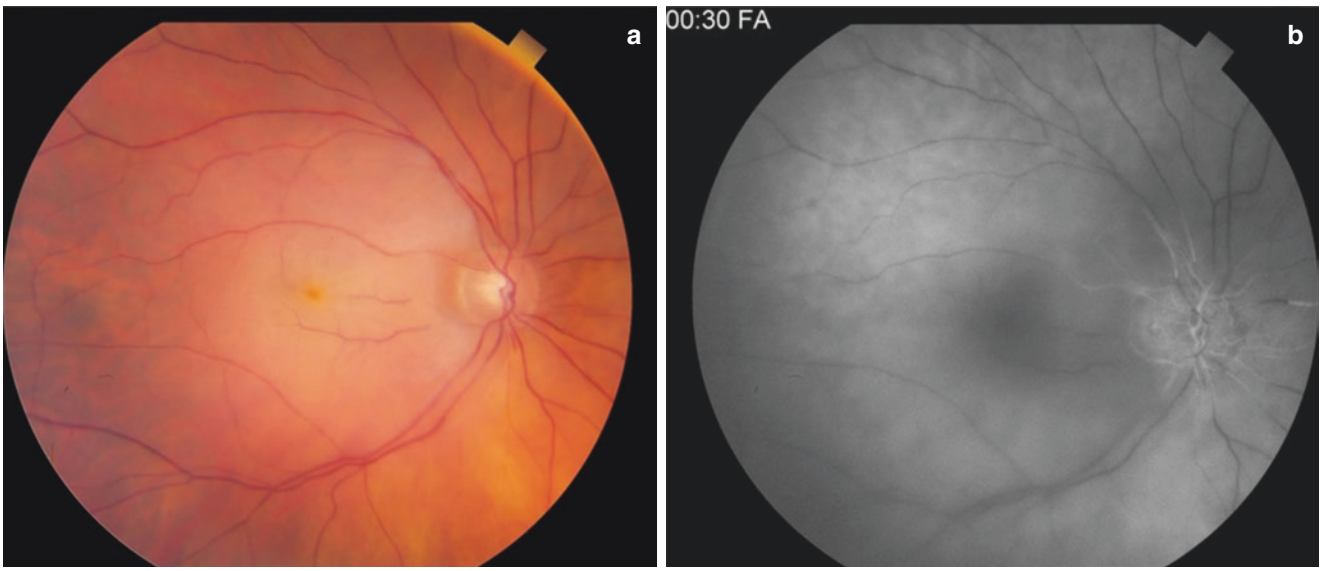

Fig. 11.10 Central retinal artery occlusion (CRAO). (**a**) Fundus photo of the right eye showing marked retinal opacity at the posterior pole with the appearance of a characteristic cherry red spot at the fovea. The vessels appear markedly attenuated. (**b**) Fluorescein angiogram of the right eye showing markedly delayed filling of the retinal arteries, as well as blocked fluorescence by extensive retinal edema

this hyperreflectivity begins to resolve and is followed by an interruption of the interdigitation zone (RPE/outer segment junction) and the ellipsoid zone (inner segment/outer segment junction or IS/OS), as well as thinning of the outer nuclear layer (ONL). Over time, symptoms may improve despite the persistence of some OCT findings including ONL thinning and interruption of the interdigitation zone (Fawzi et al. 2012) (Fig. 11.17).

PAMM was introduced by Sarraf et al. while documenting lesions similar to AMN but involving the middle macular region above the outer plexiform layer (Sarraf et al. 2013). Sridhar et al. described three distinct *en face* OCT patterns in PAMM: arteriolar, fern-like, and globular (Sridhar et al. 2015). As with AMN, PAMM lesions may pass into thinning of the affected layers, primarily the inner nuclear layer (INL) (Rahimy et al. 2015) (Fig. 11.18).

As a result, SD-OCT and OCTA, in addition to near-infrared reflectance and red-free imaging, are the current imaging modalities for the detection of the subtle retinal changes associated with PAMM and AMN.

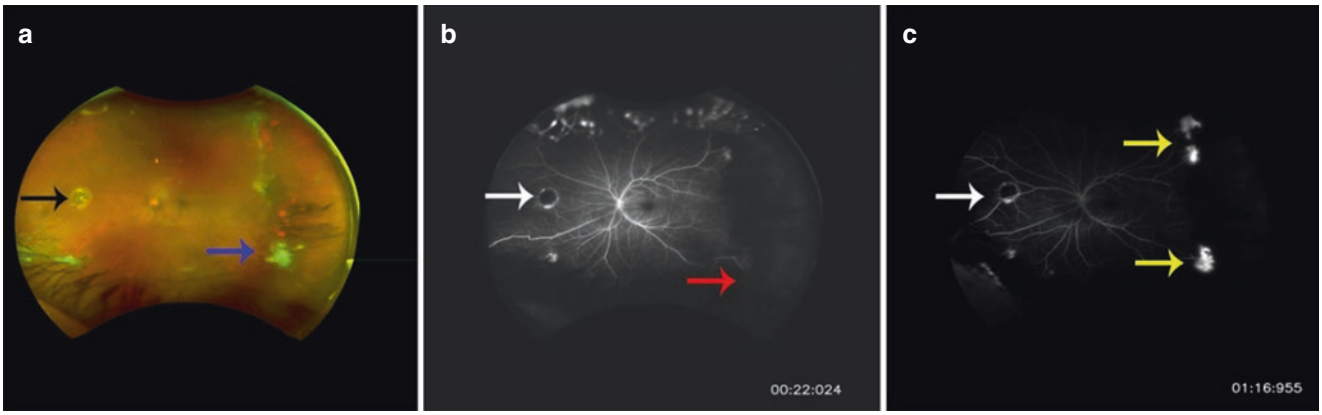

Fig. 11.11 Proliferative sickle cell retinopathy. (**a**) Wide-field fundus photo (Optos) of the left eye showing markedly attenuated peripheral arteries and a black sunburst (black arrow) in the retina. There are extensive neovascularization and fibrovascular membrane formation (blue arrow) at the temporal periphery. (**b**) Wide-field fluorescein angiogram of the left eye during the early venous phase showing an area of blocked fluorescence nasally (black sunburst) (white arrows) as well as extensive peripheral non-perfusion (red arrow). (**c**) Fluorescein angiogram of the left eye during the late phases showing additional hyperfluorescent leaking neovascularization (yellow arrows) at the temporal periphery as well as inferonasally

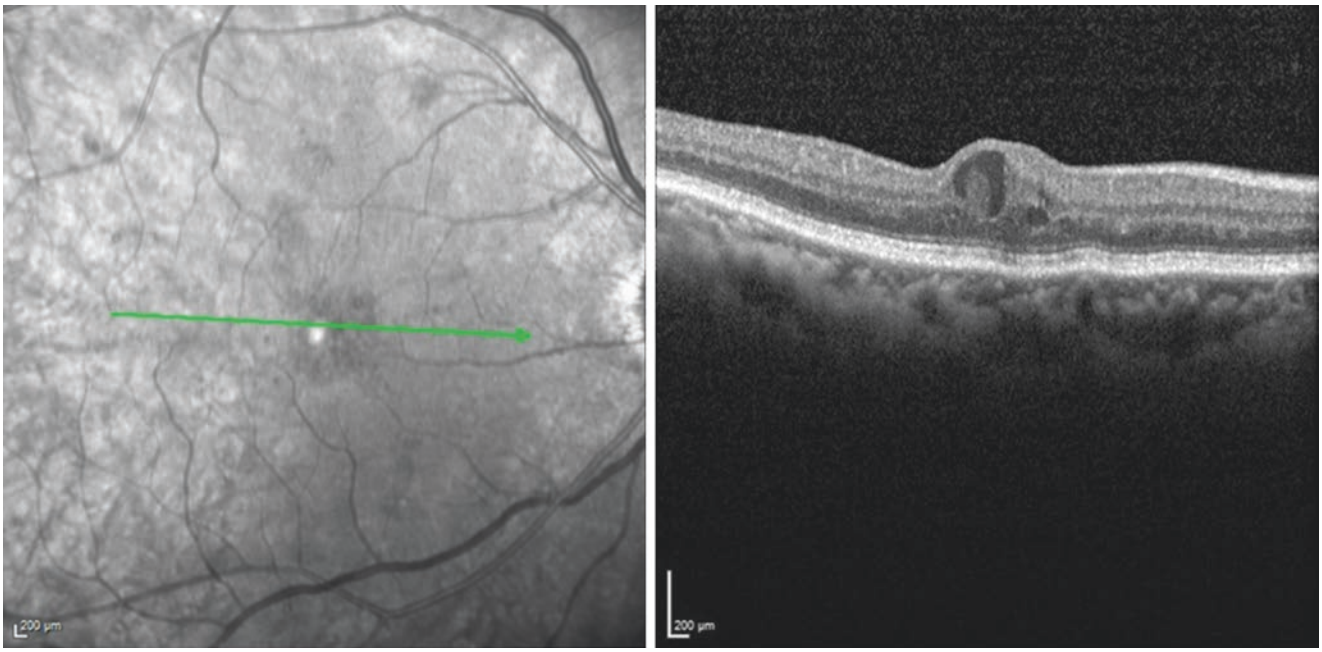

Fig. 11.12 Diabetic macular edema (DME). Spectral domain optical coherence tomography (SD-OCT) showing retinal thickening and formation of intraretinal cystic spaces involving the fovea

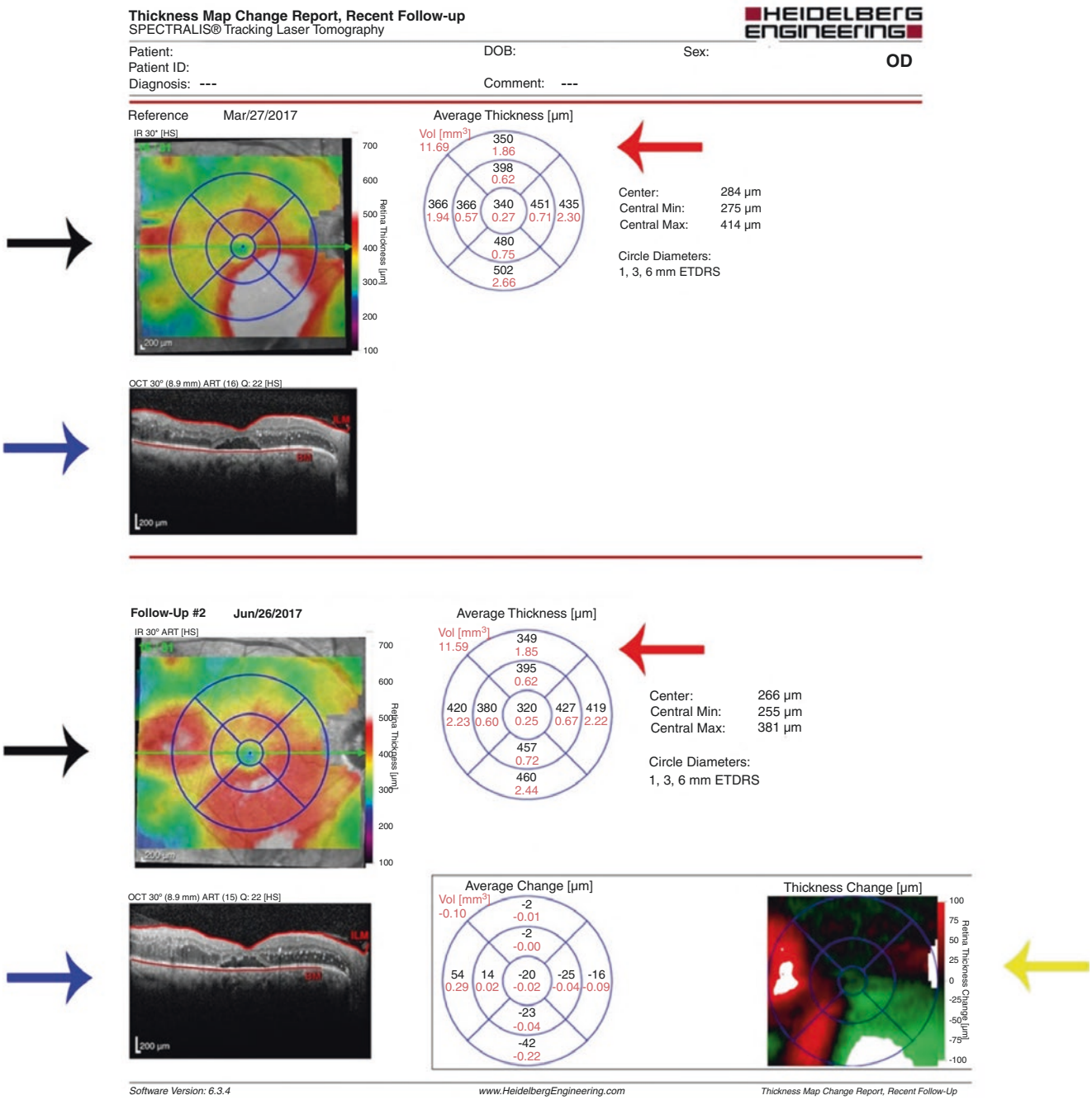

Fig. 11.13 OCT retinal thickness map. Optical coherence tomography retinal thickness map of the right eye of a patient with center involving diabetic macular edema. A 3-month follow-up scan (below) reveals a decrease in the central foveal thickness, as well as in overall volume. Blue arrows show B scans from both visits. Black arrows show color coded maps of retinal elevation. Red arrows indicate retinal thickness in the nine ETDRS sectors. Yellow arrow shows the difference in retinal thickness between both visits using ETDRS sectors and a color coded map

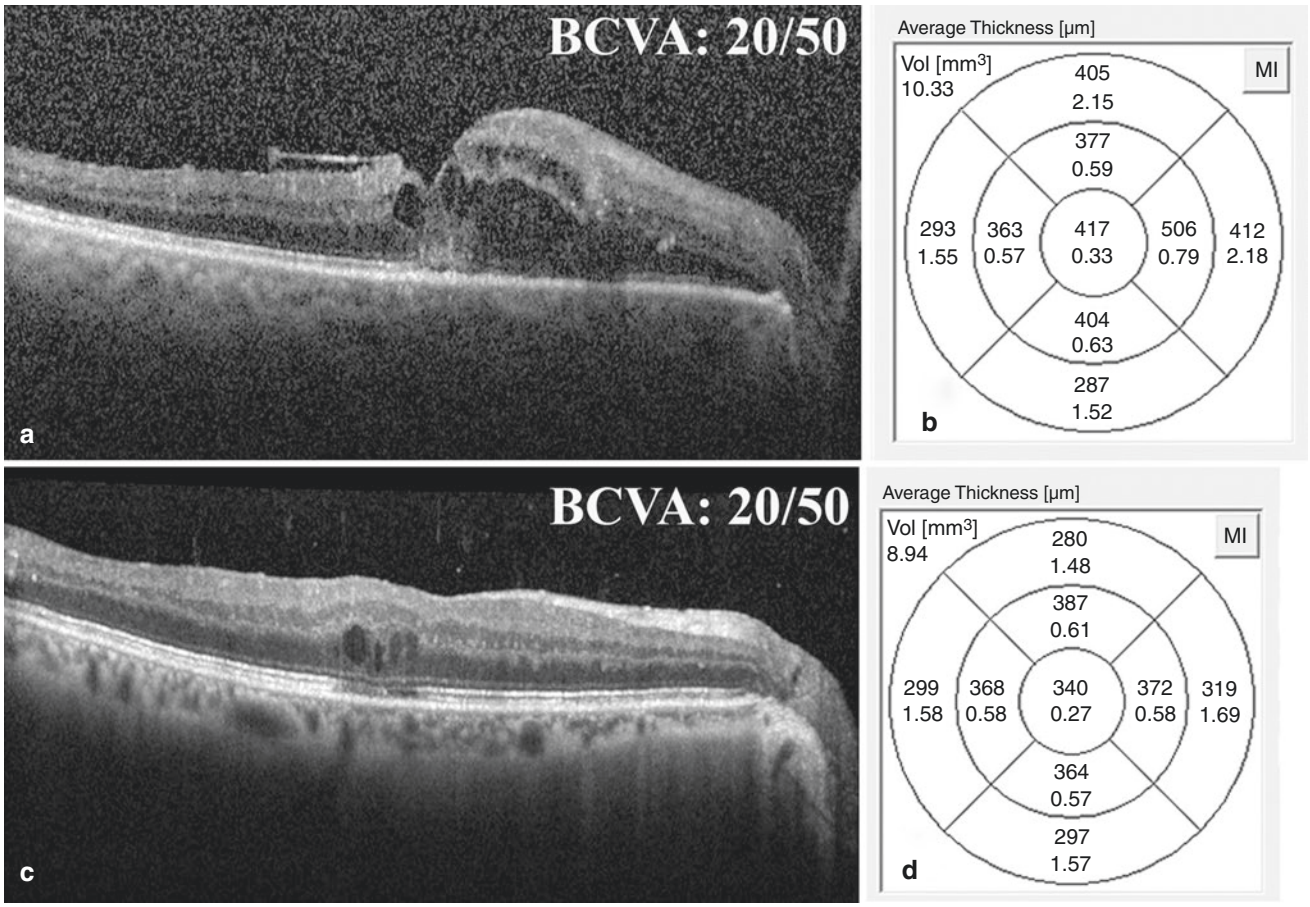

Fig. 11.14 BCVA does not correlate with retinal thickness. (**a** and **c**) SD-OCT of the right eye of two patients with DME and NPDR. (**b**) Retinal thickness map of patient (**a**). The central foveal thickness (CFT) is 417 µm and the retinal volume is 10.33 mm^3. (**d**) Retinal thickness map of patient (**c**). The CFT is 340 µm while the retinal volume is 8.54 mm^3. Both patients had a BCVA of 20/50 despite the difference in retinal thickness

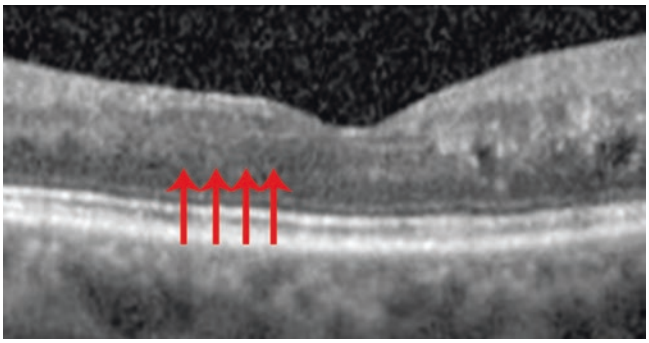

Fig. 11.15 Disorganized retinal inner layers (DRIL). Spectral domain optical coherence tomography (SD-OCT) of the right eye. There is predominant retinal thinning temporally, with clear disorganization of the inner retinal layers (DRIL) (red arrows)

Sickle Cell Retinopathy

SD-OCT is helpful in demonstrating the consequences of sickle ischemic maculopathy, even in cases that are undetectable on FA. Murthy et al. found atrophy of the inner retinal layers of patients with sickle cell retinopathy (Murthy et al. 2011). This finding was also corroborated by Witkin et al. and was attributed to the occurrence of a macular infarction as a result of an ischemic vaso-occlusive episode (Witkin et al. 2006) (Fig. 11.19). Chen et al. demonstrated preferential ischemia of the DCP in sickle cell retinopathy, which resulted in selective atrophy of the middle layers of the macula on SD-OCT (Chen et al. 2015).

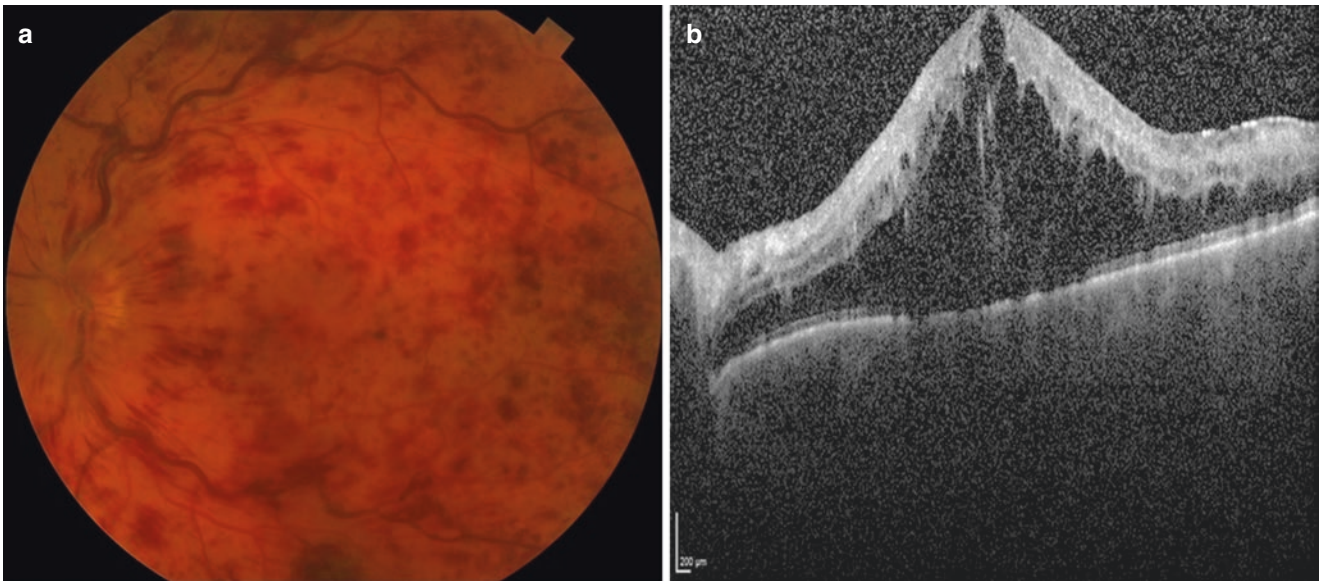

Fig. 11.16 OCT of CME in CRVO. (**a**) Fundus photo of the left eye showing markedly dilated and tortuous veins, with extensive retinal hemorrhage and cotton wool spots. The optic disc is swollen and hyperemic and the macula appears edematous. (**b**) Spectral domain optical coherence tomography (SD-OCT) showing cystoid macular edema with multiple intraretinal cysts extending from the outer plexiform layer

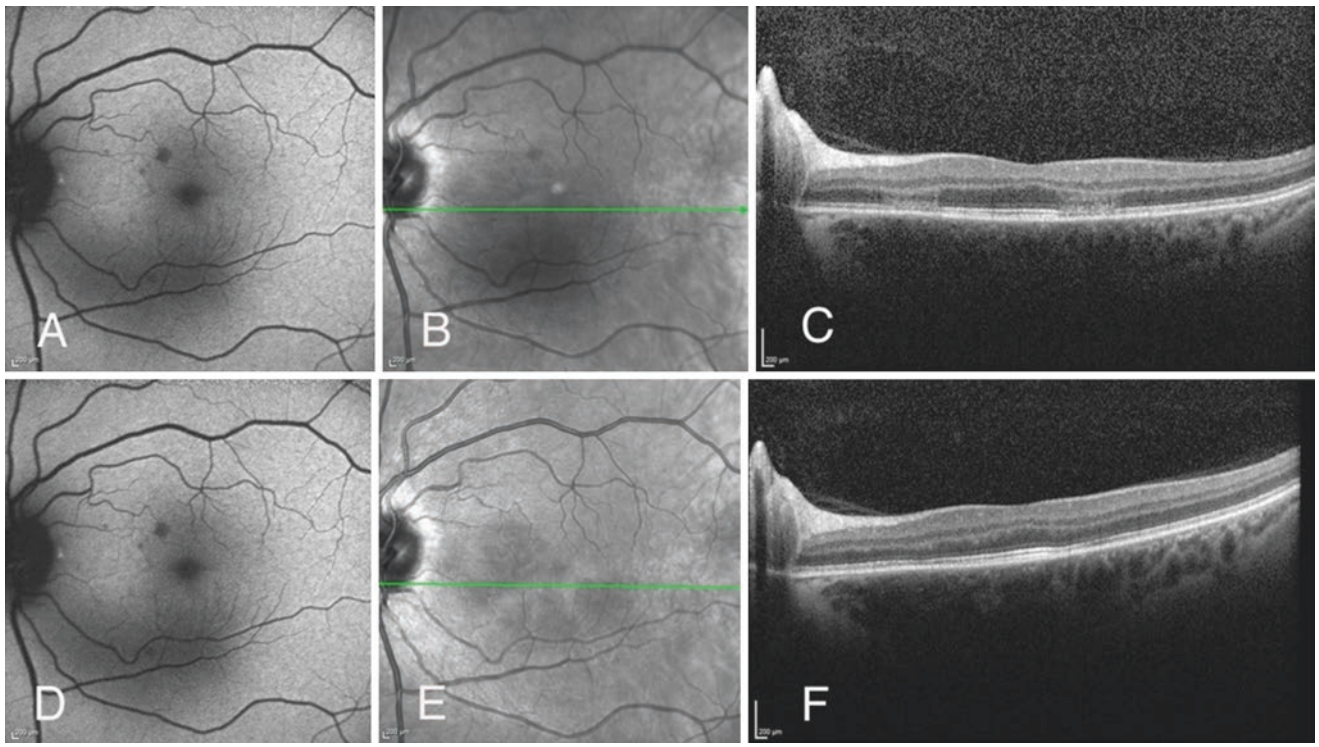

Fig. 11.17 Acute macular neuroretinopathy (AMN). (**a** and **b**) Fundus autofluorescence and infrared images of the left eye with AMN not clearly showing the hyporeflective lesions during the early phase. (**c**) Spectral domain optical coherence tomography (SD-OCT) showing hyperreflectivity of the outer nuclear layer. (**d**) FAF 1 month later with no significant change. (**e**) IR 1 month later showing a more clear image of the hyporeflective perifoveal lesions. (**f**) SD-OCT 1 month later showing marked improvement of the outer retinal layers with slight residual affection of the interdigitation zone (OS/RPE junction)

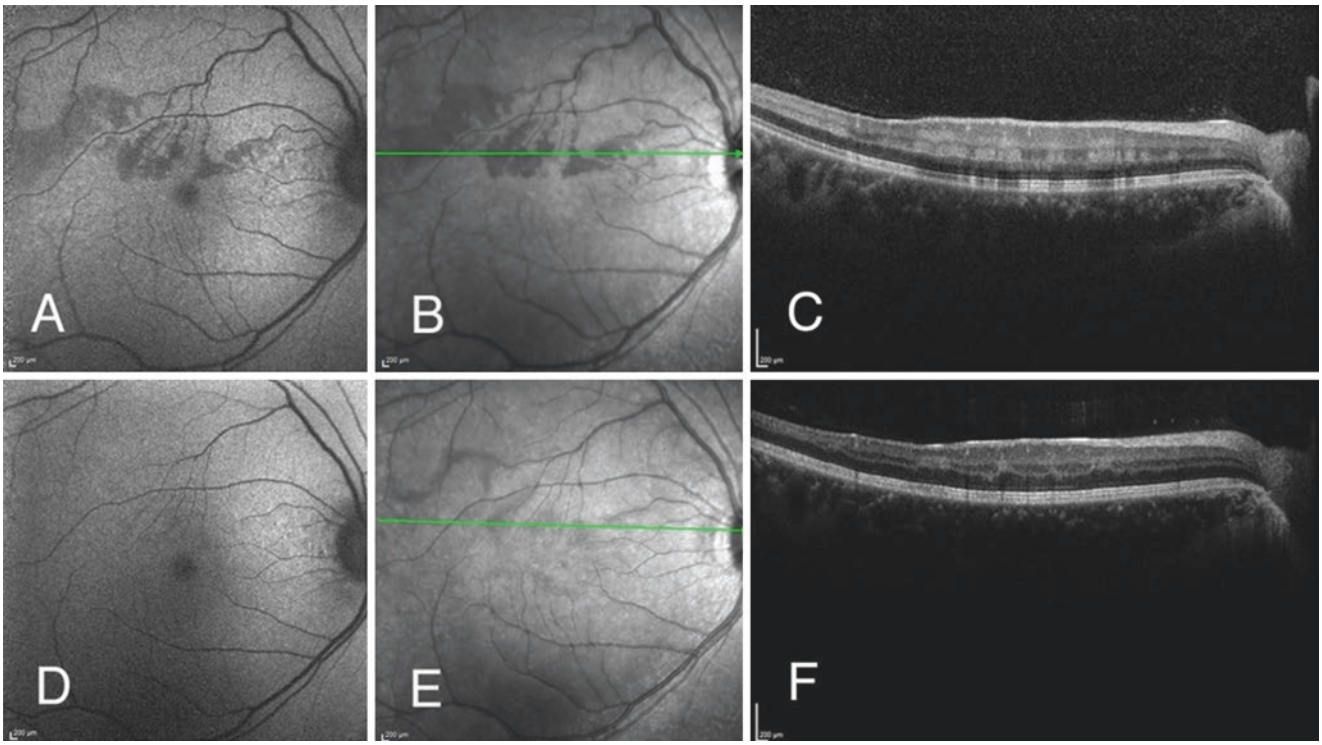

Fig. 11.18 Paracentral acute middle maculopathy (PAMM) in the setting of a small retinal branch superior vein occlusion. (**a**) Fundus autofluorescence photo of the right eye with PAMM showing areas of patchy hypoautofluorescence superior and temporal to the fovea corresponding to the swollen non-perfused area. (**b**) Infrared photograph of the right eye showing the hyporeflective perifoveal lesions. (**c**) Spectral domain optical coherence tomography (SD-OCT) showing multiple hyperreflective bands affecting the outer plexiform, inner nuclear, and inner plexiform layers. (**d** and **e**) FAF and IR 2 months later showing marked resolution of the perifoveal lesions. (**f**) SD-OCT 2 months later showing atrophy of the inner nuclear layer

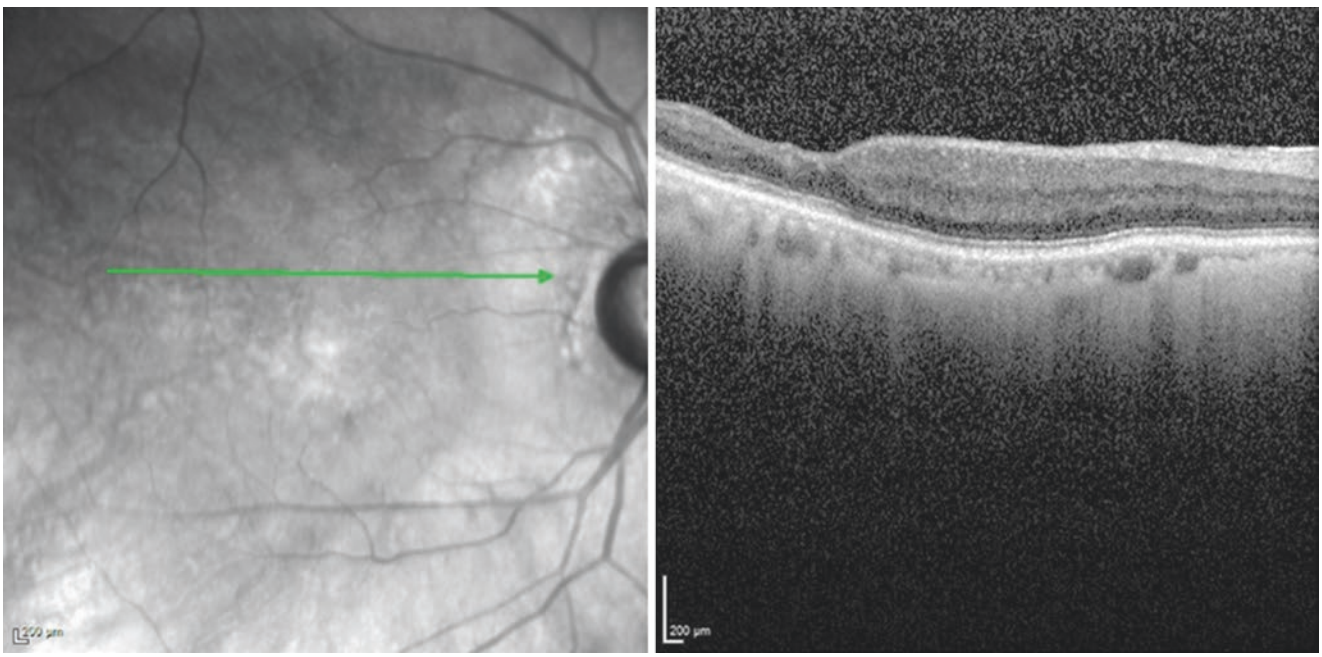

Fig. 11.19 OCT in sickle cell retinopathy. IR photo and SD-OCT of the right eye showing areas of marked inner retinal thinning superotemporal to the fovea in a patient with sickle cell retinopathy

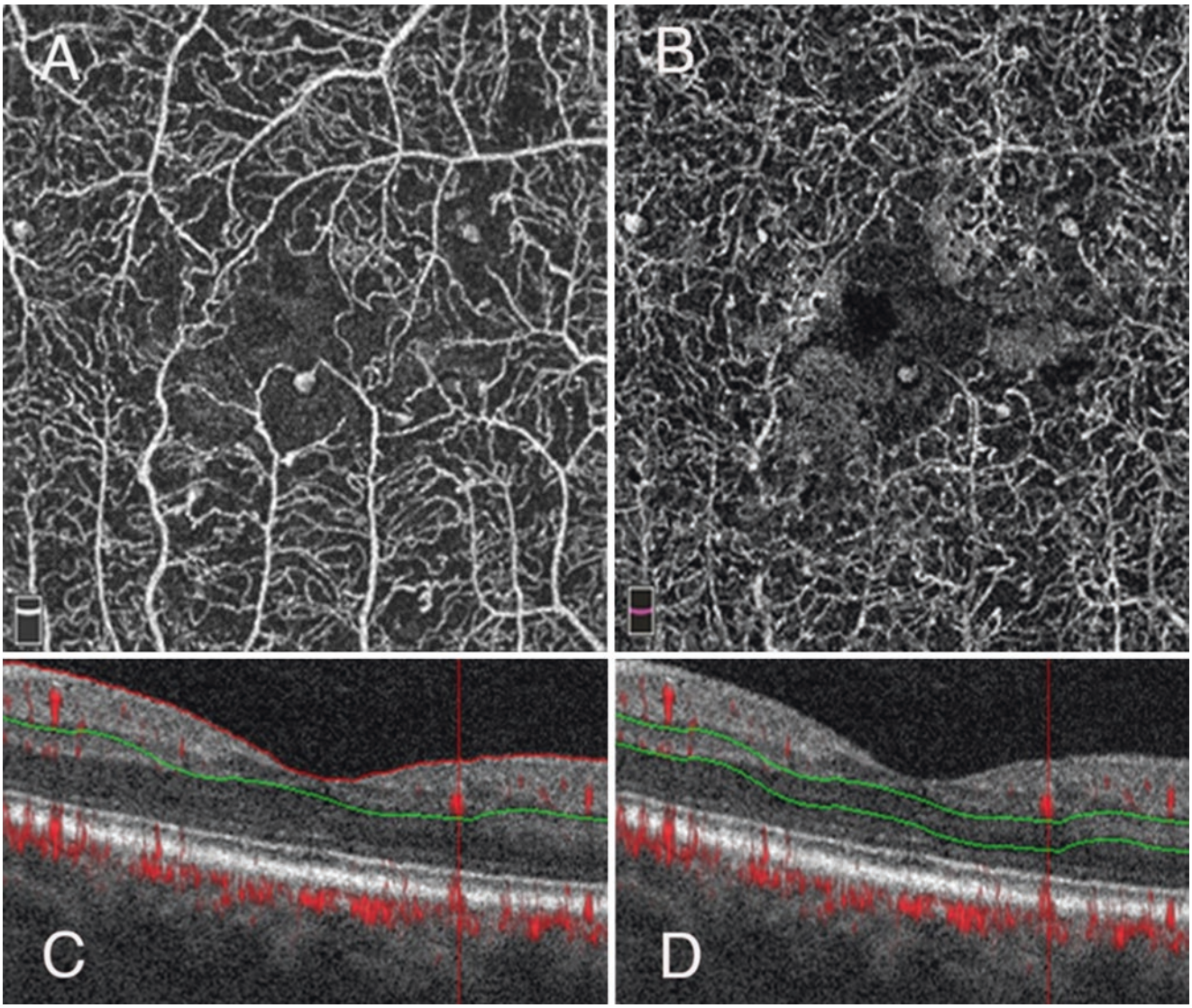

Fig. 11.20 OCTA of microaneurysms. A 3 × 3 mm OCT angiogram segmented at the superficial (**a**) and deep (**b**) retinal capillary plexus. Microaneurysms appear as multiple dilated saccules arising at the ends of capillary branches. B-scan OCTA segmented at the superficial (**c**) and deep (**d**) plexuses. Notice the microaneurysm in (**c**) at the junction between the red and green lines

Optical Coherence Tomography Angiography in Retinal Vascular Disease

Diabetic Retinopathy

In DR, OCTA shows microaneurysms as focally dilated capillaries contiguous with neighboring capillaries (Fig. 11.20). The visualization of microaneurysms can be enhanced by separating the vascular layers into SCP, MCP, and DCP, which enabled Choi et al. to determine that microaneurysms tend to be more detectable in the intermediate plexus (Huang et al. 2017; Choi et al. 2017).

OCTA is beneficial in cases where IRMAs may be confused with areas of NVE by assessing the level of these vessels with respect to the internal limiting membrane (ILM). *En Face* images of the SCP will identify IRMAs whereas images above the ILM will detect NV extending into the vitreous (de Carlo et al. 2016) (Fig. 11.21).

The advantage of OCTA over FA is that it consistently provides images that present a more accurate description of capillary non-perfusion, NV, and size of the FAZ because the image is not occluded by dye leakage (Al-Sheikh et al. 2016; Samara et al. 2017; Couturier et al. 2015). Images obtained by OCTA have the added advantage of separating

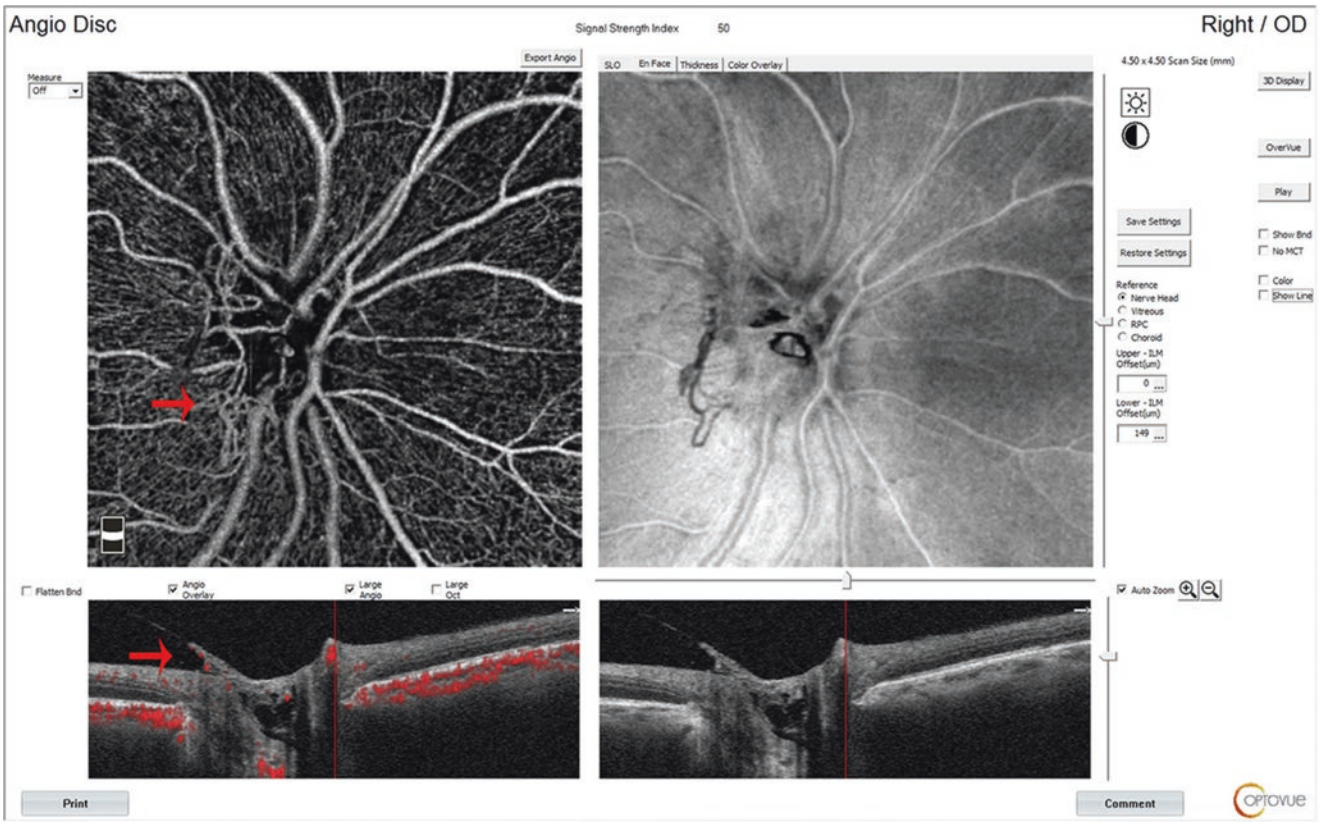

Fig. 11.21 OCTA of NVD. 4.5 × 4.5 mm optical coherence tomography angiography (OCTA) scan segmented to visualize the vessels of the optic nerve head showing areas of neovascularization (red arrow) arising along the nasal border of the optic nerve, with a B scan showing neovascularization extending to the vitreous

retinal vessels into distinct layers (up to 3 in the macular area), which allows a more thorough examination of the effect of non-perfusion in each layer.

OCTA has also been helpful in understanding the contribution of the DCP to the oxygen requirements of the photoreceptor and outer retinal layers. Scarinci et al. found areas of capillary disruption in the DCP that corresponded to photoreceptor disruption on the SD-OCT, suggesting the importance of the DCP for the metabolic demand of the photoreceptors (Scarinci et al. 2016).

Retinal Vein Occlusion

Compared to FA, OCTA has the additional advantage of demonstrating the SCP and DCP with less interference of the retinal hemorrhage and dye leakage (Rispoli et al. 2015) (Fig. 11.22). Coscas et al. determined that, in RVO, the grayish non-perfused areas and the disrupted and dilated capillary network were more frequent in the DCP than the SCP (Coscas et al. 2016). This provides evidence that retinal vein occlusion affects the deeper plexus more severely than it affects the superficial plexus.

OCTA is also effective in the evaluation of the ischemic non-perfused areas in the retina, especially those involving the macula (Cardoso et al. 2016). This can be a very important prognostic tool in the prediction of visual recovery in some cases. Both Suzuki et al. and Chung et al. found that OCTA was superior in detecting eyes with capillary non-perfusion when compared to FA because it provided higher-resolution images (Suzuki et al. 2016; Chung et al. 2017). On the other hand, OCTA cannot detect non-perfused areas in the peripheral retina which are readily picked up by wide-field FA due to limited field of view (Suzuki et al. 2016).

Iida et al. used OCTA to challenge previously reported patterns of arteriovenous crossing in cases of BRVO by documenting a higher number of cases with venous overcrossing than FA was able to detect. They also noticed more venous narrowing and macular non-perfusion in these cases (Iida et al. 2017).

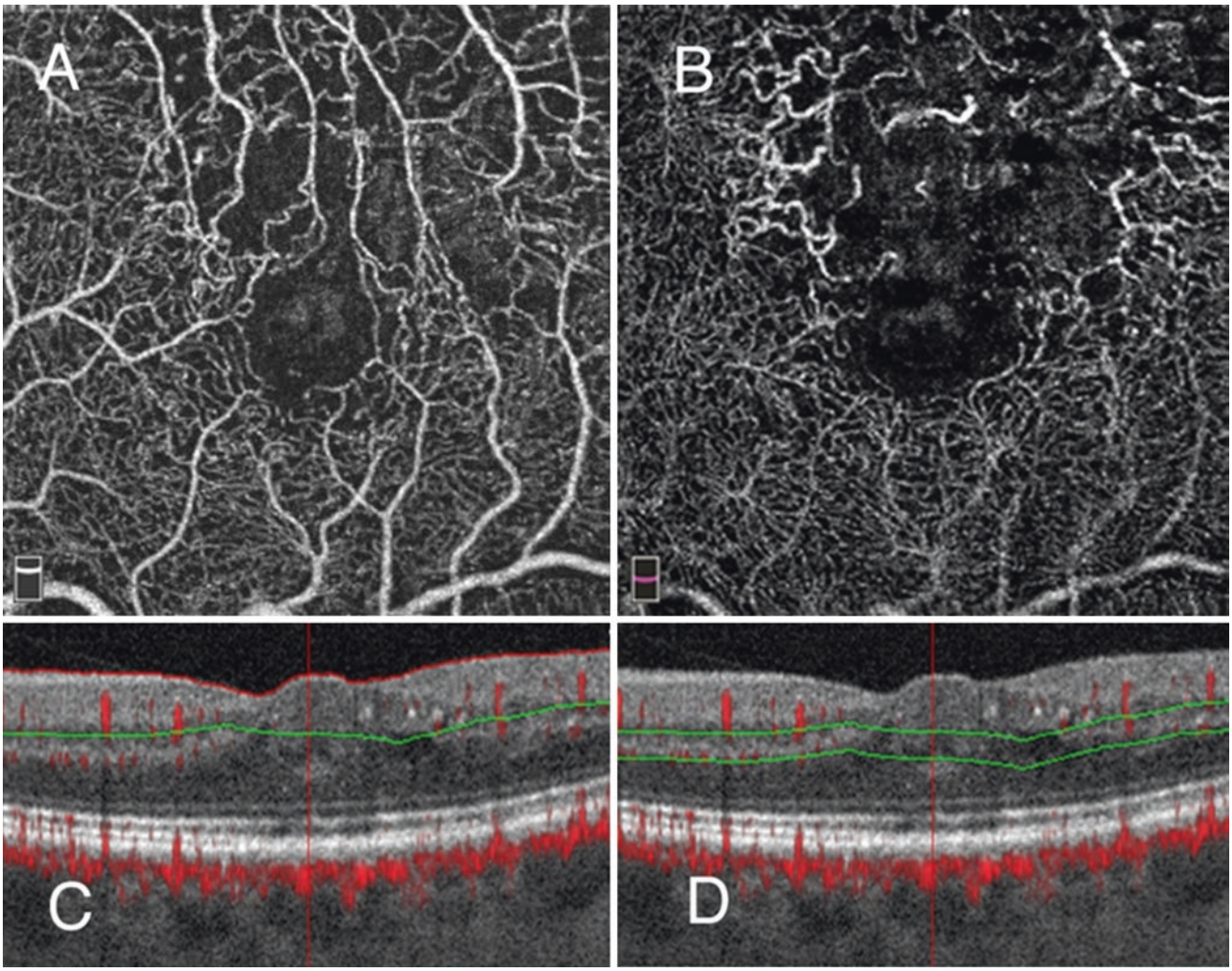

Fig. 11.22 OCTA of BRVO. 3 × 3 mm optical coherence tomography angiography (OCTA) centered around the fovea and segmented to show the superficial (**a**) and deep (**b**) retinal capillary plexuses. The vessels superior to the foveal avascular zone are enlarged and irregular and appear separated by the accumulating retinal fluid. These changes are more evident in the deeper plexus. (**c** and **d**) B scan OCTA segmented at the superficial (**c**) and deep (**d**) plexuses showing spongy retinal edema with a few intraretinal cystic spaces

Retinal Artery Occlusion

Bonini Filho et al. (2015) described areas of non-perfusion in both SCP and DCP using OCTA. de Castro-Abeger et al. determined that OCTA was superior to FA in detecting perfusion defects in the SCP. This is due to the ability of OCTA to better visualize the vasculature in areas with retinal swelling (de Castro-Abeger et al. 2015).

Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy

Patients with AMN and PAMM present with hyperreflective retinal layers, thought to represent the effect of a retinal vascular insult. This hypothesis can be validated using OCTA by demonstrating areas of DCP defects (Pecen et al. 2015) (Fig. 11.23).

Sickle Cell Retinopathy

OCTA provides high-resolution images of the ischemic changes affecting the macula, which can shed light on the prognosis of visual affection and recovery in patients with sickle cell retinopathy. Minvielle et al. identified rarefied and dilated capillaries and enlargement of the FAZ in both SCP and DCP in all their patients with sickle cell retinopathy (Minvielle et al. 2016). They also noted capillary non-perfusion in the SCP of 72.2%, and in the DCP of 27.8% of their patients. Most capillary abnormalities were located in the temporal juxtafoveal region and might extend to the superior and inferior juxtafoveal regions.

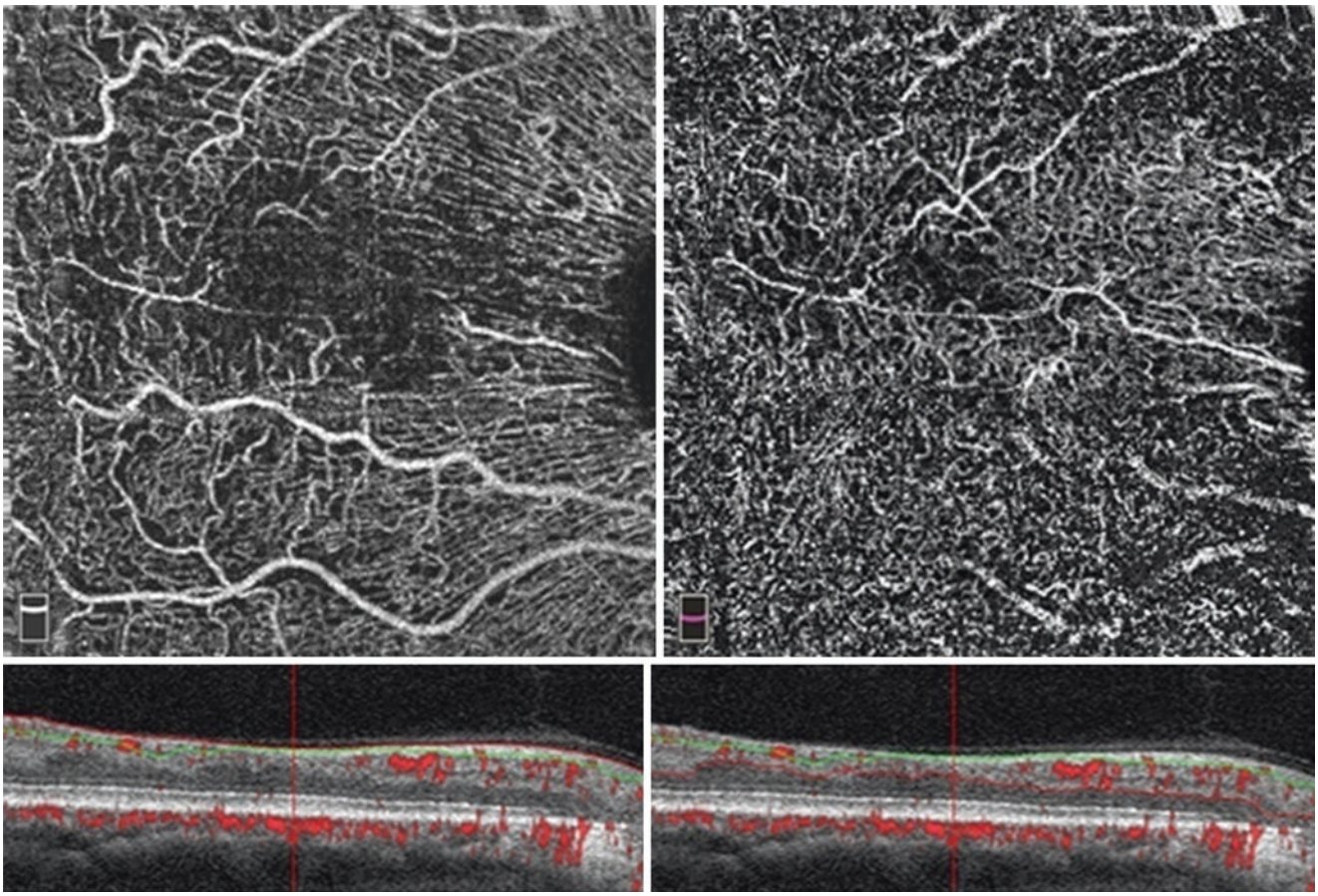

Fig. 11.23 OCTA of PAMM. 3 × 3 mm *en face* OCTA centered around a PAMM lesion temporal to the optic disc and segmented to show the superficial (left) and deep (right) retinal capillary plexuses. They show areas of capillary non-perfusion (as evident by both *en face* and flow projection) corresponding to the atrophic areas of the inner nuclear layer

In sickle cell retinopathy, OCTA can also be used to visualize abnormal NV developing at or around the optic disc as well as surrounding the macula. However, due to its limited access to the retinal periphery where most of the pathology is, wide-field FA remains superior to OCTA in the assessment of sickle cell retinopathy, especially in the proliferative stages.

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Susac's Syndrome

12

David Dao and Alan Sheyman

Introduction

Susac's syndrome is microangiopathy defined by a triad of encephalopathy, sensorineural hearing loss, and multiple branch retinal artery occlusions. First case reports appeared in the literature in 1973 (Weidauer and Tenner 1973; Pfaffenbach and Hollenhorst 1973) and in 1979, Dr. John O. Susac published reports of microangiopathy of the brain and retina in two young women (Susac et al. 1979). Since first reported in the 1970s, approximately 300 case reports have been published on the disease. Susac's syndrome most commonly affects young women and was initially only thought to affect females, however, it has been reported in males also. A recent systematic case review of all reported cases found a 3.5 to 1 female to male predominance and an average age of onset between 21 and 35 years (Dörr et al. 2013).

Diagnosis of Susac's syndrome is mainly based on presence of the characteristic clinical triad, however, many patients present with only the central nervous system, eye, or ear involvement. A review of the reported cases found that the average delay between initial symptoms and the development of the complete clinical triad was about 21 weeks, however, many patients took longer or never developed the complete triad (Dörr et al. 2013). As vision loss related to multiple branch retinal artery occlusions (BRAO) may be a presenting symptom it is important to be aware of Susac's syndrome as an ophthalmologist (Rennebohm et al. 2010). High clinical suspicion is critical for diagnosis and although treatment options are limited, early diagnosis and aggressive immunosuppressive therapy are effective in select cases.

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Etiopathogenesis

Due to the relative rarity of the disease, the pathogenesis of Susac's syndrome remains unclear. Some reports propose viral infection, hypercoagulability, and vasospasm as possible factors (Petty et al. 1998; Saw et al. 2000). The microvascular changes in Susac's syndrome appear to mimic dermatomyositis and research has suggested that Susac's syndrome is an immune-mediated vascular endotheliopathy (Jarius et al. 2009). Anti-endothelial cell antibodies have been implicated in other autoimmune syndromes such as Behcet disease, dermatomyositis, and scleroderma, where these antibodies have been shown to cause endothelial cell necrosis and C4d deposition in the microvasculature (Negi et al. 1998; Pope-Harman et al. 2003). In a study of 12 patients with Susac's syndrome, anti-endothelial cell antibodies were found in all but one of the patients with clinical features of Susac's syndrome (Magro et al. 2011). An antibody-mediated endotheliopathy supports the histologic finding of multiple retinal arterial wall plaques first described by Gass et al. (1986). The retinal arterial wall plaques were thought to arise from focal immune-mediated damage to the arterial wall that allowed the accumulation of lipids and thrombogenic material at sites of damage. Termed Gass plaques, these retinal arterial wall plaques, are distinct in appearance and pathology from other causes of BRAO such as cholesterol emboli, calcium plaques, and platelet–fibrin emboli (Egan et al. 2003). On fundoscopy, Gass plaques appear as yellow, non-refractile plaques located between arteriole bifurcations and can be either occlusive and nonocclusive (Fig. 12.1). Fluorescein angiography is critical in the diagnosis of Susac's syndrome as many patients who present with the syndrome may or may not be symptomatic (Fig. 12.2). On fluorescein angiography, Gass plaques appear with prominent small, focal arterial hyperfluorescence in areas of occlusion (Fig. 12.3) (Martinet et al. 2007; Boukouvala et al. 2014). Notably, venous and choroidal circulations are uninvolved in Susac's syndrome, which differentiates it from other autoimmune vasculopathies such as

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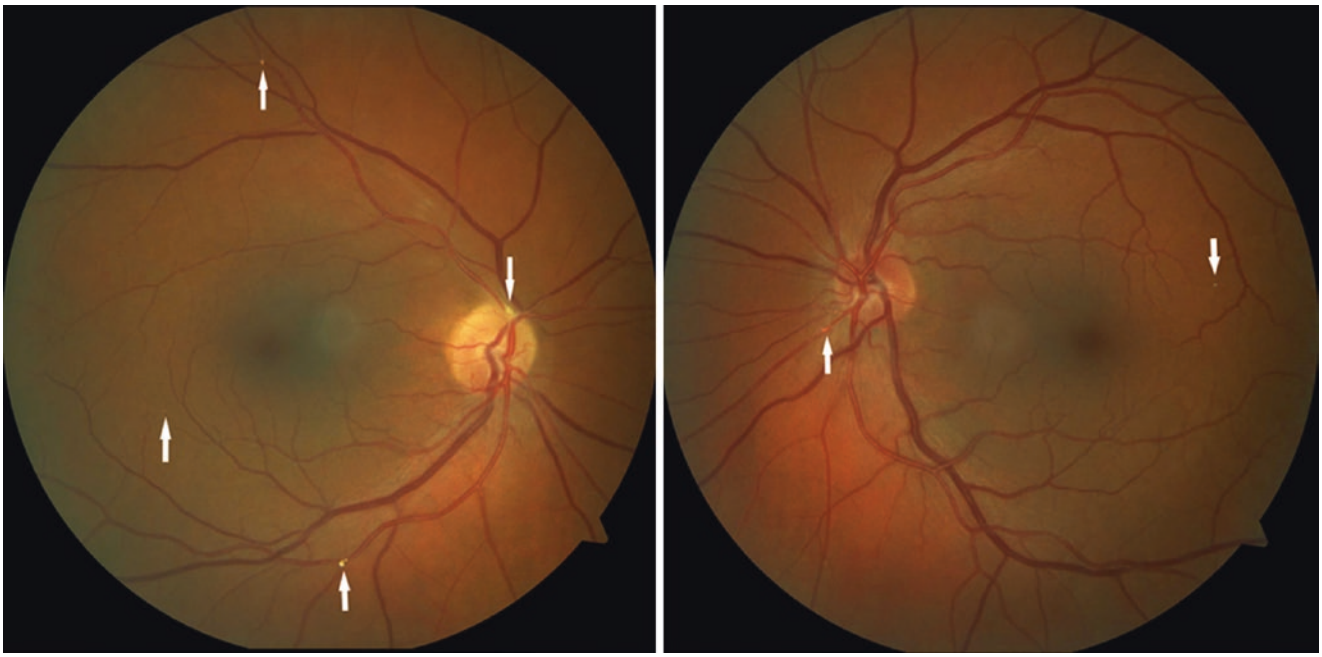

Fig. 12.1 Color fundus photo showing multiple yellow, non-refractile Gass plaques in a 57-year-old woman diagnosed with Susac's syndrome (Courtesy of Ramesh R. Shah MD, FACS, FICS)

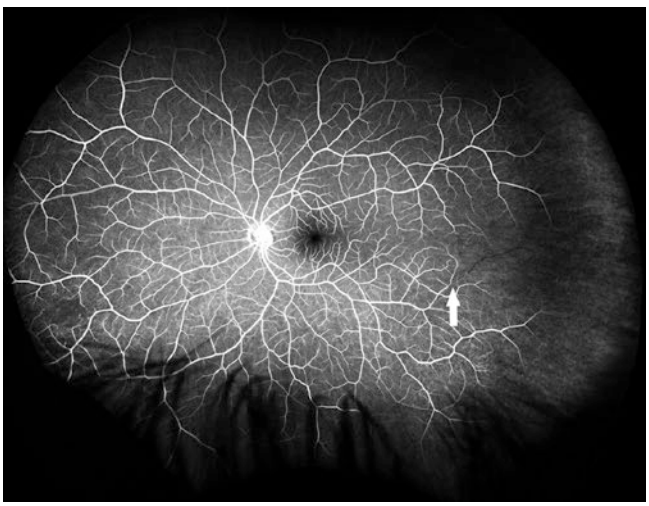

Fig. 12.2 Widefield fluorescein angiography demonstrating a branch retinal artery occlusion in the temporal periphery of the left eye in a patient with Susac's syndrome (Courtesy of Sumit Sharma, MD)

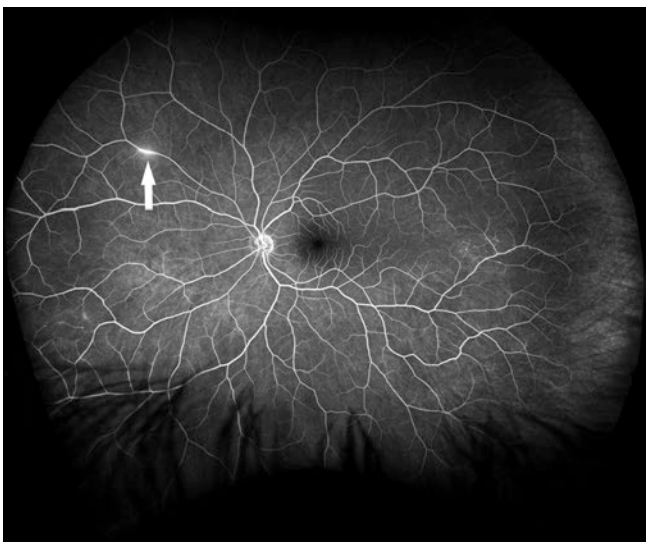

Fig. 12.3 Widefield fluorescein angiography demonstrating localized segmental wall hyperfluorescence in the left eye (Courtesy of Sumit Sharma, MD)

Behcet's disease, giant cell arteritis, and systemic lupus erythematosus (Matsuo et al. 1999; Gharbiya et al. 2006).

Clinical Features

Due to lack of serum diagnostic tests for Susac's syndrome, diagnosis is generally based on clinical suspicion and the presence of the clinical triad of encephalopathy, branch retinal artery occlusions, and sensorineural hearing loss. The most common presenting symptom of central nervous system involvement is headache following by cognitive or psychiatric changes (Vodopivec et al. 2015). Classic MRI findings show multiple T2-enhancing lesions in the white matter of the corpus callosum which is pathognomonic during the acute encephalopathic phase of Susac's syndrome (Fig. 12.4) (Demir and Case 2009; Xu et al. 2004; Susac et al. 2003). Sensorineural hearing loss has been described as occurring either acutely or later on in the disease course and

is due to arteriolar occlusion at the apex of the cochlea (Susac et al. 2007). Symptoms include difficulties with speech discrimination, vertigo, and tinnitus. Jerk nystagmus associated with vertigo may also be a sign of infarction of the vestibular system.

Vision changes such as photopsias and scotomas due to BRAO are present in a high percentage of Susac's syndrome cases (Dörr et al. 2013). However, it is important to be aware that the presence of BRAO can be a delayed manifestation of Susac's syndrome with some cases reporting the development of BRAO weeks to months after the onset of encephalopathy (Dörr et al. 2009, 2013; Susac et al. 2007). In addition, even in the absence of visual symptoms, fluorescein angiography is recommended in all patients with Susac's syndrome on the differential, as Gass plaques are frequently sub-clinical. Even in the presence of initially normal angiography, serial examinations have been recommended as Gass plaques and BRAO can present later in the course of Susac's syndrome and can serve as clinical indicators of disease progression or response to immunosuppressive therapy (Mallam et al. 2009; Egan et al. 2010).

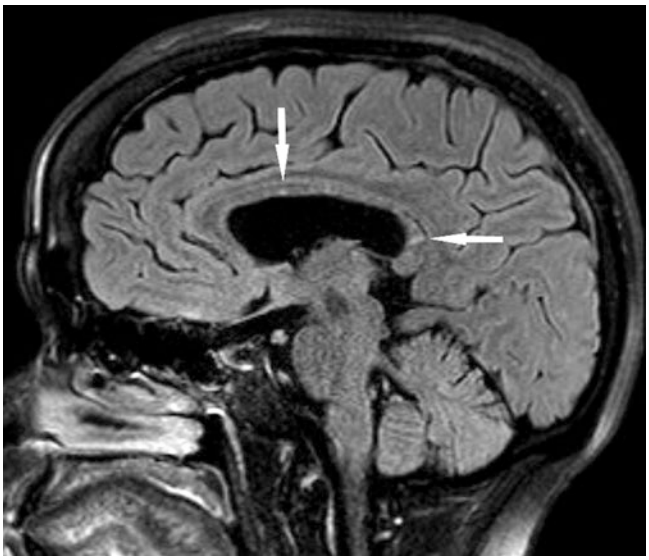

Fig. 12.4 Sagittal FLAIR MRI with hyperintensities demonstrating characteristic "snowball" and "spoke" lesions of the corpus callosum in a patient with Susac's syndrome (Courtesy of Sumit Sharma, MD)

Optical coherence tomography (OCT) has been used in several studies of Susac's syndrome to monitor retinal nerve fiber layer (RNFL) thinning due to branch retinal artery occlusions and serve as an aid in differentiating multiple sclerosis from Susac's syndrome (Fig. 12.5) (Bernard et al. 2014; Brandt et al. 2012). Recent developments in OCT angiography also provide additional diagnostic options for the evaluation of retinal ischemia in the deep capillary plexus from branch retinal artery occlusions in Susac's syndrome (Spiess and Martínez 2017).

Management

While data on the clinical course of Susac's syndrome is limited by the rarity of the disease, current evidence suggests that there are two major modes of the disease course: monocyclic and polycyclic (Dörr et al. 2013; Rennebohm et al. 2008a). In a review of all published cases, approximately

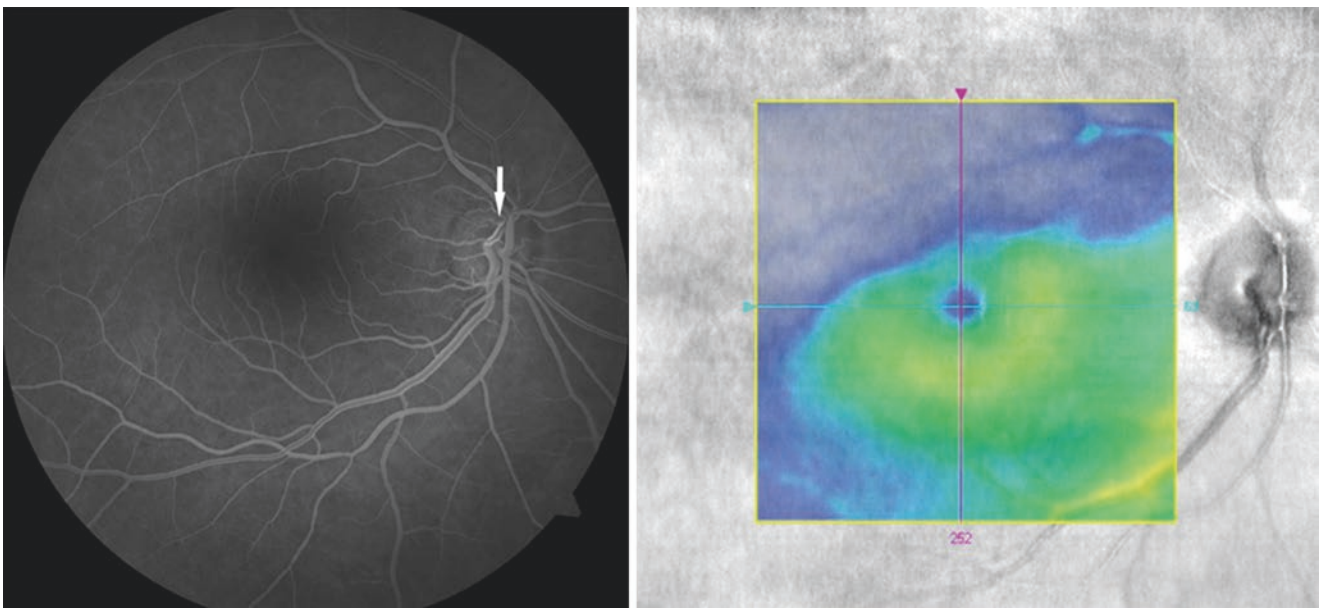

Fig. 12.5 Fluorescein angiography demonstrating delayed filling of the superotemporal arcade from an occlusive Gass plaque and corresponding thinning of the superior macula on optical coherence tomography (Courtesy of Ramesh R. Shah MD, FACS, FICS)

Table 12.1 Conventional combination treatment of Susac's syndrome

Medication	Dosage	Length	Notes
IV Methylprednisolone	1 g/100 ml D5W over 2 h	Three pulsed doses 20–24 h apart	Slow oral prednisone taper starting at 60–80 mg/day
Intravenous immunoglobulin (IVIG)	2 g/kg	Every 4 weeks for a total of six treatments	For more severe disease, can increase to every 2 weeks for the first 1–2 months
IV Cyclophosphamide	0.5–1 g/m^2 BSA	Induction monthly for 6–7 pulses Maintenance pulse every 3 months after induction	Alternatively, mycophenolate mofetil can be used for induction and maintenance Recommend addition of methotrexate if mycophenolate mofetil is used

Adapted from Rennebohm et al. (2008b)

54% of patients had monocyclic and 42% had polycyclic disease (Dörr et al. 2013). A small percentage of cases (4%) appeared to have a possible chronic-continuous manifestation of Susac's syndrome, however, the clinical significance of these cases is unclear. The active phase of the disease appears to last around for 2 years. Interestingly, the presence of encephalopathy along with hearing loss and BRAO during the active phase appears to be associated with the monocyclic (encephalopathic) form of the disease. Patients with Susac's syndrome who present with only BRAO and/or hearing loss without developing encephalopathy within 2–3 years tend to follow a polycyclic course with recurrent BRAO and hearing loss (Dörr et al. 2013).

Treatment of Susac's syndrome is currently based on pathogenic similarities to the microvascular endotheliopathy found in juvenile dermatomyositis (Magro 2005). Due to the rarity of the disease, there are limited data on which to draw treatment guidelines. Immunosuppressive therapy is the mainstay of treatment, however, reported responses have been variable and in many cases it is unclear whether improvement is due to therapy or spontaneous remission (Tashima et al. 2001; Aubart-Cohen et al. 2007). Current consensus recommends early aggressive immunosuppressive therapy to prevent disability during the active phase of the disease, especially when encephalopathy is present (London et al. 2016; Vodopivec and Prasad 2016). The treatment protocol recommended by Rennebohm et al. consists of a combination of high dose IV methylprednisolone, oral prednisone, and IVIG during the first week of treatment following by chronic maintenance with cyclophosphamide or mycophenolate mofetil and methotrexate to prevent recurrence (Rennebohm et al. 2008a, b). The authors also suggest the addition of low-dose aspirin but do not recommend anticoagulation (Table 12.1). Recommendations for the treatment of the polycyclic form differ as the chronicity of this form of Susac's syndrome requires long-term immunosuppressive therapy to maintain remission as recurrent episodes can lead to permanent vision and hearing loss.

Treatment response should be monitored closely clinically using repeated brain MRI. Eye examinations should be performed routinely even after remission has been achieved. There is no definitive way to differentiate the monocyclic and polycyclic form of Susac's syndrome and recurrence has been reported as long as 18 years after remission (Petty et al. 2001). Based on a review of all reported cases, the average number of recurrences was 2.4 per patient and males were more likely to have the monocyclic form (Dörr et al. 2013). Vodopivec et al. recommend maintenance immunosuppressive therapy for at least 2 years after remission, however, there are no clear guidelines (Vodopivec et al. 2015). Monitoring for recurrent BRAO with fluorescein angiography, visual fields, and multifocal electroretinography can be sensitive indicators for recurrence and can guide long-term treatment (Xu et al. 2004; Mallam et al. 2009; Förl et al. 2007).

Acknowledgments and Attributions

Figures 12.2, 12.3, and 12.4 contributed by Sumit Sharma, MD at Cole Eye Institute at the Cleveland Clinic.

Figures 12.1 and 12.5 contributed by Ramesh R Shah MD, FACS, FICS

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Artificial Intelligence in Retinal Vascular Imaging

13

Ursula Schmidt-Erfurth, Sophie Riedl, Martin Michl, and Hrvoje Bogunović

Introduction

Artificial intelligence (AI) has flourished in the last decade due to the emergence of *deep learning*, a class of *machine learning* algorithms dedicated to building large artificial neural network models capable of learning through exposure to large amounts of data. Ophthalmology, and especially retinal science, are at the forefront of AI applications in medicine, with a fully autonomous AI image-based diagnostic system that has recently been approved by the FDA as a first of its kind in medicine (Abramoff et al. 2018; Topol 2019).

The potential and ability of AI in retina was prominently displayed in Gulshan et al. and Ting et al., where they showed that a deep learning network can be successfully trained from a large dataset to grade diabetic retinopathy (DR) stages from color fundus photographs (CFP) at the level of a board-certified ophthalmologist (Gulshan et al. 2016; Ting et al. 2017). By improving the reference standard used for tuning the model, the performance was further increased to be at the level of retinal specialists (Krause et al. 2018). A similar performance of AI at the level of a specialist was demonstrated in performing a referral recommendation based on optical coherence tomography (OCT) scans (De Fauw et al. 2018; Kermany et al. 2018). Finally, a prospective clinical trial showed that AI can fully autonomously screen for referable DR from CFP with a high performance (90% specificity, 87% sensitivity; see section "Diabetic Retinopathy") (Abramoff et al. 2018).

Retinal imaging, achieved with noninvasive and fast imaging modalities, provides the necessary context for AI models to learn to make a diagnosis. The methods of AI-based retinal image analysis are diverse and allow wide applicability in different retinal diseases. The overall potential includes screening, diagnostic grading as well as guidance of therapy by automatically detecting disease activity, recurrence, and measuring therapeutic effects (Schmidt-Erfurth et al. 2018).

Retinal vascular imaging provides a direct, noninvasive observation of the circulation. Retina's function makes it a tissue with a high metabolic rate, needing a dual vascular supply where the choroid supplies the outer retina, and the retinal vessels supply the inner retina and midretina, and being particularly susceptible to interruptions in blood supply. Thus, both ophthalmic and systemic vascular conditions can present themselves in the retina (Abramoff et al. 2010) and consequently the ability to analyze the retinal vasculature with AI is of great interest.

In this chapter, we review prominent examples of applying AI in image analysis that involves the retinal vasculature, demonstrating the huge potential this technology has to offer. After giving an overview of technical aspects of state-of-the-art AI methods in section "AI in Retinal Imaging: Technical Aspects", we highlight relevant clinical applications in section "Clinical Applications". Various imaging modalities are considered, from fundus photos to OCT and OCT angiography (OCT-A).

AI in Retinal Imaging: Technical Aspects

The power of deep learning is manifested in its ability to learn from a set of examples with the association of raw image data and the desired output, e.g., a diagnosis. This so-called *end-to-end learning* avoids the need to first specify and extract a set of predefined measurements of interest from the image, which has been the main paradigm of the traditional machine learning approaches. The deep learning architecture found to be most suitable for imaging data is that of a convolutional neural network (CNN). CNN encodes properties into the network that are inspired by the mammalian visual cortex. Such a network applies a mathematical image filtering operation known as convolution, emulating

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neuronal response to visual stimuli. The network processes the input image with successive layers of convolutional filters, obtaining multiple levels of image representations that gradually progress from capturing low- to high-level concepts. In the process of training, these filters defined by the network's weights are being adjusted in order for the network to achieve the specific task it is being trained for. Thus, trained with a large set of examples in a well-defined task, CNNs can learn to effectively recognize visual patterns.

The ability to learn directly from raw images offers a huge advantage over traditional machine learning approaches, but it also presents a drawback. Mainly, the obtained neural network model acts as a "black-box." It is thus of importance to be able to interrogate the model to understand what visual features the model is relying on to solve the task. This is important for three reasons: First, to verify that the model is not exploiting an image artifact; second, to build trust when the features used are clinically supported, and lastly, to be able to learn from AI and generate new hypotheses, when it is able to solve tasks that humans are incapable of (e.g., predicting chronological age from fundus photos). Typically, the interpretability is achieved in the form of an overlaid heatmap, where the regions of the image responsible for a particular diagnosis are highlighted. A recent study by Sayres et al. 2019 on using AI for supporting DR screening showed that experts using such an interpretable model perform better than either the model or the experts alone (Fig. 13.1) (Sayres et al. 2019).

Two dominant AI-based image analysis paradigms are image *classification* and image *segmentation*. The first paradigm is used when an image is associated with a single label, typically a diagnosis or a disease stage (Fig. 13.1). The second paradigm is used when pixels in the image are associated with a label. This is typically applied to detect vessels (Fig. 13.2) or lesions in an image, in order to measure and quantify their shape and appearance.

Classification and segmentation are examples of *supervised learning*, where the training consists of a set of annotated and labeled examples. In contrast, *unsupervised learning* does not require the annotated labels as it aims at learning the structure in the data to identify main groups or clusters of imaging patterns. In both cases, data for learning and evaluation is first split into training, validation, and test sets. The training set is used to adjust the neural network weights in order to solve the task of interest. A validation or tuning set is used to adjust the parameters of the network, like its depth, size, and learning characteristics. Once the network's weights and parameters are fixed, the test set serves to evaluate its performance on a previously unseen dataset.

Fig. 13.1 Illustration of experimental conditions: (left) unassisted, (center) grades only, and (right) grades plus heatmap (Reproduced from Sayres et al. 2019)

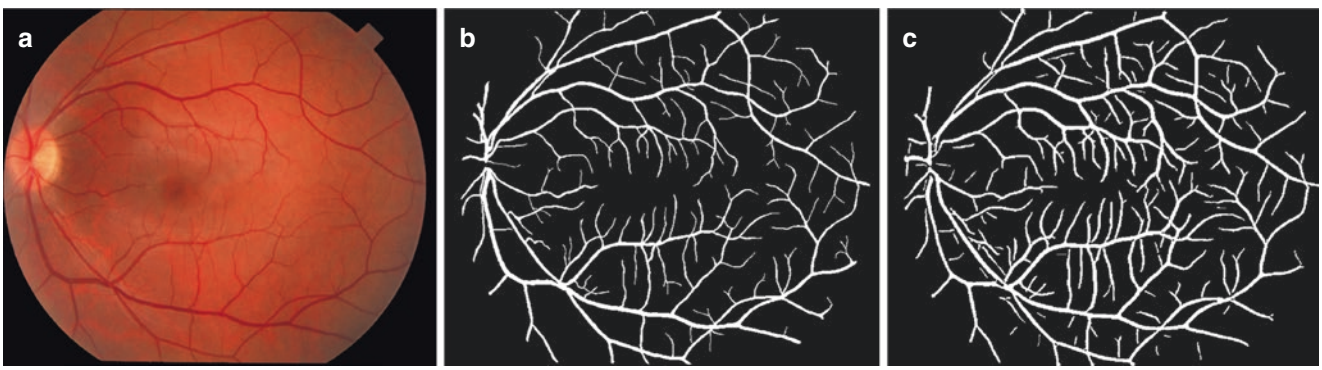

Fig. 13.2 Retinal vessel segmentation. (**a**) Color fundus image, (**b**) manual segmentation, and (**c**) automated segmentation (Reproduced from Memari et al.)

Clinical Applications

Structural Assessment of the Retinal Vasculature and Vessel-Based Prediction of Systemic Disease

Depth Resolved Vascular Imaging: Optical Coherence Tomography Angiography

Optical Coherence Tomography Angiography (OCT-A) presents the most recent addition to the diagnostic armamentarium in ophthalmic imaging. Unlike fluorescein angiography, OCT-A has the advantage of being quick and non-invasive. It allows the visualization of individual vascular networks in a three-dimensional cross-sectional manner and is amenable to automated analysis.

Commercial instruments generate images in an en face view of so-called slabs. Default settings compile a sequence of slabs, each slab offering visualization of vessels between predefined retinal layers, based on automated layer segmentation. The type of technical approach to layer segmentation depends on the instrument manufacturer. OCT-A furthermore relies on automated algorithms dealing with the removal of various imaging artifacts, such as projection artifacts caused by the inner retinal layers (Spaide et al. 2018). By these means, OCT-A offers—for the first time—in vivo visualization of 2–4 distinct capillary plexuses, in line with histologic studies: the superficial vascular plexus, intermediate capillary plexus, deep capillary plexus, and the radial peripapillary capillary plexus. Furthermore, OCT-A has enabled visualization of the respective interconnecting layers (Figs. 13.3 and 13.4) (Campbell et al. 2017).

In addition to regular retinal vasculature, OCT-A is capable of detecting choroidal neovascularization (CNV), the hallmark of neovascular age-related macular degeneration and complicating feature of numerous other retinal diseases. The clinical assessment of OCT-A images is above all a qualitative one. Nevertheless, efforts have been underway to enable an automated, quantitative analysis. Projection artifacts and segmentation errors present the main challenges in this respect. Automated quantification of CNV has been achieved by several approaches. Advanced unsupervised machine learning techniques applying cluster analysis, showed promising results, especially regarding the lesions' boundaries (Fig. 13.5) (Xue et al. 2018). OCT-A has entered clinical practice and research. Efforts in automated image analysis will definitely consolidate the role OCT-A plays in retinal imaging.

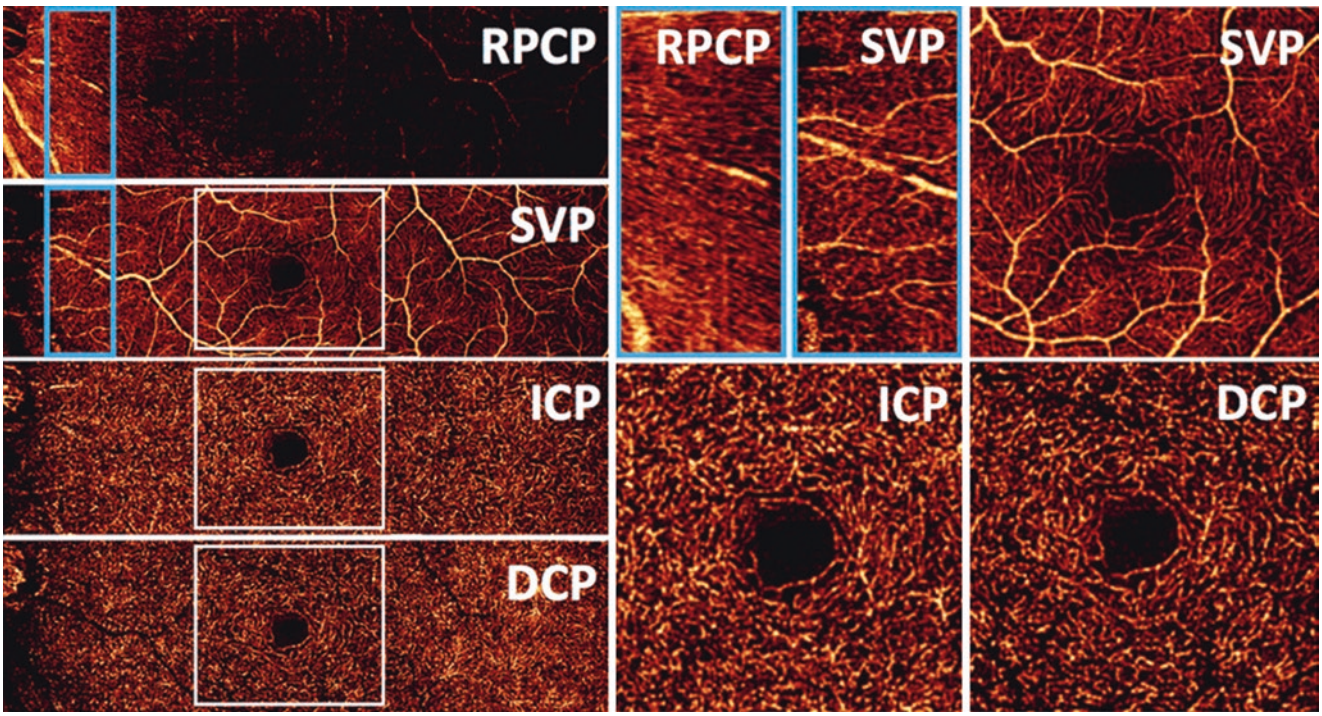

Fig. 13.3 *En face* projection-resolved OCT angiograms of the four retinal vascular plexuses in a healthy subject. Angiograms are formed by the montage of four 2 × 2 mm scans. The radial peripapillary capillary plexus (RPCP) is found in the nerve fiber layer slab. The superficial vascular plexus (SVP) slab was predominantly located in the ganglion cell layer, and was segmented as the inner 80% of the ganglion cell complex (GCC), defined as nerve fiber + ganglion cell + inner plexiform layer, excluding the nerve fiber layer. The intermediate capillary plexus (ICP) was segmented between the outer 20% of the GCC to the inner 50% of the inner nuclear layer. The deep capillary plexus was segmented between the outer 50% of the inner nuclear layer and the outer plexiform layer. High magnification images are presented at the right, from corresponding sections indicated with white squares (Reproduced from Campbell et al.)

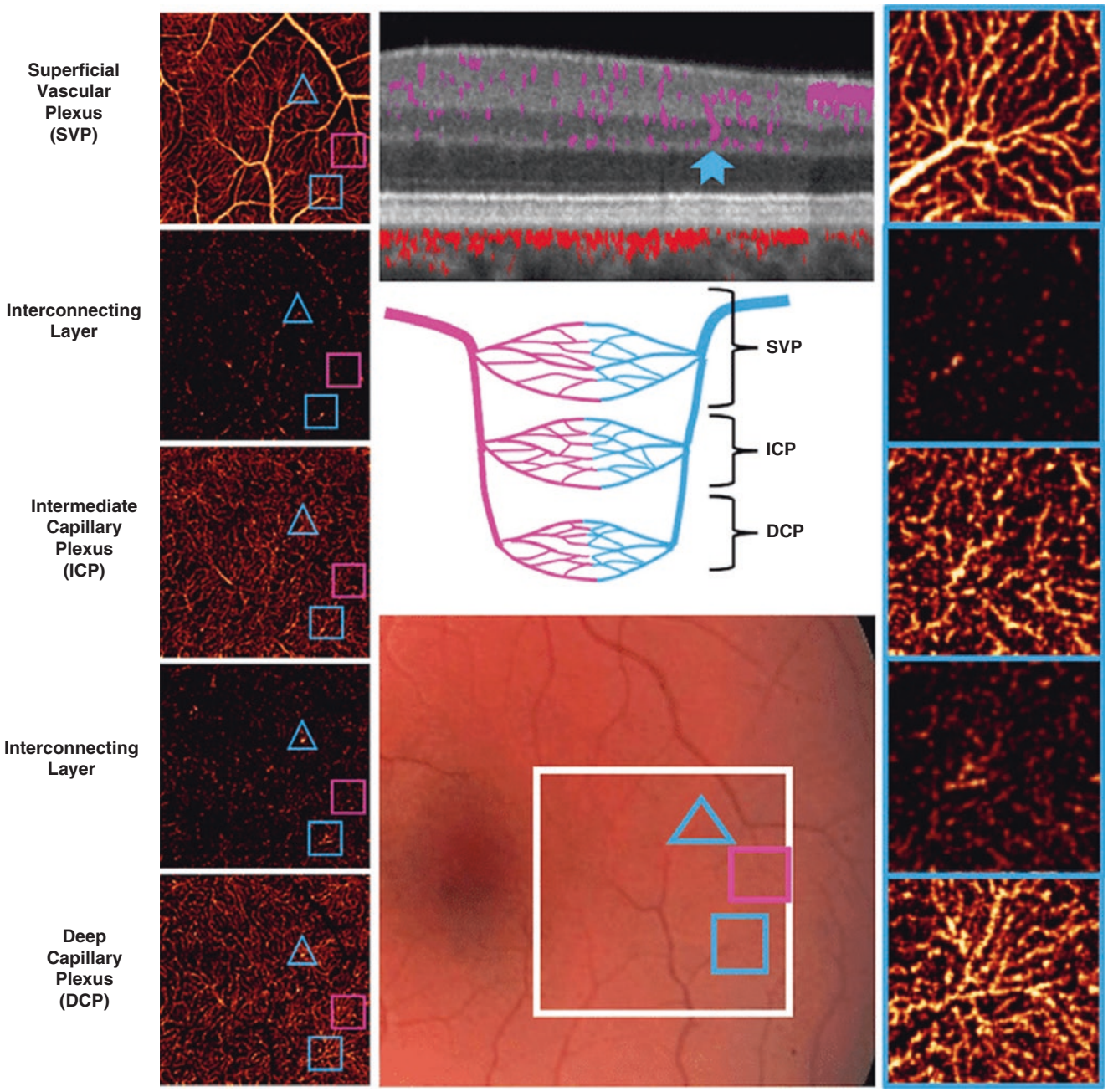

Fig. 13.4 Retinal vascular plexuses and interconnecting layers in the macula. Color fundus photograph (middle bottom panel) demonstrates the 2 × 2 mm region of scan (white square). The *en face* PR-OCTA (left panels) are arrayed from superficial on top to deep at the bottom. The blue hollow triangles enclose a diving venule (identified on color fundus photograph) that can be seen in the cross-sectional PR-OCT (middle top panel) traversing from the SVP to the DCP (blue arrow). The hollow pink squares enclose a diving arteriole that can be seen in the SVP, ICP, DCP, and the interconnecting layer between the ICP and the DCP. The hollow blue squares enclose a diving venule that is clearly seen in all magnified *en face* PR-OCTA slabs (right panels). This venule gives rise to a radiating network of capillaries in all three plexuses. The cartoon (center panel) depicts the anatomical relationships between arterial and venous systems in the three vascular plexuses and the interconnecting layers (Reproduced from Campbell et al.)

Vessel Characterization by Means of Color Fundus Photography

Leaving aside the latest developments in the field of OCT-A, clinical, and scientific assessment of the retinal vasculature has been a domain of color fundus photography (CFP). As vascular abnormalities in various diseases are specific to either arteries or veins, the classification of vessels into these subtypes is a further prerequisite for automated, large-scale image analysis following the milestone of automated segmentation of retinal vessels (outlined in the section "AI in Retinal Imaging: Technical Aspects").

Fig. 13.5 Projection resolved en face outer retina angiogram on the left. Performance evaluation of the unsupervised machine learning (middle) and the saliency (right) method for extracting CNV vessels. Blue arrows point at positions that saliency method cuts the full length of vessels at boundaries, whereas, the unsupervised system recognize the boundaries well (Reproduced from Xue et al.)

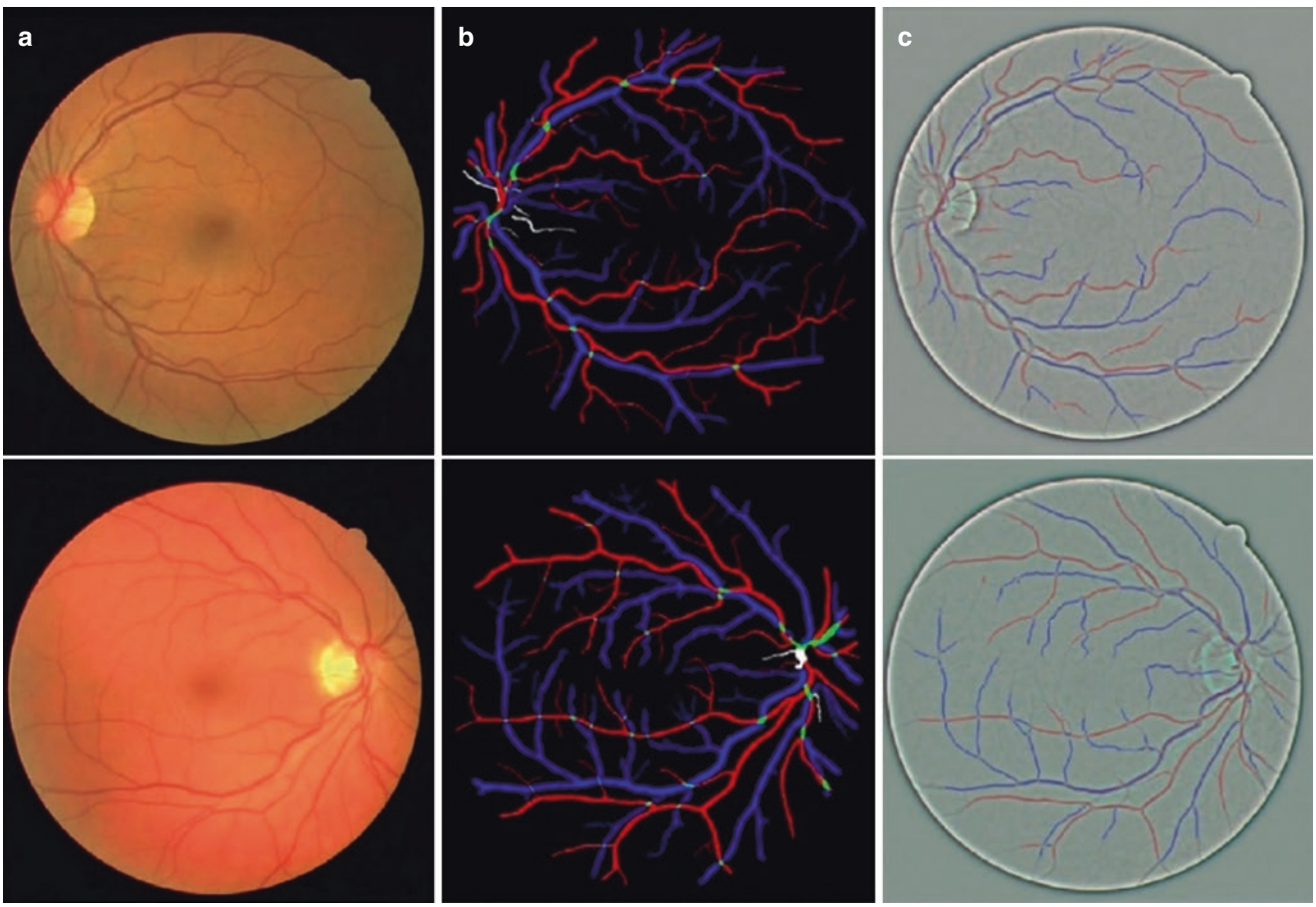

Fig. 13.6 Sample classification results. (**a**) Original fundus images. (**b**) Truth images from human experts. (**c**) Automatic classification results (Reproduced from Xu et al.)

Differences in background color between the center and periphery of images due to inhomogeneous illumination present one of the challenges tackled by preprocessing. In tree-based (e.g., graph-based) approaches, retinal vessels are segmented into biological trees and then classified into an arterial and venous tree, depending on the type of each intersection point throughout the image (Dashtbozorg et al. 2014). An inherent downside to this approach is the risk of mislabeling an entire tree due to a single misclassification. Feature-based, pixel-wise approaches, on the other hand, are based on colorimetric and geometric differences between arteries and veins (Fig. 13.6). Such features, extracted as the

basis for subsequent vessel classification, commonly include properties related to vessel width, central light reflex (mainly in arteries), color and texture (such as boundary sharpness and coarseness within vessels) (Xu et al. 2017). In more complicated feature sets, that include a large number of properties, advanced feature selection procedures for machine learning, (e.g., as genetic algorithms) may be applied (Fig. 13.7) (Huang et al. 2018).

Retinal Vessels: Markers of Cardiovascular Disease

Retinal fundus images and vascular changes, in particular, are known to contain markers of cardiovascular diseases, such as hypertension, arteriosclerosis, cerebral small vessel disease, and diabetes (Cheung et al. 2011; Doubal et al. 2010; Klein et al. 2006; Seidelmann et al. 2016). Several computer-assisted software systems, such as the Singapore "I" Vessel Assessment (SIVA; National University of Singapore, Singapore; Fig. 13.8) facilitate the assessment of potentially important markers, such as vessel caliber, arteriolar-to-venular diameter ratio, tortuosity, bifurcation, and fractal dimensions.

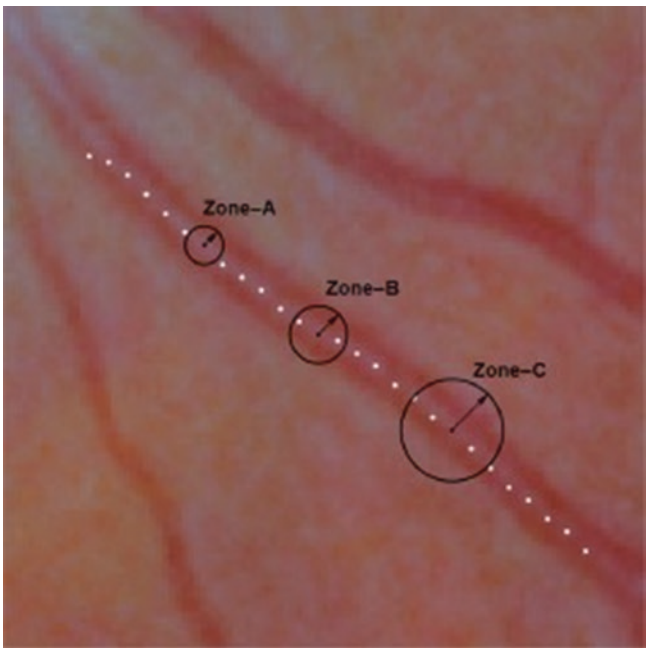

Fig. 13.7 Three circular regions centered at each centerline pixel with a radius of 0.5, 1, and 2 times the vessel width are drawn, named zone A, zone B, and zone C, respectively. The mean, standard deviation, median, minimum, and maximum of the intensity values within each region are used as features

Outpacing "feature engineering" methods, a Google research group has recently achieved the deep learning-based prediction of cardiovascular risk factors, previously unknown to be assessable by retinal imaging (Poplin et al. 2018). These included age, gender, smoking status, systolic blood pressure, and the occurrence of major adverse cardiac events. Heat mapping of anatomical regions that are relevant for the prediction revealed a substantial role of retinal vessels (Fig. 13.9). Scientific developments of this sort do not only promote the shift toward population-wide screening efforts, as is already the case with diabetic retinopathy (see section "Diabetic Retinopathy"), but furthermore propel future research.

Diabetic Retinopathy

Why Automated Screening?

The number of patients living with diabetes is on the rise, and with that, the demand for qualified ophthalmologists to regularly performs retinal examinations for the diagnosis and prevention of diabetes-related eye complications. To prevent vision loss associated with diabetic retinopathy (DR), adherence to regular check-ups at an early stage is crucial. Disease progression is higher in patients with mild disease compared to those with no disease, further highlighting the need for a screening program that is easy to access and, most importantly, reliable (Sabanayagam et al. 2019).

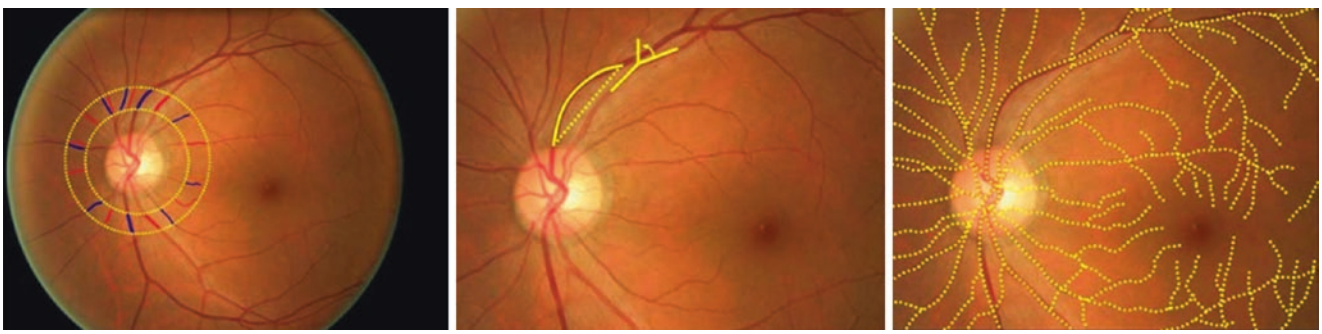

Fig. 13.8 SIVA (Singapore "I" Vessel Assessment). From left to right: assessment of retinal arteriolar (red) and venular (blue) caliber; retinal branching angles and tortuosity; retinal fractal dimension (Reproduced from https://www.accelerate.tech/qws/slot/u50299/InnovationOfferings/ReadytoSignLicense/SIVA/Brochure/SIVA%20ebrochure_v3.pdf)

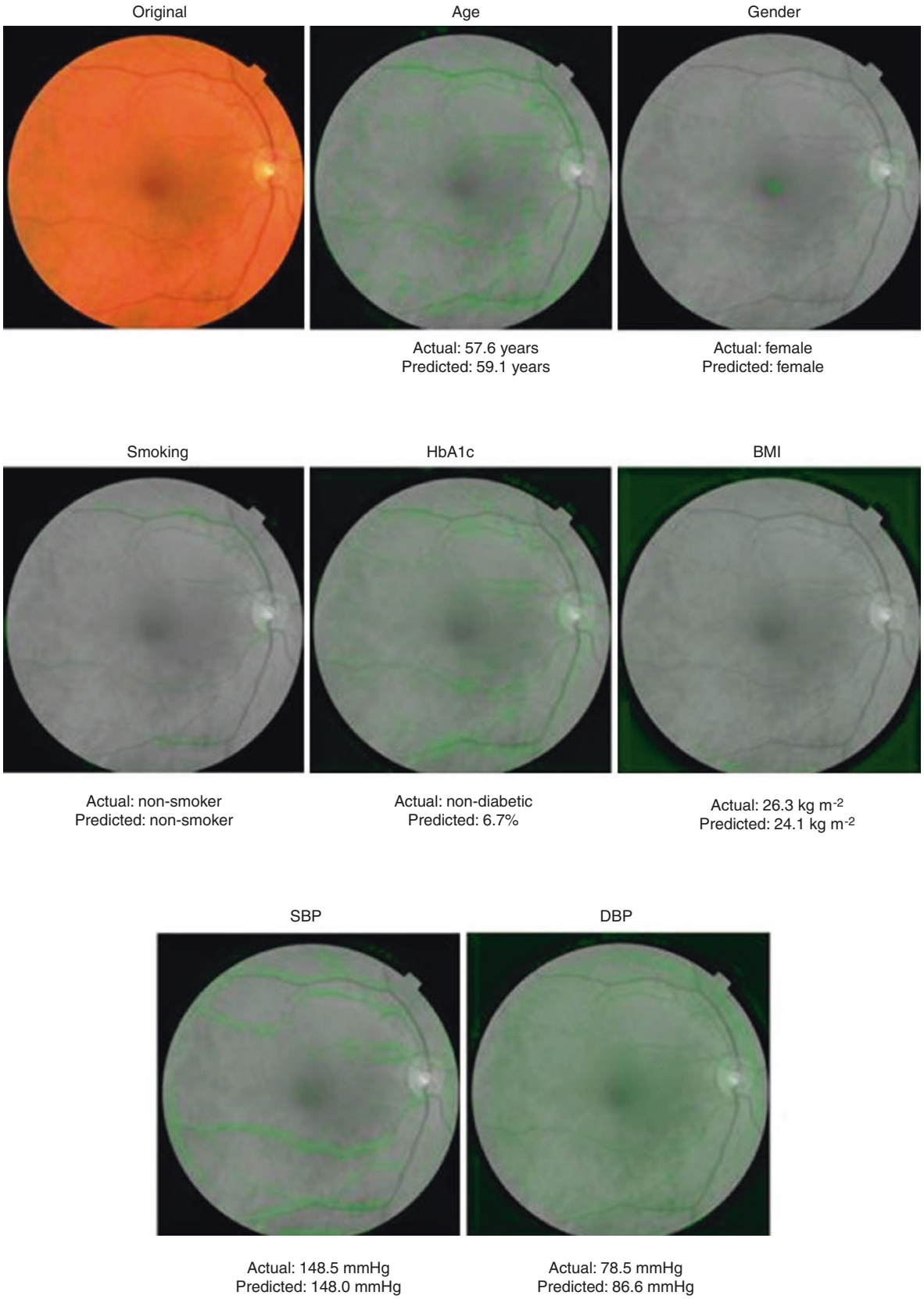

Fig. 13.9 Attention maps for a single retinal fundus image. The top left image is a sample retinal image in color from the UK Biobank dataset. The remaining images show the same retinal image, but in black and white. The soft attention heat map for each prediction is overlaid in green, indicating the areas that the neural-network model is using to make the prediction for the image. HbA1c values are not available for UK Biobank patients, so the self-reported diabetes status is shown instead (Reproduced from Poplin et al.)

Development of IDx-DR: What Is It Based on?

Over the last two decades, multiple studies have evaluated different approaches to automatically detect DR-related changes of the retina, including microaneurysms (MA), hemorrhages, cotton wool spots, intraretinal microvascular abnormalities (IRMA), venous beading, exudates, and neovascularization. This effort led to the FDA-clearance of IDx-DR, the first-ever autonomous AI system that provides a diagnostic decision. By using a fundus camera, a trained operator captures two color images per eye that are then submitted to and analyzed by the IDx-DR analysis system. Within one minute, the AI system produces a disease output (more than mild DR/no or mild DR) and follow-up care instructions (www.eyediagnosis.co; accessed on 1/30/2019). The advantages of such a diagnostic system, if implemented in a screening program, not only mean a substantial economical advantage, but also a reallocation of resources to patients who benefit from a more comprehensive examination.

Two Core Algorithms: Quality Assessment and Biomarker Detection

Sufficient image quality is a prerequisite to any automated, image-based screening program. Quality assessment in IDx-DR is facilitated by image structure clustering and depends on the identification of certain image structures, such as the optic disc, fovea, or vasculature (Niemeijer et al. 2006).

In case of sufficient image quality, multiple validated detectors (mostly multilayer CNNs) are used for the identification of DR-characteristic lesions (Fig. 13.10). Red lesions, such as MAs and intraretinal hemorrhages are detected by a hybrid system (Niemeijer et al. 2005). Large hemorrhages can also be detected with a splat feature classification method, where the characteristics of each splat of a fundus image are described relative to its surroundings, with regard to its pixels' color and location (Fig. 13.11). A further machine-learning computer program was developed that can identify bright lesions in digital color fundus photographs, including drusen, (hard) exudates, and cotton wool spots (Fig. 13.12) (Niemeijer et al. 2007).

Detection of Intra- and Subretinal Fluid in Retinal Disease

The accumulation of fluid within the retinal layers is a finding that characterizes and complicates numerous retinal diseases, such as age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO). The occurrence of intra- and subretinal fluid is an important biomarker that plays a major role in (re-)treatment decisions and is prognostic of visual rehabilitation. Recent structure–function correlations have further highlighted the importance of distinguishing IRF from SRF, as both features have different implications on visual function: While IRF has been shown to substantially contribute to visual loss, the presence of SRF might entail a positive effect on vision (Sharma et al. 2016; Waldstein et al. 2016).

In light of the immense volume of OCT data that is now acquired in clinical routine, a thorough OCT assessment by a clinician that accounts for absolute volume of retinal

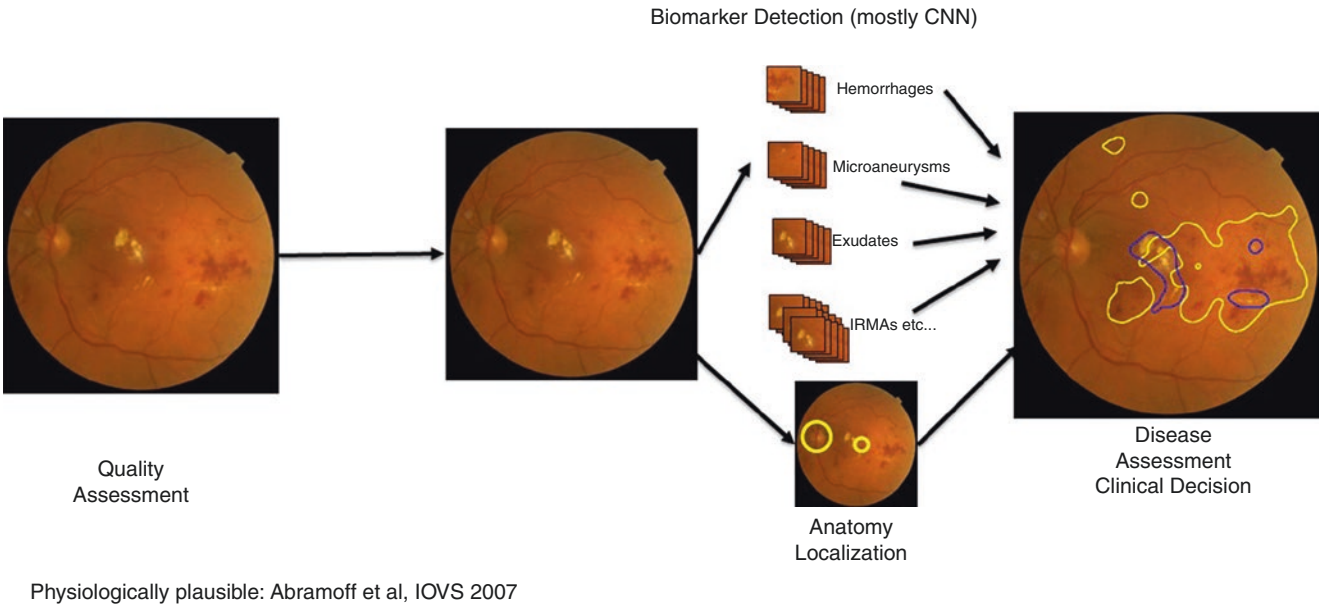

Fig. 13.10 The detection of DR-specific retinal changes depends on a first assessment of image quality. The individual changes are then detected and localized by multiple, lesion-specific diagnostic algorithms, and a disease level output is generated

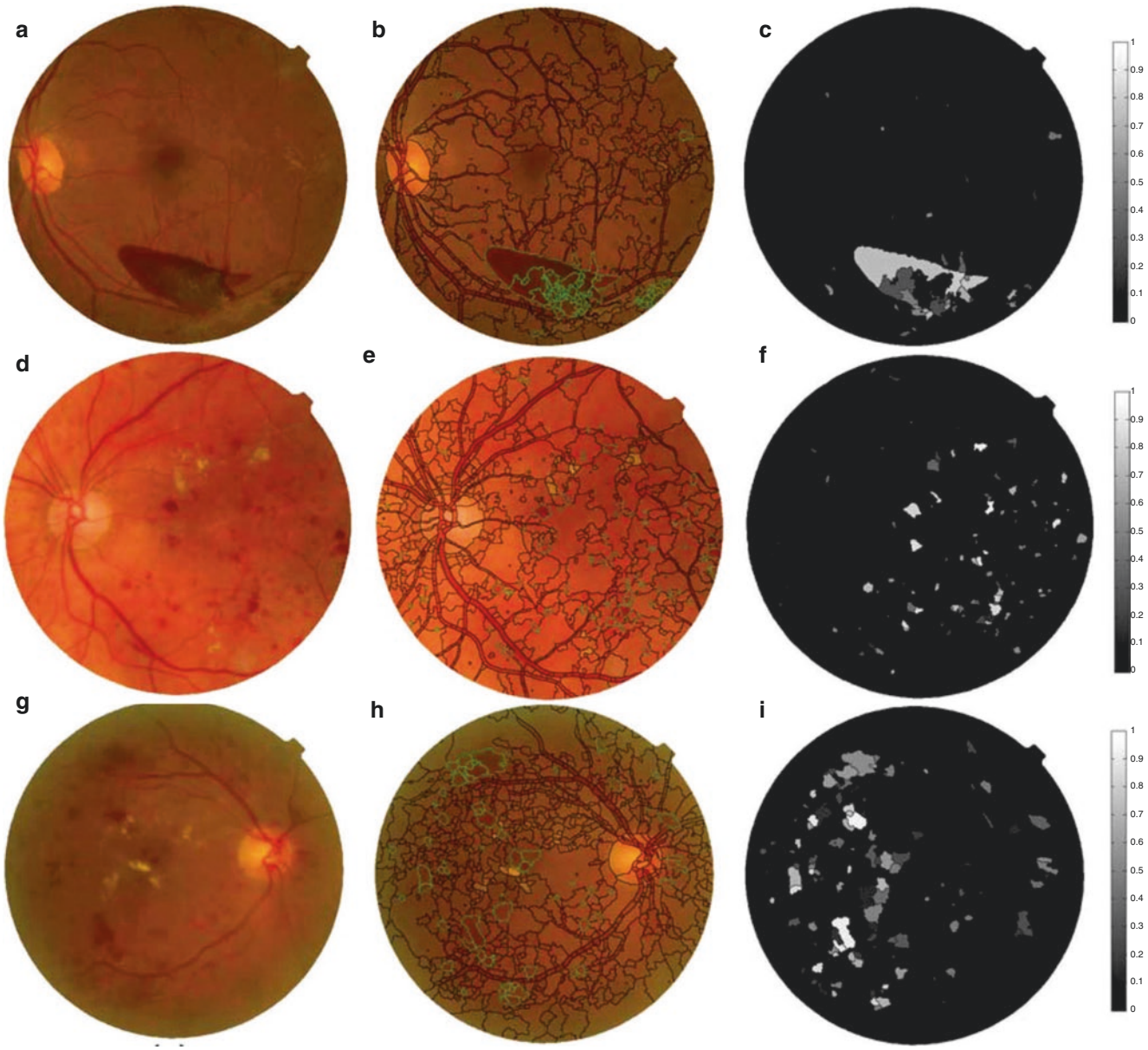

Fig. 13.11 Big hemorrhages are detected with the help of splat-based feature classification: (**a**, **d**, **g**) fundus images (**b**, **e**, **h**) expert annotations of vessels and hemorrhages 1; (**c**, **f**, **i**) hemorrhageness map (Tang et al. 2013)

fluid has become largely unrealistic. The advent of AI-based systems now allows us to objectively quantify and localize intra- and subretinal fluid: A fully automated segmentation approach based on deep learning CNN that was trained on annotated OCT volumes of eyes affected by neovascular AMD, RVO, and DME achieved high precision and accuracy for the detection of retinal fluid (Fig. 13.13) (Schlegl et al. 2018). Additionally, the quantification of fluid complied very well with that of a manual expert assessment.

Assessment of Ischemia by Optical Coherence Tomography Angiography

OCT-A can be a useful tool for evaluating ischemia in retinal vascular diseases such as RVO and DR (Anegondi et al. 2018). Macular ischemia, an important finding in patients with diabetic retinopathy and retinal vein occlusion, correlates closely with vision loss and impacts the potential for visual rehabilitation (Ganjee et al. 2018; Ghashut et al. 2018; Hwang et al. 2016). Capillary nonperfusion (CNP) as a key

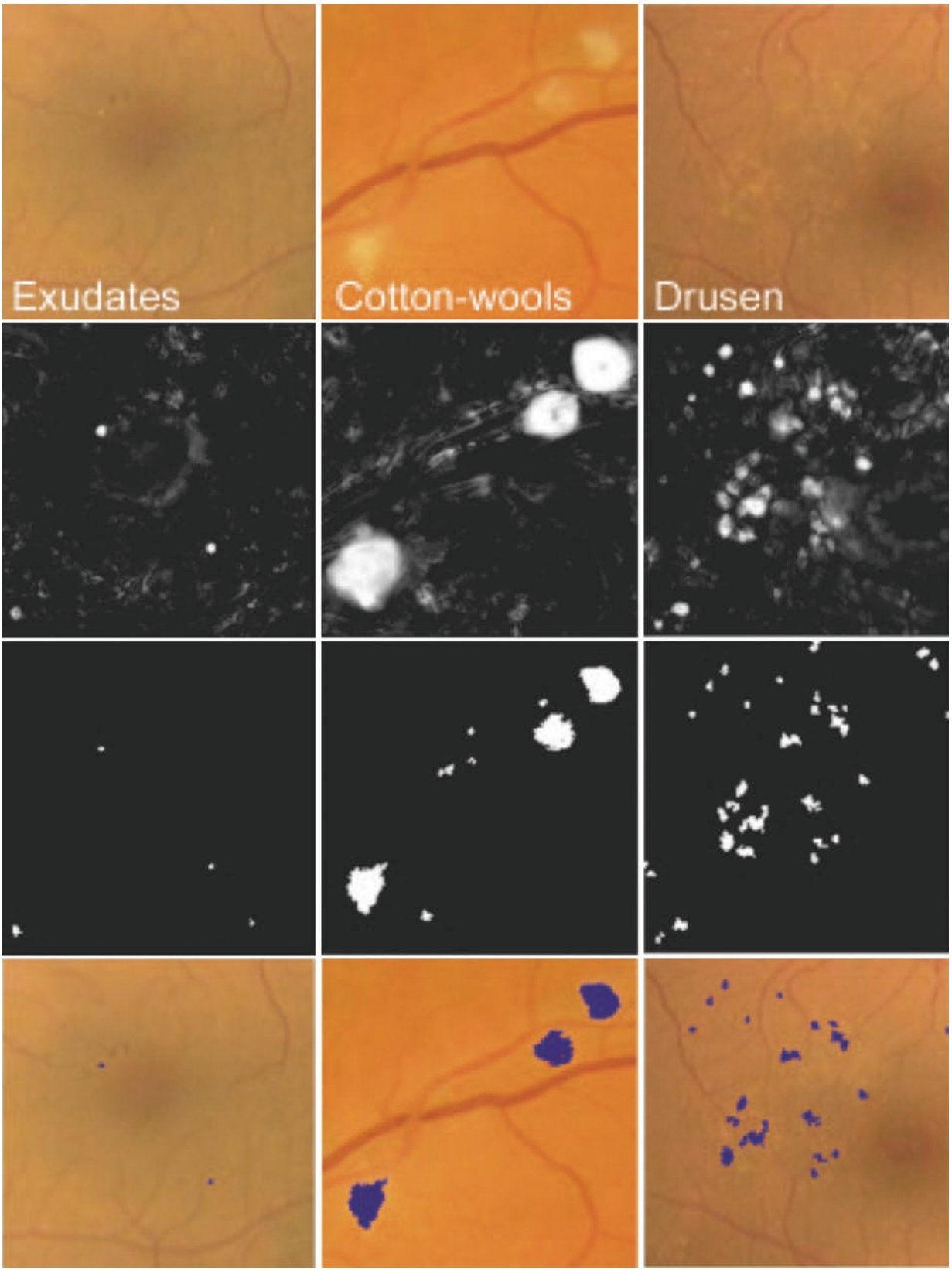

Fig. 13.12 Identification of bright lesions: Machine learning algorithm steps performed to detect and differentiate bright lesions. From *left* to *right* columns: exudates, cotton wool spots, and drusen. From *top* to *bottom*: first row shows the relevant region in the retinal color image, *second row:* posterior probability map after the first classification step; *third row*: pixel clusters that are probable bright lesions (potential lesions); *bottom row*: objects that the system classified as true bright lesions overlaid on the original image (Reproduced from Niemeijer 2007)

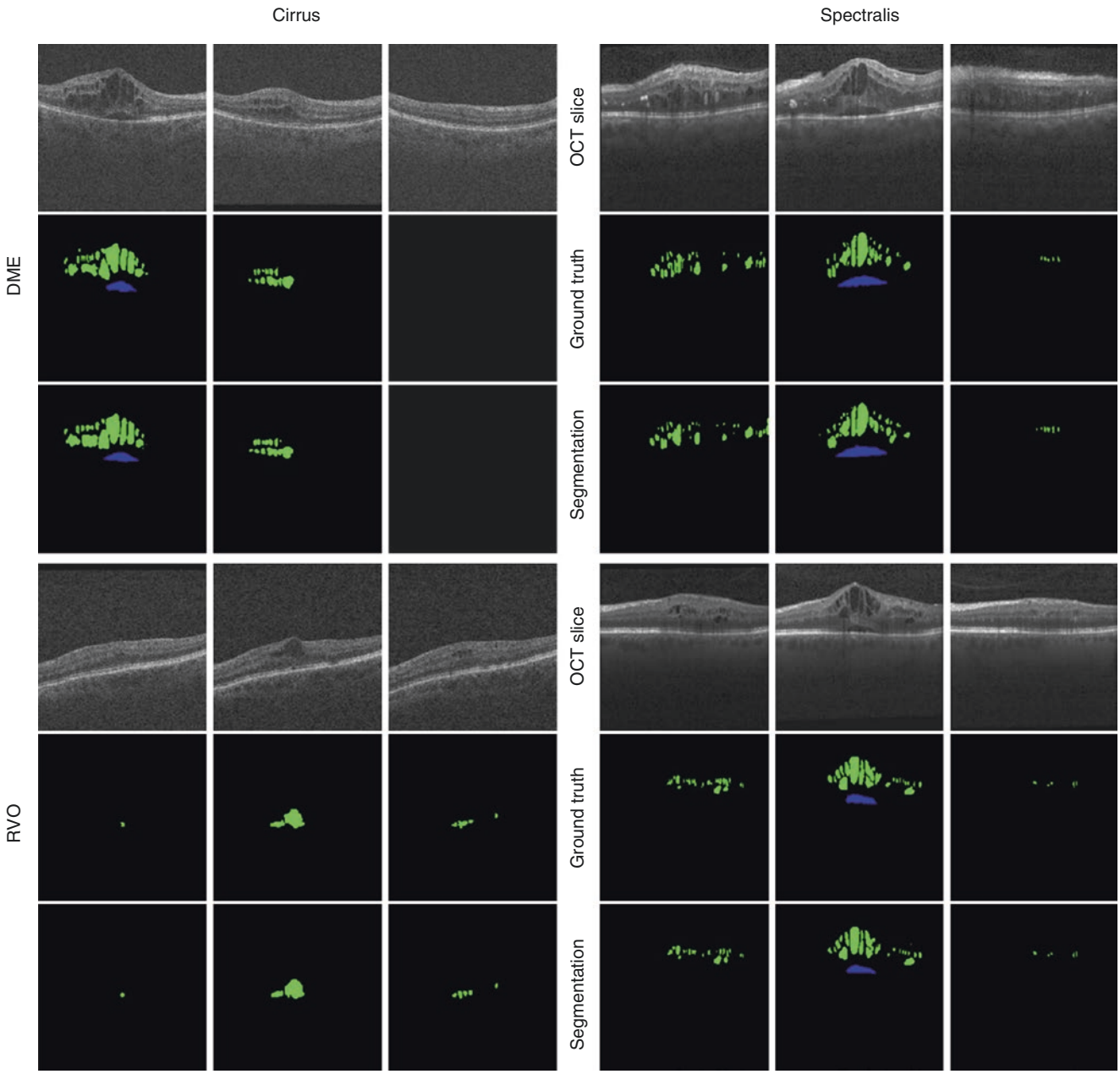

Fig. 13.13 Example cases of segmentation results on OCT scan acquired with Cirrus or Spectralis devices of diabetic macular edema (DME) and retinal vein occlusion (RVO) cases. The first row shows OCT slices, the second row shows manual labels by certified graders, and the bottom row shows the automated segmentation results (intraretinal cystoid fluid [IRC] in green, SRF in blue) (Reproduced from Schlegl 2018)

feature found in diabetic macular ischemia has been shown to increase with the severity of DR, thus making it a potential biomarker for this disease. To this end, the exact, objective and reproducible quantification of CNP is an important prerequisite that could further be optimized with its automated quantitative evaluation (Fig. 13.14) (Anegondi et al. 2018). Thus, the automated quantification of the foveal avascular zone (FAZ) has been of special interest in the OCT-A-based assessment of ischemia. In summary, the visualization of individual capillary networks in OCT-A not only allows an earlier detection of microvasculopathy, but also increases diagnostic accuracy.

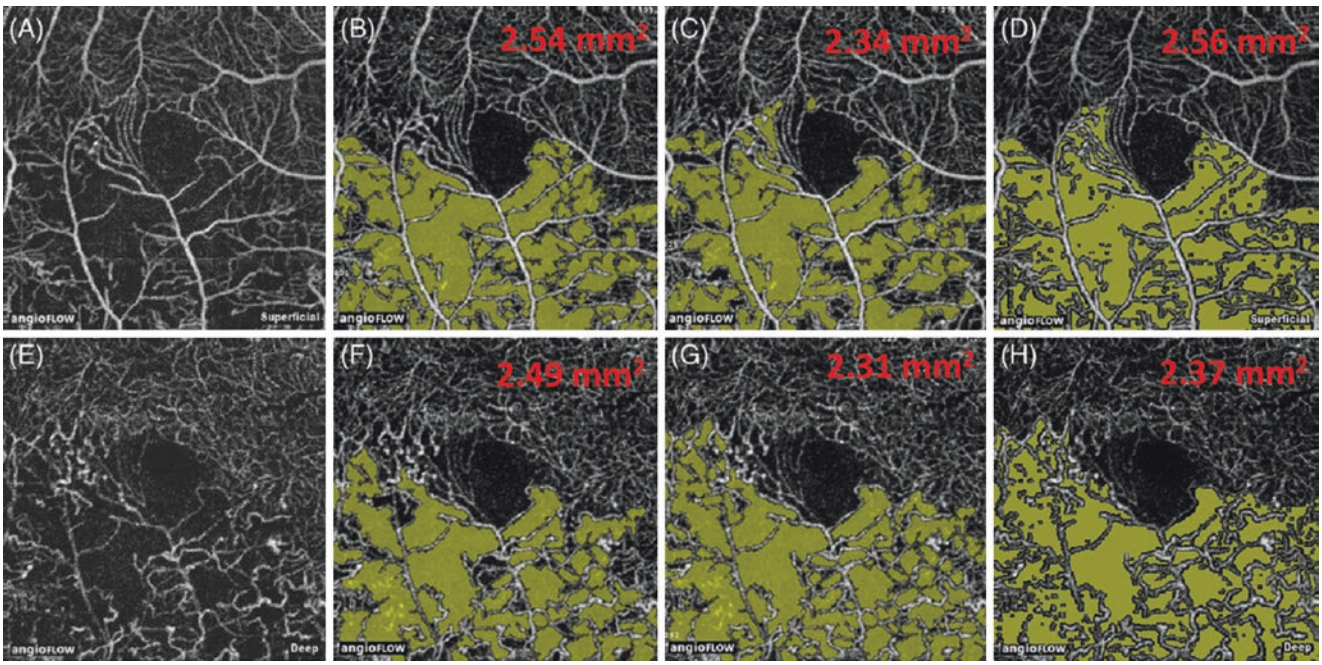

Fig. 13.14 Areas of capillary nonperfusion (CNP) are detected by using a local fractal method. OCT-A image of a BRVO eye, manually marked CNP region by observer 1 (**b** and **f**), manually marked CNP region by observer 2 (**c** and **g**) and automated CNP area detection (**d** and **h**) by a local fractal method in superficial retinal vascular plexus (**a**–**d**) and deep retinal vascular plexus (**e**–**h**). The magnitude of CNP areas are indicated in red (Reproduced from Anegondi 2018)

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Sickle Cell Retinopathy

14

Ru-ik Chee, Sarwar Zahid, and Jennifer I. Lim

Introduction

Sickle cell disease refers to a group of inherited hemoglobinopathies characterized by abnormal hemoglobin genes. The resulting abnormal hemoglobin protein results in sickling of erythrocytes, intravascular hemolysis, defective oxygen transport, and tissue damage due to ischemia and necrosis. Sickle cell disease manifests systemically in many organs such as the brain, lungs, heart, liver, spleen, kidneys, joints, bones, and skin (Yawn et al. 2014).

Periocular involvement in sickle cell disease is uncommon, but infarctions of orbital bones during vaso-occlusive crises, orbital hematomas, retrobulbar ischemic optic neuropathy, and lacrimal gland involvement have been reported (Lim 2012). Anterior segment findings include conjunctival vessel dilation, segmental iris atrophy, and anterior uveitis. A lower threshold for intervention is needed for sickle cell patients with hyphema, due to increased risk for obstruction of aqueous outflow and acute increase in intraocular pressures. In particular, oral carbonic anhydrase inhibitors should be avoided to minimize acidification and thus increased sickling in the anterior chamber (Walton et al. 2002).

Clinical fundus findings in early nonproliferative sickle retinopathy include salmon patch hemorrhages, iridescent spots, and black sunbursts, while proliferative sickle retinopathy progresses from arteriolar occlusions and arteriovenous anastomoses to sea-fan neovascularization, vitreous hemorrhage, and retinal detachment in advanced disease (Goldberg 1977).

Recent advances in optical coherence tomography (OCT), optical coherence tomography angiography (OCTA) and wide-field fundus photography have facilitated novel approaches to evaluating patients with sickle cell retinopathy. We review some of these characteristic imaging findings in this chapter.

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Genetics, Epidemiology, and Risk Factors for Proliferative Sickle Retinopathy

Hemoglobin consists of four globular protein subunits. Hemoglobin A (HbA), the normal adult form of hemoglobin, contains two alpha and two beta subunits. Fetal hemoglobin, or HbF, contains two alpha and two gamma subunits. The sickle cell gene mutation resulting in hemoglobin S (HbS) arises from a single nucleotide mutation (GAG to GTG) at the sixth position of the beta chain in HbA on chromosome 11, resulting in substitution of valine for glutamic acid. A different single nucleotide mutation (GAG to AAG) results in the substitution of lysine for glutamic acid, resulting in hemoglobin C (HbC). Inclusion of valine or lysine in place of glutamic acid leads to increased risk of polymerization in environments of low oxygen tension, due to the presence of hydrophobic regions within the abnormal hemoglobin. Thalassemias are a group of blood disorders that result in decreased production of alpha (alpha-thalassemia) or beta (beta-thalassemia) subunits. Individuals with sickle cell disease are homozygous (HbSS), while individuals with sickle cell trait (HbAS), SC disease (HbSC), sickle-thalassemia disease (HbSThal) are heterozygous. Homozygous HbCC results in mild hemolytic anemia.

Polymerization of hemoglobin leads to sickling of erythrocytes, decreasing cell deformability, and increasing the risk of vascular occlusion. In the retina, subsequent ischemia increases production of VEGF and other pro-angiogenic factors, leading to neovascularization and proliferative sickle retinopathy.

Sickle cell disease is the most common inherited hematological disorder, with an incidence of 1 in 500 African Americans. Sickle cell trait, believed to be protective against malarial infection, is present in 1 in 12 African Americans. Among African Americans in North America, SC disease is found in 0.2%, and SThal in 0.03% of individuals.

SC disease patients generally have a milder systemic clinical course compared to individuals with SS disease, but proliferative sickle retinopathy (PSR) is more common in SC

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(33%, up to 70%) and Sthal (14%) disease compared to SS disease (3%) (Fox et al. 1990). Theories behind this phenomenon include an intermediate level of vaso-occlusion that produces retinal ischemia and neovascularization in SC and SThal disease, compared to a higher rate of auto-infarction as a result of more significant vaso-occlusion in SS disease (Condon and Serjeant 1980).

In SS disease, high total Hb in males and low HbF in both males and females were found to be risk factors in the development of PSR (Hayes et al. 1981). In HbSC disease, high mean cell volume and low fetal hemoglobin were associated with PSR in females (Hayes et al. 1981).

Clinical Classification and Features

In 1977, Goldberg provided a detailed description of the different stages in the natural course of sickle retinopathy (Goldberg 1977). Fundus findings in nonproliferative sickle retinopathy include small retinal hematomas with a salmon patch appearance, iridescent hemosiderin deposits, and black sunburst lesions. Angioid streaks are known to be associated with sickle cell disease (Figs. 14.1 and 14.2) (Paton 1959).

Salmon patch hemorrhages are areas of hemorrhage that arise from occluded arterioles that subsequently rupture. These superficial hemorrhages have been shown to be located between the retina and internal limiting membrane in histopathological analysis (Romayanada et al. 1973). The red color of an acute hemorrhage adopts a salmon-colored hue after progressive hemolysis (Fig. 14.3).

Separation of the internal limiting membrane due to superficial hemorrhage may lead to the creation of a schisis cavity. Macrophage phagocytosis of erythrocytes degrades hemoglobin to hemosiderin. The hemosiderin-laden macrophages then appear on ophthalmoscopy as iridescent deposits within the space of the old superficial hematoma (Figs. 14.4 and 14.5).

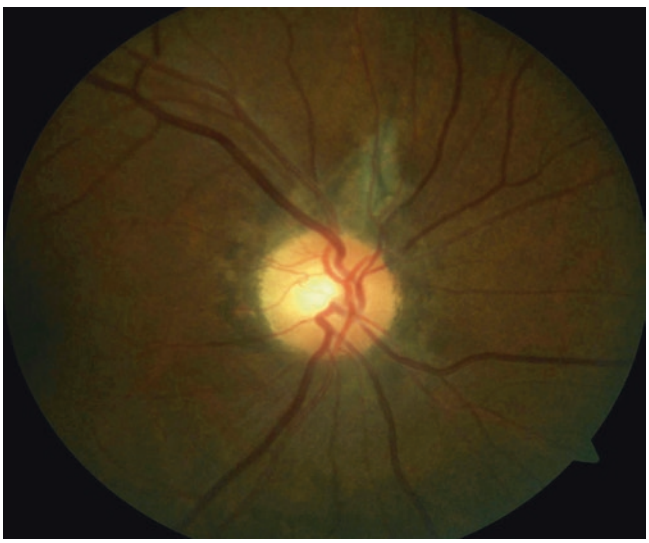

Fig. 14.1 Color fundus photograph of the right eye in a patient with sickle cell disease. Angioid streaks are notable in the juxtapapillary area

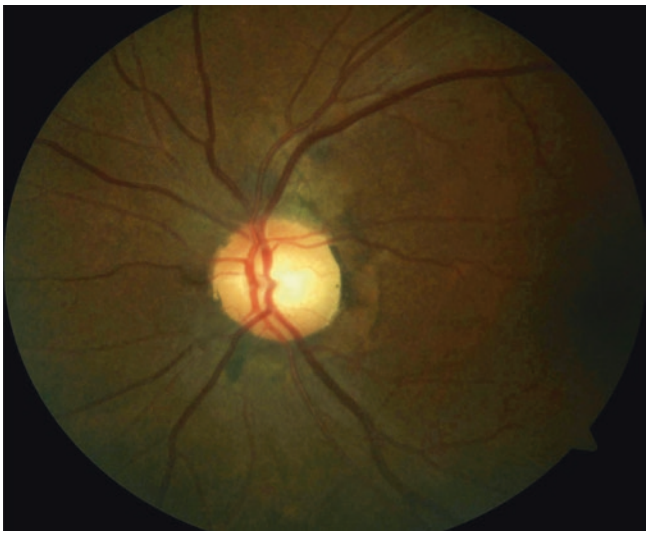

Fig. 14.2 Color fundus photograph of the left eye in a patient with sickle cell disease. Angioid streaks are notable in the juxtapapillary area

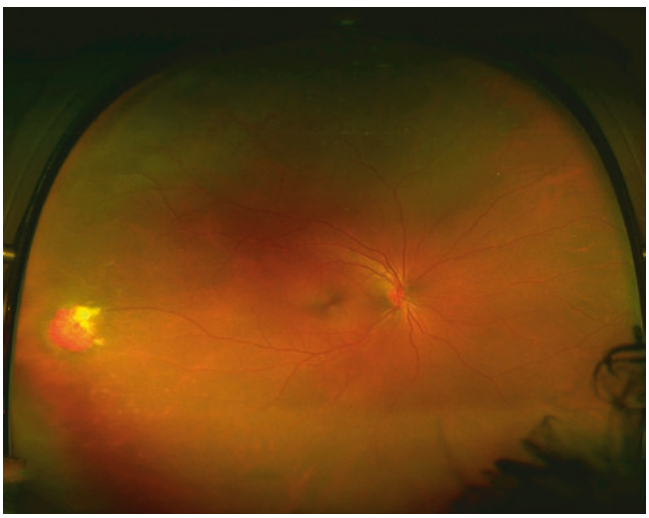

Fig. 14.3 Color fundus photograph illustrating a temporal salmon patch hemorrhage

Blood within a salmon patch hemorrhage may rupture anteriorly causing mild vitreous hemorrhage, or migrate posteriorly into the subretinal space. Histological evaluation of pigmented lesions with a black sunburst appearance revealed diffuse deposition of iron, which is present in hemoglobin (Romayanada et al. 1973). Focal retinal pigment epithelium (RPE) hypertrophy and outer retinal thinning are associated with histological findings in black sunburst lesions (Fig. 14.6).

Subsequent proliferative stages of sickle retinopathy are further subclassified into five Goldberg stages:

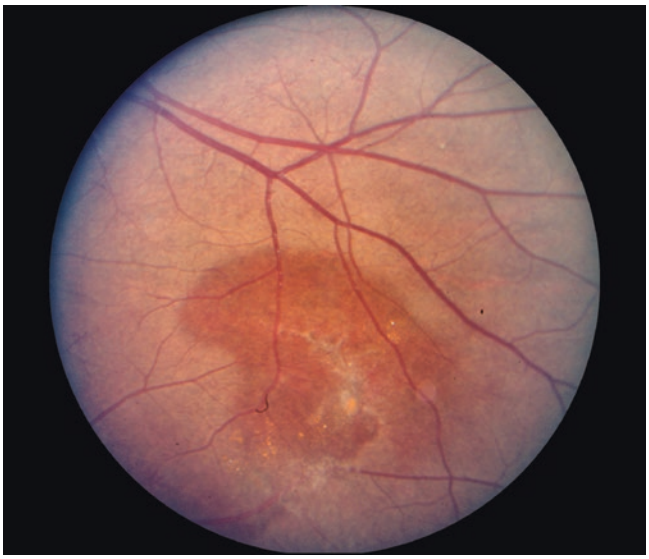

Fig. 14.4 Iridescent spots within a resolving area of old retinal hemorrhage

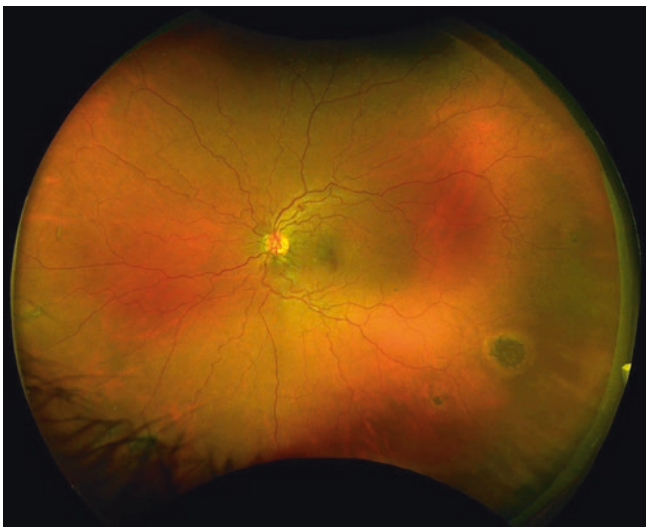

Fig. 14.6 Ultra-widefield color fundus photograph illustrating black sunburst lesions in the inferotemporal peripheral retina

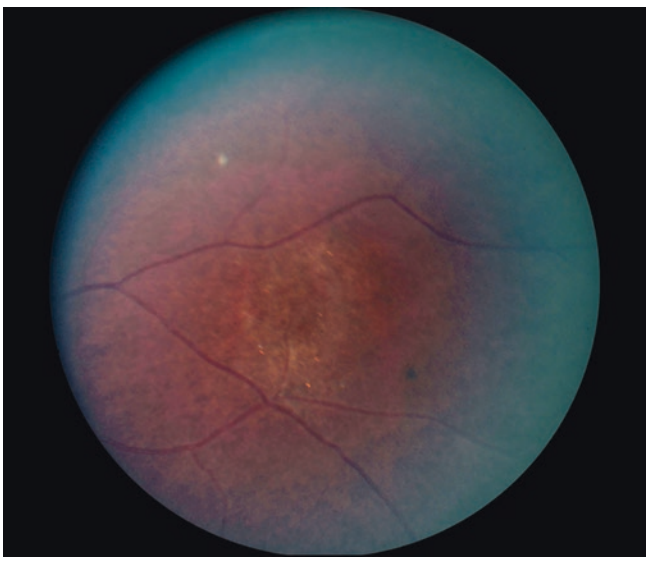

Fig. 14.5 Iridescent spots within an area of resolved hemorrhage

Stage I: Arteriolar occlusion

Arteriolar occlusion primarily occurs in the peripheral temporal retina. Sickling of erythrocytes is more common in the temporal retina, due to greater vascular transit distances and times, leading to increased deoxygenation of hemoglobin (Fig. 14.7a, b).

Stage II: Arteriovenous Anastomosis

At the junction of perfused and ischemic retina distal to a vaso-occluded site, vascular remodeling of retinal arterioles and venules result in the formation of arteriovenous anastomoses (Figs. 14.8, 14.9, and 14.10). These anastomoses are characterized by a lack of leakage on fluorescein angiogram, distinguishing it from true neovascularization seen in Stage III sickle retinopathy.

Stage III: Sea-Fan Neovascularization

Ischemic drive from non-perfused retina results in increased production of pro-angiogenic factors such as vascular endothelial growth factor and fibroblastic growth factor. New vessels are more permeable than normal mature vessels, and are more likely to lead to leakage of intravascular contents and bleeding. The classic clinical findings in Stage III proliferative sickle retinopathy are sea-fan fronds, which resemble sea fans in clinical appearance, and leak on fluorescein angiography (Figs. 14.11, 14.12 and 14.13).

Stage IV: Vitreous Hemorrhage

Fibrovascular proliferation in the neovascularization process may lead to increased traction, and vitreous hemorrhage occurs when the delicate wall structure of new vessels has been compromised to an extent where erythrocytes leak into the extravascular vitreous cavity (Figs. 14.14, 14.15, and 14.16). The hemorrhage may be localized within a subhyaloid bursa resulting in a preretinal hemorrhage (Fig. 14.17) or diffused throughout the vitreous cavity, which is typically associated with decreased vision.

Stage V: Retinal Detachment

Progressive traction on the retina may lead to tractional retinal detachments, typically occurring in the peripheral retina in sickle retinopathy. Breaks in the retina may develop as a result of retinal atrophy/thinning from chronic ischemia, or mechanical traction from fibrovascular tissue, resulting in rhegmatogenous in addition to tractional retinal detachments (Fig. 14.18).

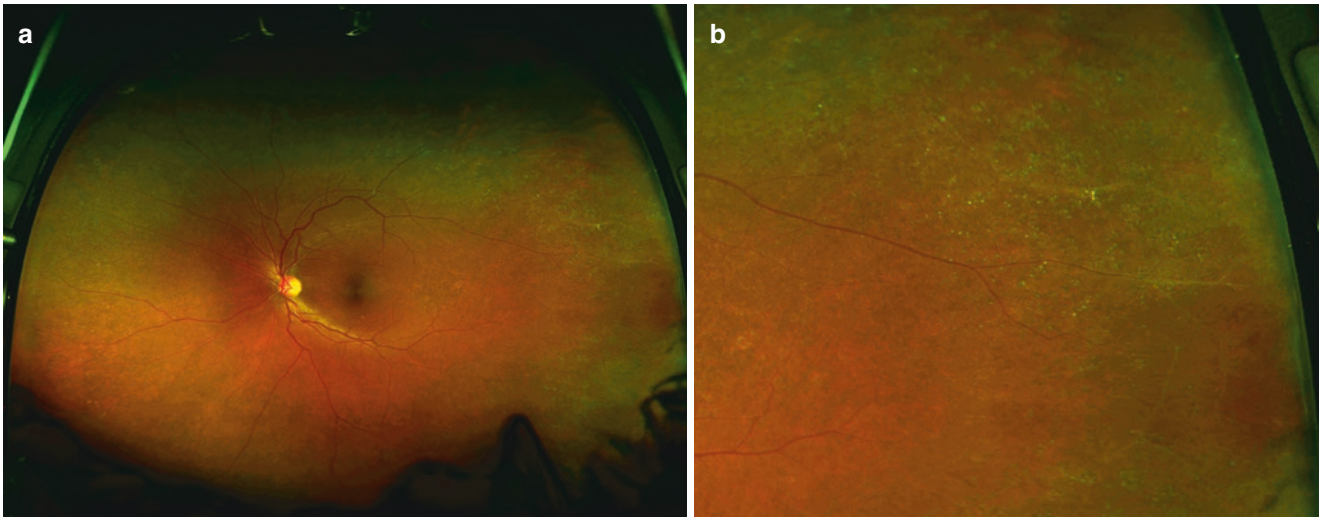

Fig. 14.7 (**a**) Ultra-widefield fundus photograph illustrating temporal arteriolar occlusion. (**b**) Magnified image of area of temporal arteriolar occlusion from (**a**)

Fig. 14.8 Ultra-widefield color fundus photograph illustrating temporal arteriovenous anastomoses in Stage II proliferative sickle retinopathy (arrows)

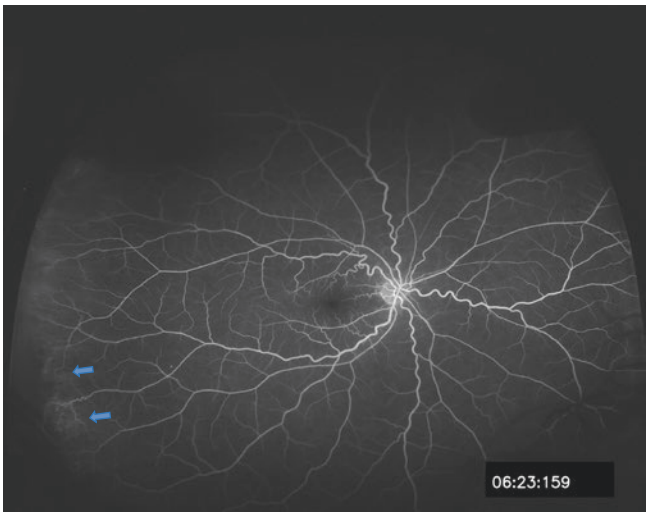

Fig. 14.9 Ultra-widefield late-phase fluorescein angiogram image illustrating temporal arteriovenous anastomoses in Stage II proliferative sickle retinopathy (arrows)

Imaging

Features on Widefield Imaging

Widefield imaging, particularly in combination with fluorescein angiography, has facilitated visualization of peripheral ischemia in sickle cell patients (Cho and Kiss 2011). Improved visualization of peripheral vascular changes enhances detection of high-risk clinical characteristics of disease, prompting earlier treatment and prevention of advanced manifestations of disease (Figs. 14.9, 14.10, 14.11, and 14.13). Peripheral ischemia, as detected on ultra-widefield fluorescein angiography, was reported to be significantly associated with presence of macular thinning documented on OCT and OCTA (Ghasemi Falavarjani et al. 2016). In addition to ultra-widefield imaging, OCT and OCTA have complementary characteristics and may contribute to a more complete evaluation of sickle cell patients when a multimodal imaging approach is adopted.

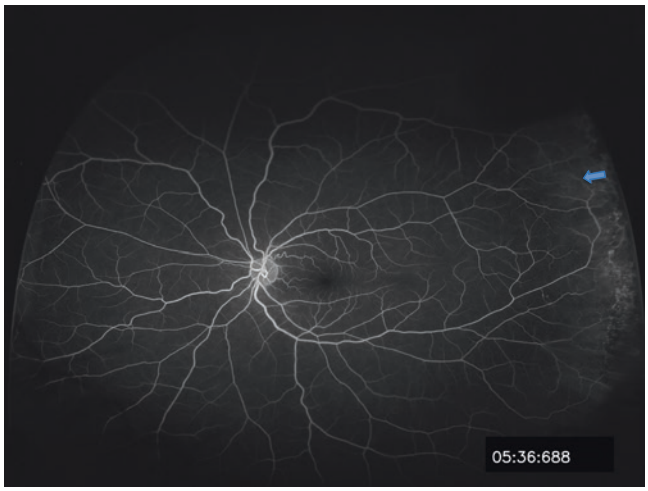

Fig. 14.10 Ultra-widefield late-phase fluorescein angiogram image illustrating temporal arteriovenous anastomoses (arrow) in Stage II proliferative sickle retinopathy

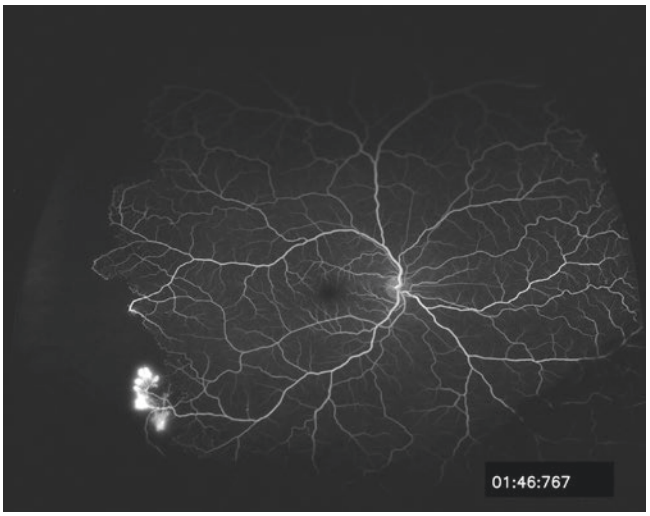

Fig. 14.11 Ultra-widefield mid-phase fluorescein angiogram image illustrating inferotemporal sea-fan neovascularization with a hyperfluorescent pattern of leakage. Temporal hypofluorescence and vascular pruning are consistent with retinal ischemia, which drives neovascularization

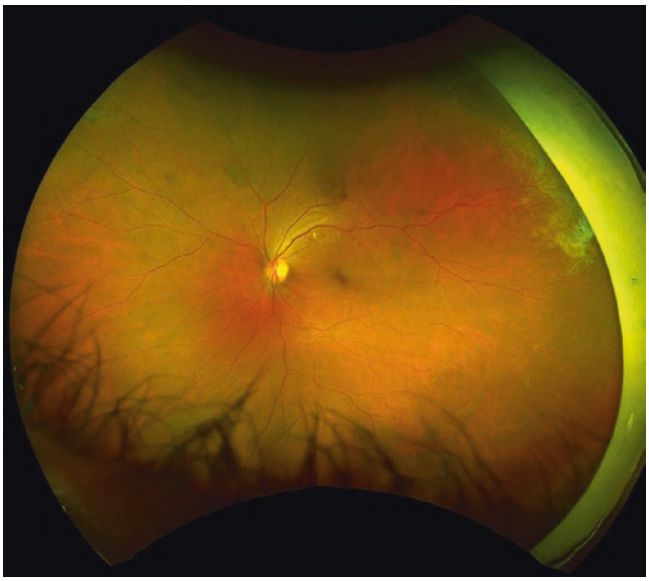

Fig. 14.12 Ultra-widefield color fundus photograph illustrating superotemporal sea-fan neovascularization

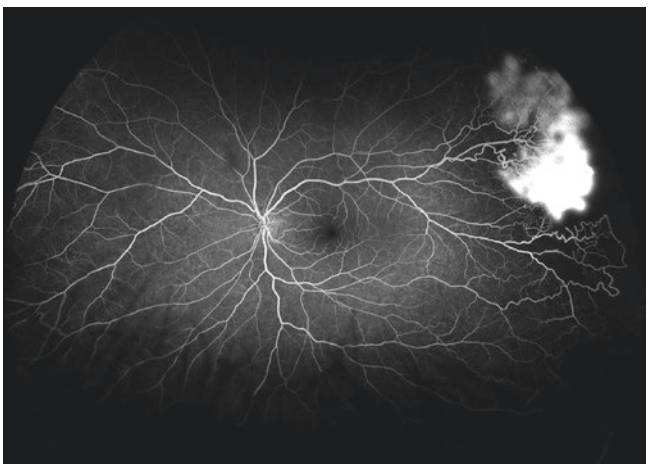

Fig. 14.13 Ultra-widefield mid-phase fluorescein angiogram image illustrating superotemporal hyperfluorescent pattern of leakage corresponding to the area of neovascularization in Fig. 14.12

Features on Spectral Domain Optical Coherence Tomography

OCT and OCTA has enabled further detailed study into the effects of ischemic retinal vascular events that occur in the posterior pole of sickle cell patients, in a disease traditionally conceived to manifest predominantly in the peripheral retina. Early studies of OCT findings in sickle cell patients reported that macular thinning, especially in the temporal region, is frequently seen in such patients (Witkin 2006; Hoang et al. 2011) (Fig. 14.19). These macular changes may occur even when patients are asymptomatic, are associated with decreased peripapillary retinal nerve fiber layer thickness (Chow et al. 2013), and have been correlated with functional changes by scanning laser ophthalmoscope microperimetry, a sensitive measurement of macular function (Chow et al. 2011). Interestingly, subsequent studies then illustrated that there appeared to be a significant association between posterior pole OCT changes and peripheral ischemia, as well as presence of proliferative sickle retinopathy (Lim and Cao 2018). These findings may ultimately contribute to a modified and updated classification of sickle cell disease, as similar "Goldberg stages" may differ widely in their OCT and OCTA findings.

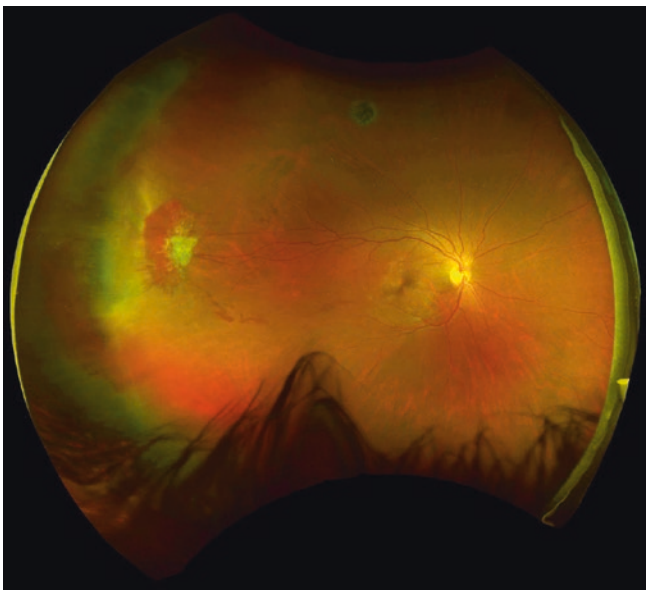

Fig. 14.14 Ultra-widefield color fundus photograph illustrating temporal neovascularization with mild vitreous hemorrhage

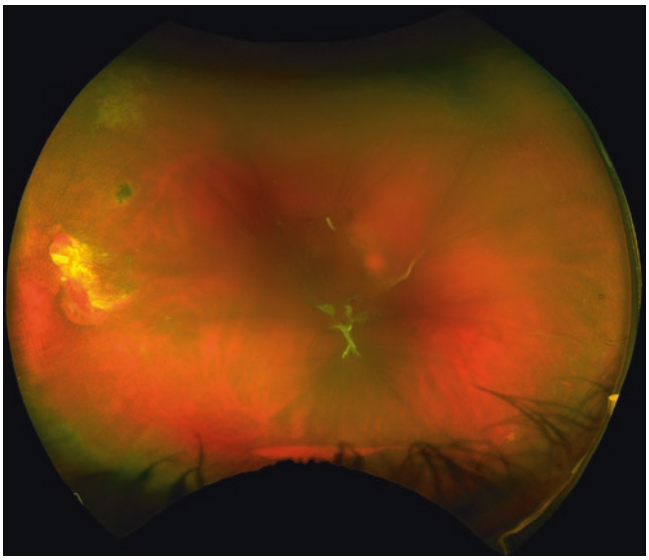

Fig. 14.16 Ultra-widefield color fundus photograph illustrating temporal neovascularization with diffuse vitreous hemorrhage and inferior subhyaloid hemorrhage

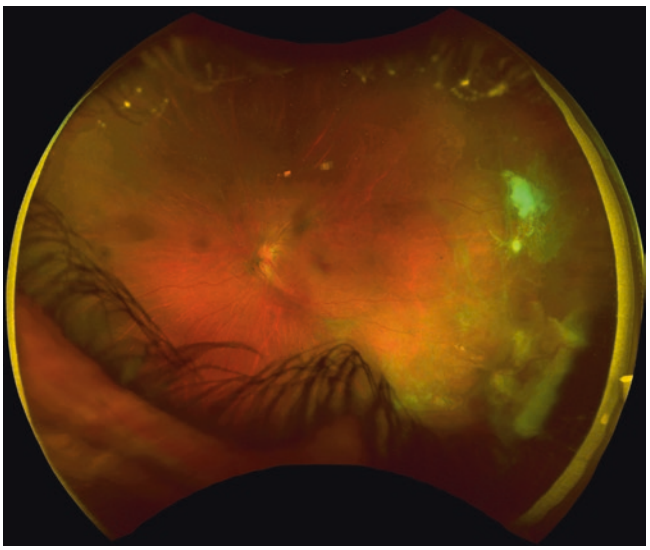

Fig. 14.15 Ultra-widefield color fundus photograph illustrating temporal neovascularization with dehemoglobinized vitreous hemorrhage

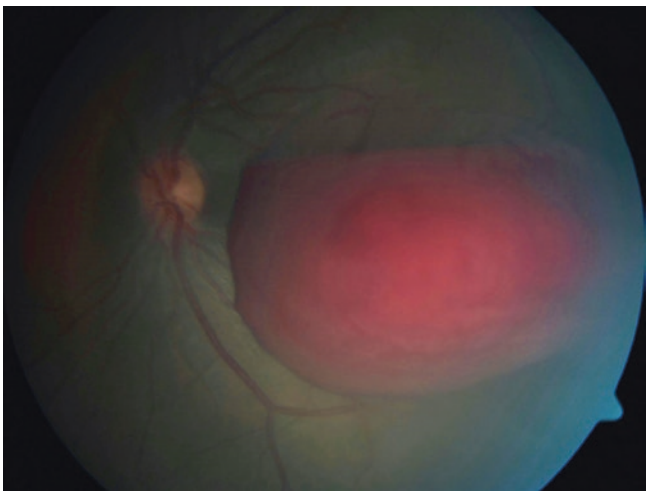

Fig. 14.17 Color fundus photograph illustrating a subhyaloid preretinal hemorrhage arising from sea-fan neovascularization in a 28-year-old sickle cell disease patient

Features on Optical Coherence Tomography Angiography

Six OCTA parameters have been described to be statistically significant in the differentiation of sickle cell disease patients and controls: (1) blood vessel tortuosity, (2) mean diameter of superficial large blood vessels, (3) vessel perimeter index, (4) area of foveal avascular zone (FAZ), (5) contour irregularity of FAZ, and (6) density of parafoveal avascular region (Alam et al. 2017).

On average, sickle cell patients have retinal vessels with 16.6% increased tortuosity and 29.4% increased dilation as compared to controls (Fig. 14.20). Vessel perimeter index represents a ratio of the perivascular surface area to the total surface area imaged on *en face* OCTA imaging, and is a marker of overall vessel length. Sickle cell disease patients had a 2.49% decrease in vessel perimeter index (Fig. 14.21). Decreased area of FAZ is another parameter consistent with occlusion and drop out of retinal vessels in sickle retinopathy. Sickle cell disease patients were found to have 52% and 53% increases in the area of FAZ in the deep and superficial capillary plexuses, respectively (Fig. 14.22).

Importantly, contour irregularity of the FAZ was reported as the most sensitive parameter in detecting the presence of sickle cell retinopathy. Increased contour irregularity results from perifoveal vascular occlusions, leading to irregularity and spiculation of the FAZ border. Sickle cell disease patients showed a 36% increase in FAZ contour irregularity compared to controls, and has been suggested as a possible non-invasive biomarker of SC disease. Density of parafoveal avascularity, especially in temporal regions, increases with increasing vascular occlusions in sickle cell disease, and was also found to be highly sensitive in detecting the presence of sickle retinopathy (Alam et al. 2017).

All six OCTA parameters with the exception of FAZ area were not significantly associated with retinal thickness measurements with OCT alone, consistent with the observation that further value can be obtained with OCTA imaging compared to traditional OCT (Alam et al. 2017). Furthermore, it has been shown in a case report that OCTA may be more sensitive than traditional fluorescein angiography in the identification of retinal ischemia in patients with sickle cell disease, highlighting the potential unique value OCTA may have in the evaluation and management of sickle retinopathy (Grover et al. 2016).

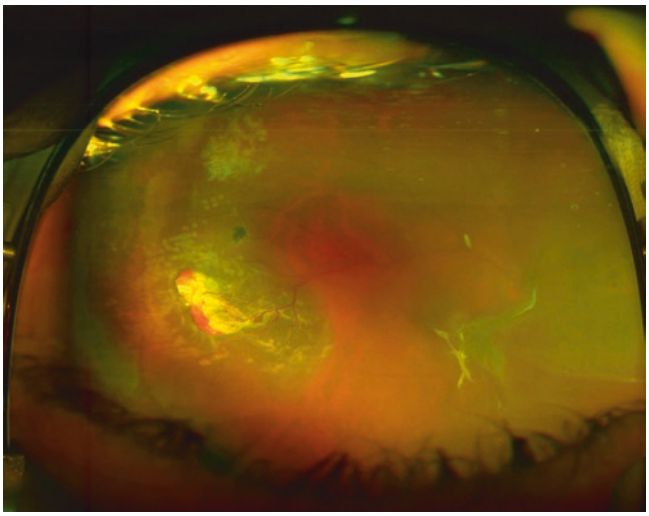

Fig. 14.18 Ultra-widefield color fundus photograph illustrating temporal retinal tear and combined tractional and rhegmatogenous retinal detachment

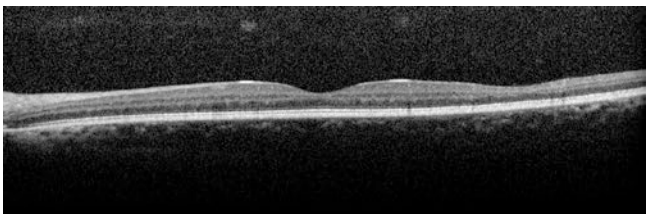

Fig. 14.19 Spectral domain optical coherence tomography image of the left eye of a sickle cell disease patient with temporal macular thinning

Ophthalmic Management

Screening

An expert panel report published in the *Journal of the American Medical Association* in 2014 recommended Ophthalmology referral for initial screening for sickle retinopathy with dilated fundus examination at 10 years of age (Yawn et al. 2014). In the setting of normal screening examination, annual to biannual follow up thereafter was recommended. The quality of evidence behind this recommendation was recognized by the panel as low, but appears to be supported by reports of median age of onset of proliferative sickle retinopathy at 13.7 years (range 9–18 years) (Gill and Lam 2008).

Observation

Close observation of early retinal abnormalities (Stages I and II) is appropriate, due to the relatively high probability of autoinfarction. The natural history of salmon patch hemor-

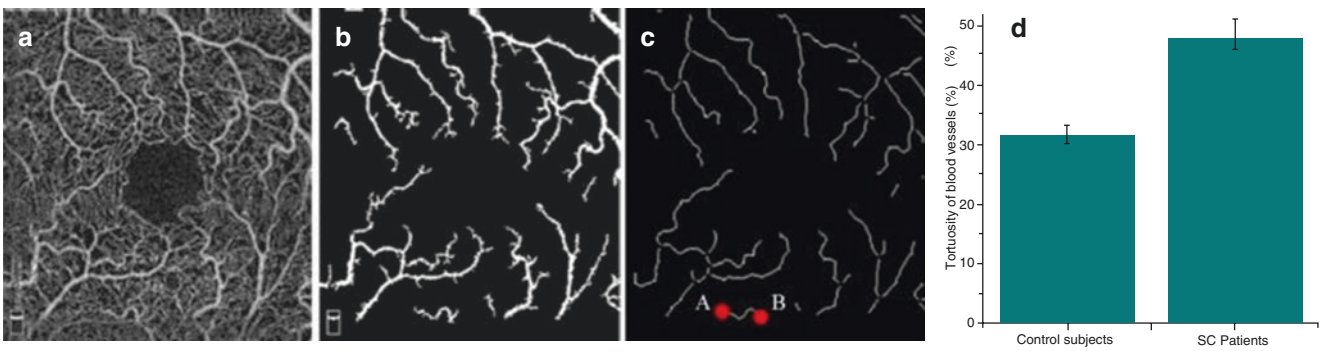

Fig. 14.20 Measuring tortuosity of OCTA images. (**a**) OCTA raw image, (**b**) segmented large blood vessel map, (**c**) skeletonized blood vessels branches with identified endpoints (for a random vessel branch, A and B endpoints are shown with red dots), (**d**) comparison of tortuosity in control and SC patients (error bars are standard deviations). Reproduced with permission (Alam et al. 2017)

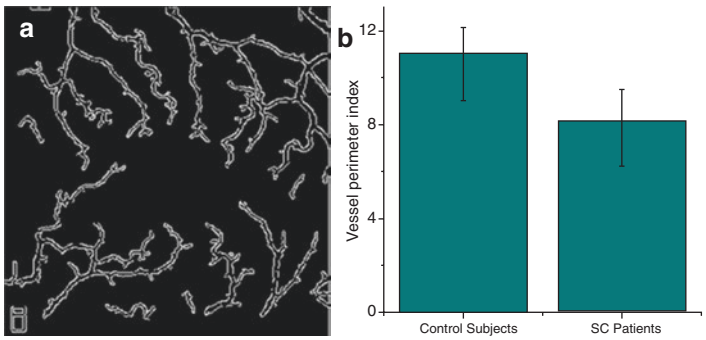

Fig. 14.21 (**a**) Vessel perimeter map, (**b**) comparison of VPI in control and SCD patients (superficial layer). Reproduced with permission (Alam et al. 2017)

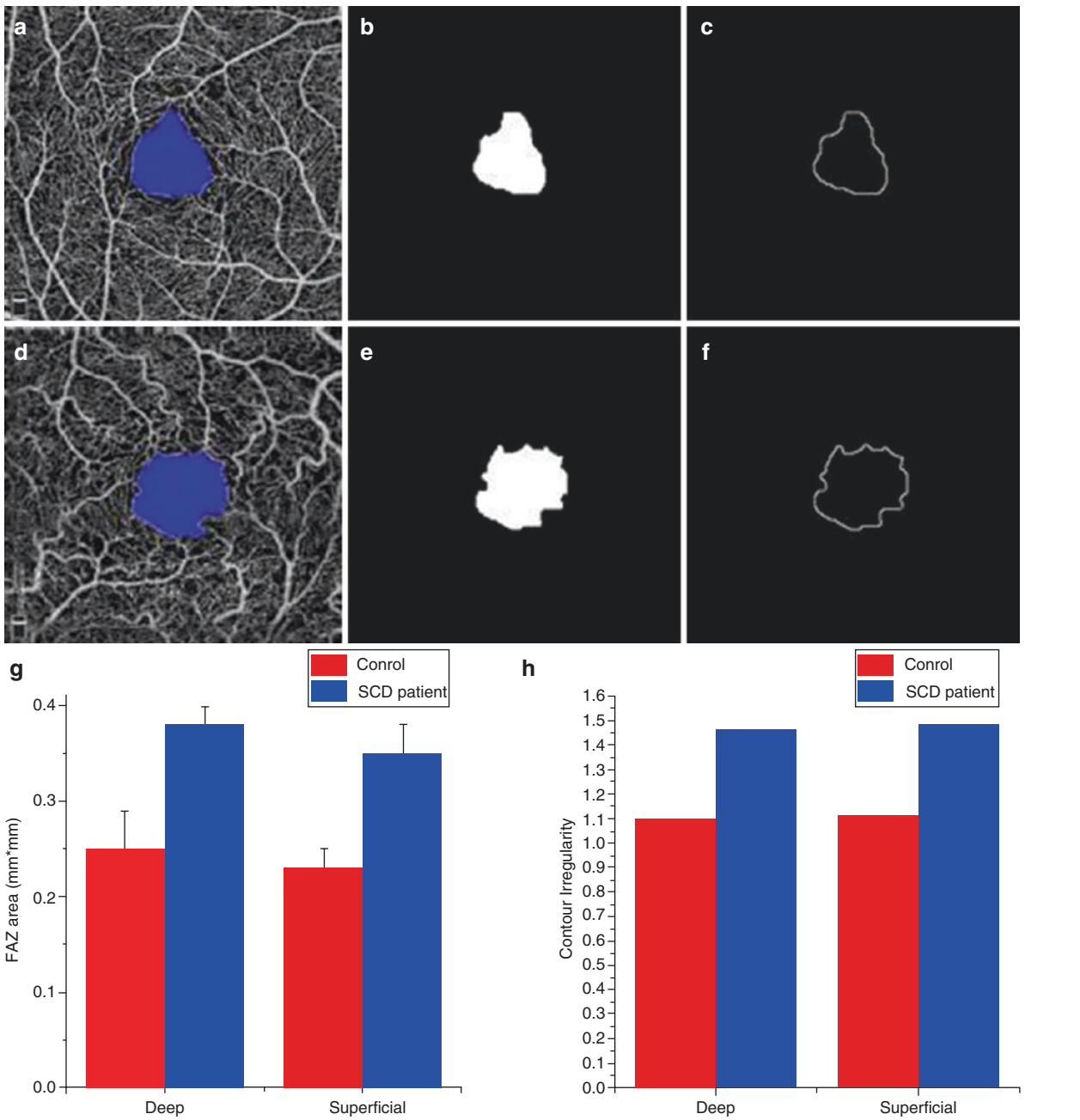

Fig. 14.22 (**a**) OCTA image with demarcation for normal eye, (**b**) segmented avascular region for normal eye (**c**) FAZ contour for normal eye, (**d**) OCTA image with demarcation for diseased eye, (**e**) segmented avascular region for diseased eye, (**f**) FAZ contour for diseased eye, (**g**) comparison of area of FAZ in control and SCD patients for deep and superficial layers, (**h**) comparison of area of FAZ in control and SCD patients for deep and superficial layers. Reproduced with permission (Alam et al. 2017)

rhages is to progress to black sunburst lesions with low risk of spontaneous hemorrhage into the vitreous cavity. These lesions rarely have clinical manifestations, as they are mostly located in the peripheral retina.

Systemic Medical Therapy

Hydroxyurea is a ribonucleotide reductase inhibitor that increases fetal hemoglobin (HbF) levels, decreases circulating leukocytes and reticulocytes, improves cellular deformability, and has been shown in multicenter prospective randomized controlled trials to improve clinical outcomes in sickle cell patients. Sickle cell retinopathy has been reported to be inversely correlated with HbF levels. By increasing HbF levels, hydroxyurea may confer a protective benefit against sickle cell retinopathy (Estepp et al. 2013).

Cryotherapy and Photocoagulation

Ablative cryotherapy or photocoagulation of ischemic peripheral retina is indicated in Stage III proliferative sickle cell retinopathy, reducing the risk of hemorrhage from neovascular vessels (Figs. 14.23 and 14.24). Ablative therapies function by reducing VEGF drive of ischemic retina, a similar concept to other retinal vascular diseases. The sickle cell study showed that laser was effective in management of PSR and is the preferred treatment. At present, no study has prospectively compared anti-VEGF to laser for PSR.

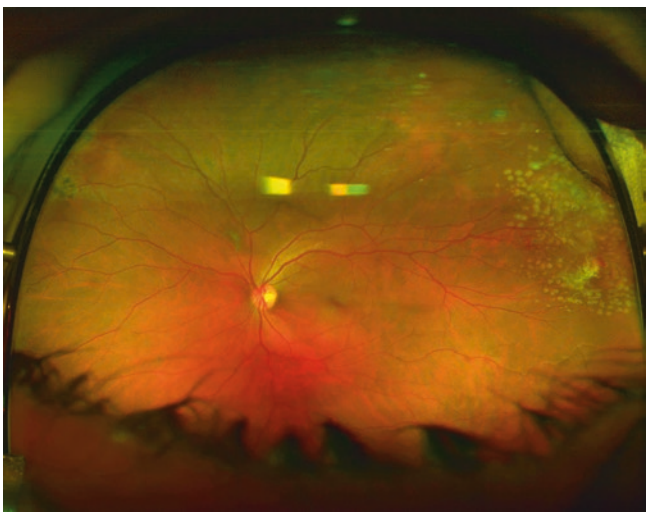

Fig. 14.23 Ultra-widefield color fundus photograph illustrating laser uptake chorioretinal scars corresponding to the superotemporal area of sea-fan neovascularization in Fig. 14.12

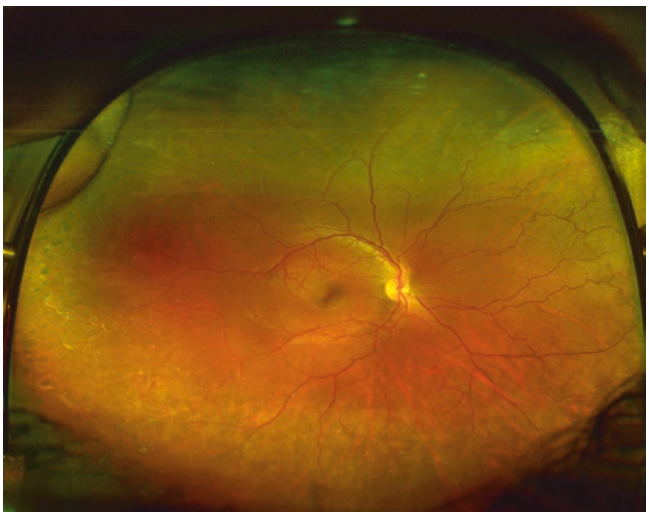

Fig. 14.24 Ultra-widefield color fundus photograph illustrating laser chorioretinal scars temporally around an area of neovascularization inferotemporally

Intravitreal Anti-VEGF Pharmacotherapy

Evidence for intravitreal anti-VEGF pharmacotherapy in the treatment of sickle cell retinopathy remains limited to individual case reports. Anti-VEGF therapy has been shown to be effective in regression of neovascularization, particularly for Stage IV proliferative sickle cell retinopathy when vitreous hemorrhage precludes a view of the fundus for laser photocoagulation and surgical intervention is not preferred (Siqueira et al. 2006; Shaikh 2008; Mitropoulos et al. 2014). Pre-surgical anti-VEGF therapy 3 days before vitreoretinal surgery for Stage V proliferative sickle retinopathy was reported to reduce vascularity and increase fibrosis of neovascular tissue, with the surgeons anecdotally noting that it decreased intraoperative bleeding and facilitated surgical maneuvers (Moshiri et al. 2013).

Vitreoretinal Surgery

Non-clearing vitreous hemorrhage in Stage IV proliferative sickle cell retinopathy is most effectively managed with pars plana vitrectomy and intraoperative endolaser application. Peripheral retina ischemia leads to atrophy and an increased propensity for retinal breaks, which requires greater intraoperative attention to minimizing iatrogenic traction. Segmentation techniques that isolate sea-fan neovascular tissue have been reported to be preferred over delamination techniques to reduce the incidence of iatrogenic retinal breaks (Williamson et al. 2009). During pars plana vitrectomy, awareness of intraocular infusion pressure is critical, due to heightened risk of complications with raised intraocular pressures in sickle cell patients.

Scleral buckles may be beneficial when there are multiple retinal breaks and sites of pathology. Buckle height, size, and site considerations are especially important, due to increased risk of anterior segment ischemia in sickle cell patients (Ryan and Goldberg 1971). An institutional case series of vitreoretinal surgery outcomes in 15 eyes with proliferative sickle retinopathy reported high rates of success with repair of retinal detachment (8 of 8 eyes), with no reported cases of anterior segment ischemia (Chen et al. 2014). Other surgical considerations include the avoidance of vasoconstrictive epinephrine in the retrobulbar anesthetic and intraocular irrigating solution.

Advances in smaller gauge vitrectomy, widefield viewing systems for intraoperative peripheral retina visualization, intraocular pressure management, and other microsurgical techniques have resulted, and will likely continue to lead to further improvements in surgical outcomes in patients with proliferative sickle retinopathy.

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