Retinal Vasculitis in Systemic Disease

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Abstract

Retinal vasculitis may be associated with various systemic vasculitides. It can result in cystoid macular edema, retinal ischemia, and occlusive disease and resultant sight-threatening sequelae such as neovascularization, vitreous hemorrhage, and neovascular glaucoma. The purpose of this chapter is to discuss the more common systemic diseases associated with retinal vasculitis, including Behçet's disease, systemic lupus erythematosus, Susac's syndrome, and ANCA-associated vasculitides. The diagnostic criteria of these multisystem disorders will be reviewed, as well as their ocular manifestations and presentations. Attention will be given to various imaging modalities including fluorescein angiography and optical coherence tomography to evaluate their utility and describe typical clinical findings.

2.1 Introduction

Vasculitis can affect the arteries, capillaries, and veins of any organ system; therefore, manifestations vary based on the site affected. For example, palpable purpura may be evident in individuals with cutaneous vasculitis, fluid retention and hematuria may occur in individuals with renal involvement, and focal neurologic deficits may manifest in those with central nervous system disease. While infectious causes of vasculitis exist, the majority appear to be autoimmune. The available evidence suggests that the dysfunction caused by vasculitis is the result of leukocyte-mediated alterations in blood vessel structure and function.

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Table 2.1 Predominant vessel type involved in various forms of ocular inflammation

Arteritis	Systemic lupus erythematosus, acute retinal necrosis syndrome, polyarteritis nodosa, granulomatosis with polyangiitis, idiopathic retinal vasculitis, aneurysms, and neuroretinitis syndrome (IRVAN), Susac's syndrome
Phlebitis	Behçet's disease, sarcoidosis, multiple sclerosis

The International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC2012) published their consensus on the nomenclature of vasculitides in 2012. Their system included groups of disease characterized by the size of vessel affected and groups such as single-organ vasculitis, vasculitis associated with systemic disease, and vasculitis associated with a probable etiology [1].

Vasculitis affecting the retinal blood vessels may occur in isolation or be associated with systemic diseases and infectious processes affecting the eye. Clinically, this vasculitis can manifest as sheathing of the blood vessels, retinal hemorrhages, cotton wool spots, vascular occlusion, and neovascularization of the retina. Together these inflammatory changes can result in vision loss, cystoid macular edema, and structural complications such as vitreous hemorrhage and retinal detachment. The primary site of retinal vascular inflammation (arteritis versus phlebitis; proximal versus distal) may narrow the differential diagnosis of retinal vasculitis (Table 2.1).

The scope of this chapter will include a summary of some of the systemic diseases that may feature vasculitis affecting the retinal and choroidal vasculature.

2.2 Behçet's Disease

Adamantiades-Behçet's disease (Behçet's disease) is a chronic, relapsing inflammatory disorder classically characterized by the presence of oral and genital aphthous ulcers, ocular inflammation, and characteristic skin lesions.

While Behçet's disease has a worldwide distribution, there are certain regions in which the incidence and prevalence are much higher. Turkey has the highest prevalence of Behçet's disease, with 420 cases per 100,000 population. The prevalence in Japan, Korea, China, Iran, and Saudi Arabia ranges from 13.5 to 22 cases per 100,000 population. The prevalence in North America and Europe is much less, with one case per 15,000–500,000 population [2].

The sex prevalence varies geographically, though the most severe manifestations of the disease including pulmonary aneurysms, uveitis, thrombophlebitis, and neurologic disease are all more common in males. Behçet's disease is most common in persons aged 20–40 years with a mean age at onset of 25–30 years [2].

The diagnosis of Behçet's disease is based on clinical findings, with the most widely used criteria published by the Research Committee of Japan and the International Study Group [3]. The clinical manifestations of the disease are broken down into major and minor criteria, and patients may only manifest a subset of these findings (Table 2.2).

Table 2.2 Research committee of Japan clinical criteria for the diagnosis of Behçet's disease

Major criteria
• Recurrent oral aphthous ulcers
• Skin lesions (erythema nodosum, acneiform pustules, folliculitis)
• Recurrent genital ulcers
• Ocular inflammatory disease
Minor criteria
• Arthritis
• Gastrointestinal ulceration
• Epididymitis
Behçet's disease classification
• Complete (four major criteria)
• Incomplete (three major criteria or ocular involvement with one other major criterion)
• Suspect (two major criteria with no ocular involvement)
• Possible (one major criterion)

Oral aphthous ulceration is the most prevalent manifestation of Behçet's disease in most series. These painful lesions have a high recurrence rate and typically appear as a cluster or crop of lesions.

Recurrent ulcerative genital lesions can occur on the scrotum and penile shaft in males and the labia, vagina, and perineum in females. Other skin manifestations include erythema nodosum and acneiform papulopustular lesions on the face, trunk, and extremities.

The disease can also affect other organ systems such as the brain (memory/recall, behavioral changes, meningoencephalitis, cerebral vasculitis), large blood vessels (pulmonary artery aneurysms, coronary vasculitis/thrombosis), and the GI system (deep intestinal ulceration).

Ocular involvement manifests in approximately 70% of patients who have Behçet's disease. In most instances, oral and genital ulceration precedes eye inflammation, though ocular disease has been observed as the initial manifestation as well. Behçet's uveitis typically consists of recurrent episodes of severe inflammation. In one series, anterior uveitis was present in 59% of cases, posterior uveitis was present in 76% of cases, and panuveitis was present in 88.1% of cases. While inflammation may present unilaterally, in most cases it progresses to involve both eyes. The classic anterior uveitis with shifting hypopyon is estimated to be present in less than one-third of patients [4].

Retinal vascular disease is the most serious complication of Behçet's uveitis with severe inflammatory arteritis and phlebitis. The initial manifestations of retinal arteritis and phlebitis may include cystoid macular edema and vascular occlusion, both of which may result in profound vision loss. Later manifestations may include secondary ischemia-induced neovascularization of the retina and optic disk. Neovascular glaucoma has been reported in eyes afflicted with severe occlusive vasculitis (Figs. 2.1 and 2.2).

The treatment for Behçet's disease is immunosuppression, particularly when ocular involvement is noted. Previous studies have demonstrated the benefit granted by

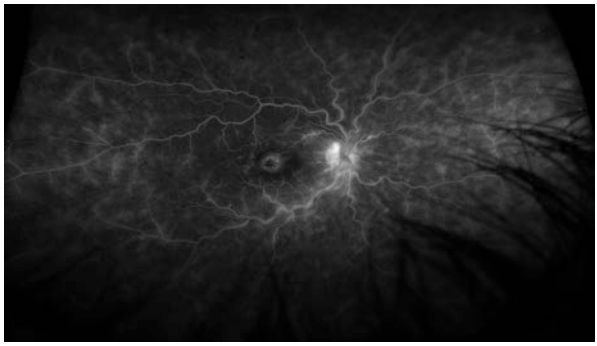

Fig. 2.1 Wide-field fluorescein angiogram of a male with Behçet's disease-associated retinal vasculitis. The photograph depicts tortuous vessels with diffuse leakage (veins and arteries) and angiographic cystoid macular edema. Courtesy: Bryn Burkholder, MD

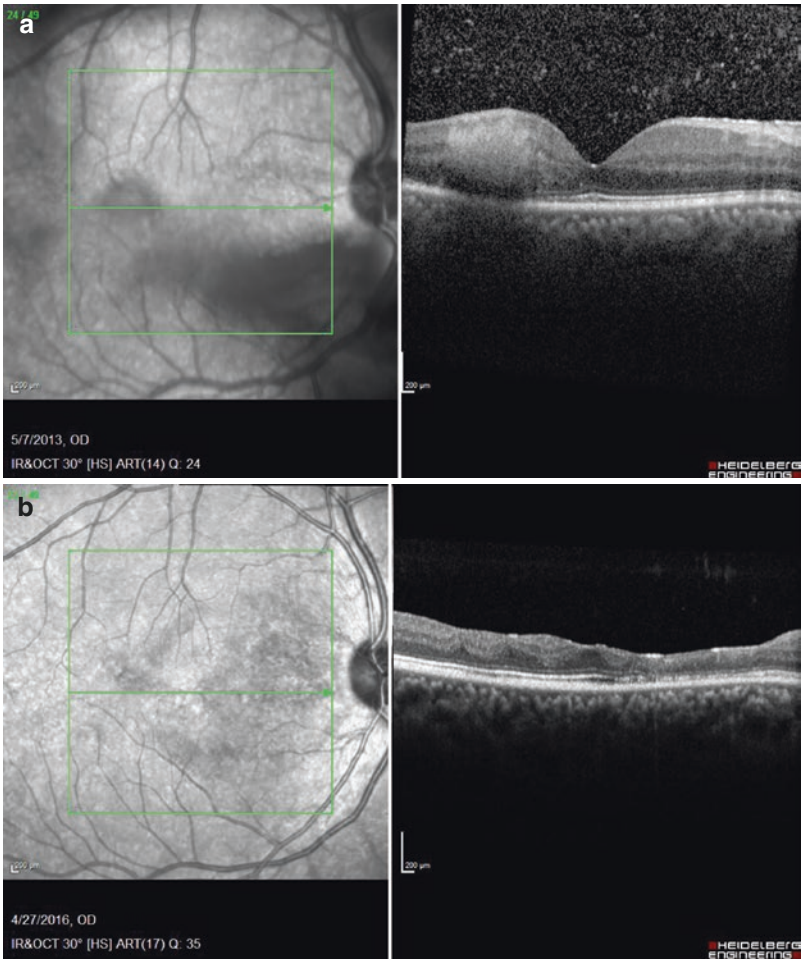

Fig. 2.2 Spectral domain OCT in a male with Behçet's disease-associated retinal vasculitis. Pictured above is a region of inner retinal edema corresponding to an acute arteriolar occlusion (**a**). Months later, after instituting therapy with infliximab, the residual inner retinal atrophic changes are noted (**b**). The patient maintained 20/35 visual acuity due to relative sparing of the fovea. Courtesy: Bryn Burkholder, MD

instituting early immunomodulatory therapy with azathioprine, alkylating agents, and, more recently, biologic mediators of inflammation such as infliximab. Given the expected chronic course, corticosteroid monotherapy is not considered to be an appropriate therapy given the side effects of long-term administration.

2.3 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of circulating autoantibodies. The majority of these autoantibodies are targeted against cell nuclei, resulting in multisystem involvement.

In North America, the annual incidence of SLE ranges between 1.8 and 7.6 per 100,000 persons per year, with a reported prevalence of approximately 50 cases per 100,000 persons. The frequency of SLE varies by race and ethnicity, with higher rates reported in blacks, Asians, and Hispanics. Worldwide, the prevalence of SLE is variable, but the highest rates of prevalence have been reported in Italy, Spain, and the UK Afro-Caribbean population. More than 90% of cases of SLE occur in women of child-bearing age, suggesting a role for hormonal factors in the pathogenesis of the disease [2].

There are a variety of clinical manifestations of SLE ranging from the classic malar, or "butterfly" rash, to arthralgias (present in up to 85%) and nephropathy (present in 50%). The American College of Rheumatology has created and updated a list of clinical manifestations and serologic patterns that serve as diagnostic criteria for SLE (Table 2.3) [5].

Patients with SLE may also develop ocular involvement. The most common manifestations are surface disease, including episcleritis, scleritis, and keratoconjunctivitis sicca.

Table 2.3 American College of Rheumatology Diagnostic Criteria for SLE

1. Malar rash	Erythema over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging
3. Photosensitivity	Skin rash as a result of reaction to sunlight
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints
6. Serositis	Pleuritis or pericarditis
7. Renal disorder	Persistent proteinuria greater than 0.5 g per day or cellular casts on urinalysis
8. Neurologic disorder	Seizures or psychosis in the absence of offending drugs or known metabolic derangements
9. Hematologic disorder	Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
10. Immunologic disorder	Anti-SM positivity or positive antiphospholipid antibodies
11. Anti-nuclear antibody	An abnormal titer of antinuclear antibody

A diagnosis is made if at least four of the listed features manifest simultaneously or serially over any length of time

The retinal and choroidal manifestations of SLE are potentially blinding and are considered to be important markers of systemic disease activity. Lupus retinopathy was initially described in 1929, by Bergmeister, and since then, numerous investigators have elaborated on its clinical signs and manifestations. The incidence of lupus retinopathy ranges from 3% in patients with mild disease to 29% in individuals with active disease affecting other organ systems. Additionally, a strong correlation between the presence of retinopathy and CNS disease has been described [2].

The most common signs of retinopathy are microangiopathic, mirroring the retinal vascular changes seen in diabetic and hypertensive retinopathy. Early on, retinal hemorrhages and cotton wool spots predominate. More advanced retinopathy includes the presence of inflammation of the retinal arterioles and/or venules. The most severe retinal lesion seen in lupus retinopathy is arterial occlusion, which can result in severe and permanent vision loss. Sudden vision loss from a central retinal vascular occlusion in a young individual without evident risk factors should prompt the clinician to consider an underlying diagnosis of SLE. Arterial occlusion in SLE can result in the same ischemic sequelae noted in other causes of retinal nonperfusion, such as neovascularization, vitreous hemorrhage, and tractional retinal detachment [6].

Individuals with retinal vasculopathy have a higher prevalence of concomitant antiphospholipid antibodies including anticardiolipin and lupus anticoagulant. In one study by Montehermoso et al., 77% of patients with SLE and retinal involvement had positive antiphospholipid antibody titers, whereas only 29% of SLE patients without retinal disease had positive titers [7].

The hemorrhages and vascular leakage noted in milder forms of lupus retinopathy are believed to be mediated by immune complex deposition and inflammation, while the histologic correlate of more severe occlusive disease is fibrinoid degeneration and necrosis without significant inflammation [8].

A rare ocular manifestation of SLE is lupus choroidopathy, presenting with exudative retinal detachment. Described in multiple case reports, choroidopathy is typically noted in patients with concurrent and highly active CNS and renal disease. Patients often have associated uncontrolled hypertension. The pathogenesis is suspected to be due to a combination of factors including the aforementioned uncontrolled blood pressure and immune complex deposition in the choriocapillaris. Anti-retinal pigment epithelium antibodies have also been implicated as a potential causative factor. Several series have indicated that choroidopathy may be a sensitive indicator of systemic lupus activity. The presence of SLE choroidopathy may be indicative of coexistent (although sometimes occult) nephropathy and CNS vasculitis [9].

The treatment for lupus retinopathy is immunosuppression, with corticosteroids used to rapidly control active inflammation, and steroid sparing immunomodulatory therapy used for long-term control. Retinal photocoagulation, intravitreal anti-vascular endothelial growth factor agents, and vitrectomy are used to treat the structural complications of advanced retinopathy and vaso-occlusive disease.

2.4 ANCA-Positive Vasculitis

The ANCA-associated vasculitides (AAV) include three clinical entities that are characterized by systemic vasculitis and a high prevalence of positive serologic testing for antineutrophil cytoplasmic antibodies. The three types of vasculitis are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA).

The worldwide annual incidence of ANCA-associated vasculitis is estimated to be 20 per million, with GPA accounting for about half in northern European populations, MPA a third, and the rest EGPA [10].

While ocular disease has been described in all of the ANCA-associated vasculitides, it has been best characterized and most frequent in GPA. The necrotizing vasculitis that characterizes GPA affects the upper and lower respiratory tracts and the kidneys. The antineutrophil cytoplasmic antibody (ANCA) occurs in 80% of patients with GPA. Ocular and orbital involvement can occur from 28% to 58% of patients with GPA. The typical inflammatory disease in individuals with GPA is scleritis, orbital inflammation, and peripheral ulcerative keratitis [2].

Posterior manifestations of ocular disease may include optic disk edema and subsequent atrophy from active orbital inflammation and serous retinal detachments from choroidal effusions in individuals with posterior scleritis.

Isolated retinal and choroidal disease is uncommon in most series, but reports of microangiopathy and occlusive retinal vasculitis have been described (Fig. 2.3). Microvascular changes such as cotton wool spots and retinal hemorrhages may be seen, as well as sequelae of retinal non-perfusion. Choroidal vascular occlusions and inflammatory masses have also been reported in individuals with GPA [11].

Similar to many autoimmune inflammatory diseases, the treatment of ANCA-associated vasculitis requires the use of corticosteroids and transition to immunomodulatory therapy including alkylating agents and biologics for long-term suppression of inflammation.

2.5 Susac's Syndrome

Susac's syndrome is an inflammatory microvasculopathy of undetermined etiology, affecting the brain, the cochlea, and the retina. This syndrome typically occurs in young women (20–40 years of age). Regarded as a rare disease, its true prevalence is unknown. At presentation, central nervous system signs and symptoms occur in 80% of patients, cochlear involvement (hearing loss) in 52%, and retinal findings in 46%. Only 20% of patients present with the complete triad, resulting in difficulty identifying the disorder. The diagnosis is based on clinical and radiographic findings, as there is no definitive laboratory test [2].

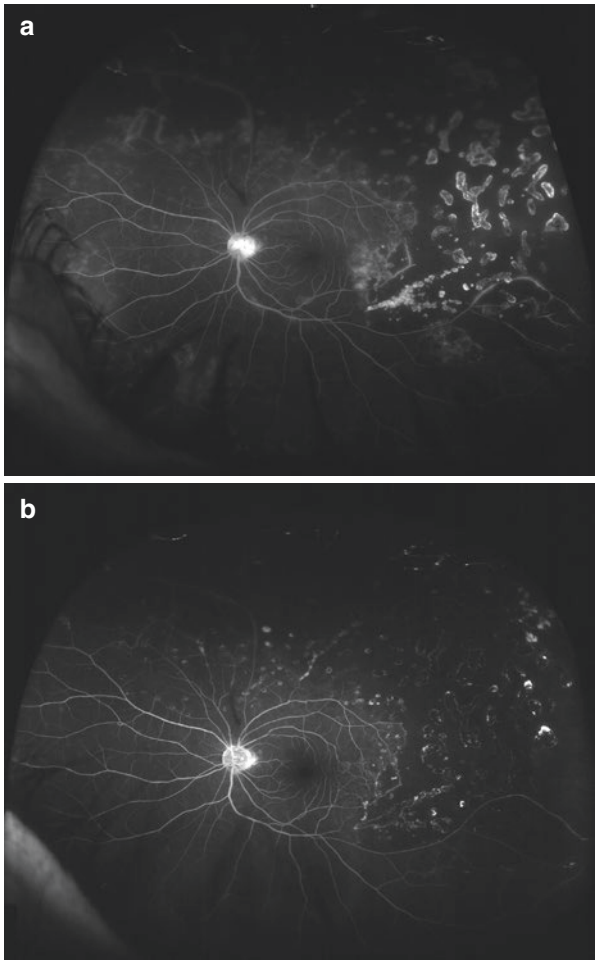

Fig. 2.3 Wide-field fluorescein angiography depicting occlusive vasculitis in an individual with GPA. There is a broad region of superior and temporal non-perfusion that was treated with laser photocoagulation (**a**). After instituting systemic anti-inflammatory therapy the patient's vasculitis stabilized with resolution of vascular leakage (**b**)

MRI findings include hyperintense foci on T2-weighted images. The lesions may occur in both gray and white matter, supratentorially or infratentorially. Lesions involving the central fibers of the corpus callosum are considered almost pathognomonic for Susac's syndrome in the appropriate clinical setting.

The ocular manifestations of this syndrome include focal arteriolar narrowing and occlusions (Fig. 2.4). Though the findings over time are usually bilateral, at the onset of disease, findings may predominate in one eye. Retinal hemorrhages and microaneurysms may be present. Over time, the occlusive retinal disease can lead to the formation of arteriolar collaterals. The vitreous and anterior chambers are usually quiet, or, at most, mildly inflamed.

The treatment of the microangiopathy generally involves immunosuppression with corticosteroids initially. Many types of steroid sparing immunosuppressive therapy have been employed with varying levels of success.

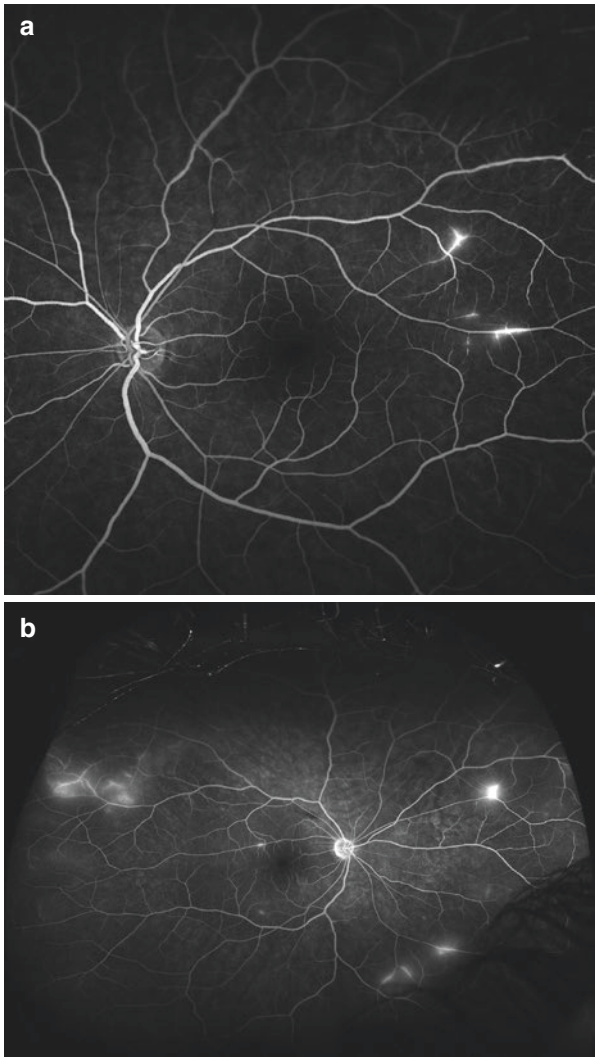

Fig. 2.4 Fluorescein angiography depicting segmental arteritis in a young female with Susac's syndrome

2.6 Other Systemic Vasculitides with Ophthalmic Manifestations

2.6.1 Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a systemic vasculitis affecting medium-sized and small muscular arteries, preferentially at bifurcations. The inflammation may result in aneurysmal dilatation which can be associated with rupture and thrombosis, yielding multisystem organ dysfunction. The skin, peripheral nerves, joints, intestines, and kidney may all be affected, in addition to the eye and orbit.

A variety of ocular manifestations have been described including scleritis, peripheral ulcerative keratitis, orbital inflammation, and retinal vasculitis. The descriptions of retinal vasculitis have included vitritis and both arterial and venous involvement (though arterial involvement has been more commonly described [12].

2.7 Kawasaki Disease

Kawasaki disease is a systemic vasculitis of children that typically affects the small- and medium-sized blood vessels of the body, in particular, the coronary arteries. It is most common in Asian children and the etiology is, as of yet, unknown.

Retinal vasculitis has not been described as a manifestation of this disease, though there is a case report demonstrating retinal ischemia suspected to be related to a thrombotic event from the systemic vasculitis [13]. The most common eye finding is bilateral conjunctival injection. Anterior uveitis, intermediate uveitis, and papilledema are less common findings. The anterior uveitis is usually bilateral and mild and responds to topical corticosteroids and systemic therapy for the vasculitis.

2.8 Takayasu's Arteritis

Takayasu's arteritis is a large-vessel granulomatous vasculitis that mostly commonly occurs in young or middle-aged Asian women. The vasculitis results in intimal fibrosis and narrowing of blood vessels, affecting pulmonary arteries and the aorta. As a result of the obstruction of the main branches from the aorta (subclavian artery, common carotid artery, brachiocephalic artery), the absence or weakening of the pulse in the upper extremities may be noted. The renal arteries may be markedly attenuated as well, leading to renovascular hypertension.

While Takayasu's arteritis is not associated with inflammation of the retinal vasculature, decreased blood flow to the retina and choroid as well as systemic hypertension may result in a variety of ocular manifestations including amaurosis fugax, hypertensive retinopathy (involvement of renal vasculature), and choroidal and retinal non-perfusion leading to ocular ischemic syndrome, retinal neovascularization, and its associated structural complications if left untreated, such as vitreous hemorrhage and neovascular glaucoma [8].

2.9 Retinal and Choroidal Imaging in Systemic Vasculitides

2.9.1 Fundus Photography

Fundus photography remains an important method for monitoring fundus changes over time and documenting findings such as hemorrhages, disk appearance, and retinal vascular caliber and branching patterns.

In addition, ultrawide-field (UWF) photography optical systems allow assessment of the retinal periphery in individuals with both media opacity and miotic pupils.

In individuals with retinal vasculitis, far peripheral vein sheathing and retinal infiltrates that denote disease activity can clearly be detected with pseudocolor imaging. Green laser and red laser separation images also provided additional informative value. Green laser light (red-free light) (532 nm) highlights the anterior retinal structures and retinal vasculature and has demonstrated utility in the visualization and quantification of lesions in the retina secondary to vasculitis. Even in patients with significant vitritis, high-definition images can be obtained to improve disease monitoring [14].

2.10 Fluorescein Angiography

The use of fluorescein angiography in ocular disease with a vasculitic component has been well established. This imaging modality allows for the direct observation of vascular hyperpermeability and capillary non-perfusion. As noted previously, the presence of predominant arteritis versus phlebitis can help narrow the differential in individuals with ocular inflammatory disease to an extent.

Behçet's disease shows a predominant phlebitis on FA, though severe arteritis and vascular occlusion may be noted rarely. Grading schema for the degree of retinal vascular leakage has been described by authors for assessing individuals with Behçet's disease and their response to treatment. Mean total vascular leakage scores based on fluorescein angiography have been shown to correlate with visual acuity over time [14].

Fluorescein angiography has been integral in diagnosing reported cases of Susac's syndrome. The pathognomonic lesions noted on FA in Susac's syndrome are multifocal, segmental areas of arteriolar narrowing with leakage of dye from the involved segments. The occlusions do not necessarily occur at the branches of the arterioles, in contrast to emboli or thrombi [12].

FA is also useful to follow treatment efficacy as steroids or other agents are tapered. The retinal and FA findings improve or resolve with treatment success and recur during flares of the syndrome. This information would allow the care team to intervene early, before further neurological or cochlear damage occurs.

The utility of ultrawide-field FA also allows for more accurate assessment of the extent of vasculitis in the retinal periphery, aiding in titration of medical therapy and also planning interventions such as laser photocoagulation.

In polyarteritis nodosa, the FA may reveal varying degrees of prolongation of the arm-to-retina circulation time given the narrowing of the proximal vessels branching from the aorta.

2.11 ICG Angiography

Angiographic evaluation with indocyanine green (ICG) can be used to study the choroidal circulation in systemic diseases.

ICG imaging has been used to visualize the choroidal circulation in lupus choroidopathy. Studies have revealed focal, transient early-phase hypofluorescence

followed by late-phase diffuse hyperfluorescence, distortion of the large choroidal vessels, and also focal clusters of choroidal hyperfluorescence in the intermediate phase. It has been postulated that the focal areas of hyperfluorescence in the intermediate frames may actually represent ICG staining of immune complexes.

Baglio et al. used indocyanine green angiography to demonstrate that subtle changes in the choroidal circulation can be seen in patients with SLE-associated nephropathy, while similar findings are not seen in SLE patients without renal involvement [15].

2.12 Optical Coherence Tomography (OCT)

OCT is a noninvasive imaging modality that is now essential in assessing individuals with retinal vasculitis. Cystoid macular edema is a common occurrence in such patients and a primary cause of vision loss, which is easily and accurately measured by OCT. OCT can be used to monitor response to both local and systemic treatments.

Additionally, the presence of inner retinal edema noted on OCT can support a diagnosis of retinal vascular occlusion.

More recently, an OCT technique termed "enhanced depth imaging" (EDI) has been utilized to provide an enhanced view of the choroid and to measure choroidal thickness. Previous studies have indicated that choroid thickness is increased during the development of Vogt–Koyanagi–Harada (VKH) disease and is greater in the acute phase of the disease than in the convalescent phase. A recent study evaluating individuals with Behçet's disease has shown that subfoveal choroidal thickness is greater in the acute phase of uveitis than in the remission phase and correlates significantly with retinal vascular leakage by fluorescein angiography [16].

OCT has also been used to evaluate retinal nerve fiber layer and central macular thickness in individuals with a history of neuro-Behçet's disease and healthy control subjects. The average RNFL in patients with neuro-Behçet's disease was significantly lower than that of healthy controls, and average central macular thickness was significantly lower [17].

Retinal vasculitis may occur in the setting of a systemic vasculitic disorder. Recognizing the systemic context in which the ocular inflammation occurs may be of critical importance, both for limiting permanent ocular sequelae and also significant systemic morbidity and mortality. Therapeutic options include local ocular treatments (local steroid, laser), but systemic immunosuppressive therapy in conjunction with these measures is paramount. Retinal imaging may serve as an integral tool for gauging both the response to therapies and the need to escalate therapy.

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