Conferences and Reviews

Retinal Vasculitis—A Primer

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Retinal vasculitis is a diagnosis that is generally suggested by an ophthalmologist. Frequently patients with the disorder are referred to nonophthalmologists for further diagnostic evaluation or treatment. The criteria for defining vasculitis differ greatly between ophthalmologists and other physicians. To facilitate collaboration between ophthalmologists and their colleagues, we have sought to clarify the term "retinal vasculitis" by discussing its subcategories, the potential role of antiphospholipid antibodies, and the etiology of retinal vasculitis. We offer guidelines for evaluating the disorder and treating patients.

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Retinal vasculitis is defined clinically as an abnormal appearance of the retinal vasculature due to inflammation. An ophthalmologist diagnoses vasculitis based on a direct visualization of the vessels and rarely has the benefit of pathologic confirmation; in contrast, vasculitis in most locations other than the eye is usually diagnosed and classified on the basis of pathologic findings (Table 1).[1] Thus, subcategories of systemic vasculitis including leukocytoclastic vasculitis, granulomatous angiitis, giant cell arteritis, systemic necrotizing vasculitis, and thromboangiitis obliterans are essentially pathologic diagnoses. In many cases, abnormalities of retinal vessels may be caused by perivascular changes rather than true disease in the vessel wall itself. Furthermore, although microvascular involvement in some organ systems may produce no symptoms, microvascular inflammation in the retina often has major and immediate visual consequences.

Many pathologic processes can affect the retinal vasculature and produce clinical findings similar to retinal vasculitis. A strict definition of retinal vasculitis excludes forms of vasculopathy due to noninflammatory processes such as atherosclerosis, congenital anomalies, or increased blood viscosity (Table 2). Inflammation may involve retinal arteries, veins, or capillaries, although venous involvement is more commonly recognized. Patients with retinal vasculitis may report reduced visual acuity, cloudy vision, diminished color appreciation, a sensation of flashing lights (photopsia), or floaters (Table 3). Some patients with retinal vasculitis are asymptomatic. The disorder by itself should not produce pain or ocular redness. One hallmark of retinal vasculitis (Table 4) is a vascular sheathing (Figure 1), which seems to correlate with a perivascular infiltrate of inflammatory cells seen on pathologic specimens.[2] Sheathing, however, is not specific for vasculitis and frequently appears, such as after a retinal vein occlusion. Inflammation involves noncontiguous portions of the vessel, is often associated with inflammatory cells in the overlying vitreous, and does not initially narrow the vessel. In contrast, sheathing due to atherosclerosis frequently occurs along with vessel narrowing, microvascular anomalies, lipid exudates, and increased light reflexes. Retinal vasculitis can result in various other nonspecific findings including cotton-wool spots or cytoid bodies (Figure 2), which are indicative of retinal ischemia; hemorrhage; Roth's spots (Figure 3), which are hemorrhages with a white center[3]; and the abrupt occlusion of retinal vessels, macular edema, or optic disc edema. Abnormal attenuation of vessels may appear as an end stage of vasculitis. Additional evidence of ocular inflammation, such as leukocytes in the vitreous humor, frequently accompanies retinal vasculitis.

Retinal vessels can be visualized directly with instruments such as a hand-held direct ophthalmoscope, an indirect ophthalmoscope, or the combination of a slit-lamp biomicroscope with an appropriate contact lens. Close scrutiny under high magnification is often required to detect vascular change. Small patches of vasculitis or peripheral retinal involvement are difficult to see by direct ophthalmoscopy. The retinal vessels are also evaluated by fluorescein angiography. The intravenous administration of sodium fluorescein permits excellent definition of the retinal vasculature. These vessels do not normally permit the extravasation of this dye. Fluorescein staining of the vessel wall does occur if the vessel is inflamed.

Retinal vasculopathy can be divided into subcategories (Table 2). Atherosclerosis, including that associated with diabetes mellitus, is the most common cause of abnormal retinal vessels but is not primarily an inflammation. Abnormal retinal vessels can result from congenital anomalies as in Coats' disease. Abnormal blood viscosity from hemoglobinopathies, leukemia, or paraproteinemias also produces abnormal retinal vessels.

Inflammatory conditions involving retinal vessels can also be subdivided. First, certain systemic illnesses (Table 5) such as Behçet's disease or sarcoidosis (Figures 4 and 5) may be associated with retinal vasculitis. Although sarcoidosis is not regarded as a systemic vasculitis, its ability to involve the wall of the retinal vasculature has been confirmed histologically.[4] Most forms of systemic vasculitis such as polyarteritis nodosa,[5] Churg-Strauss vasculitis,[6] or Wegener's granulomatosis[7] can involve retinal vessels. These are rare diseases, however, that only infrequently manifest as a retinal vasculitis. Temporal arteritis is well known for its ability to cause retinal ischemia through involvement of the ophthalmic or

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central retinal artery, but involvement of branch retinal arteries or veins has not to our knowledge been described. Multiple sclerosis[8] and Crohn's disease[9] have also been reported in association with retinal vasculitis. Systemic lupus erythematosus frequently produces retinal ischemia as manifested by cotton-wool spots,[10] but these are usually asymptomatic. Visually significant retinal vasculitis in association with systemic lupus is well described but uncommon.[11]

TABLE 1.—*Differences Between Retinal and Systemic Vasculitis*

	Vasculitis	
Basis for Diagnosis	*Retinal*	*Systemic*
Size of vessel involvement	Microvascular to small	Variable, but microvascular involvement not clinically important
Histologic findings	No	Yes

TABLE 2.—*Classification of Retinal Vasculopathy*

Disease	*Example*
Noninflammatory	
Atherosclerosis	Diabetes mellitus
Congenital anomalies	Coats' disease
Increased blood viscosity	Hemoglobinopathies, paraproteinemias
Inflammatory	
Secondary to chorioretinal inflammation	Toxoplasmosis, cytomegalovirus
As part of systemic disease	Sarcoidosis, Behçet's syndrome, polyarteritis
Vaso-occlusive disease	Anticardiolipin antibody-mediated
Primary retinal vasculitis	Eales disease, frosted branch angiitis

TABLE 3.—*Symptoms Associated With Retinal Vasculitis*

Reduced visual acuity	Central scotoma
Cloudy vision	Unusual numbers of floaters
Photopsia	Reduced color appreciation

TABLE 4.—*Physical Findings Associated With Retinal Vasculitis*

Vascular sheathing	Roth's spots
Attenuated vessels	Optic disc edema
Occluded vessels	Macular edema
Cytoid bodies	Optic nerve pallor
Cotton-wool spots	

TABLE 5.—*Systemic Illnesses Associated With Retinal Vasculitis**

Sarcoidosis	Churg-Strauss vasculitis
Behçet's disease	Antiphospholipid antibody syndrome
Systemic lupus erythematosus	Tuberculosis
Syphilis	Subacute bacterial endocarditis
Crohn's disease	Primary Sjögren's syndrome
Polyarteritis nodosa	Multiple sclerosis
Wegener's granulomatosis	Whipple's disease
Relapsing polychondritis	Malaria

*Excludes illnesses associated with vasculopathy rather than vasculitis.

A second subcategory of retinal vasculitis occurs in a localized area of chorioretinal inflammation. For example, in toxoplasmosis, acute retinal necrosis, or retinitis due to cytomegaloviral infection (Figure 6), retinal vessels adjacent to the area of chorioretinitis are frequently abnormal. The characteristics of the accompanying chorioretinal lesion should help direct the diagnostic evaluation of these diseases.

A third form of vascular abnormality appears primarily as vaso-occlusive disease. Antiphospholipid antibodies such as the lupus anticoagulant or anticardiolipin antibodies have definitely been associated with vaso-occlusive disease.[12] Increasing evidence suggests that these antibodies can be associated with retinal occlusive disease in patients with systemic lupus erythematosus[13] and in others who do not meet diagnostic criteria for lupus.[14,15] A search for these antibodies should be made in any patient who has evidence of an occlusive form of retinal vasculopathy. Patients with lupus who have retinal vascular disease secondary to anticardiolipin antibodies are more likely to have central nervous system disease. A rare microangiopathic syndrome resulting in the occlusion of retinal and cerebral vessels has been described.[16,17] The role of antiphospholipid antibodies in this condition is unknown.

Finally, many patients fall outside all of these disease subcategories and suffer from an idiopathic syndrome that has no apparent systemic correlate (Figures 7 and 8). We suggest that this disorder be labeled primary retinal vasculitis to indicate its distinctness from the subcategories we have discussed. Examples of primary retinal vasculitis include Eales disease[18] and frosted branch angiitis.[19] Eales disease refers to a periphlebitis that involves primarily vessels in the periphery of the retina (Figure 1).

In theory, the distinction between inflammatory and noninflammatory forms of vasculopathy should be clear-cut. Nonetheless, regardless of its cause, ischemia can produce secondary inflammatory changes.[20] Vascular changes due to emboli can easily be confused with an inflammatory event originating in the vessel wall. Further, occlusive disease frequently coexists with other vascular abnormalities. Systemic lupus erythematosus is a classic example of an illness that produces both occlusive vascular changes and vascular sheathing, as seen in a primary vasculitis.

Etiologic Considerations

With rare exceptions, such as toxoplasmosis or antiphospholipid antibody-mediated disease, the cause of retinal vasculitis is unknown. Tuberculosis, an extremely rare cause of uveitis in this country, was once presumed to be a common cause of retinal vasculitis. A delayed hypersensitivity response to purified protein derivative has been reported in nearly 50% of patients with Eales disease.[18] The role of this immune response in the pathogenesis of the vasculitis is not clear at this time. Antituberculous therapy has not been useful in patients with Eales disease or forms of retinal vasculitis unaccompanied by tuberculous uveitis.

Retinal vasculitis can be produced experimentally in animals by provoking an immune response against rhodopsin kinase, also known as retinal S antigen.[21] A chorioretinitis occurs along with the retinal vessel involvement. Increasing evidence supports the concept that the microvascular endothelium is intrinsically different from large-vessel endothelium.[22] It may be that unique antigens expressed by retinal vascular endothelial cells expose the vessel to immune-medi-

ated damage. Alternatively, retinal vessels may be unique in their response to specific immune complexes.

Laboratory Evaluation

The laboratory evaluation of cases of retinal vasculitis is determined largely by the results of a patient's history and physical examination. If present, a systemic illness such as Behçet's disease, polyarteritis nodosa, or systemic lupus erythematosus should be suggested by a thorough medical history. Despite the potential for a systemic process to involve retinal vessels, most patients with retinal vasculitis have no evidence of a disease process outside the eye. A recently

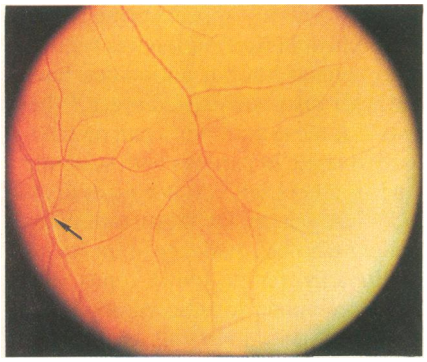

Figure 1.—The photograph shows a peripheral retinal vessel of a patient with idiopathic retinal vasculitis (Eales disease). The arrow indicates an area with significant vascular sheathing.

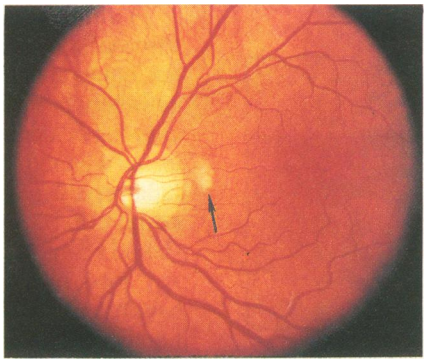

Figure 2.—A cotton-wool spot **(arrow)** indicates that local retinal ischemia is present just temporal to the optic nerve.

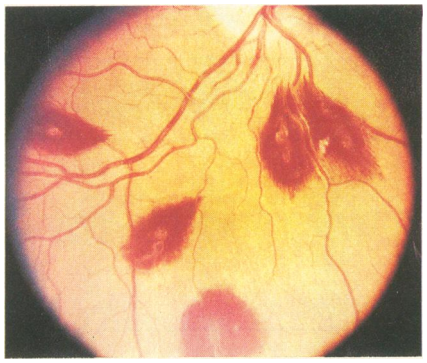

Figure 3.—Multiple Roth's spots on the fundus of a patient with acute leukemia are evident as hemorrhages with a white center.

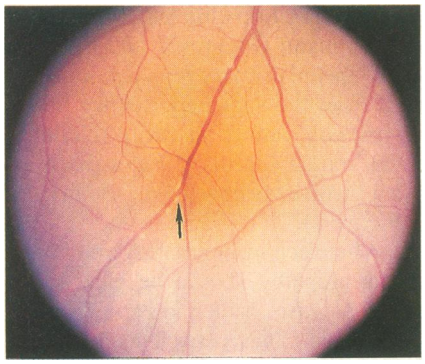

Figure 4.—The fundus photograph shows the peripheral retinal vessels of a patient with known sarcoidosis. The whitish perivascular infiltrates **(arrow)** are called candle-wax dripping.

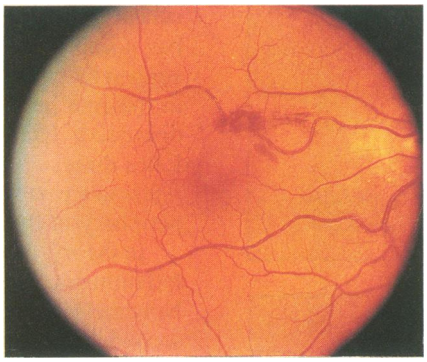

Figure 5.—In this fundus photograph of a patient with sarcoidosis, there is an area of hemorrhage and interruption of vascular flow.

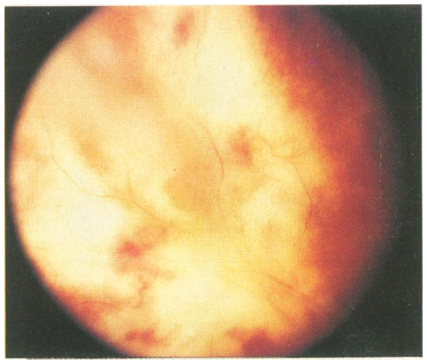

Figure 6.—The fundus of a patient with the acquired immunodeficiency syndrome and cytomegalovirus retinitis is shown. In association with the whitish areas of confluent retinitis, the retinal vessels are clearly abnormal with areas of attenuation, tortuosity, and hemorrhage.

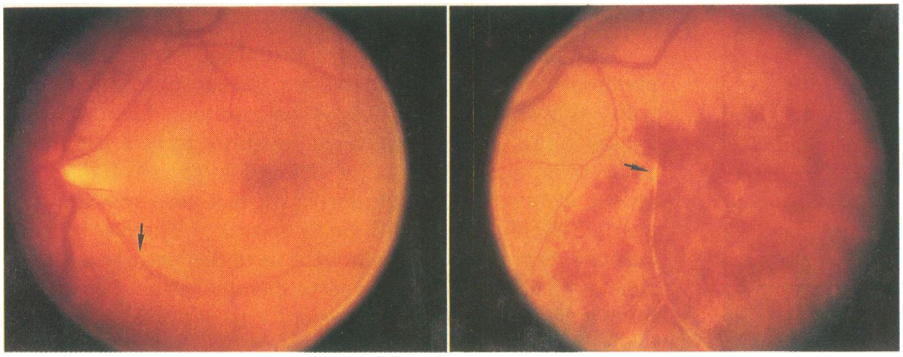

Figure 7.—Left, The fundus of the left eye of a patient with a primary retinal vasculitis shows abnormal vessels in the posterior pole. Note particularly the irregularity of the artery for the inferior temporal arcade **(arrow)**. The haze or reduced clarity of the photograph is due to associated inflammation in the vitreous. **Right,** In another photograph of the same eye, the vessel in the periphery **(arrow)** is occluded with surrounding hemorrhage.

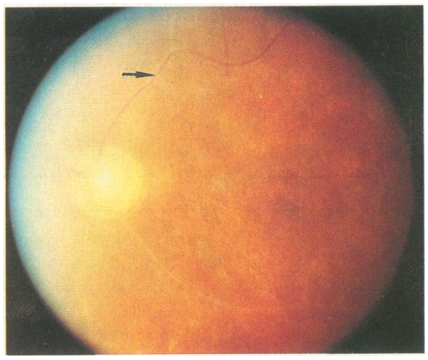

Figure 8.—The photograph shows the posterior pole of the same eye depicted in Figure 7 taken 2½ years later. Despite aggressive therapy including oral corticosteroids, periocular corticosteroids, azathioprine, intravenous cyclophosphamide, and cyclosporine at various times, the eye disease has progressed. The inferior temporal artery is now occluded, and the superior temporal artery has obvious sheathing **(arrow)**. The disc shows marked pallor.

reported southern California survey of patients with uveitis included 41 with retinal vasculitis.[23] In 38 of these patients, no underlying illness was found. In the remaining 3 patients, the vasculitis was presumed to be secondary to a systemic viral illness. In contrast, a recent British study found that many patients with retinal vasculitis do have a systemic illness, usually Behçet's disease or sarcoidosis.[24] Our own clinical experience concurs with the California report in that Behçet's disease is rare in our patient population. It accounts for about 0.4% of patients with intraocular inflammation in our demographic group. If a chorioretinal lesion accompanies the vasculitis (secondary retinal vasculitis), a specific disorder, such as toxoplasmosis, acute retinal necrosis, or cytomegaloviral infection, may be suggested. Occlusive lesions should prompt a search for antiphospholipid antibodies, and emboli arising from the heart or great vessels should be excluded.

Without signs or symptoms pointing to a specific illness, we frequently obtain a complete blood count; a chemistry screen that includes liver and renal function studies, the quantitation of serum globulin levels, and serum glucose values; a urinalysis to exclude glomerular involvement; and a sedimentation rate. These tests are rarely useful in arriving at a specific diagnosis, but they are relatively inexpensive and generally provide baseline values that could be affected by several therapeutic choices.

A chest roentgenogram is a more critical study. The chest film may show adenopathy suggestive of sarcoidosis, a disease often initially symptomatic in the eye.[25] In addition, we prefer the chest x-ray study over a purified protein-derivative skin test as a screening device for tuberculosis because skin tests are frequently positive in patients with retinal vasculitis but have no therapeutic implication. Finally, syphilis can present as a retinal vasculitis[26] and should be excluded by a serologic study such as a fluorescent treponemal antibody absorption test. Many patients with retinal vasculitis that seems confined to the eye have systemic immunologic abnormalities such as detectable circulating immune complexes.[27,28] An association with HLA-DR4 has also been reported.[29] We do not routinely search for these abnormalities because present knowledge does not assign them therapeutic or prognostic importance. Similarly, a test that is positive for antinuclear antibodies does not establish a diagnosis of systemic lupus erythematosus.[30] This test is therefore done only if other aspects of the presentation suggest this diagnosis.

Treatment

The treatment of retinal vasculitis depends on the detection of an associated condition, the severity of the disease, and whether the process is unilateral or bilateral. If its cause is infectious, the disorder should be managed with appropriate antibiotic therapy. In the absence of a specific infection, the periocular administration of corticosteroids may help control the inflammation. We elect not to institute any therapy for many patients with retinal vasculitis. For example, patients with Eales disease often have a smoldering course, and the peripheral nature of the disease spares central acuity. Because present therapy is palliative rather than curative, patients may need to accept some degree of visual loss rather than undergo potentially toxic therapy. If the disease is bilateral and interferes considerably with activities of daily living, parenteral corticosteroid therapy at an initial dose equivalent of 40 to 60 mg of prednisone per day is sometimes effective. No controlled studies have been done on the treatment of retinal vasculitis. We reserve systemic immunomodulatory therapy beyond corticosteroids for those patients with active inflammation, bilateral inflammation, and a best-corrected vision of no better than 20/50. The use of cyclosporine has been beneficial in a limited number of patients.[31] We have used azathioprine or cyclophosphamide at dosages comparable to what has been suggested for patients with systemic vasculitides.[1] Many authorities recommend anticoagulation for vascular disease due to antiphospholipid antibodies.[15] The prognosis for retinal vasculitis is variable, reflecting the heterogeneous nature of this group of disorders.

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