REVIEW

Retinal Vasculitis

ABSTRACT  Retinal vasculitis is a sight-threatening intraocular inflammation affecting the retinal vessels. It may occur as an isolated ocular condition, as a manifestation of infectious or neoplastic disorders, or in association with a systemic inflammatory disease. The search for an underlying etiology should be approached in a multidisciplinary fashion based on a thorough history, review of systems, physical examination, and laboratory evaluation. Discrimination between infectious and noninfectious etiologies of retinal vasculitis is important because their treatment is different. This review is based on recently published articles on retinal vasculitis and deals with its clinical diagnosis, its link with systemic diseases, and its laboratory investigation.

KEYWORDS  Retina; vasculitis; fluorescein angiography; laboratory diagnosis

INTRODUCTION

Retinal vasculitis is a sight-threatening inflammatory eye disease that involves the retinal vessels. It may occur as an isolated idiopathic condition, as a complication of infective or neoplastic disorders, or in association with systemic inflammatory disease (Table 1).

Clinical Findings

Retinal vasculitis may be either symptomatic or asymptomatic. If the retinal vascular changes are in the periphery of the fundus without vitreous involvement, patients may have minimal or no symptoms. Patients with inflammation of the posterior retinal blood vessels and/or vitreous cells, however, may experience a decrease in vision or may notice floaters. Visual field scotomata may develop and are usually related to the areas of ischemia.

Active vascular disease is characterized by sheathing or cuffing of blood vessels, and vitreous cells. Inflammation of macular blood vessels can cause macular edema. Occlusive retinal vasculitis may cause cotton-wool spots representing microinfarcts, retinal edema, and intraretinal hemorrhage. Late changes secondary to vascular occlusion and remodelling include telangiectasis, microaneurysms, and ischemia-induced neovascularization. These clinical signs may be confirmed by fluorescein angiography, which demonstrates leakage of the dye due to breakdown of the inner blood-retinal barrier, and staining of the blood vessel wall with fluorescein. Fluorescein angiography is a more sensitive technique and will frequently show that the vasculitis is more extensive than the
TABLE 1  Disorders associated with retinal vasculitis.

Infectious disorders
- Bacterial disorders (tuberculosis, syphilis, Lyme disease, Whipple’s disease, brucellosis, cat-scratch disease, endophthalmitis)
- Viral disorders (human T-cell lymphoma virus type 1, cytomegalovirus, herpes simplex virus, varicella zoster virus, Rift Valley fever virus, hepatitis, acquired immunodeficiency syndrome, West Nile virus infection)
- Parasitic disorders (toxoplasmosis)
- Rickettsial disorders (Mediterranean spotted fever)

Neurologic disorders
- Multiple sclerosis
- Microangiopathy of the brain, retina, and cochlea (Susac syndrome)

Malignancy
- Paraneoplastic syndromes
- Ocular lymphoma
- Acute leukemia

Systemic inflammatory disease
- Behçet’s disease
- Sarcoidosis
- Systemic lupus erythematosus
- Wegener’s granulomatosis
- Polyarteritis nodosa
- Churg-Strauss syndrome
- Relapsing polychondritis
- Sjögren’s A antigen
- Rheumatoid arthritis
- HLA-B27-associated uveitis
- Crohn’s disease
- Postvaccination
- Dermatomyositis
- Takayasu’s disease
- Buerger’s disease
- Polymyositis

Ocular disorders
- Frosted branch angiitis
- Idiopathic retinal vasculitis, aneurysms, and neuroretinitis
- Acute multifocal hemorrhagic retinal vasculitis
- Idiopathic recurrent branch retinal arterial occlusion
- Pars planitis
- Birdshot retinochoroidopathy

clinical examination suggests. In our experience, optical coherence tomography is a highly effective method for the diagnosis of macular edema in uveitis as it provides highly reproducible measurements of retinal thickness in micrometers. In addition, it is of great value in assessing the results of treatment for uveitic cystoid macular edema (Fig. 1). The two main causes of visual loss are cystoid macular edema and new blood vessel formation resulting from retinal ischemia that can lead to vitreous hemorrhage and traction retinal detachment.¹

Retinal vasculitis affecting predominantly the veins has been described in association with Behçet’s disease, tuberculosis, sarcoidosis, multiple sclerosis, pars planitis, retinal vasculitis associated with tuberculoprotein hypersensitivity (Eales’ disease), and human immunodeficiency virus (HIV) infection. In certain diseases with predominantly arterial involvement (e.g., systemic lupus erythematosus and polyarteritis nodosa), the retinal arteries bear the brunt of the disease. Intraretinal infiltrates are characteristic of infectious processes; however, in the absence of these, they are pathognomonic of Behçet’s disease. Cotton-wool spots are most often found in association with a systemic vasculitis. Swelling of the optic nerve head is a common nonspecific finding related to intraocular inflammation, but may also represent infiltrative disease of the nerve itself or optic nerve head vasculitis as in patients with Behçet’s disease.

INFECTIOUS RETINAL VASCULITIS

Tuberculosis

*Mycobacterium tuberculosis* is an aerobic acid-fast bacillus that causes human tuberculosis. The most common manifestation of ocular tuberculosis in patients with pulmonary tuberculosis is choroiditis.² Retinal periphlebitis with a marked tendency to peripheral retinal capillary closure leading to new vessel formation has been reported to be the presenting sign of tuberculosis.³

Ocular manifestations of tuberculosis can be due to direct infection or to indirect hypersensitivity mechanisms to mycobacterial antigens when there is no defined active systemic lesion elsewhere or the lesion is thought to be inactive.³ In addition to the retinal periphlebitis caused by direct infection, there is evidence

**FIGURE 1**  (A) Optical coherence tomography (OCT) of the left eye of a 26-year-old man with retinal vasculitis secondary to Behçet’s disease showing cystoid macular edema. Macular thickness measured by the retinal thickness map was 445 µm. Visual acuity was 20/100. (B) Ten months after starting infliximab therapy, OCT displays normal anatomy of the macula with a reduction of macular thickness to 207 µm. Visual acuity improved to 20/25.
to support an immune-mediated cause of retinal periphlebitis in patients with tuberculoprotein hypersensitivity (Eales’ disease). Eales’ disease manifests as an obliterative periphlebitis (Fig. 2) affecting the retina in multiple quadrants, starting at or anterior to the equator and progressing posteriorly. This inflammation-induced vascular occlusion (Fig. 3) can lead to a proliferative vascular retinopathy with sequelae such as recurrent vitreous hemorrhage and traction retinal detachment (Fig. 4). The disease appears most commonly to affect healthy young adults in the third and fourth decades of life. Men may be affected more often than women. The disease appears to be more prevalent in India, Pakistan, and Afghanistan.2

Although the clinical characteristics and natural course of Eales’ disease are well known, the etiopathogenesis is not yet well understood. Of the several etiologies proposed, most favored are tuberculosis and hypersensitivity to tuberculoprotein. Recently, *M. tuberculosis* complex DNA was detected in vitreous fluid samples of Eales’ disease patients using polymerase chain reaction.4 Another study demonstrated the presence of *M. tuberculosis* DNA by nested polymerase chain reaction technique in epiretinal membrane specimens from patients with Eales’ disease.5 Bacteriological examination of vitreous fluid samples did not reveal the presence of acid-fast bacilli.4 In addition, Biswas et al.6 found statistically significant, higher phenotype frequencies of (HLA) B5 (B51), DR1, and DR4 in patients with Eales’ disease compared with healthy people. It is postulated that individuals with the HLA predisposition may develop retinal vasculitis as a result of a cell-mediated immunological tissue damage triggered by a sequestered *M. tuberculosis* antigen in an inactive form and clinically present as Eales’ disease.5

The diagnosis of intraocular tuberculosis has been reviewed.2 A definitive diagnosis of intraocular tuberculosis requires the identification of *M. tuberculosis* organisms in ocular tissues or fluids. Because of the difficulty and potential ocular morbidity associated with obtaining biopsy material from the eye, the diagnosis of intraocular tuberculosis in the majority of reported cases is presumptive. The presence of active or inactive extracellular tuberculosis infection does not prove that intraocular tuberculosis exists. In the investigation of these patients, a chest x-ray should be performed routinely, although ocular tuberculosis has been reported to occur without demonstrable evidence of pulmonary infection. Recently, computed chest tomography was found to reveal the presence, dimensions, and activity of tuberculous mediastinal lymphadenopathy which routine chest x-rays were unable to detect in patients with presumed tuberculous retinal vasculitis.7 Extrapulmonary tuberculosis may occur without clinically or radiographically apparent pulmonary disease. The tuberculin skin testing provides a simple and easily performed investigation. The definitive systemic diagnosis is made by culture of *M. tuberculosis* from body fluids or biopsy material. Bronchoscopy, gastric lavage, liver biopsy, lymph node biopsy, or fecal culture must be performed as
required by the clinical history. A definitive diagnosis of ocular tuberculosis requires smears and cultures of aqueous humor or vitreous. Molecular biologic techniques have been developed. Polymerase chain reaction has added a new dimension for the detection of *M. tuberculosis* in intraocular fluid samples from patients with tubercular retinal vasculitis. Recently, Sakai et al. demonstrated that the detection of anticord factor antibody may be useful to support the diagnosis of ocular tuberculosis. A positive result for anticord factor antibody may indicate that tubercle bacilli are present in some organ(s) of the patient even in the absence of active systemic disease. There are no sufficient data to justify the diagnosis of ocular tuberculosis on the basis of response to isoniazid.

The management of active tuberculous retinal vasculitis or retinal vasculitis associated with tuberculo-protein hypersensitivity (Eales’ disease) requires the use of systemic steroids and appropriate antituberculous therapy to avoid reactivation of systemic illness. Rosen et al. reported a series of patients with intraocular tuberculosis in which one of the patients with retinal vasculitis and no evidence of active systemic disease at presentation developed miliary tuberculosis following treatment with corticosteroids alone. New vessel formation associated with retinal vasculitis and capillary closure responds to panretinal photocoagulation. Early vitrectomy and adequate endolaser photocoagulation should be considered in eyes with non-resolving vitreous hemorrhage associated with active fibrovascular proliferation.

**Syphilis**

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. The incidence of syphilis has markedly increased since the mid-1980s. Because of the protean manifestations of the disease, it has been called the ‘great imitator’. The ability of syphilis to mimic different ocular disorders can lead to misdiagnosis and a delay in appropriate antimicrobial therapy. Syphilis, therefore, needs to be excluded in all patients with retinal vasculitis. Posterior segment complications include vitritis, chorioretinitis, retinal vasculitis, venous and arterial occlusive disease, exudative retinal detachment, macular edema, neuroretinitis, optic neuritis, optic atrophy, choroidal neovascular membranes, and pseudoretinitis pigmentosa. Leuetic vasculitis is more commonly arterial, but an isolated periphlebitis has also been reported. The diagnosis of syphilis is based on clinical history, physical examination, and laboratory tests including the Venereal Disease Research Laboratory (VDRL) test, the fluorescent treponemal antibody absorption testing (FTA-ABS), and micro-hemagglutination-T pallidum test (MHA-TP). Because syphilitic uveitis may occur in later stages of syphilis when screening VDRL will be falsely negative, it is mandatory to perform a confirmatory FTA-ABS or MHA-TP test.

**Lyme Disease**

Lyme disease is caused by the tick-borne spirochete, *Borrelia burgdorferi*. This spirochete is transmitted to humans from infested deer, birds, or field mice by the bite of an infected tick of the *Ixodes* genus. The clinical manifestations of classical, untreated, Lyme disease occur in three stages. Stage 1 is the localized annular skin rash and flu-like symptoms. Stage 2 follows weeks or months later with varied systemic symptoms with dermatologic, neurologic, cardiac, and musculoskeletal involvement. Stage 3 consists of chronic arthritis and neurologic symptoms. Ocular manifestations can involve any of the ocular structures and they can occur at any stage of Lyme borreliosis. Posterior segment inflammation may manifest as intermediate uveitis, vitritis, multifocal chorioretinitis, retinal vasculitis, cystoid macular edema, exudative retinal detachment, branch retinal artery occlusion, branch retinal vein occlusion, or panophthalmitis. Retinal vasculitis can be complicated by neovascularization and vitreous hemorrhage. Retinal vasculitis is frequent in patients with intraocular inflammation. Subsequently, Lyme borreliosis should be taken into account in the differential diagnosis of retinal vasculitis, especially in areas endemic for the disease. Diagnosis is based on clinical history, clinical ocular and systemic findings, determination of antibodies to *B. burgdorferi* using enzyme-linked immunosorbent assay and immunoblot analysis, detection of *B. burgdorferi* DNA by polymerase chain reaction, and exclusion of other infectious and inflammatory causes. Cytologic examination of vitreous specimens of patients with posterior uveitis may demonstrate *B. burgdorferi.*

**Cat-Scratch Disease**

*Bartonella henselae* has been demonstrated to be the principal cause of cat-scratch disease, with the reservoir
for *B. henselae* in domestic cats. Contact with kittens and cats under one year of age is documented in about 90% of cat-scratch disease cases. The transmission of *B. henselae* from cats to humans usually occurs via scratches or by the contamination of surface wounds. A local macula, papula, or vesicle occurs at the inoculation site (sometimes accompanied by a febrile syndrome) and is followed by tender, regional lymphadenopathy that resolves over several months. Numerous ocular manifestations have been reported in cat-scratch disease. Parinaud’s oculoglandular syndrome with granulomatous conjunctivitis and preauricular lymphadenopathy is the most common. Other ocular manifestations include neuroretinitis, optic neuritis, papillitis, vitritis, pars planitis, nongranulomatous anterior uveitis, acute multifocal inner retinitis, focal retinitis, focal choroiditis and serous retinal detachment, branch retinal arteriolar and venular occlusions, retinal vasculitis, and peripapillary angiomatosis. The diagnosis of ocular cat-scratch disease, given the broad range of findings, requires a high index of suspicion. The primary inoculation site and regional lymphadenopathy must be sought.

*B. henselae* infection may be identified by serologic evaluation of antibody titers or by polymerase chain reaction molecular techniques. Although the cat-scratch skin test (prepared from aspirated pus) is sensitive and specific, the fear of pathogen contamination and lack of standardization have led to its general avoidance.24–26

**Toxoplasmosis**

Toxoplasmosis is caused by the obligate intracellular parasite, *Toxoplasma gondii*. The cat is the definitive host, while humans are incidental hosts. Human infections may occur by either the congenital or the acquired route. Ocular lesions primarily affect the retina. The hallmark of ocular toxoplasmosis is focal necrotizing retinitis, ultimately resulting in characteristic atrophic scars. Reactivation is frequently situated adjacent to an old atrophic scar with hyperpigmentation along the borders, indicating an old infection (satellite formation). Anterior uveitis, which may be granulomatous, and a secondary rise in intraocular pressure may also be noted. There may be an associated retinal vasculitis, which may be either near to or distant from the focus of active retinochoroiditis27 (Fig. 5). In rare cases, the vasculitis may be occlusive, resulting in retinal infarction and consequent visual field defects. Recently, a case of frosted branch angiitis secondary to toxoplasmic retinochoroiditis was reported.28 In addition, Diaz-Valle et al.29 reported a case of acute frosted branch angiitis without necrotizing chorioretinitis associated with acquired toxoplasmosis. That patient developed late peripheral retinochoroidal scarring. Similarly, Holland et al.30 reported the development of intraocular inflammatory reactions including vitritis, iridocyclitis, and retinal vasculitis without necrotizing retinal lesions in individuals with acquired *T. gondii* infection. Foci of retinitis or inactive retinochoroidal scars were seen in the same eyes during follow-up examinations suggesting that the initial inflammation may be caused by the presence of parasites in retinal tissue. These data strongly suggest that acquired *T. gondii* infection should be considered in the differential diagnosis of patients with retinal vasculitis, especially in the presence of constitutional symptoms suggesting systemic toxoplasmosis. More severe or atypical ocular presentations occur in immunocompromised patients.

Diagnosis is based on clinical history and fundus examinations and is supported by serologic evidence of *T. gondii* exposure. The high incidence of IgG antibodies against *Toxoplasma* in the population can be explained primarily by past acquired infections; therefore, a positive IgG test is not discriminatory for ocular disease and may not even be related to the eye lesion. Because a negative test is thought to rule out the diagnosis of ocular toxoplasmosis, ophthalmologists have often urged that tests be performed with undiluted serum. Demonstration of the local synthesis of *Toxoplasma* antibodies in the eye by intraocular fluid analysis is a valuable diagnostic tool. Intraocular antibody production is considered to have taken place if the relative amount of specific antibodies compared with total immunoglobulin level found in the aqueous exceeds the relative amount of these antibodies in the serum (Goldmann-Witmer coefficient). Cytologic identification of *T. gondii* from
vitreous specimens has been described. The diagnosis of congenital disease in newborns is established by the detection of specific IgM or IgA antibodies or the demonstration of stable or rising titers of IgG antibodies for a period of several months after birth. Intraocular fluid samples may be assessed by the polymerase chain reaction for *Toxoplasma* DNA. Rarely is a choriretinal biopsy performed to show *T. gondii* organism or cyst.31−33

**Human T-Cell Lymphoma Virus Type 1 (HTLV-1)-Associated Uveitis**

Human T-cell lymphotropic virus type 1 (HTLV-1), a single-stranded RNA retrovirus, is the first retrovirus to be associated with human disease. HTLV-1 is transmitted by sexual contact, by blood transfusion, transplacentally from mother to child, and via breast feeding. The infection is diagnosed by serology, demonstrating antibodies to the virus, and confirmed by Western blot analysis. HTLV-1 infection is endemic in Japan, the Caribbean islands, and parts of Central Africa and South America. The major target cell of HTLV-1 is the CD4 T-cell. HTLV-1 infection is the established cause of adult T-cell leukemia/lymphoma (ATL, an aggressive malignancy of CD4+ lymphocytes), HTLV-1-associated myelopathy ((HAM)/tropical spastic paraparesis (TSP), ademyelinating inflammatory disease of the spinal cord), and HTLV-1 uveitis (HU, defined as uveitis of undetermined etiology in an HTLV-1 carrier). Clinically, HU has been described as acute granulomatous or nongranulomatous uveal reactions that are accompanied by vitritis and retinal vasculitis. The ocular disease is considered benign, resolving over weeks in response to corticosteroid treatment, with low incidence of complications and good visual prognosis. Gray-white granular deposits scattered on the retinal vessels in the posterior pole have been noted. Similar material has also been found to deposit on the vitreoretinal interface of the foveal areas. In addition, retinal vasculitis with sheathing of retinal veins in the periphery has been described in patients with HTLV-1-associated myelopathy.34−36 Recently, Nakao and Ohba37 reported three HTLV-1-positive Japanese teenagers presenting with extensive retinal periphlebitis resembling frosted branch angiitis. The retinal vascular disease responded poorly to systemic corticosteroids, had a smoldering course, and eventually resulted in diffuse chorioretinal degeneration. Levy-Clarke et al.38 reported a patient with ATL presenting as bilateral retinal vasculitis associated with necrotizing retinitis. These cases suggest that HTLV-1 should be included in the differential diagnosis of retinal vasculitis, particularly in patients from endemic areas.

**Cytomegalovirus**

In the majority of cases, cytomegalovirus (CMV) retinitis is a manifestation of AIDS and the most common ocular infection in AIDS patients. The classic description of CMV retinitis is one of scattered yellow-white areas of necrotizing retinitis with variable degrees of hemorrhage and mild vitreous inflammation (‘cottage cheese with catsup’ or ‘pizza pie’ retinopathy). The pathway of expanding lesions can be predicted by the appearance of venous sheathing or white dots distal to the leading edge. CMV retinitis is often accompanied by varying amounts of retinal vasculitis consisting primarily of perivenous sheathing.39,40 Frosted branch angiitis has been described in patients with AIDS associated with small patches of CMV retinitis.31,42 Perivasculitis of the peripheral vessels involving veins more often than arteries has been described in patients with AIDS, CMV retinitis was not seen in these patients. The vasculitis was thought to be a noninfectious retinopathy associated with AIDS.43,44 Recently, Fine et al.45 reported a case of an HIV-infected child with frosted branch angiitis without CMV retinitis that was refractory to specific anti-CMV therapy. The angiitis only improved after subsequent treatment with systemic corticosteroids, suggesting that the frosted branch angiitis in this patient was not caused by CMV.

**Acute Retinal Necrosis**

Acute retinal necrosis is caused by the herpes group of viruses, mainly varicella zoster, herpes simplex types 1 and 2, and, rarely, CMV.46 It was demonstrated that acute retinal necrosis in a patient older than 25 years of age was more likely to be caused by varicella zoster or herpes simplex 1, whereas this type of necrosis in a patient younger than 25 years of age was more likely to be caused by herpes simplex virus type 2. A history of central nervous system infection in a patient with acute retinal necrosis syndrome suggests that herpes simplex virus is likely to be the viral cause.46 A history of neonatal herpes, triggering events such as neurosurgery, periocular trauma, and high-dose corticosteroids, and chorioretinal scars were present in patients with herpes
simplex virus type 2-related acute retinal necrosis, suggesting that herpes simplex virus type 2 retinitis reflects reactivation of herpes simplex virus type 2 infection.\textsuperscript{47}

The prominent features of acute retinal necrosis include peripheral necrotizing retinitis, retinal arteritis, and a prominent inflammatory reaction in the vitreous and anterior chamber (Fig. 6). Optic neuritis occurs in many affected eyes, and complicated rhegmatogenous retinal detachments are often encountered as a late sequela of the condition.\textsuperscript{48} The disease can progress rapidly with vision loss due to macular involvement, retinal detachment, or optic neuropathy.

In the earlier reported cases, the patients were immunocompetent. However, acute retinal necrosis is known to occur in immunocompromised individuals. Rochat et al.,\textsuperscript{49} for example, demonstrated impaired cellular immunity in apparently immunocompetent acute retinal necrosis patients. In addition, Kezuka\textsuperscript{50} demonstrated the absence of delayed hypersensitivity reactivity to varicella zoster virus antigens (i.e., immune deviation) in patients with acute retinal necrosis. These findings suggest that acute retinal necrosis may develop in association with an imbalance of the immune system.

Polymerase chain reaction is a highly sensitive, specific, and rapid way of detecting viral DNA in intraocular fluid samples.\textsuperscript{46,51} The Goldmann-Witmer coefficient was used to demonstrate intraocular antibody production to varicella zoster virus or herpes simplex virus.\textsuperscript{52}

**Rift Valley Fever Virus**

Rift valley fever is an arthropod-borne phlebovirus disease caused by *Bunyaviridae*, an RNA virus with a diameter of 94-100 nm that is transmitted to humans through a bite by infected mosquitoes or through direct contact with infected animals. Rift Valley fever virus can cause retinitis, occlusive retinal vasculitis, cotton-wool spots, retinal hemorrhages, and retinal edema\textsuperscript{53,54} (Fig. 7).

**Whipple’s Disease**

Whipple’s disease is a rare disease caused by infection with the gram-positive bacterium *Tropheryma whippelii*. The most common presenting manifestations are weight loss, diarrhea, migratory, nondeforming seronegative polyarthralgias, and abdominal pain. Extraintestinal involvement primarily includes the central nervous system (CNS), lungs, and heart, although any other site, including the eye, may be affected. The diagnosis is based on clinical findings as well as microscopic examination of biopsy specimens and, more recently, polymerase chain reaction analysis, which has high sensitivity and specificity. Although the organism historically has been difficult to culture, several recent attempts have been successful. Current treatment is based on the administration of trimethoprim-sulfamethoxazole for at least one year. Ocular manifestations have usually been secondary to CNS involvement and include gaze palsy, nystagmus, and, most frequently, ophthalmoplegia. Intraocular manifestations have been reported with or without CNS involvement and include uveitis, vitritis, vitreous hemorrhage, retinal hemorrhage, papillitis, papilledema, multifocal chorioretinitis, and retinal vasculitis.\textsuperscript{55,56} Diagnostic polymerase chain reaction on vitreous samples and recognition of key presenting symptoms in patients with ocular Whipple’s disease allows earlier definitive diagnosis.\textsuperscript{56}

**West Nile Virus Infection**

West Nile virus (WNV) is a single-stranded RNA flavivirus endemic to Africa, Asia, Australia, and Europe.
It was first detected in the United States in 1999 during a meningoencephalitis epidemic in New York City. It belongs to the group including the Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, and Kunjin virus. Birds are the natural hosts for the virus, and the virus can be transmitted from them to humans and other animals by the bite of an infected mosquito. The incubation period of the WNV ranges from 3 to 14 days. Approximately 20% of infected humans become symptomatic with fever, and typically only half of them are ill enough to seek medical attention. More severe symptoms include fever, malaise, anorexia, nausea, vomiting, eye pain, headache, myalgia, arthralgia, rash, and lymphadenopathy. The infection can progress to a meningoencephalitis with symptoms of headache, stiff neck, weakness, and confusion. Advanced age, immunosuppression, and diabetes are risk factors for poorer clinical outcomes. In addition to the clinical findings, the diagnosis is confirmed by laboratory detection of the IgM antibody to the virus in serum or cerebrospinal fluid. At present, there is no effective treatment for WNV infection. Recent reports have suggested that acute WNV may cause anterior uveitis, vitritis, multifocal chorioretinitis, optic neuritis, optic nerve head edema, retinal hemorrhages, white-centered retinal hemorrhages, subretinal hemorrhages, serous retinal detachment, macular star, cystoid macular edema, optic disc edema, branch retinal artery occlusion, and branch retinal vein occlusion. These reports show a striking similarity in both the funduscopic and angiographic appearance of the chorioretinal lesions. Kaiser et al. also reported a patient with occlusive retinal vasculitis with confirmed WNV infection.

**Mediterranean Spotted Fever**

Mediterranean spotted fever (MSF) is endemic in Mediterranean countries. The disease is transmitted to humans by the dog tick *Rhipicephalus sanguineus*. The etiologic agent for this infection is *Rickettsia conorii*, a small coccobacillary intracellular bacterium. The main reservoir of infection is domestic dogs, rabbits, and rodents. In rickettsiosis, proliferation of the organism in the vascular endothelium results in vasculitis and microinfarcts. The initial clinical presentation of MSF develops after a 5-7-day incubation period and includes high fever, headache, and malaise. A local skin lesion, termed traché noire (black spot), occurs in 50-75% of the patients. The skin rash, usually maculopapular in type, appears over the next few days. The prognosis is usually good; however, systemic complications sometimes occur and the mortality rate is 2-3%.

Diagnosis of MSF is usually based on clinical features confirmed by serologic detection of antibodies to *R. conorii*. Systemic manifestations of *R. conorii* infection are effectively treated with oral tetracyclines. Retinal vasculitis was reported in 45-55% of the patients and is considered to be an important clinical sign of MSF in endemic areas. Other posterior segment manifestations include mild vitreous inflammation, white retinal lesions, intraretinal hemorrhages, white-centered retinal hemorrhages, subretinal hemorrhages, serous retinal detachment, macular star, cystoid macular edema, optic disc edema, branch retinal artery occlusion, and branch retinal vein occlusion. The presence of any of the aforementioned posterior segment changes in a patient with fever and/or skin rash living in or returning from a specific endemic area, especially during the spring or summer, strongly suggests a diagnosis of *R. conorii* infection.

**RETINAL VASCULITIS ASSOCIATED WITH NEUROLOGIC DISEASES**

**Multiple Sclerosis**

Multiple sclerosis (MS) is a chronic disease of unknown etiology that causes demyelination and sclerosis in the central nervous system. Predominantly, the disease affects young adults, with the age of onset typically between 20 and 40 years of age. More females than males are affected.

Various ocular inflammatory changes have been described in patients with MS and may be the presenting sign of the disease. They include nongranulomatous and granulomatous iridocyclitis, intermediate uveitis, retinitis, periphlebitis (Fig. 8), and optic neuritis. Retinal periphlebitis has been described as a common manifestation of MS. It has been observed with

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**Figure 8** (A) Peripheral retina of a 24-year-old woman with multiple sclerosis showing perivenous sheathing. (B) Fluorescein angiogram showing focal venous leakage.
an average frequency of 11.5% in more than 3000 published cases of MS examined for sheathing. In an autopsy series of 93 eyes from patients with definite MS, segmental lymphoplasmacytic perivenous infiltrates were found in seven eyes and focal lymphocytic or granulomatous retinitis was present in five. The foci of granulomatous retinal inflammatory cells were noted in the inner retina and overlying vitreous and corresponded to white plaques visible on the inner retinal surface on gross examination. Round dot-like opacities, the diameter of a medium-sized vein, visible in the vitreous immediately overlying the retina were originally described by Rucker. These have come to be known as ‘Rucker bodies’. It has been demonstrated that demyelinative plaques in the brain typically encircle a venule and that, in an active lesion, perivenular infiltrates are present. These changes appear similar to the periphlebitis occurring in the retina. The periphlebitis can progress to occlusive peripherial vasculitis, which results in peripheral retinal neovascularization and tractional or rhegmatogenous retinal detachments or both. Peripheral scatter photocoagulation and vitrectomy may be required to stabilize the proliferative retinopathy. Magnetic resonance imaging scans that show periventricular foci of hyperintensity in conjunction with cerebrospinal fluid oligoclonal bands are the most sensitive for detecting MS.

**Microangiopathy of the Brain, Retina, and Cochlea (Susac Syndrome)**

Susac syndrome is a rare disease of unknown pathogenesis. It is caused by microangiopathy affecting the arterioles of the brain, retina, and cochlea, giving the classic triad of encephalopathy, branch retinal arterial occlusions, and sensorineural hearing loss. The underlying process is believed to be a small-vessel vasculitis causing microinfarcts of the retina, brain, and cochlea. Susac syndrome usually occurs in young women, but can affect men. In those cases in which a brain biopsy was performed, histopathologic examination results showed microinfarcts and perivascular inflammatory infiltrates of small vessels consistent with an active small-vessel angiitis. Magnetic resonance imaging of the brain often shows lesions suggestive of MS. Fluorescein angiography may show arteriolar wall hyperfluorescence. Early recognition of the syndrome is important because treatment with systemic immunosuppression including parenteral or oral corticosteroids or cyclophosphamide may minimize permanent cognitive, audiologic, and visual sequelae. In patients in whom rapid diagnosis has led to early administration of immunosuppressive therapy, recovery can be almost complete.

**RETINAL VASCULITIS SECONDARY TO MALIGNANCY**

**Paraneoplastic Syndromes**

Cancer-associated retinopathy is an uncommon paraneoplastic event accompanying neoplasias that occur distant from the site of the tumor and is typically secondary to small-cell carcinoma of the lung followed by gynecologic and breast cancers. Autoimmunity has been proposed as a contributing factor to paraneoplastic vision loss. Circulating antibodies that recognize retinal photoreceptor, bipolar, and ganglion cells have been demonstrated. These patients present with a retinitis pigmentosa-like disease with progressive night blindness, visual loss, visual field loss, and attenuated retinal arterioles. Retinal phlebitis and vitritis have also been reported. Melanoma-associated retinopathy is a visual paraneoplastic syndrome occurring in some patients with metastatic cutaneous malignant melanoma. These patients present with a sudden onset of night blindness. Melanoma-associated retinopathy is characterized by a negative electroretinogram, similar to the pattern seen in congenital stationary night blindness. Autoantibodies from serum of patients were shown to stain rod bipolar cells in the retina. Retinal periphlebitis was reported in a patient with melanoma-associated retinopathy.

**Ocular Lymphoma**

Ocular lymphoma usually presents as a chronic uveitis, occurring in the elderly and responding poorly to corticosteroids. Arterial and venous sheathing has been described. Ocular lymphoma, therefore, should be considered in the differential diagnosis of patients with the unexplained onset of retinal vasculitis.

If clinical suspicion is high, magnetic resonance imaging and lumbar puncture should be performed. Ultrasonography may be helpful to identify subtle chorioretinal thickening. A vitreous biopsy should be performed if the diagnosis remains unclear.
Acute Leukemia

Retinal infiltration producing perivascular sheathing has been described in patients with acute leukemia. Lumbar punctures are positive for leukemic cells. Appropriate leukemic therapy is effective in inducing the resolution of this condition. A case of retinal vasculitis and recurrent posterior uveitis which occurred in hairy cell leukemia has also been reported.

RETINAL VASCULITIS ASSOCIATED WITH SYSTEMIC INFLAMMATORY DISEASE

Behçet’s Disease

Behçet’s disease is a multisystem inflammatory disorder whose principal manifestations are oral and genital ulcerations as well as inflammation of the eye and skin. Patients with Behçet’s disease are clustered along the ancient Silk road, extending from the Mediterranean basin to the Far East. HLA-B51 is strongly associated with the susceptibility of Behçet’s disease. The diagnosis is made using criteria proposed by the International Study Group for Behçet’s Disease in 1990. The criteria require recurrent oral ulceration as an essential symptom plus two or more symptoms of genital ulceration, eye lesions, skin lesions, and a positive pathergy test to make the diagnosis. Inflammatory eye disease generally appears later than the oral ulceration and develops in about 70% of patients in Japan. The ocular inflammation associated with Behçet’s disease represents one of the most challenging forms of uveitis to treat. The ocular manifestations of Behçet’s disease typically include recurrent attacks of anterior uveitis, with or without hypopyon, cellular infiltration and opacification of the vitreous, retinal vasculitis (Fig. 9), retinal infiltrates (Fig. 10) and hemorrhages, cystoid macular edema, and disc hyperemia. Retinal vasculitis and recurrent vaso-occlusive episodes are the major cause of visual morbidity. Inflammatory retinal vein occlusions are also strongly associated with Behçet’s disease.

Sarcoidosis

Ocular involvement manifests in 25–50% of patients with systemic sarcoidosis. The most common ocular manifestations are uveitis and conjunctival nodules. Sarcoid-associated anterior uveitis may present as either acute iridocyclitis or as a chronic granulomatous uveitis with large ‘mutton fat’ keratic precipitates, granulomatous nodules of the iris, anterior chamber angle, and granulomas located on trabecular meshwork. Intermediate uveitis with vitritis, peripheral vasculitis, and snowball infiltrates may also be encountered. Genuine snow banking may be occasionally observed. Characteristic funduscopic findings
in posterior segment involvement include retinal periphlebitis (usually non-occlusive, sometimes subclinical and only visible on fluorescein angiography) associated with typical segmental cuffing or more extensive sheathing and perivenous exudates, which are usually indicated as ‘candle wax drippings’. Multiple small round chorioretinal lesions are frequently seen in the peripheral fundus. Peripheral multifocal chorioretinitis and choroidal granuloma have been described. Optic disc swelling may be caused by uveitis, raised intracranial pressure, or optic nerve infiltration. Arterial macroaneurysms, occurring in elderly female patients with peripheral multifocal chorioretinitis, have been described and associated with severe cardiovascular disease.97

The definitive diagnosis of sarcoidosis requires the finding of noncaseating epithelioid cell granulomas in biopsy specimens. Because more than 90% of the patients with sarcoidosis exhibit pulmonary or mediastinal involvement at some stage, much diagnostic attention has focused on pulmonary imaging (chest radiograph, high-resolution computed tomography) or cytology (bronchoalveolar lavage, endobronchial or transbronchial lung biopsy, mediastinal biopsy). High-resolution computed tomography has been shown to have high sensitivity not only for mediastinal node involvement, but also for lung parenchymal infiltration. Bronchoalveolar lavage fluid may be obtained to analyze lymphocytes; lymphocytosis with an increased CD4+/CD8+ ratio is considered supportive for the diagnosis of sarcoidosis. The use of elevated angiotensin-converting enzyme levels to aid the diagnosis of sarcoidosis has been well established, but elevated levels may be seen in many diseases or in healthy children or adolescents. Hypercalcemia and hypercalciuria occur in some patients as a result of increased calcium absorption after increased production of 1.25 dihydroxycholecalciferol. The gallium scan, which detects concentrated radioactive gallium in areas of inflammation, can be useful in showing involvement of other organs such as the lungs, lacrimal glands, and parotid glands. Pulmonary function tests can be useful in evaluating patients with suspected sarcoidosis. Anergy on skin testing is also seen in sarcoidosis patients and may help support the diagnosis. Other tests include a diffuse rise in gamma globulins and a raised erythrocyte sedimentation rate. The fear of transmitting infectious agents has led to the abandonment of the Kveim test.97, 98

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by autoantibody formation and may cause small-vessel occlusion in different organs. Retinal vascular lesions are the most common ophthalmic manifestations of SLE and are due to arachoid occlusion. The retinopathy generally consists of cotton-wool spots with or without retinal hemorrhages and may occur in the absence of hypertension. The prevalence ranges from 3%99 to 29%100 and depends on the patient population studied. By contrast, a less common but more severe retinal vaso-occlusive disease characterized by diffuse arteriolar occlusion with extensive capillary nonperfusion has been described.101 A more focal vascular disease, including retinal artery or vein occlusion, may occur. Patients with SLE and raised antiphospholipid antibodies have a higher risk of developing occlusive retinal vascular disease.102 Recently, a patient with severe SLE-associated frosted branch periphlebitis and exudative maculopathy was reported.103 The underlying pathological process is probably secondary to immune complex deposition in the vessel wall. These changes are found in all arterioles, including those of the retina and choroid.104 Exacerbations of disease activity might manifest only in the retina as a retinal vascular occlusion.105 Immunological abnormalities are common and include high titers of anti-double-stranded DNA antibodies, antinuclear antibody, positive lupus erythematosus cell preparation, reduced serum complement, raised circulating immune complexes, and hypergammaglobulinemia.

Wegener’s Granulomatosis

Wegener’s granulomatosis is a necrotizing granulomatous vasculitis with a predilection typically for the upper and lower airways and the kidneys. Ocular involvement has been reported to occur in 28–58% of patients with Wegener’s granulomatosis and may precede the involvement of other organs.106 Ocular manifestations, which have been described, include orbital involvement secondary to invasion by paranasal granulomata, nasolacrimal duct obstruction, episcleritis, scleritis, corneal ulceration, optic nerve vasculitis, retinal artery occlusion, choroidal arterial occlusion, and retinal vasculitis.106–110 The diagnosis of Wegener’s granulomatosis is based on typical clinical findings and supporting histologic data. Typical histopathologic features include inflammation of small- and, less often,
medium-sized vessels, necrosis, and granuloma formation. Antineutrophil cytoplasmic antibodies (ANCAs) have been recently described as specific markers for a group of closely related vasculitic conditions. Two distinct classes of ANCAs have been described, differentiated by characteristic immunofluorescence patterns, using neutrophils as substrate for indirect immunofluorescence assay. The classic ‘cytoplasmic’ staining pattern (cANCA) is seen in Wegener’s granulomatosis, while the perinuclear pattern (pANCA) is associated with necrotizing and crescentic glomerulonephritis (renal vasculitis) and microscopic polyarteritis.

**Polyarteritis Nodosa**

Polyarteritis nodosa typically affects small- and medium-sized arteries, leading to necrotizing vasculitis in various organs, which compromises their functions. Vasculitis commonly involves the heart, kidneys, liver, gastrointestinal tract, and central nervous system. Ocular involvement is present in 10–20% of patients with polyarteritis nodosa. Ocular manifestations include peripheral ulcerative keratitis, necrotizing scleritis, non-granulomatous iritis, vitritis, and conjunctival vessel involvement producing pale, yellow, friable lesions. Papilledema, papillitis, or ischemic optic neuropathy may occur due to optic nerve vascular involvement. Inflammation of the orbital vessels may lead to exophthalmos. Central nervous system involvement may result in extraocular muscle palsies, amaurosis, homonymous hemianopia, or nystagmus. Retinal vascular involvement is primarily arterial and gives rise to retinal vasculitis, cotton-wool spots, edema, hemorrhage, and central retinal artery occlusion. The disease also may involve choroidal vessels. Recently, Curi et al. reported aggressive retinal vasculitis involving both arteries and veins in a patient with polyarteritis nodosa. Current therapy usually consists of corticosteroids and cyclophosphamide.

**Churg-Strauss Syndrome (Allergic Granulomatous Angiitis)**

The hallmarks of Churg-Strauss syndrome include severe bronchial asthma and disseminated necrotizing vasculitis. The protean manifestations include fever, eosinophilia, and multisystem involvement associated with a histologic pattern of necrotizing arteritis, eosinophilic tissue infiltration, and extravascular granulomata. There are only a few reports of ocular involvement in Churg-Strauss syndrome. Ocular manifestations include orbital inflammatory pseudotumor, conjunctival granulomas, marginal corneal ulceration, cranial nerve palsies, ischemic optic neuropathy, amaurosis, central retinal vein occlusion, branch retinal artery occlusion, central retinal artery occlusion, retinal vasculitis, and retinal infarction.

**Relapsing Polychondritis**

Relapsing polychondritis is a rare connective tissue disease. The cardinal features are inflammatory episodes involving the auricular, nasal, or laryngotracheal cartilage and an inflammatory arthritis. Ocular manifestations include episcleritis, scleritis, proptosis, corneal infiltrates and thinning, iridocyclitis, optic neuritis and ischemic optic neuropathy, exudative retinal detachment, chorioretinitis, retinopathy consisting of microaneurysms, hemorrhage, and cotton-wool spots, and retinal vascular occlusion associated with retinal vasculitis.

**Autoantibodies to Sjögren's Syndrome A Antigen**

Recent interest has focused on autoantibodies directed against a cytoplasmic protein-ribonucleic acid conjugate termed the Sjögrens’s syndrome A or Ro antigen. These autoantibodies are found in patients with systemic lupus erythematosis and lupus-like disorders, Sjögrens’s syndrome, Waldenstrom’s hypergobulinemic purpura, progressive systemic sclerosis, and hypocomplementemic urticarial vasculitis. Farmer et al. reported severe retinal arteriolitis in two patients with mild systemic lupus-like illness. Both patients had autoantibodies to Sjögrens’s syndrome A antigen, suggesting that such autoantibodies be searched for in patients with retinal arteriolitis.

**Rheumatoid Arthritis**

Retinal vasculitis has been described in patients with rheumatoid arthritis. Fluorescein angiography disclosed diffuse leakage from the retinal capillaries and cystoid macular edema. In another study employing fluorescein angiography, retinal vasculitis was found in 18% of the examined patients with rheumatoid arthritis even though no clinical and ophthalmoscopic signs of retinal vessel inflammation were present.
HLA-B27-Associated Uveitis

Retinal vasculitis is rarely reported in association with HLA-B27. Retinal vasculitis was found in association with the HLA-B27 haplotype in nine patients and ankylosing spondylitis was present in five. Mild peripheral vasculitis was the most common finding. The disease was complicated by macular edema and serous retinal detachment. In addition, Rodriguez et al. reported retinal vasculitis in seven patients with uveitis, who had a positive HLA-B27 haplotype. Four of these patients had a nonspecific arthropathy, three of whom had ankylosing spondylitis, Reiter syndrome, and psoriatic arthritis, respectively.

Crohn’s Disease

Crohn’s disease is a chronic, relapsing, inflammatory bowel disease of unknown origin. Extraintestinal complications frequently occur during the course of the disease and the eye is involved in 4–10% of patients. Several reports have documented occlusive retinal arteritis and phlebitis in Crohn’s disease.

Common Variable Immunodeficiency Syndrome

Common variable immunodeficiency syndrome is a heterogenous group of disorders in children and adults, distinguished by recurrent infections and autoimmune disorders associated with varying degrees of hypogammaglobulinemia. It can be sporadic or familial, with different modes of inheritance. Defects in B-cell function, regulatory T cells, and macrophage function have been reported. Three patients with common variable immunodeficiency syndrome have been reported, all of whom had bilateral retinal vasculitis with optic nerve and macular edema.

LOCAL RETINAL VASCULITIS WITHOUT SYSTEMIC DISEASE

Frosted Branch Angiitis

Frosted branch angiitis, first described in 1976 by Ito et al., occurs in young, healthy individuals who typically have acute bilateral (sometimes unilateral) visual loss, associated with anterior and posterior segment inflammation. The retinal findings include swelling of the retina and severe sheathing of the retinal venules, creating the appearance of frosted tree branches. Additional findings include intraretinal hemorrhages, hard exudates, and serous exudative detachments of the macula and periphery (Fig. 11). Fluorescein angiography demonstrates leakage of dye from the vessels, but no evidence of decreased blood flow or occlusion. The disease usually responds rapidly to systemic corticosteroids with rapid resolution of the vascular sheathing. The visual prognosis is usually good and there is no recurrence in most patients. The term ‘acute frosted retinal periphlebitis’ was suggested by Kleiner et al. to describe the condition. Recently, Kleiner classified the patients who have the appearance of frosted branch angiitis into three subgroups. First are the patients with lymphoma or leukemia, whose disease is due to infiltration with malignant cells (frosted branch-like appearance). Second is the group of patients who have associated viral infections or autoimmune disease. Frosted branch angiitis was reported in patients with systemic lupus erythematosus, Crohn’s disease, toxoplastic retinochoroiditis, human T-cell lymphoma virus type 1 infection, AIDS associated with small patches of retinitis, HIV without CMV retinitis, and herpes simplex virus infection. The frosted branch angiitis in these patients is a clinical sign, possibly of immune complex deposition (secondary frosted branch angiitis). Finally, there is the group of otherwise healthy young patients (acute idiopathic angiitis). It is likely that the frosted branch angiitis that developed in these patients represents an immune reaction to a number of different stimuli. Recently, a case of frosted branch angiitis complicated by bilateral retinal and optic nerve head neovascularization secondary to severe peripheral retinal ischemia was reported. We also reported the unusual association between severe retinal periphlebitis resembling frosted branch angiitis and nonperfused central retinal vein occlusion.
Idiopathic Retinal Vasculitis, Aneurysms, and Neuroretinitis (IRVAN)

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) is a rare clinical entity characterized by bilateral retinal arteritis, numerous aneurysmal dilations of the retinal and optic nerve head arterioles, peripheral retinal vascular occlusion, neuroretinitis, and uveitis (Fig. 12). This syndrome typically affects young healthy individuals, has a female predominance, and is not associated with any systemic abnormalities. Visual loss is due to exudative maculopathy and neovascular sequelae of retinal ischemia. Recently, we reported a patient who presented with features typical of IRVAN in whom medical evaluation disclosed allergic fungal sinusitis. Several reports have described the resolution of aneurysmal dilatations of the retinal arterioles in patients with IRVAN treated with systemic steroids and peripheral retinal photocoagulation.

Acute Multifocal Hemorrhagic Retinal Vasculitis

Acute multifocal hemorrhagic retinal vasculitis has been described in a small group of otherwise healthy patients who develop abrupt onset of unilateral or bilateral visual loss associated with mild anterior uveitis, retinal vasculitis (predominantly periphlebitis), variable retinal hemorrhage, nonconfluent posterior retinal infiltrates, vitritis, and papillitis. Angiographically, these patients demonstrate areas of retinal capillary nonperfusion and neovascular complications including retinal, disc, choroidal, and iris new vessels requiring photocoagulation. Oral prednisone is of some benefit. The etiology is unknown.

Idiopathic Recurrent Branch Retinal Arterial Occlusion

This clinical syndrome is characterized by recurrent multiple branch retinal arterial occlusions of unknown cause in one or both eyes of healthy middle-aged patients. Ophthalmoscopic and fluorescein angiographic findings have suggested focal arteritis and arteriolitis as the cause of the obstructions. Eyes that have large areas of retinal ischemia may subsequently develop preretinal neovascularization. The prognosis for maintaining good visual acuity is good. Detailed investigation of these patients has failed to reveal a systemic etiology. Vestibuloauditory and/or transient sensorimotor symptoms were detected in 50% of patients. It is postulated that many of the patients have mild or partial manifestations of the microangiopathic syndrome of encephalopathy, hearing loss, and retinal arteriolar occlusions.

Diagnostic Evaluation

The search for a cause in patients with retinal vasculitis often involves a multidisciplinary approach and laboratory investigation (Table 2). Discrimination between infectious and noninfectious etiology of retinal vasculitis is important because their treatment is different. Immunosuppressive therapy may be essential in certain disorders, but it might be deleterious in infectious entities. Once an infectious cause is believed to be unlikely, an associated systemic disease should be considered and an appropriate investigation instituted. In cases of diagnostic doubt, malignancy must be ruled out and should certainly be considered if, after an initial improvement with therapy, the patient’s disease rapidly becomes refractory to treatment. The ophthalmologist, therefore, has a major role in clarifying the nosologic and diagnostic debate in patients with retinal vasculitis.

The laboratory workup of a patient with retinal vasculitis should be based on a differential diagnosis derived from a detailed history, review of systems, and
TABLE 2 Diagnostic studies performed on patients with retinal vasculitis.

<table>
<thead>
<tr>
<th>Laboratory tests</th>
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<tr>
<td>- Complete blood count with differential</td>
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<tr>
<td>- Erythrocyte sedimentation rate</td>
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<tr>
<td>- C-reactive protein</td>
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<tr>
<td>- Serum chemistry panel with tests for renal and liver functions</td>
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<tr>
<td>- Blood sugar</td>
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<tr>
<td>- Urinalysis</td>
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<tr>
<td>- Venereal Disease Research Laboratory (VDRL) test, fluorescent treponemal antibody absorption (FTA-ABS) test</td>
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<tr>
<td>- Tuberculin skin testing</td>
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<tr>
<td>- Toxoplasmosis serology</td>
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<td>- Lyme disease serology</td>
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<tr>
<td>- Cat-scratch disease serology</td>
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<tr>
<td>- Human immunodeficiency virus, human T cell virus type 1, cytomegalovirus, herpes simplex virus, varicella zoster virus, hepatitis virus, and West Nile virus serology</td>
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<tr>
<td>- Polymerase chain reaction to identify pathogens in ocular specimens</td>
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<tr>
<td>- Serum angiotensin-converting enzyme</td>
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<tr>
<td>- Rheumatoid factor</td>
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<td>- Antinuclear antibody</td>
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<tr>
<td>- Anti-DNA</td>
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<tr>
<td>- Antineutrophil cytoplasmic antibody</td>
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<tr>
<td>- Antiphospholipid antibodies (lupus anticoagulants and antiphospholipid antibodies)</td>
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<tr>
<td>- Serum complement, CH50, AH50</td>
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<tr>
<td>- Extractable nuclear antigen</td>
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<tr>
<td>- Serum protein electrophoresis</td>
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<tr>
<td>- Serum cryoglobulins</td>
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<tr>
<td>- Human leukocyte antigen testing</td>
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<tr>
<td>- Vitreous biopsy</td>
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<tr>
<td>- Cerebrospinal fluid cytology and cell count</td>
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<tr>
<td>Imaging</td>
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<tr>
<td>- Fluorescein angiography</td>
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<tr>
<td>- Optical coherence tomography</td>
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<td>- Ultrasonography</td>
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<tr>
<td>- Chest x-ray</td>
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<td>- CT scanning</td>
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<td>- Magnetic resonance imaging</td>
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<tr>
<td>- Gallium scan</td>
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<td>- Sacroiliac x-ray</td>
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The diagnostic workup should be tailored according to the patient's medical history, review of systems, and physical examination.

physical examination. If the patient's medical history, review of systems, or ocular examination suggests an underlying systemic disease, then the diagnostic workup should be tailored for that disease. The absence of any diagnostic clues from history makes idiopathic retinal vasculitis most likely. If, however, the patient has no signs or symptoms suggestive of an associated disease, then the workup of the patient is limited to a fluorescein angiogram, complete blood count, erythrocyte sedimentation rate, VDRL, FTA-ABS, blood chemistry, urinalysis, tuberculin skin testing, HIV serology, and chest radiograph. Numerous studies have shown that little additional information is gained by 'blind' investigation of the patient and that pursuing this is neither time- nor cost-effective.

Evaluation of patients with suspected infectious retinal vasculitis may include ocular and/or systemic cultures, serologic tests, polymerase chain reaction, and tuberculin skin testing. Tuberculin skin testing is often negative in sarcoidosis and in immunosuppressed individuals. In patients with suspected tuberculosis or Eales' disease, chest radiograph and/or computed tomography of the chest may aid in the evaluation.

In patients with suspected noninfectious systemic diseases, the diagnostic evaluation typically focuses on systemic vasculitis syndromes. Evaluation of these patients should include rheumatoid factor, antinuclear antibody, anti-double-stranded DNA antibodies, antineutrophil cytoplasmic antibodies, extractable nuclear antigens, levels of complement, antiphospholipid antibodies, C reactive protein, and imaging studies.

The study of human leukocyte antigen (HLA) testing may be helpful in certain forms of systemic disease associated with retinal vasculitis. These HLA associations include birdshot retinochoroidopathy and HLA-A29, Behçet’s disease and HLA-B51, and systemic lupus erythematosus and HLA-DR3.

If intraocular lymphoma is suspected, then vitreous biopsy is mandatory. Furthermore, because of the association between this disease and central nervous system lymphoma, a full neurological evaluation, including magnetic resonance imaging and cerebrospinal fluid cytological analysis, is needed.

**COMPLICATIONS AND PROGNOSIS**

The causes of poor vision in retinal vasculitis are multifactorial, although cystoid macular edema is a significant contributory factor. Cystoid macular edema, when adequately treated with immunosuppressive therapy, is associated with a good prognosis. Poor visual outcome in some patients with retinal vasculitis despite adequate therapy may be explained by the presence of macular ischemia on fluorescein angiography. Palmer et al. demonstrated that patients with ischemic
retinal vasculitis have a significantly worse visual outcome than those with non-ischemic retinal vasculitis. Inflammation-induced vascular occlusion and ischemia can lead to a proliferative vascular retinopathy, with sequelae such as recurrent vitreous hemorrhage, traction retinal detachment, ruberosis iridis, and neovascular glaucoma that can lead to functional loss of the eye.\(^{10,67,74,101,124,126,134}\) Recently, we demonstrated that aggressive treatment of Eales’ disease, an oblitative retinal periphlebitis, with systemic steroids and antituberculous therapy, full panretinal photocoagulation, and early vitrectomy improve prognosis of retinal vasculitis associated with tuberculin protein hypersensitivity (Eales’ disease).\(^{10}\)

Inflammatory branch retinal vein occlusions are strongly associated with Behcë’t disease.\(^{10}\) Retinal arterial occlusions are also reported in patients with retinal vasculitis.\(^{105,110,113,116,126,142,143}\)

**SUMMARY**

Not only may retinal vasculitis be sight-threatening, but more importantly, it could be the first sign of a potentially lethal systemic disease. Prompt diagnosis and institution of the appropriate therapy will help control the ocular disease and, more importantly, the systemic disease. Thus, it is essential that a thorough history, review of systems, and physical examination are performed in patients with retinal vasculitis. A multidisciplinary team approach is essential in the evaluation and treatment of these patients. The diagnostic evaluation should be focused, guided by the information obtained in the patient’s history and in their ophthalmic and physical examinations.

**REFERENCES**


