Algorithm for Workup of Retinal Vasculitis

Ahmed M. Abu El-Asrar

Contents

Introduction

In this chapter, a practical approach to the diagnosis of retinal vasculitis is discussed based on ophthalmoscopic and fundus fluorescein angiographic findings (Tables 1 and 2).

Fundus Fluorescein Angiography

Intravenous fluorescein angiography is an essential component of the evaluation and management of retinal vasculitis. Characteristic features seen with fluorescein angiography in active vasculitis include leakage of dye due to breakdown of the inner blood-retinal barrier and staining of the blood vessel wall with fluorescein. Such leakage may be focal as seen in sarcoidosis or multiple sclerosis or more diffuse as seen in Behçet's disease and retinal vasculitis associated with tuberculoprotein hypersensitivity. Diffuse capillary leakage is also a common finding in many conditions such as Behçet's disease and birdshot chorioretinopathy.

Identification of the Involved Retinal Vessels

Retinal vasculitis affecting predominantly the veins (phlebitis) has been described in association with Behçet's disease, tuberculosis, sarcoidosis, multiple sclerosis, pars planitis, retinal vasculitis associated with tuberculoprotein hypersensitivity, and human immunodeficiency virus infection. Retinal arteritis is more commonly seen in acute retinal necrosis; idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN); and systemic vasculitides such as systemic

A. M. Abu El-Asrar (✉)
College of Medicine, Department of Ophthalmology, King Abdulaziz University Hospital, King Saud University, Riyadh, Saudi Arabia

Dr. Nasser Al-Rashid Research Chair in Ophthalmology, Riyadh, Saudi Arabia
e-mail: abuelasrar@yahoo.com; abuasrar@KSU.edu.sa

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Table 1 Disorders associated with retinal vasculitis

Infectious Disorders
Bacterial disorders: tuberculosis, syphilis, Lyme disease, Whipple's disease, brucellosis, cat scratch disease, endophthalmitis, post-streptococcal syndrome.
Viral disorders: human T cell lymphoma virus type 1, cytomegalovirus, herpes simplex virus, varicella zoster virus, Epstein-Barr virus, Rift Valley fever virus, hepatitis, acquired immunodeficiency syndrome, West Nile virus infection, Dengue fever virus.
Parasitic disorders: toxoplasmosis.
Rickettsial disorders: Mediterranean spotted fever, Rocky Mountain 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
Granulomatosis with polyangiitis (GPA)
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
Pars planitis
Birdshot chorioretinopathy

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lupus erythematosus (SLE), polyarteritis nodosa, and granulomatosis with polyangiitis (GPA); Churg-Strauss syndrome; and cryoglobulinemia.

Cotton-Wool Spots

Cotton-wool spots representing microinfarcts of the retina due to precapillary retinal arteriolar occlusion are most often found in association with systemic vasculitides such as SLE, polyarteritis nodosa, granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome, and cryoglobulinemia. Susac syndrome is a rare disease of unknown pathogenesis. It is also 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.

Table 2 Differential diagnosis of retinal vasculitis based on ophthalmoscopic findings

Ophthalmoscopic finding	Possible diagnoses
Phlebitis	Behçet's disease, tuberculosis, sarcoidosis, multiple sclerosis, pars planitis, human immunodeficiency virus infection
Arteritis	Acute retinal necrosis, idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN), systemic vasculitides such as systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome, and cryoglobulinemia
Cotton-wool spots	Systemic vasculitides such as SLE, PAN, granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome, and cryoglobulinemia and Susac syndrome
Intraretinal infiltrates	Behçet's disease, rickettsial infection, cat scratch disease
Necrotizing retinitis	Ocular toxoplasmosis, acute retinal necrosis, cytomegalovirus retinitis
Aneurysmal dilatations of the retinal and optic nerve head arterioles	IRVAN, sarcoidosis
Frosted branch angiitis	Idiopathic, infiltration with malignant cells (lymphoma or leukemia), SLE, Crohn's disease, toxoplasmic retinochoroiditis, human T cell lymphoma virus type 1 infection, acquired immunodeficiency syndrome, human immunodeficiency virus infection, herpes simplex virus infection, Epstein-Barr virus infection
Retinal ischemia	Tuberculosis, Behçet's disease, multiple sclerosis (rare), sarcoidosis (rare)
Inflammatory branch retinal vein occlusion	Behçet's disease, tuberculosis, sarcoidosis (rare)
Retinal arterial occlusions	SLE, PAN, granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome, Crohn's disease, Susac syndrome, cat scratch disease, Mediterranean spotted fever, ocular toxoplasmosis

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Intraretinal Infiltrates

Intraretinal infiltrates are characteristic of infectious processes, but in the absence of these, they are pathognomonic of Behçet's disease. These transient white patches of retinitis often with small adjacent hemorrhages are almost always seen in patients with active posterior Behçet's uveitis. Typically, they are silent on fundus fluorescein angiography.

Necrotizing Retinitis

Retinal vasculitis may be associated with necrotizing retinitis due to ocular toxoplasmosis, acute retinal necrosis, cytomegalovirus (CMV) retinitis, and rarely human T cell lymphoma virus type 1 (HTLV-1) associated uveitis.

Aneurysmal Dilatations of the Retinal and Optic Nerve Head Arterioles

IRVAN is a rare clinical entity characterized by bilateral retinal arteritis, numerous aneurysmal dilatations of the retinal and optic nerve head arterioles, peripheral retinal vascular occlusion, neuroretinitis, and uveitis. Visual loss is due to exudative maculopathy and neovascular sequelae of retinal ischemia. Arterial macroaneurysms, occurring in elderly female patients with sarcoidosis associated with peripheral multifocal chorioretinitis, have been described. These patients had severe cardiovascular disease.

Frosted Branch Angiitis

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. Fluorescein angiography demonstrates leakage of dye from the vessels, but no evidence of decreased blood flow or occlusion. Patients who have the appearance of frosted branch angiitis are classified into three subgroups. First are 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, toxoplasmic retinochoroiditis, human T cell lymphoma virus type 1 infection, AIDS associated with small patches of retinitis, HIV without CMV retinitis, herpes simplex virus infection, and Epstein-Barr virus infection. In these patients, frosted branch angiitis 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).

Retinal Ischemia

Ischemic retinal vasculitis is frequently seen secondary to tuberculosis and retinal vasculitis associated with tuberculoprotein hypersensitivity. Ischemic retinal vasculitis may also be secondary to Behçet's disease and multiple sclerosis. Retinal periphlebitis associated with sarcoidosis is usually nonocclusive, 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." Development of capillary nonperfusion and subsequent neovascularization as well as branch and central retinal vein occlusions have been described.

Diagnostic Evaluation

The search for a cause in patients with retinal vasculitis often involves a multidisciplinary approach and laboratory investigation (Table 3). Discrimination between infectious or noninfectious etiology of retinal vasculitis is important because treatment is different. 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 laboratory workup of a patient with retinal vasculitis should be based on differential diagnosis derived from a detailed history, review of systems, and 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.

Key Points

- Differential diagnosis of retinal vasculitis is based on ophthalmoscopic and fluorescein angiographic findings.
- Multidisciplinary team approach is essential in evaluation and treatment.
- Thorough history, review of systems, and physical examination are essential.
- The diagnostic workup should be tailored according to the patient's medical history, review of systems, and physical examination.

Table 3 Diagnostic studies performed on patients with retinal vasculitis

A. Laboratory Tests:
Complete blood count with differential
Erythrocyte sedimentation rate
C-reactive protein
Serum chemistry panel with tests for renal and liver functions
Blood sugar
Urinalysis
Venereal Disease Research Laboratory (VDRL) test, Fluorescent treponemal antibody absorption (FTA-ABS) test
Tuberculin skin testing
Interferon-γ release assays for tuberculosis
Toxoplasmosis serology
Lyme disease serology
Dengue virus serology
Cat scratch disease serology
Rickettsial serology
Human immunodeficiency virus, human T cell lymphoma virus type 1, cytomegalovirus, herpes simplex virus, varicella zoster virus, hepatitis virus, and West Nile virus serology
Polymerase chain reaction to identify pathogens in ocular specimens
Serum angiotensin-converting enzyme
Rheumatoid factor
Antinuclear antibody
Anti-dsDNA
Antineutrophil cytoplasmic antibody
Antiphospholipid antibodies (lupus anticoagulants and anticardiolipin antibodies)
Serum complement, CH50, AH50
Extractable nuclear antigen
Serum protein electrophoresis
Serum cryoglobulins
Human leukocyte antigen testing
Vitreous biopsy
Cerebrospinal fluid cytology and cell count
B. Imaging
Fluorescein angiography
Indocyanine green angiography
Optical coherence tomography
Ultrasonography
Chest x-ray
Chest CT scanning
Magnetic resonance imaging
Gallium scan
Sacroiliac x-ray

Modified from Abu El-Asrar et al. (2010)

Suggested Reading

Abu El-Asrar AM, Jestaneiah S, Al-Serhani AM. Regression of aneurysmal dilatations in a case of idiopathic retinal vasculitis, aneurysms and neuroretinitis (IRVAN) associated with allergic fungal sinusitis. Eye. 2004;18:197–9.

Abu El-Asrar AM, Herbort CP, Tabbara KF. Retinal vasculitis. Ocul Immunol Inflamm. 2005;13:415–33.

Abu El-Asrar AM, Herbort C, Tabbara KF. A clinical approach to the diagnosis of retinal vasculitis. Int Ophthalmol. 2010;30:149–73.

Ganatra JB, Chandler D, Santos C, Kuppermann B, Margolis TP. Viral causes of the acute retinal necrosis syndrome. Am J Ophthalmol. 2000;129:166–72.

Graham EM, Stanford MR, Sander MD, Kasp E, Dumonde DC. A point prevalence study of 150 patients with idiopathic retinal vasculitis: I. Diagnostic value of ophthalmological features. Br J Ophthalmol. 1989;73:714–21.

Kestelyn P, Lepage P, Van de Perre P. Perivasculitis of the retinal vessels as an important sign in children with AIDS-related complex. Am J Ophthalmol. 1985a;100:614–5.

Kestelyn P, Van de Perre P, Rouvroy D, Lepage P, Bogaerts J, Nzaramba D, Clumeck N. A prospective study of the ophthalmologic findings in the acquired immune deficiency syndrome in Africa. Am J Ophthalmol. 1985b;100:230–8.

Kleiner RC. Frosted branch angiitis: clinical syndrome or clinical sign? Retina. 1997;17:370–1.

Kleiner RC, Kaplan HJ, Shakin JL, Yannuzzi LA, Crosswell Jr HH, McLean Jr WC. Acute frosted retinal periphlebitis. Am J Ophthalmol. 1988;106:27–34.

Levy-Clarke GA, Buggage RR, Shen D, Vaughen LO, Chan CC, Davis JL. Human T-cell lymphotropic virus-type 1 associated T-cell leukemia/lymphoma masquerading as necrotizing retinal vasculitis. Ophthalmology. 2002;109:1717–22.

Nakao K, Ohba N. Human T-cell lymphotropic virus type 1-associated retinal vasculitis in children. Retina. 2003;23:197–201.

O'Halloran HS, Pearson PA, Lee WB, Susac JO, Berger JR. Microangiopathy of the brain, retina, and cochlea (Susac syndrome). A report of five cases and a review of the literature. Ophthalmology. 1998;105:1038–44.

Rothova A, Lardenoye C. Arterial macroaneurysms in peripheral multifocal chorioretinitis associated with sarcoidosis. Ophthalmology. 1998;105:1393–7.

Samuel MA, Equi RA, Chang TS, Mieler W, Jampol LM, Hay D, Yannuzzi LA. Idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis (IRVAN): new observations and a proposed staging system. Ophthalmology. 2007;114:1526–9.

Verougstraete C, Snyers B, Leys A, Caspers-Velu LE. Multiple arterial ectasias in patients with sarcoidosis and uveitis. Am J Ophthalmol. 2001;131:223–31.