

Eye and Vasculitis

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Abstract

Vasculitis is not an uncommon diagnosis, however ocular manifestations of vasculitis may at times be presenting symptoms of the disease, requiring an earnest effort on part of the ophthalmologist. In the eye, retinal vessels are the most susceptible to inflammation and sometimes, ocular signs may provide vital clues to the systemic etiology. This review of ocular manifestations of vasculitis is structured in accordance with latest Chapel Hill nomenclature encompassing both local and systemic forms of the disease. It is a synopsis of latest clinical manifestations and diagnostic criteria's of vasculitis, with a summary on newer investigations and treatment guidelines. It attempts to provide an overview for not only ophthalmologists but also rheumatologist, as proper management of vasculitis requires a multi-disciplinary approach with urgent inter departmental referral that could at times be both sight and lifesaving for the patient.

Keywords: Vasculitis; Connective tissue disorders; Retina; Chapman-Hill classification; Eales' disease

Introduction

Vasculitis is defined as inflammation of the blood vessel wall. Inflammation along with necrosis occurring secondary to abnormal immune response, lead to destruction and occlusion of vessels, resulting in poor perfusion and ischemia of the end organ. It can present as multi-organ vasculitis or as a local form affecting only a particular organ.

Vasculitis can affect all blood vessels across the body including those of the eye, in particular, the retinal vessels. In some situations, subtle ocular clues may unveil grave systemic illnesses, underlining the importance of meticulous ocular examination [1]. The clinical features of the eye vasculitis can vary from conjunctivitis, episcleritis, scleritis, peripheral ulcerative keratitis (PUK), proptosis, retinal vasculitis, orbititis to uveitis, depending on the site and distribution of the vessels involved [2]. Hence, prompt recognition of these ocular symptoms as a part of systemic involvement maybe life saving for the patient [3-5].

As retinal vasculitis is the most common presentation of vasculitis, herein we shall focus on causes and varied presentations of retinal vasculitis in local as well as systemic form.

Microanatomy of Retinal Vasculature and Pathogenesis

General

The central retinal artery is a branch of ophthalmic artery, which on entering the retina divides into superior and inferior ramification. These immediately give rise to temporal and nasal arcades, which supply all 4 quadrants of retina. The corresponding retinal veins drain these quadrants, finally joining as the central retinal vein, which eventually drains into the cavernous sinus.

Microanatomy

Retinal vasculature is a complex network composed of different cell populations. The arterial wall is composed of (from inside to outside) a single layer of endothelial cells with subendothelial elastica, a media of smooth muscle cells with a poorly demarcated external elastic lamina, and an adventitia consisting of collagen fibrils. Similarly retinal veins are made up of a single layer of endothelial cells having a thin basement membrane, media comprising of predominantly elastic fibers and muscle cells, and a thin adventitia. As we move to periphery veins loose muscle cells which get replaced with pericytes. Capillary walls comprise of endothelial cells, basement membrane, and intramural pericytes [6].

Pathogenesis

In vasculitis, immunological homeostasis gets disrupted with aberrant recognition of self-proteins as antigens. This leads to T and B lymphocyte proliferation, production of auto-antibodies culminating in an attack on end structures such as vascular endothelium, vessel wall, intracytoplasmic granules, and intranuclear proteins of nucleated cells. These immunopathological mechanisms are responsible for the ocular manifestations of the vasculitides [7]. For example, conjunctivitis might be caused by eosinophilic infiltration, granuloma formation, and inflammatory microangiopathy in the vessels of the conjunctiva. Similarly, antibody-mediated destruction of the peripheral cornea is an important mechanism in ANCA (Anti-Nuclear Cytoplasmic Antibody) positive vasculitis. Also, deposition of immune complexes in the sclera, limbal and retinal vessels results in recruitment of inflammatory cells responsible for tissue necrosis and ischemia.

Classification

Since separate clinical and histological classifications led to confusion and duplication, American College of Rheumatology (Chapel Hill) developed a nomenclature to evaluate and describe

systemic vasculitis in a standard fashion [8]. It was recently updated to include forms of vasculitis that were not included earlier (Table 1) [9]. However, none of the classifications mention ocular manifestations in detail. Hence we attempt to structure our discussion in accordance with the latest Chapel Hill Nomenclature.

Eye Vasculitis can be categorized as:

- Eye Vasculitis without Systemic Involvement
- Eye Vasculitis with Primary Systemic Vasculitis
- Eye Vasculitis with Autoimmune Disorders
- Eye Vasculitis associated with probable infectious etiology

Eye Vasculitis
Eye vasculitis without systemic involvement
Single-organ– Retinal Vasculitis.
Pars Planitis
Birdshot Chorioretinopathy
Idiopathic Retinal Vasculitis, Aneurysm and Neuroretinitis Syndrome (IRVAN)
Eales' Disease
Eye vasculitis with primary systemic vasculitis
a. Small vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
b. Medium vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
c. Large vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Eye vasculitis associated with autoimmune disorders
a. Variable vessel vasculitis
Behcet's disease
Cogan's Syndrome
b. Vasculitis associated with systemic disease
Sarcoid vasculitis
Lupus vasculitis
Spondyloarthropathies
Eye Vasculitis associated with probable infectious etiology
a. Vasculitis secondary to infection
Endogenous Endophthalmitis

Viral Retinitis
Tuberculosis
Acquired Syphilis
Lymes Disease
Toxoplasma
Toxocara
b. Vasculitis with Masquerade syndromes
Vasculitis associated with Malignancies
Drug Associated Vasculitis

Table 1: Classification of Eye vasculitis according to Chapel Hill nomenclature.

Eye Vasculitis without Systemic Involvement

Pars Planitis

It is a subset of Intermediate Uveitis (IU) where primary site of inflammation is the intermediate part of the uveal layer (ciliary body), with absence of any underlying infection or systemic disease [10]. It is characterized by deposition of exudation in characteristic pattern called snow banking and snowball formation [11]. Rarely patients show a benign course and most patients have a severe and prolonged disease with episodic exacerbations. Patients should be investigated for multiple sclerosis, sarcoidosis, lymes disease, syphilis, tuberculosis etc. to rule out IU with systemic involvement [12]. Common posterior segment complications are cystoid macular edema, epiretinal membrane formation, vitreous condensation, neovascularization, vitreous hemorrhage, retinal detachment and cyclitic membranes [13,14]. Recently, retinoschisis has also been reported as a frequent complications [15].

Birdshot chorioretinopathy (BCR)

It is HLA-A29 associated, and hypothesized to be due to an autoimmune response to retinal S antigens [16]. It is a bilateral, chronic posterior uveitis with characteristic hypopigmented lesions [17]. Hypopigmented lesions are typically ¼ to ½ optic disc diameters, radiating from the optic nerve towards the periphery, involving predominantly the inferior and nasal peripapillary area [18]. Recently formulated diagnostic criteria for BCR include 1) Bilateral disease, 2) At least 3 peripapillary lesions inferior or nasal to disc in at least one eye, 3) Low grade anterior segment inflammation [19]. Advanced stages may show cystoid macular edema, vascular attenuation, optic atrophy and subretinal neovascularization [18,20]. Disease is chronic in nature and does not regress. HLA A29 antigen testing might be positive in nearly 100% [21].

Idiopathic retinal vasculitis, aneurysm and neuroretinitis syndrome (IRVAN)

It is a rare entity presenting with arteritis and multiple aneurysmal dilatation of arteriolar branches and on the optic nerve head, along with anterior uveitis and vitritis [22]. Neuroretinitis with disc edema and macular star is seen [23]. Marked exudation around the disc may be seen due to leakage. These unique findings have resulted in greater recognition of this syndrome. A newer staging system has graded

IRVAN into 5 stages. Stage 1 includes macroaneurysms, exudation, neuroretinitis, retinal vasculitis, stage 2 has angiographic evidence of capillary nonperfusion, stage 3 comprises of neovascularization of disc or elsewhere with/without vitreous hemorrhage, stage 4 shows anterior segment neovascularization (rubeosis iridis), with stage 5 finally culminating in neovascular glaucoma [24]. Earlier stages with early treatment have showed good prognosis.

Eales' disease

Eales' disease is considered as a diagnosis of exclusion, and confirmed only after ruling out all possible infections and systemic etiologies [25]. It is characterized by peripheral retinal vasculitis in the earlier stages and by proliferative changes later during the course of the disease. In the early stage there is perivascular exudation (cuffing of vessels), perivascular retinal edema and retinal hemorrhages in the affected segment. These changes may resolve spontaneously but with time evolve into the proliferative phase in a significant number of patients. The proliferative phase is characterized by development of new vessels on the retinal surface (neovascularization elsewhere, NVE) or optic disc (neovascularization on the disc, NVD). As these new vessels are very fragile, they easily rupture producing vitreous hemorrhage and severe loss of vision. The involvement is bilateral and usually seen in young healthy adults (usually men) in the Indian subcontinent and has good prognosis [26-29]. Although its association with tuberculosis has been debated before, recent reports have also reiterated similar findings [30]. Neurological involvement such as stroke and transient ischemia has been reported due to leptomeningeal vasculitis.

Eye Vasculitis with Primary Systemic Vasculitis

Depending on the vessel size, primary vasculitis can be divided into small vessel, medium vessel and large vessel disease. Vasculitis commonly having ocular involvement is mentioned below.

Small vessel vasculitis

Microscopic polyangiitis: It is characterized by necrosis of small vessels and associated with focal segmental necrotizing glomerulonephritis [31]. Renal dysfunction can progress rapidly to renal failure. Lung involvement is common resulting in dyspnea and haemoptysis [32]. Ocular manifestations mainly involve the anterior segment. Peripheral ulcerative keratitis (PUK) is the most common presenting symptom often leading to corneal perforation [33]. Conjunctival and lid involvement in the form of nodules with central ulcerations can also be seen [34]. Rarely, visual loss may be attributed to the development of longstanding extensive exudative retinal detachment secondary to marked choroidal inflammation associated with the recurrent episodes of necrotising scleritis [35]. Although central retinal artery occlusion has been reported recently [36], retinal vasculitis is rare. Currently, most likely diagnosis in ANCA-positive patient with diffuse pulmonary hemorrhage and hemosiderosis is microscopic polyangiitis [37]. MPA long-term prognosis is less severe, although relapses are frequent [38]. End-stage renal failure is a frequent complication of MPA.

Granulomatosis with polyangiitis (Wegener's Granulomatosis): It is characterized by the classical triad of respiratory tract vasculitis, focal segmental glomerulonephritis and necrotizing vasculitis of small arteries and veins [39]. Orbital and ocular involvement is seen in nearly half of the patients [40,41]. Orbital inflammation may lead to

diplopia, proptosis, restrictive myopathy, exposure keratopathy and compressive optic neuropathy [41]. It is also associated with peripheral ulcerative keratitis, corneal granuloma, episcleritis and necrotizing scleritis [42]. Neurological involvement such as nerve palsy has also been reported [43]. Posterior segment manifestations such as retinal inflammation, occlusive retinal vasculitis, choroiditis, posterior scleritis and ischemic optic neuritis have been documented [44]. C-ANCA with antigen specificity to PR 3 is considered diagnostic. However biopsy still remains gold standard. There is a nine-fold increase in risk of death compared with the general population in the first year. Infection, active vasculitis and acute kidney injury are leading causes of mortality. Thereafter, the risk falls until the eighth year when there is an unexpected peak [45].

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome): It is an allergic granulomatous angiitis affecting small sized arteries and veins. Three major histological criteria required for its diagnosis are a) prominent eosinophilic infiltration, b) necrotizing/granulomatous small-vessel vasculitis, and c) extra-vascular granulomas [46]. Patients commonly have fatal cardiac involvement such as congestive heart failure and restrictive cardiomyopathy [47]. It can have orbital involvement such as granulomas involving the lids or ocular involvement such as conjunctivitis, episcleritis and marginal ulcerative keratitis [48]. Branch vein occlusion, optic disc vasculitis and retinal infarction are common posterior segment manifestations [49]. Neurological complications such as ischemic optic neuropathies and cranial nerve palsy have been reported [50,51]. Eosinophilia with p-ANCA positivity seems to be diagnostic. Earlier the condition was mostly fatal, but with better treatment options the prognosis has improved.

Medium vessel vasculitis

Polyarteritis nodosa (PAN): It mainly causes necrotizing inflammation of vessel wall at branching sites. PAN has renal involvement (75%) and cardiac involvement (80%) which may lead to fatal consequences. Mononeuritis multiplex is the most common symptom and gastrointestinal manifestations are most severe [46,52]. Orbital involvement may present as exophthalmos secondary to orbital vessel inflammation. Although, ocular involvement may present as conjunctivitis, episcleritis and scleritis, peripheral ulcerative keratitis (PUK) is commonly the initial presenting symptom [33,53]. Posterior segment findings in PAN are choroidal infarction, retinal vasculitis, central retinal artery occlusion, optic atrophy, and posterior scleritis [54]. These occur due to systemic hypertension or renal disease. Papilledema, papillitis and optic atrophy have been seen. Neurological manifestations such extra ocular muscle palsies, homonymous hemianopia and Horner's syndrome can also occur [55]. According to American College of Rheumatology presence of 3 out of 10 features such as weight loss of 4 kg or more, livedo reticularis, testicular pain/tenderness, myalgia or leg weakness/tenderness, mononeuropathy or polyneuropathy, diastolic blood pressure greater than 90 mm/Hg, elevated blood urea nitrogen, hepatitis B virus blood test positivity, arteriographic abnormalities, and biopsy of small and medium sized arteries are considered diagnostic. Prompt diagnosis and early treatment initiation has vastly improved survival of such patients [56].

Kawasaki disease (KD): It is a systemic vasculitis of unknown etiology that affects the medium sized blood vessels of the body, particularly the coronary arteries early in childhood [57]. Coronary artery aneurysm is a lethal complication of KD [58]. The common ophthalmological findings in KD are conjunctival injection,

iritidocyclitis, superficial punctate keratitis, vitreous opacities, papilledema and subconjunctival hemorrhage [59]. Retinal vasculitis is however reported rarely. Classical complete form of KD is diagnosed when patients present with fever of five days or more, with at least 4/5 features - bilateral conjunctival injection, changes in the lips and oral cavity, cervical lymphadenopathy, extremity changes, and polymorphous rash [60]. Transthoracic echocardiography is the imaging modality of choice to detect cardiac artery abnormalities [61]. With newer treatments the prognosis has improved [62].

Large vessel vasculitis

Giant cell arteritis (GCA): It is a necrotizing vasculitis with predilection for medium and large vessels of the head and neck [63]. Jaw claudication and scalp tenderness are important manifestations of GCA [63,64]. Most of the patients remain asymptomatic even though autopsy reports confirm large vessel involvement. It may present as cerebral infarctions and hearing loss [65]. GCA can lead to sudden vision loss secondary to ischemic optic neuropathy or central retinal artery occlusion [64]. Episcleritis, scleritis, corneal edema and anterior uveitis may be present [66]. Elevated ESR and C reactive protein are highly suggestive of GCA. Temporal artery biopsy is diagnostic. Although, GCA has a self-limiting course, partial or permanent visual loss may be seen in 15-20% of patients [67].

Takayasu Arteritis: It is chronic autoimmune vasculitis of the large vessels. It can have grave complications such as congestive heart failure and stroke [68]. Renal impairment and ischemia of gastrointestinal tract have also been reported. Ocular manifestations include cataract, glaucoma and ischemic optic neuropathy [69]. Retinal vascular changes secondary to peripheral ischemia may result in Takayasu Retinopathy as coined by uyama [70]. It has 4 stages, stage 1 comprises of dilatation of small vessels, stage 2 has microaneurysms and cotton wool spots +/- haemorrhage, Stage 3 shows arterial venous anastomosis at disc or elsewhere and stage 4 is associated with proliferative vitreoretinopathy, vitreous haemorrhage and tractional retinal detachment [71]. Angiography is useful in studying the extent of retinal ischemia [71]. Recently, inflammatory pseudotumor and anterior scleritis have also been reported [72,73]. Milder form of disease has good prognosis where as others may tend to deteriorate considerably.

Eye Vasculitis with Autoimmune Disorders

Autoimmune disorders may present as secondary systemic vasculitis. Common disorders having ocular involvement are discussed.

Variable vessel disease

Behcets' Disease: It is an autoimmune disease characterized by aphthous ulcers, genital ulcers and skin lesions along with uveitis [41]. Arthritis, neurological and gastrointestinal involvement is also seen. Ocular involvement is common with presence of non-granulomatous uveitis, hypopyon, posterior synechiae and hyphema [74]. Posterior segment examination may reveal vitritis, occlusive arteritis, phlebitis, retinal infiltrates and branch retinal vascular occlusion [75]. Optic disc edema with subsequent optic atrophy may be seen [74]. International criteria for diagnosis of behcets disease requires presence of oral ulceration alongwith 2 features out of recurrent genital ulceration, eye lesions, skin lesions or pathergy test [76]. HLA-B51 and pathergy test are useful in confirming the diagnosis. Prognosis of mucocutaneous

disease is better than cases where eye and central nervous system involvement is present [77].

Cogan Syndrome: It is characterized by sensorineural hearing loss and vestibular dysfunction [78]. Other manifestations may include arteritis, aortitis, aortic aneurysms, and valvulitis [79]. Ocular manifestations include conjunctivitis, episcleritis, scleritis and uveitis [80]. It is also one of the causes of a very distinctive corneal involvement known as interstitial keratitis [78]. Posterior segment is rarely involved. Atypical Cogan syndrome can manifest with posterior segment findings such as retinal vasculitis, papillitis, central retinal vein occlusion, and vasculitic optic neuropathy [81,82]. Leukocytosis and elevated erythrocyte sedimentation, sometimes C-reactive protein may also be elevated, but none are considered to be diagnostic [83,84]. Almost 90% of the patients suffer severe hearing loss or total bilateral deafness, while ocular sequelae are rare [85,86].

Vasculitis associated with systemic disease

Sarcoidosis: It is a chronic disorder with non caseating granulomatous inflammation, commonly involving the lung and the lymph nodes [87]. It has a bimodal age of presentation, one occurring in young age and the other, at an elderly age. Presenting features include dyspnea on exertion, with bilateral hilar lymphadenopathy with ocular and skin lesions [88]. Retinal vasculitis is a periphlebitis, with venous sheathing, macular edema, and neovascularization [89]. Dalen-Fuchs nodules are deep yellow lesions thought to be small choroidal granulomas, may also be seen in some patients [90]. Optic disc swelling may be present [89]. CT chest and serum ACE levels are routinely done to confirm the diagnosis. The International Workshop on Ocular Sarcoidosis established diagnostic criteria, classifying ocular sarcoidosis as definitive, presumed, probable and possible on the basis of clinical signs and laboratory investigations [91]. Definite diagnosis was made when there was positive biopsy with compatible uveitis. The course of ocular involvement could be could be monophasic, relapsing or chronic [92]. Young patients may have an acute onset with spontaneous resolution in 2 years. Others have a more chronic course with disease persistence beyond 2 years.

Systemic lupus erythematosus (SLE): It is a chronic, immune complex mediated autoimmune disease. Anteriorly, it may present as episcleritis, scleritis, stromal keratitis and keratoconjunctivitis sicca [93]. Posteriorly, retinal vasculitis along with haemorrhage, cotton wool spots and macular edema is commonly seen [94,95]. Choroidopathy with resultant serous retinal detachment may also occur [95]. ANA testing shows high sensitivity. New SLE classification criteria (SLICC-2012) have been developed for better diagnosis. It is divided into 11 clinical and 6 immunological criteria's. Presence of more than 4 of these criteria or biopsy proven SLE with ANA or Anti-DNA is considered to be diagnostic [96]. Although, prognosis of SLE has improved with newer treatments, long-term prognosis remains poor [97].

Spondyloarthropathies: They are a group of disorders featuring HLA-B27 positivity and enthesitis [98]. It comprises of ankylosing spondylitis, psoriatic arthritis, reactive arthritis and spondyloarthropathy with inflammatory bowel disease [99]. It presents with severe anterior uveitis with intense fibrinous reaction, hypopyon and posterior synechie [100]. Posterior segment findings like vitritis, retinal vasculitis and papillitis are less common [100].

Eye Vasculitis associated with probable infectious etiology

Eye vasculitis secondary to infections

Microorganisms can directly invade vascular endothelium leading to cellular injury and death. Antigenic components of microorganisms may form immune complexes and deposit at the blood vessel wall, activating complement, and produce acute inflammation.

Endogenous endophthalmitis (EE): Infections, both fungal and bacterial can result in endophthalmitis via spread from distant foci [101]. Metastatic spread may occur in case of intravenous drug abuse, indwelling catheters, septic joint, immunocompromised and diabetic patients [102-104]. Patients are generally systemically unstable. Fungal EE has lesser involvement of anterior chamber and present mainly as vitritis and chorioretinitis [105]. Typically fluffy balls or string of pearls can be seen. Bacterial EE has severe anterior segment reaction with fibrinous reaction and hypopyon [106]. Posterior segment has severe vitreous inflammation and debris [105]. Early cases may show retinal vasculitis with surrounding infiltrates. Although, aqueous and vitreous samples can be taken, blood culture is considered most reliable for diagnosis [107]. EE has poor prognosis and can result in complete vision loss, especially if missed early on and treatment delayed [108].

Viral retinitis: Viruses such as cytomegalovirus (CMV), Herpes Simplex Virus (HSV) and varicella zoster commonly cause retinitis. With use of HAART therapy, CMV has become less common. CMV can cause full-thickness retinal necrosis and HPE shows characteristic cytomegalic cells with intranuclear inclusions [109]. Lesions show marked retinal edema with confluent areas of retinal whitening, retinal hemorrhage, and vascular sheathing [110]. On the other hand HSV and VZV cause necrotizing retinitis such as Acute Retinal Necrosis (ARN) in immunocompetent [111] and Progressive Outer Retinal necrosis (PORN) in immunocompromised patients [112]. ARN may present as anterior uveitis, vitritis and retinal vasculitis with patchy or confluent cream colored lesions in the periphery early in the disease with eventual posterior involvement [113,114]. PORN has paucity of uveal inflammation and vasculitis, and shows only outer retinal discoloration [112]. PCR of intraocular samples can be done in doubtful cases. With early treatment complications can be prevented, however risk of retinal detachment during the course of disease remains a concern [115].

Tuberculosis: It is caused by *Mycobacterium tuberculosis*, commonly affecting the lungs, although extrapulmonary manifestations are not uncommon [116]. Ocular involvement secondary to hematogenous spread is common. It may present as anterior uveitis and panuveitis apart from posterior segment findings such as retinitis and chorioidopathy [117]. Retinal vasculitis is associated with vitritis, retinal hemorrhage, neovascularization, and neuroretinitis [117,118]. Choroidal tubercles, choroidal tuberculoma, subretinal abscess and serpiginous like chorioidopathy may be seen [119,120]. Mantoux and Quantiferon gold test are supportive of diagnosis. Diagnostic criteria for ocular tuberculosis include at least one or more clinical sign along with positive PCR or demonstration of AFB under microscope or culture of ocular fluids [117]. Prognosis is variable and depends on early diagnosis and treatment.

Acquired syphilis: It can be caused either by the direct invasion of the spirochete *Treponema pallidum* or an allergic reaction due to the pathogen [121]. It may present as anterior segment flare and cells, and posterior segment manifestation like patchy diffuse neuroretinitis with

hemorrhagic areas [122]. VDRL and RPR test are considered confirmative. Patients with ocular syphilis should undergo CSF testing to rule out neurosyphilis [123]. Patients with syphilis should be tested for HIV infection due to similar risk factors for acquisition.

Lyme disease: It is caused by spirochete, *Borrelia burgdorferi*, and is transmitted through tick bite. Annular skin lesions develop after several days, followed by neurological and cardiac manifestations [124]. Chronic arthritis, polyneuropathy and encephalopathy may also occur [124]. Uveitis may be anterior, intermediate or posterior [125]. Anterior segment findings like conjunctivitis, keratitis, iritis, scleritis and episcleritis has been reported [126]. Retinal vasculitis, neuroretinitis and multifocal chorioiditis may be seen [127]. ELISA positivity is highly sensitive for lyme disease.

Toxoplasma: It is caused by intracellular parasite *T. gondii* and can persist as latent infection in host cell vacuoles (tissue cysts) [128]. After cyst rupture focal necrotizing retinitis may occur followed by scar formation [129]. Anterior uveitis and vitritis may occur due to hypersensitivity [121]. Classically new lesions develop at the edges of old scars [128,130]. Secondary complications such as cataract, glaucoma and cystoid macular oedema may occur. *Toxoplasma* IgG and IgM serology are definitive of diagnosis. Although the disease is self-limiting, early treatment can hasten recovery [131].

Toxocara: It is caused by *Toxocara canis*, and is a common diagnosis in children [132]. Systemic manifestations can range from mild eosinophilia to fatal pneumonia, congestive heart failure or convulsions [133,134]. In eye it can present as chronic endophthalmitis, posterior pole granuloma or peripheral granuloma [135]. Acute inflammation may present as yellow infiltrates of vitreous and retina [136]. Retinal vasculitis may be seen rarely. Eosinophilia and vitreous sampling for PCR are supportive of diagnosis. Total IgE, along with anti-toxocara IgG antibody (ELISA), may also be useful for the diagnosis [137].

Vasculitis with Masquerade Syndromes

Vasculitis associated with Malignancies

It is mostly uncommon finding accompanying malignancies. Autoimmunity against self-antigens contributes to vision loss [138]. Antibodies target retinal photoreceptor, bipolar, and ganglion cells [139]. They show retinitis pigmentosa like picture with night blindness and vascular attenuation [140]. Retinal phlebitis and vitritis may also be present [140]. Arterial and venous sheathing may be seen in ocular lymphoma [141]. Retinal infiltrates and sheathing can be seen in cases of acute leukemia [142].

Drug induced vasculitis

Although rare, inhalations of methamphetamine and intravenous immunoglobulins have been implicated [143,144]. Other drugs such as opioids, hydralazine, antifibrotics, antibiotics and leukotrienes have also been reported to cause vasculitis [7].

Clinical Assessment and Diagnosis

A comprehensive ophthalmic assessment should include not only a complete history of ocular complaints along with past treatment history, but also a probing history of any associated systemic complaints in detail. Previous medical history of any rheumatological disease, infection, neoplasm and drug-sensitivity must be taken to

differentiate primary vasculitis from secondary forms [145]. Ophthalmic examination might reveal decreased visual acuity, visual field defects, raised intraocular pressure (IOP) and abnormal color vision [146]. Anterior segment findings such as keratic precipitates, anterior chamber cells and flare, hypopyon, inflamed iris, iris nodules, posterior synechiae and complicated cataract may also be present [147]. Posterior segment may show vitritis with signs of retinal vasculitis like attenuation, sheathing, cotton wool spots, microaneurysms, hemorrhage, edema, infiltrates and peripheral ischemia [148,149]. Complete ocular examination should be complemented with meticulous examination of skin, joints, extremities, nasal and oral mucosa, and neurologic system to determine any systemic involvement [150].

An ophthalmologist can be vital in the diagnosis and treatment of systemic vasculitis, as there maybe patients who present for the first time with ocular symptoms. He may also play an important role in referred patients by assessing ocular involvement and determining disease activity, and at times a timely intervention may prevent irreversible vision loss.

Investigations

Management of a case of vasculitis requires multidisciplinary approach. Our aim is to identify and classify vasculitis, noting its local and systemic involvement. Minimal testing is required initially such as complete blood count, erythrocyte sedimentation rate, acute phase proteins, protein electrophoresis, blood chemistry and chest radiograph. More specific investigations can be tailored according to each case (Table 2).

Diagnosing associations of Retinal vasculitis	
Primary systemic vasculitis	
Microscopic polyangiitis	Renal biopsy, ANCA
Wegener's Granulomatosis	c-ANCA, chest XRAY
Churg Strauss syndrome	Eosinophilia, p-ANCA, chest XRAY, biopsy
Polyarteritis nodosa	HBV,ESR, Urine microscopy, Biopsy
Kawasaki disease	ESR, Echocardiography, ECG
Takayasu arteritis	Arteriography, chest CT
Giant cell arteritis	ESR, CRP, biopsy
Autoimmune disorder	
Behcet's disease	HLA B51, pathergy test
Sarcoid vasculitis	Serum ACE, Chest X-ray, chest CT
Lupus vasculitis	ANA
Spondyloarthropathies	HLA B27, X-ray of relevant joint, CT scan
Infective etiology	
Endogenous endophthalmitis (always under physician guidance)	Blood culture, Chest X-Ray, USG abdomen and pelvis, MRI head, lumbar puncture, Urine examination and culture
Viral retinitis	PCR, Serum ELISA as suspected

Tuberculosis	Mantoux, IGR assays, Chest X-ray, Sputum AFB, Chest CT
Acquired syphilis	VDRL, TPHA, FTA Abs, RPR
Lymes disease	ELISA assay
Toxoplasma	Serum ELISA assay
Toxocara	Eosinophilia, PCR
Masquerade syndromes	As suggested by clinical features

Table 2: Diagnosing associations of Retinal vasculitis

Treatment

The aim of therapy is to induce remission, maintain remission and prevent relapse [151]. In cases of ocular involvement only, unilateral cases may be treated with topical and periocular steroids, however bilateral cases and vision threatening involvement may necessitate added systemic treatment [25]. However, before considering steroid therapy, infectious causes must be ruled out. Ocular manifestations in a patient with systemic diseases mostly require systemic treatment, as local treatment is seldom beneficial [7]. Although, steroids can be life-saving, they can have serious complications in patients on long term systemic therapy [152,153]. Therefore, in order to prevent the potential risks, high dose steroids are advocated for brief periods to achieve the desired result, with slow tapering and with eventual discontinuation [154]. In steroid responders patients can be given immunosuppressive. They have also been shown to be effective in combination with steroids to induce remission [155]. In patients with poor response to treatment, intravenous immunoglobulins have also been tried with good results [156].

In patients with proliferative changes, as a sequel of retinal vasculitis, prompt treatment with laser photocoagulation is helpful in reducing the risk of severe vision loss [157]. Advanced cases with vitreous haemorrhage and tractional retinal detachment may require surgical intervention [158].

Conclusion

Diagnosis of vasculitis affecting the eye lies in an accurate, detailed and relevant history. When presented with a patient with eye vasculitis, specific questions regarding the presence of a multisystem inflammatory disorder should be asked. Eye vasculitis can be sight threatening, hence requires a thorough diagnostic work up guided by the patient's symptoms and signs. Prompt diagnosis and initiation of appropriate treatment is useful in preventing both systemic and ocular morbidity.

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