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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Orbital Vasculitides–Differential Diagnosis

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Abstract

Purpose of Review The orbit is subject to a variety of vascular insults that manifest with both specific and nonspecific patterns of vision compromise. The aim of the following review is to highlight the ophthalmic clinical features of systemic vasculitides that most frequently involve the orbit and differentiate them from the most common non-vasculitic orbital disorders.

Recent Findings New studies continue to explore the autoimmune nature of vasculitic disease and seek to determine optimal use of newer therapies such as biologic agents.

Summary The pattern of ocular involvement in the context of clinical history allows the knowledgeable physician to distill a differential diagnosis into a specific or likely cause. Establishing a diagnosis in a timely fashion allows for a custom-tailored approach to therapy.

Keywords Vasculitis · Behcet's disease · IgG4 disease · Cogan's disease · Granulomatosis with polyangiitis · Takayasu arteritis

Introduction

The eye is an important indicator of systemic vasculitis. Vasculitis is an inflammatory process that attacks the blood vessels. Several etiologies including autoimmune, infectious, neoplastic, and drug-related causes can result in vasculitis. Vasculitis is often systemic affecting several organs at once; however, certain primary vasculitides tend to cause localized inflammation. Inflammation disrupts normal blood flow to end organs leading to ischemia and necrosis. When this occurs in the orbit, vision compromise is devastating. Ophthalmic disorders can often be the first diagnostic manifestation of these potentially life-threatening vasculitides because the vasculature is visible around the eyes, and even deeper orbital vasculitis leads to changes in vision which become symptomatic earlier than damage caused to internal organs. Therefore, it is important to be able to recognize ocular findings and distinguish vasculitis from other closely presenting non-vasculitic disorders of the orbit.

This review of ocular manifestations of vasculitis will discuss a group of systemic vasculitides which have defining ophthalmologic findings. We will also summarize the classic characteristics of the differential diagnosis for symptoms of both vasculitic and non-vasculitic orbital inflammation.

Ophthalmologic Manifestations

A wide variety of ocular manifestations can occur including inflammation of the cornea, conjunctiva, lacrimal gland, episclera, sclera, uvea, retina, and orbital blood vessels. Vascular inflammation occurs in response to the production of aberrant auto-antibodies that initiate an attack on vascular endothelium, vessel wall, intracytoplasmic granules, or intranuclear proteins of nucleated cells [1]. While ocular symptoms can be variable and nonspecific, some patterns of involvement can suggest a particular disease (Table 1) [2–5].

Differentiation of Primary Vasculitides

Orbital vasculitis can occur with and without systemic involvement (Table 2). Examples of orbital vasculitis without systemic involvement are known as ocular vasculitides such as retinal vasculitis (e.g., CMV, HIV retinitis), pars planitis, birdshot chorioretinopathy, idiopathic retinal vasculitis

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Table 1 Ocular manifestations of vasculitis with associated systemic vasculitides

	Conjunctivitis (keratoconjunctivitis sicca *)	Keratitis {interstitial*, peripheral ulcerative**)	Episcleritis/scleritis	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Retinal vasculitis	Optic neuropathy	Ophthalmoplegia	Periorbital inflammation
Typical ocular symptoms	Red eye, burning sensation, tearing	Red eye, eye pain, tearing, blurry vision, light sensitivity, foreign body sensation	Red eye, eye pain, light sensitivity, pain with eye movements	Blurry vision, red eye, eye pain, light sensitivity, seeing floaters, headache			Decreased vision, blind spots (scotomas)	Painless vision loss, transient vision loss (amaurosis fugax)	Double vision, pain on eye movements	Proptosis, eye pain, eyelid edema
Behcet's			++	+++	+++	+++++	+++++	++		
Cogan's	+++	++++*	+++		+++					
Churg Strauss		+	+					+	+	
Giant cell arteritis							++	+++++	+	
Granulomatosis with polyangiitis	++++	++**	++++		++			+	+	++++
Henoch-Schonlein Purpura		+	+	+						
Kawasaki	++			+				+		
Polyarteritis nodosa		+++	+++				+++			
Rheumatoid arthritis	+++ *	++**	++				+++			
SLE	+++*	+	+++	++			++++	++++	++	
Sarcoidosis				++++	+++	+++	+++	+++		
Takayasu arteritis			+		+		+++	++		

Key: "+" rarely < 2%, "++" infrequently < 10% of the time, "+++" sometimes > 10–40%, "++++" frequently > 40–75%, "+++++" almost always > 75%

Table 2 Differential diagnosis of orbital vasculitis

Associated with autoimmune disorders
- Sarcoidosis
- Lupus
- Rheumatoid arthritis
- Sjogren disease
- Spondyloarthropathies (Reiter's, HLA-B27 associated)
- Crohn's disease
- Scleroderma
- Sclerosing cholangitis
- Dermatomyositis, Polymyositis
- Juvenile idiopathic arthritis

Associated with primary systemic vasculitis
- Small vessel disease
  - Granulomatosis with polyangiitis (Wegener's syndrome)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
  - Microscopic polyangiitis
  - Henoch-Schonlein purpura
- Medium vessel disease
  - Polyarteritis nodosa
  - Kawasaki disease
- Large vessel disease
  - Takayasu arteritis
  - Giant cell arteritis
- Variable vessel disease
  - Cogan's syndrome
  - Behcet's disease
  - Buerger's disease (small-to-medium)
  - IgG4-related disease (medium-to-large)

Without systemic involvement
- Retinal vasculitis
- Pars planitis
- Scleritis, including posterior scleritis
- Birdshot chorioretinopathy
- Idiopathic retinal vasculitis, aneurysm and neuroretinitis Syndrome (IRVAN)
- Eales disease
- Acute multifocal hemorrhagic retinal vasculitis

Associated with systemic infection
- Bacterial
  - Endogenous endophthalmitis
  - Tuberculosis
  - Syphilis
  - Lymes disease
  - Bartonella henselae
  - Brucellosis
  - Post streptococcal syndrome
  - Whipple's disease
- Viral
  - Acquired immunodeficiency syndrome
  - Cytomegalovirus
  - Herpes simplex virus
  - Varicella zoster virus
  - Epstein-Barr virus
  - West Nile virus
  - Dengue fever virus
  - Human T cell lymphoma virus type 1
- Parasitic
  - Toxoplasma
  - Toxocara

Associated with Masquerade syndromes
- Neoplasms/Malignancies
  - Acute leukemia
  - Ocular lymphoma
  - Lymphoproliferative disorders (lymphomatoid granulomatosis, angiolymphoid hyperplasia)
  - Paraneoplastic syndromes
- Drug-associated
  - Post vaccination
  - Methamphetamine inhalation, opioids, hydralazine, antifibrotics, antibiotics and leukotrienes

Associated with neurologic disorders
- Multiple sclerosis
- Susac syndrome

aneurysms and neuroretinitis syndrome, Eales disease, and acute multifocal hemorrhagic retinal vasculitis. Primary systemic vasculitis with orbital involvement have been categorized into small, medium, large, or variable vessel disease which can be accompanied by both specific and nonspecific patterns of vision compromise [6].

A retrospective multi-center cohort of 1286 patients by Rothschild et al. showed that 16.6% of patients presenting with systemic vasculitis had various ocular manifestations at time of diagnosis [7]. The most common primary vasculitides associated with eye involvement are giant cell arteritis (GCA) and granulomatosis with polyangiitis (GPA). In a multicenter longitudinal observational cohort of 838 patients diagnosed with systemic vasculitides, ocular involvement was recorded at diagnosis in 30% of GCA, 26% of GPA, 7% of Takayasu arteritis (TAK), 6% of polyarteritis nodosa (PAN), 4% of eosinophilic granulomatosis with polyangiitis (EGPA), and 0% of the microscopic polyangiitis (MPA) patients [8]. Over the 6-year period of observation, the cumulative ocular involvement was found to include 35% of GCA, 38% of GPA, 9% of

TAK, 12% of PAN, 14% of EGPA, and 12% of MPA. The timing of onset of new manifestations was not significantly associated with disease duration.

Although orbital inflammation can occur with vasculitis, there is a whole host of non-vasculitic orbital inflammatory diseases that need to be distinguished from orbital vasculitides (Table 3). Idiopathic orbital inflammation (IOI) is a prime example of the difficulties in establishing diagnostic criteria for orbital processes. Mombaerts et al. have proposed a consensus diagnostic criteria of IOI using a modified Delphi approach to meet virtually with orbital experts [9•]. The criteria exclude symptoms such as eyelid swelling, redness, ptosis, proptosis, motility deficit, and visual dysfunction as they are nonspecific to differentiate IOI from any other orbital disease. Findings that were considered significant included orbital pain of acute onset, absence of history of orbital-related systemic disease, unilaterality, pathologic findings, and radiologic imaging [10••].

Small-Medium Vessel Vasculitis

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) is a systemic autoimmune disease that widely affects small- and medium-sized vessels throughout the body. Similarly, it can affect nearly every structure in the orbit from the external structures of the eyelids to the internal structures such as the retina, choroid, optic nerve, and even the sclera and cornea. The prevalence ranges from 20 to 160 cases per 1 million people across Europe, UK, and Japan; however, in the USA, the prevalence is 26 per 1 million (based on hospitalizations) and the annual incidence is 1.8 cases for pediatric-onset GPA and 12.8 per million for adult-onset GPA in the US [10••, 11]. The disease primarily affects Caucasians, is rare in black populations, and has a slight female preponderance [12].

A recent review by Sfiniadaki et al. classifies GPA into limited and systemic forms [13]. The limited form has only upper and lower respiratory tract involvement, whereas the systemic form involves both respiratory tract, kidneys, and additional organs. Studies seem to suggest that the chronic nasal carriage of *S. aureus* is linked to relapse of GPA [14]. Systemic GPA is associated with c-ANCA (80–95%) and p-ANCA (5–20%). ANCA is also found in association with the limited form (50–60%) [15]. Orbital involvement is the most frequent manifestation of both limited and systemic GPA occurring in 45–50% of patients [15, 16•]. This is further corroborated in a case series by Tan et al. including 247 patients with orbital inflammation: 15% were diagnosed with GPA and only 22% had systemic manifestations [17]. A study evaluating patients with lacrimal gland inflammation resulted in GPA diagnosis in 10% [18].

Common presenting eye symptoms include epiphora, painful eye, erythema, reduced vision, and proptosis. Proptosis is a key clinical sign and its combination with respiratory airway disease or renal disease implies diagnosis. Proptosis and deformation of eyelids can result in exposure keratopathy leading to corneal ulceration and blindness. Painful ophthalmoplegia can result from extension of orbital mass into neighboring structures in the cavernous sinus. With chronic proptosis, subsequent enophthalmos can ensue due to fibrotic changes [14]. Epiphora can occur with nasolacrimal duct obstruction related to the sinus disease. Diplopia can arise from vasculitis of the vessels supplying the extraocular muscles. Other orbital manifestations include globe perforation from necrotizing scleritis or peripheral ulcerative keratitis, vision threatening orbital compartment syndrome due to compressive periorbital soft tissue swelling, and ischemic optic neuropathy arising from central retinal artery occlusion [12, 14, 15, 19–21, 22••]. Uveitis occurs in approximately 10% of patients, with retinal and choroidal manifestation occurring less frequently. Retinal vein occlusion can occur due to compressive soft tissue swelling but is usually associated with vasculitis. Retinitis, chorioretinitis, macular edema, exudative detachment, and retinal necrosis are all posterior segment findings which can be identified on fluorescein angiography that reveals delayed filling of blood vessels in areas of ischemia [14, 15].

Imaging such as CT, MRI, and ultrasound is useful in orbital involvement to demonstrate masses, extent of tissue damage, and comorbid sinus disease, but it is not specific; therefore, biopsy is used to confirm the diagnosis (Fig. 1). Isa et al. reported that even for ANCA-negative cases of GPA, cytokine staining for IL-17 and IL-23 was significantly greater in GPA samples than in sarcoid and IOI disease. These cytokines may prove to be useful biomarkers for early diagnosis of orbital GPA [23]. Although the pathogenesis of GPA remains to be seen, the pathophysiologic mechanisms are better understood creating more potential targets for therapy. Rosenbaum et al. have found that gene expression in orbital biopsy tissue can distinguish between IOI and other causes of orbital inflammation such as thyroid eye disease and sarcoidosis, however, the gene expression was unable to distinguishable between GPA and IOI and it is hypothesized that many cases of IOI may actually be non-specific cases of GPA [24, 25].

Fifteen years ago, the prognosis for GPA was dismal with a median survival rate of 5 months and > 80% mortality at 1 year [26]. The first-line therapy is considered intravenous glucocorticoids plus cyclophosphamide, methotrexate, or azathioprine, which has improved prognosis significantly to survival rates as high as 95% at 5 years [27]. The latest studies show promise with

Table 3 Differential of non-vasculitic orbital inflammation

Differential	Classic Presentation
Infection	
Bacterial orbital cellulitis	H/o recent or chronic sinusitis, preseptal cellulitis, dacryocystitis, styes, or midfacial skin or dental infection; H/o facial trauma; rapid painful ophthalmoplegia, decreased vision, double vision, proptosis, possible afferent pupillary defect, possible choroidal folds and optic disc swelling
Fungal orbital infection (e.g., Mucormycosis)	H/o diabetic ketoacidosis or immunosuppression, recent upper respiratory infection or sinusitis; slow progression of periorbital swelling, double vision and visual loss, infarction superimposed on septic necrosis leading to black eschar on palate, turbinates, skin, and eyelids, possible retinal vein occlusion
Dacryocystitis	H/o tearing, acute or chronic sinusitis; acute or chronic onset of medial canthal area pain, may have concomitant preseptal cellulitis or conjunctivitis, pressure over lacrimal sac results in mucopurulent canalicular reflux
Infective dacryoadenitis	H/o viral infection with Epstein-Barr Virus, mumps, or Cytomegalovirus; unilateral swelling of lateral aspect of eyelid with an S-shaped ptosis, injection of palpebral portion of lacrimal gland causing down and inward dystopia
Vascular lesions	
Acute orbital hemorrhage	Associated with trauma, orbital surgery (retrobulbar block, fracture repair) or rare vascular anomalies, associated risk of acute orbital compartment syndrome and compressive optic neuropathy leading to irreversible blindness
Cavernous sinus thrombosis	H/o sinusitis, orbital or preseptal cellulitis, or otitis; rapid onset of headache, nausea/vomiting, unilateral or bilateral pulsatile proptosis, chemosis, congestion of conjunctiva and retinal veins or vein occlusion, reduced vision, ophthalmoplegia with cranial nerve III-IV palsies
Carotid-cavernous fistula	H/o head injury; triad of pulsatile proptosis, conjunctival chemosis and whooshing noise in head; elevated intraocular pressure
Neoplasia	
Rapidly progressive retinoblastoma	Diagnosis of childhood: usually diagnosed within the first year of life in bilateral cases or around 2 years old in unilateral tumor; leukoria from intraretinal dome-shaped calcified white lesion, strabismus, painful red eye with secondary glaucoma and buphthalmos with orbital invasion, poor vision, orbital inflammation mimicking orbital or preseptal cellulitis
Lacrimal gland tumor (e.g., adenoma, carcinoma)	Superolateral painless smooth and firm mass, slowly progressive growth, upper lid swelling, possible dystopia, proptosis, ophthalmoplegia, or choroidal folds
Lymphoma	Can be asymptomatic or present with discomfort, double vision, eyelid mass, conjunctival lymphoma often presents with boggy pink conjunctival lesion
Rhabdomyosarcoma	Diagnosis of childhood: typical onset 5–7 years old; Rapidly progressive painless unilateral proptosis mimicking orbital cellulitis, poorly defined mass can arise from orbit such as conjunctiva and uvea, diplopia frequent
Leukemia	Ocular features generally present due to secondary changes such as anemia, hyperviscosity, thrombocytopenia, and opportunistics infections which lead to intraocular bleeding, infection, and vascular occlusion, retinal heme, roth spots, and cotton wool spots
Lymphangioma	Usually presents in childhood; proptosis due to spontaneous bleed may lead to chocolate cysts that regress spontaneously with time, episode may follow an upper respiratory tract infection
Neuroblastoma	Common childhood malignancy, presents with rapid onset proptosis, a superior orbital mass and eyelid ecchymosis
Endocrine	
Thyroid eye disease	H/o thyroid disease; Most common cause of unilateral and bilateral proptosis, middle age female, congestive inflammatory injection, painless motility defects, diplopia, lid retraction, possible end-stage optic neuropathy
Non-neoplastic inflammation	
Idiopathic orbital inflammatory disease	Acute or subacute periocular swelling and pain, pyrexia (common in children, rare in adults), mild to severe ophthalmoplegia, if posterior orbit involved can lead to vision loss, optic nerve swelling or choroidal folds, course involves spontaneous remission after weeks of prolonged inflammation followed by intermittent episodes of inflammation
Tolosa hunt syndrome	Ipsilateral periorbital or hemicranial pain, oculomotor dysfunction, sensory loss along V1-V2
Ruptured dermoid cyst	Superolateral eyelid or orbital swelling due to rupture of a childhood choristoma

Rituximab, an anti-CD20 therapy which prolongs B cell depletion. Rituximab has been shown to have less adverse effects when compared to cyclophosphamide [28] and has shown benefit in treating orbital symptoms of GPA. The RITIZAREM study due out in 2020 will be the largest trial to compare repeated intravenous Rituximab to the

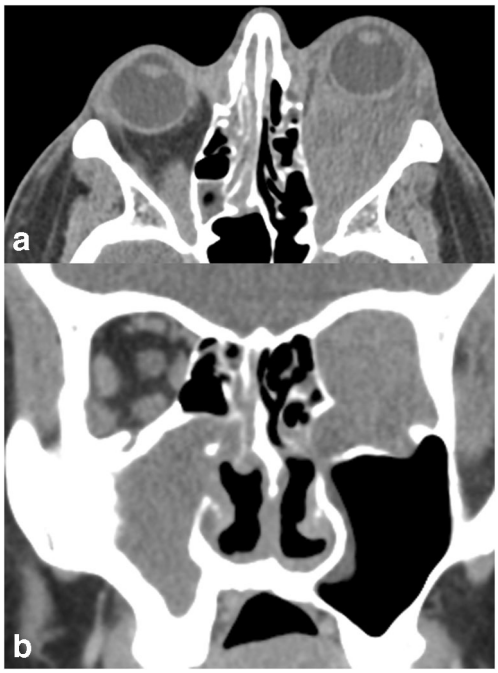

Fig. 1 **a** Axial CT scan of a 27-year-old male with granulomatosis with polyangiitis showing marked proptosis of the left eye with diffuse orbital inflammatory disease. **b** Coronal CT scan of the same patient showing right-sided maxillary sinus disease and left orbital inflammation with bony changes along the inferomedial orbit

current standard of daily oral azathioprine to prevent relapse and induce remission of ANCA-associated vasculitis [29]. Intravenous immunoglobulin has also shown to be useful when first-line therapy fails [30, 31].

Large Vessel Vasculitis

Giant Cell Arteritis

GCA is the most common vasculitis that affects adults over 50 years of age. The age affected peaks at 70–80 years old. It primarily affects Caucasian women of northern European descent [6]. The mechanism of GCA remains unknown; however, literature supports a combination of genetic causes such as racial predisposition and environmental risk factors. Currently, HLA-DRB1 has been consistently linked with GCA in addition to PTPN22 and REL loci, which is involved in T cell recognition [32, 33]. Several studies have suggested possible associations with viral infections including VZV, CMV, and parvovirus B19, but none have demonstrated a conclusive link [34, 35].

Common symptomatology includes, from least to greatest: headache, jaw claudication, constitutional B-symptoms (fever, weight loss, and fatigue), polymyalgia rheumatica, and scalp tenderness. Though there are several presentations of GCA, ocular manifestations are a consistent presentation. Visual symptoms occur in 20–50% of patients and manifest with diplopia (5–15%), transient (10–30%), and permanent (5–19%) defects from optic nerve ischemia [36•, 37•, 38–41]. It is important to note that approximately one in five patients with ocular symptoms only, without constitutional or other symptoms, are diagnosed with occult GCA [42]. In general, most patients have unilateral involvement at presentation, and if untreated, the second eye is affected within 7 days [43]. Arteritic anterior ischemic optic neuropathy (A-AION) is the most common ocular manifestation affecting nearly 80% of patients due to ischemia of the posterior ciliary arteries which are branches of the ophthalmic artery that supply the optic nerve head [44]. In the acute phase, the optic nerve demonstrates a chalky white appearance. Subsequent optic atrophy usually develops in 6–8 weeks with diffuse or segmental pallor. Less commonly, arteritic posterior ischemic optic neuropathy (A-PION) can occur when the site of ischemia is retrobulbar and not visible on fundoscopic exam. Clinically, the patient will have decreased visual acuity, visual field defects, afferent pupillary defect, and abnormal color vision. Both AION and PION necessitate an urgent work-up to prevent bilateral blindness.

Other ocular findings include choroidal and retinal ischemia due to retinal artery occlusion and cotton wool spots (CWS). Fundoscopic appears to demonstrate a retinal pallor, vessel attenuation, and parafoveal cherry red spot. A recent study reported central retinal artery occlusion in 14% of patients with GCA. More common is occlusion of the cilioretinal artery (85%), an artery that supplies the papillomacular bundle and causes central vision loss. CWS have been reported in 30% of GCA patients that present with early vision loss [45]. Anterior segment ischemia can result from vasculitic changes to the vasa vasorum that supply the anterior ciliary arteries which travel in the rectus muscles. Therefore, diplopia and motility defects may occur. Furthermore, hypotony can ensue from reduced aqueous humor production as a result of ischemia of the PCAs or ACAs [46, 47]. Scleritis and peripheral ulcerative keratitis have been noted but occur less frequently. Anisorcoria, an asymmetry between pupil sizes, can be associated with third cranial nerve palsy, rarely a Horner' syndrome, and tonic pupil in GCA due to microvascular ischemia of the sympathetic pathway at the ciliary ganglion or post-ganglionic short ciliary nerves [36, 46–48].

First-line treatment remains high-dose glucocorticoids; however, the treatment-related morbidity of long-term steroids has piqued interest in steroid sparing agents. Methotrexate and TNF-alpha inhibitors have shown little to no benefit [49, 50]. Recent elucidation of GCA pathogenesis has led to an increased interest in biologic agents. Two randomized control trials have reported significant increase in remission rates with an IL-6 targeted agent, tocilizumab, in GCA. The phase II study by Villiger et al. showed 85% relapse-free survival at 52 weeks vs. 20% in placebo [51•]. The phase III GIACTA

study further supports tocilizumab success demonstrating sustained remission at 52 weeks in 53% vs 17% in glucocorticoid monotherapy group [52]. Although tocilizumab is promising, further investigation of adverse effects and timeline of treatment approach are needed. Other therapies being investigated with limited success include anakinra [53] and JAK-STAT inhibitors [54].

Takayasu Arteritis

Takayasu arteritis (TAK) has been considered a rare disease in the West and was thought to be more common in the Far East. The disease was first described in middle-aged Japanese women; however, recent surveys show that the disease is seen in all ethnicities with increasing prevalence rates [55•]. Takayasu arteritis is a granulomatous pan-arteritis that affects the aorta and major branches. Delay in diagnosis stems from indistinct symptoms of presentation and the body's unique ability to generate collateral vessels in the face of chronic ischemia.

Ischemic ocular complications can lead to complete loss of vision and coincide with vasculitic destruction of the carotid arteries and collateral blood supply to the eye. Patients may present with amaurosis fugax (transient vision loss) or they may have progressive permanent vision loss [22••]. Ocular manifestations of TAK include microaneurysm formation, small-vessel dilatation, cotton-wool spots, arteriovenous anastomosis, retinal ischemia due to vasculitic destruction of carotid arteries or ophthalmic artery. Poor perfusion of the retina from arteriovenous shunts and retinal capillary dropout are easily recognized on fluorescein angiogram by delayed choroidal and retinal circulation [22••, 56]. As a result of chronic hypoperfusion, neovascular glaucoma and ocular ischemic syndrome can develop. Ocular ischemic syndrome is due to global ischemia that presents with subacute vision loss, ocular angina, neovascularization, and is highly associated with extensive carotid disease. On examination, congested episcleral vessels along with rubeosis iridis will be the most obvious signs; however, additional findings on posterior segment exam may include retinal neovascularization with or without intravitreal hemorrhage leading to significant vision loss. A cross-sectional study showed the occurrence of retinopathy in TAK to be 15%, 7% for ocular ischemic syndrome, and 16% for hypertensive retinopathy [57]. Other ocular findings such as uveitis and scleritis are less common but have occurred in case reports [58, 59].

Diagnosis for TAK using fluorescein angiogram has been replaced by MRA and FDG-PET in recent years. In terms of therapy options, there is a paucity of controlled clinical therapeutic trials for TAK. Nevertheless, a recent systematic review showed promising results of leflunomide, TNF-alpha inhibitors, and tocilizumab in steroid refractory TAK [60•].

Variable Vessel Vasculitis

Cogan's Syndrome

Cogan's syndrome (CS) is a rare systemic vasculitic disorder with variable clinical manifestations that are characterized by involvement of the visual and auditory systems. The association with systemic vasculitis in CS is also well documented and occurs in approximately 15–21% of patients [61]. It is a disease the primarily affects young adult Caucasians with median age 25 without gender predominance [61, 62]. The disease is classified as typical or atypical based on timing. The typical presentation is a non-infectious interstitial keratitis arising within 2 years of a Meniere's-like vestibuloauditory syndrome with sudden onset of vertigo, tinnitus, and a sensorineural hearing loss. Interstitial keratitis (IK) is a non-ulcerating inflammation of the corneal stroma that leads to scarring and neovascularization of the cornea without involvement of the epithelium or endothelium [5]. The leading cause of IK world-wide is syphilis, though viral infections are most common in the USA, namely Herpes simplex virus. Atypical more commonly consists of non-IK ocular inflammation including conjunctivitis, episcleritis, glaucoma, and uveitis, and is characterized by a gap of more than 2 years between ocular and vestibuloauditory symptoms [63–65]. Hearing loss can be profound despite treatment; in a literature review by Grasland et al., 60 of the 111 patients with typical CS remained with bilateral deafness despite treatment [66]. Aside from ocular and vestibulo-auditory manifestations, approximately 70% of CS patients have systemic symptoms such as cardiovascular, neurological, and gastrointestinal involvement [62]. The most common cardiac manifestation is aortitis with aortic insufficiency [67, 68]. Intracranial vasculitic involvement has led to hemiparesis or aphasia, and gastrointestinal involvement can include mesenteric arteritis [62, 69–71].

There is currently no specific serum autoantibody used for the diagnosis of Cogan's disease, however several autoimmune markers have been implicated. Anti-heat-shock-protein 70 antibodies have been found in typical Cogan's syndrome [72]. Several case reports point to a possible ANCA-associated CS, especially with ocular retinal vasculitis and glomerulonephritis [73, 74]. However, clinical importance of testing biomarkers in CS will require more study to target therapy. The first-line therapy is still high-dose glucocorticoids which has been shown to produce vestibulo-auditory and ocular improvement [75]. Biologics such as infliximab have shown promise in the treatment of CS with a French study by Durtette et al. showing an 80% response in vestibulo-auditory symptoms after 6 months [76]. Infliximab was also able to keep elapse rates low with 13% at 5 years and 31% at 10 years compared to steroid alone and DMARDs groups which included cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine. Padoan

et al. have gone so far as to recommend that infliximab be used as first-line therapy with glucocorticoids at an early stage in the disease process to prevent permanent damage [77].

Behcet's Disease

Behcet disease (BD) is an idiopathic and variable-vessel vasculitis that typically presents as an multisystemic disease and is characterized by episodic attacks [78]. The prevalence is highest in patient with Mediterranean and Asian descent, particularly Turkish males. The male ratio is 3.5:1 [79, 80]. As with other primary vasculitides, the pathophysiology involves both genetic predisposition and aberrant dysregulation of the immune system leading to increase in inflammatory mediators, abnormal heat shock protein response, and oxidative stress [81–83]. A recent meta-analysis demonstrated a strong association between BD and HLA-B51, especially in Eastern Europe and Asia, but not in Western Europe [83].

A case series in Iran showed that 58% of BD patients demonstrate ocular manifestations [84]. Intraocular inflammation is a diagnostic criterion in up to 70% of patients and is key in prognostication [78]. The typical constellation of findings includes intraocular inflammation, skin lesions, oral and genital ulceration, cutaneous and GI involvement. Patients present with bilateral symptoms in 50% [79, 80]. Uveitis is the most common ophthalmologic finding. Anterior uveitis is associated with a shifting hypopyon in 30% of cases [79, 80]. Panuveitis has been reported to be the most common (89.4%) presentation in the Middle East [85•]. Unfortunately, posterior segment involvement accounts for the more devastating vision loss. In a recent retrospective study, a Behcet disease Ocular Attack Scoring system (BOS24) was utilized to evaluate recurrence of uveitis attack at 5 years and the rate of attack was found to be the most significant prognosticator of visual prognosis [86]. In chronic ocular inflammation, ocular hypertension can result from anterior synechiae which may occlude the anterior chamber drainage angle 360 degrees, pupillary block which traps fluid behind the iris diaphragm, or from secondary corticosteroid use. When ocular inflammation extends into the posterior segment, the patient can develop vision loss from a secondary cataract. Posterior segment disease is variable, however, about a third of patients have retinal vasculitis [81, 86]. Retinitis can include retinal hemorrhage, edema, exudates, and ischemia from retinal vein occlusion [87, 88]. Inflammation can result in macular edema and ischemia with subsequent subretinal neovascularization and possible epiretinal membranes. Involvement of the optic nerve can result in hyperemic disc edema and neovascularization.

Fluorescein angiography is the standard to monitor retinal vasculitis (Fig. 2). Ultra-wide field imaging was able to detect peripheral retinitis in 85% of patient without findings on funduscopic exam and can reliably be used to monitor disease.

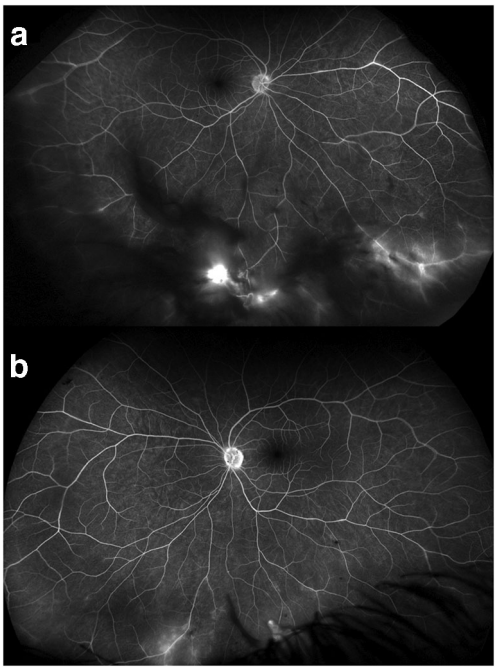

Fig. 2 Fluorescein angiography of the right (**a**) and left (**b**) eyes in a 22-year-old female with diagnosis of Behçet syndrome with mild inferior vitreous hemorrhage with temporal and inferior leakage in late phases of angiography. Photograph courtesy of Gabriel Andrade, MD

Laser flare photometry is a device not approved by the FDA that measures flare in the A/C, which has been reported to correlate with FA leakage [89]. Due to the difference in disease course and severity between patients, the variability in patient outcome measures has made it difficult to agree on the best management strategy. There is a need to develop uniform outcome measures to further investigate.

Treatment of BD is generally tailored to the organ affected. It is important to note that males with early onset disease have more severe presentation and may have multi-system involvement including ocular, GI, and neurological effects [90]. Ocular involvement in Behcet's requires significant attention since it has the highest rate of morbidity [91]. First-line therapy for anterior uveitis includes topical steroid eye drops plus cycloplegic agents. If uncontrolled, the next step includes the addition of corticosteroids, which is the general the treatment for posterior segment uveitis and/or retinal vasculitis [90]. For intraocular inflammation that remains unabated despite chronic systemic corticosteroid use, immunosuppressives such as azathioprine and cyclosporine are should be implemented as second-line therapy to decrease steroid burden [92–94]. International clinical studies have supported the use of IFN-alpha or anti-TNF alpha (e.g., Infliximab, adalimumab) therapies as second line. In severe cases with macular edema or vision limiting retinal vasculitis, first- and second-line treatments can be combined [91]; TNF-alpha inhibitors have shown to decrease uveitis flares and severe complications of retinal vasculitis [95]. Other randomized control studies have

demonstrated favorable use of methotrexate, mycophenolate mofetil, and rituximab as third line treatments [96–98]. The latest review of 398 references demonstrates promising results of interleukin-1 inhibitors such as anakinra and canakinumab to control mucocutaneous and ocular manifestations [99].

IgG4-Related Disease

IgG4-related disease (IgG4-RD) is a multi-organ inflammatory disorder that causes densely lymphoplasmacytic infiltrate and fibrosing lesions. The most frequent manifestations include, but are not limited to, autoimmune pancreatitis, sclerosing cholangitis, nephritis and renal fibrosis, lacrimal and submandibular glands, and lymph node enlargement [100–103]. Rheumatologists describe orbital manifestations as IgG4-related ophthalmic disease (IgG4-ROD). IgG4-RD tends to affect middle-aged to elderly men; however, IgG4-ROD tends to affect men and women equally [104–106]. Orbital manifestations can affect nearly every structure including the lacrimal duct and gland, periorbital soft tissue, sclera, extraocular muscles, trigeminal nerves, and orbital bones [100]. In a recent retrospective analysis at Massachusetts General Hospital by Curruthers et al., 13 of 21 (62%) patients had involvement of lacrimal gland, 3 of 21 (14%) had EOM involvement, 6 of 21 had soft tissue involvement (29%), 1 of 21 had scleritis (4.7%), and 1 of 21 (4.7%) had nasolacrimal duct involvement [100]. There was a predominance for bilateral cases, and 15 of 21 (71%) had extra-orbital manifestations. The most common extra-orbital sites of involvement were the submandibular glands (5 of 21, 24%) and parotid gland (4 of 21, 19%), with less common manifestations involving the trigeminal nerve, scleritis, xanthogranuloma, and destructive bone lesions. Vision loss is a main presenting symptom, especially in those who present with IOI. An observational study demonstrated vision loss in 21% of IgG4-ROD patients [107]. The link with extra-orbital manifestation was strongest in those with lacrimal gland involvement or bilateral IgG4-ROD, therefore, screened for systemic lesions should be performed in these cases [108, 109••].

The challenge with selecting a therapy for IgG4-RD exists due to limited access to data on conventional immunosuppressive therapeutic outcomes. However, Detiger et al. composed a systematic review identifying 35 studies and case series demonstrated that success of treatment with DMARDs is limited and is highly variable with success ranging from 36 to 75%; however, rituximab has shown a 93% in IgG4-ROD [109••]. A French study by Ebbo et al. corroborates these findings: 13 of 19 patients who relapsed after the first course of glucocorticoids were treated with conventional DMARDs MTX, Mycophenolate mofetil, and azathioprine [101]. At the 60-month follow-up, 72.2% still required prednisone or prednisone plus DMARD. Rituximab response was associated with near complete clinical response.

Conclusions

Ocular presentations of vasculitic and non-vasculitic orbital inflammation can be difficult to distinguish. Familiarity and early identification of ophthalmic presentations are important for a comprehensive approach to the management of orbital and systemic vasculitis and can even be life saving for the patient.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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