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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Ocular Vasculitis

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Abstract Vasculitis is the inflammation of blood vessels that leads to loss of perfusion and ischemia with necrosis. When this occurs in the orbit, the consequences are typically very conspicuous and can be devastating with decreased quality of life and loss of vision. Systemic vasculitides are often related to ophthalmic disorders, which can serve as the first diagnostic manifestation of potentially life-threatening disease. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (e.g., granulomatosis with polyangiitis), Behcet's disease, rheumatoid arthritis, sarcoidosis, and systemic lupus erythematosus are a few of the diseases commonly associated with ocular vasculitis. Collaboration between ophthalmologists and rheumatologists is important in the successful diagnosis and treatment of patients with vasculitis.

Keywords Ocular vasculitis · Autoimmune disease · Behcet's disease · Biologics · Granulomatosis with polyangiitis · Ocular inflammation · Rheumatoid arthritis · Uveitis · Vasculitis · Treatment · Corticosteroids · Adalimumab · Etanercept · Infliximab · Rituximab

Introduction

Orbital inflammation can affect any structure of the eye and orbit. Visualization of ocular vasculature provides us with a unique opportunity to diagnose and treat a wide variety of diseases. While each area of involvement creates a distinct constellation of findings and symptoms, it can be difficult to determine the exact cause of the symptoms due to frequent overlap of findings. Ocular inflammation is a potentially sight-threatening event that can be the harbinger of further systemic diseases that can also be life threatening. Uveitis is a significant contributor to visual impairment and blindness in developed countries with a rate of up to 34 % noted outside the United States and approximately 10–15 % in the United States [1]. Early investigation for systemic disease is important in the management of these patients, although new therapeutic modalities have not yet shown significant benefit in visual outcome, there has been significant improvement in morbidity and mortality of systemic diseases [2••, 3•].

This article is part of the Topical Collection on *Vasculitis*

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Anatomical Considerations

Vasculitis can directly or indirectly affect every part of the orbit. The cornea is naturally an avascular structure whose health depends on an intact tear film externally and aqueous humor internally. The proximity of limbal vasculature allows the peripheral cornea to be most susceptible to direct infiltration. This leads to peripheral ulcerative keratitis, which is the thinning and ulceration at the corneal margin. Central corneal involvement is typically related to infectious etiologies; however, interstitial keratitis has been seen in the rare vasculitis known as Cogan syndrome which is associated with hearing loss [4]. Dry eye syndrome may be caused by inflammatory involvement of the lacrimal gland or accessory glands in the conjunctiva. This causes keratopathy that can predispose to infection, leading to blurred vision and foreign body sensation. Keratic precipitates can be seen on the inner aspect of the cornea which can help diagnose intraocular inflammation and distinguish between granulomatous and non-granulomatous inflammation.

The conjunctiva, episclera, and sclera have a rich network of vessels that can be involved in many immune-mediated disorders. Conjunctivitis, or a red eye, is the most recognized sign of ocular inflammation but is typically non-specific as many conditions can cause a secondary conjunctivitis. Conjunctival

biopsy has low risk and can be helpful in the diagnosis of several disorders, notably relapsing polychondritis, ANCA-associated vasculitides, and sarcoidosis [5••, 6, 7]. Episcleritis is the inflammation of the tissue between the conjunctiva and the sclera. This erythema typically blanches on application of topical phenylephrine and is non-tender to palpation. This differentiates it from scleritis, in which symptoms of red eye, light sensitivity, and eye irritation are accompanied by a marked pain and tenderness to palpation. Scleritis can occur anteriorly or posteriorly, although approximately 94 % will be anterior [8]. Posterior scleritis will typically be diagnosed with imaging such as ultrasonography showing thickening of the sclera surrounding the optic nerve. In a study by Sainz de la Maza et al., episcleritis was found to be associated with connective tissue or vasculitic diseases in 15 % of patients, while scleritis was associated in 25 % [8]. Scleritis led to the diagnosis of connective tissue or vasculitic disease in 39 % of those cases. Episcleritis, however, is generally considered to be a self-limited disease that is only occasionally associated with systemic diseases (less than 5 %) and the high incidence in this study may be related to the nature of a tertiary referral center [8, 9].

The uveal tract is the term used to denote the highly vascularized middle layer of the eye. It includes the iris, ciliary body, and choroid. Its major function is to provide nourishment for the intraocular tissues including the retina, lens, and cornea. Uveitis is subdivided based on the anatomic region of the eye that is affected: anterior (ciliary body and iris), intermediate (vitreous and peripheral retina), posterior (choroid and posterior retina), and panuveitis (all three levels) [10]. Symptoms of anterior uveitis include light sensitivity, blurred vision, tearing, and aching eye pain, although this is uncommon in early juvenile idiopathic arthritis [11•]. Chronic anterior inflammation commonly results in band keratopathy (calcium deposits in the inner Bowman's layer of the cornea), posterior synechiae (adhesions of the iris tissue to the lens), glaucoma (elevated pressure in the eye), and cataract formation.

Intermediate uveitis will typically present as painless decreasing vision with floaters [12]. Inflammation spills over into the vitreous where they cast shadows on the retina perceived as floaters. Collections of white cells may form collagen bands and create vitreous neovascular membranes and subsequently cause vitreoretinal traction and retinal detachment. Posterior uveitis occurs in the choroidal vessels adjacent to the retina. The use of indocyanine green angiography has been critical in the evaluation and differentiation of choroidal vascular involvement; although it is not a widespread practice among retinal specialists, it is still utilized in uveitis centers [13, 14]. The most common cause of visual decrease in uveitis is macular edema [1].

Retinal vasculitis is the classic ocular vasculitis in which the affected blood vessels can be directly visualized (Fig. 1). Findings result from occlusive events in the retinal arterioles, capillaries, or venules. Hemorrhage, vascular sheathing, focal ischemia with cotton wool spots, and necrosis of the retina occur. The pattern of involvement can be characteristic of certain diseases, with arterial involvement in systemic lupus erythematosus (SLE), granulomatosis with polyangiitis (GPA), and polyarteritis nodosa; predilection for veins occurs in Behcet's disease, sarcoidosis, and multiple sclerosis [15•]. Secondary effects of these events can lead to retinal and subretinal neovascular membranes, macular edema, and epiretinal membrane formation. Fluorescein angiography is very helpful in characterizing retinal vasculitis as predominantly phlebitis, capillaritis, or arteriolitis, and can evaluate the extent of retinal ischemia.

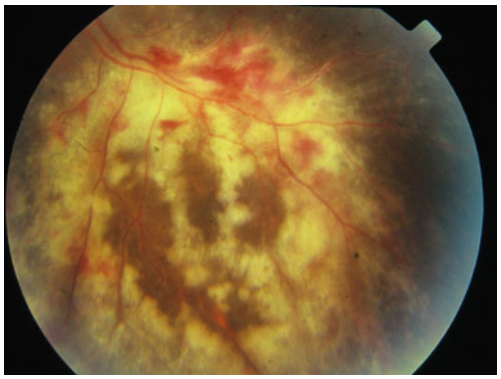

Fig. 1 CMV retinitis: hemorrhagic CMV retinitis is seen in this case. Necrotizing retinitis shows as retinal whitening; retinal hemorrhage accompanies. There is perivascular sheathing presenting as white cuffing around the veins. Later, retinal whitening resolves and leads to necrotic thin retina with underlying pigmentary RPE changes, mostly as stippled depigmentation

Orbital vasculitis is often very nonspecific and can be mistaken for idiopathic orbital inflammatory disease. Idiopathic orbital inflammatory disease is a diagnosis of exclusion; however, it is not unusual to coexist with known systemic rheumatologic disease due to inability to determine exact causality [16]. Manifestations may include eyelid edema, blurred vision, double vision, and varying degrees of periorbital pain. In more extreme cases, the orbital apex structures are involved which causes severe proptosis, ophthalmoplegia, pain, and glaucoma. Loss of vision with optic neuropathy can occur related to vasculitis or secondary to compressive sequelae of the inflammation. Vasculitic diseases most commonly associated with orbital disease are the ANCA-associated vasculitides, Cogan's syndrome, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, and giant cell arteritis [10].

Disorders

There are a multitude of conditions that have effect on the orbital tissues. Table 1 includes a non-exhaustive list of the more commonly observed and described diseases.

Table 1 Entities associated with ocular inflammation

Differential diagnoses for ocular vasculitis

Infectious disorders

- *Bacterial disorders*
  - Brucellosis
  - Cat scratch disease
  - Endophthalmitis
  - Lyme disease
  - Post-streptococcal syndrome
  - Syphilis
  - Tuberculosis
  - Whipple's disease
- *Parasitic disorders*
  - Mediterranean spotted fever
  - Rickettsial disorders
  - Rocky Mountain spotted fever
  - Toxoplasmosis
- *Viral disorders*
  - Acquired immunodeficiency syndrome
  - Cytomegalovirus
  - Dengue fever virus
  - Epstein-Barr virus
  - Hepatitis
  - Herpes simplex virus
  - Human T cell lymphoma virus type 1
  - West Nile virus infection
  - Varicella zoster virus

Malignancy

- Acute leukemia
- Ocular lymphoma
- Paraneoplastic syndromes

Neurologic disorders

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

Ocular disorders

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

Systemic inflammatory diseases

- Behçet's disease
- Buerger's disease
- Churg-Strauss syndrome (Eosinophilic granulomatosis with polyangiitis)
- Crohn's disease
- Dermatomyositis
- Henoch-Schonelein Purpura
- HLA-B27-associated uveitis
- Juvenile idiopathic arthritis
- Microscopic polyangiitis
- Polyarteritis nodosa
- Polymyositis
- Postvaccination
- Relapsing polychondritis
- Reiter's syndrome
- Rheumatoid arthritis
- Sarcoidosis
- Sjögren's A antigen
- Systemic lupus erythematosus
- Takayasu's disease
- Temporal arteritis
- Wegener's granulomatosis (Granulomatosis with polyangiitis)

We will focus on a few of the systemic vasculitides in which ophthalmic symptoms can be crucial in diagnosis and management decisions.

Granulomatosis with polyangiitis (aka Wegener's Granulomatosis)

The most common ocular manifestation of granulomatosis with polyangiitis (GPA) is orbital granuloma; however, GPA-associated vasculitis can affect the retinal and choroidal vessels, extraocular muscles, and corneal, episcleral and scleral vessels. Eye involvement has been noted to occur in approximately 29–58 % of patients with GPA [17–19]. In a study by Harper et al. reviewing 47 patients who presented with GPA-associated ophthalmic disease, ocular inflammation resulted in the diagnosis in 68 % with the following distribution: 38 % had undiagnosed systemic manifestations prior to presentation, 9 % had only ocular signs with evidence of systemic disease on further investigation, 9 % developed systemic disease long after diagnosis, and 44 % had purely ocular findings [17]. Scleritis was present in 74 %, with most associated with peripheral corneal disease. There is likely some referral bias in this study, as Hoffman et al. found that only 15 % of patients with GPA presented with ocular or orbital disease. In my practice, almost all patients diagnosed with GPA presented with nasolacrimal duct obstruction secondary to sinus inflammation. Nasolacrimal duct obstruction is a fairly common side effect of GPA, developing secondarily in up to 18 % of patients [19]. This may present primarily to the ophthalmologist as a patient with increased tearing with a history of nose bleeds and unrecognized septal perforation.

The American College of Rheumatology has given guidelines showing that the presence of two or more of the following is 88 % sensitive and 92 % specific for GPA: oral ulcers or nasal discharge; abnormal chest radiograph; abnormal urinary sediment; and granulomatous inflammation on biopsy [20]. Cytoplasmic antineutrophil cytoplasmic antibody (cANCA) has been found to be positive in up to 96 % of active generalized systemic cases of GPA, 67 % of cases of limited GPA, and only in 41 % of patients in full remission of GPA [19, 21, 22].

Therapies include high-dose corticosteroids, cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, leflunomide, and rituximab [5••, 23]. The use of etanercept has been shown to be ineffective and potentially detrimental for patients with this disease [24]. Early recognition of symptoms and diagnosis of this disease along with improvements in therapy over the last four decades has improved survival and reduced relapse rate [2••]. Even so, more than 50 % of patients are likely to suffer at least one severe or life-threatening event or die early due to disease [24].

Rheumatoid Arthritis

The most common findings in rheumatoid arthritis (RA) are keratoconjunctivitis sicca, marginal keratitis, peripheral ulcerative keratopathy, and anterior scleritis. Keratoconjunctivitis sicca, or dry eye syndrome, can be present in up to 90 % of RA patients, with the diagnosis of secondary Sjogren's syndrome present in 10–30 % [25]. In studies of scleritis, RA is the most common connective tissue disease that accounts

for 18–33 % of the cases [8, 26]. RA patients are particularly associated with the rare scleromalacia perforans variant of scleritis in which the sclera atrophies without apparent external inflammation. Patients reported in 1984 by Foster et al. with necrotizing scleritis and/or peripheral ulcerative keratitis who were treated with conventional therapy alone had a 53 % mortality rate over a 10-year period, while patients treated with long-term immunosuppression only had a 6 % rate. [27]. In a more recent study by Kapetanovic et al., they followed patients diagnosed with rheumatoid arthritis after 1980 and found that the mortality rate was not significantly increased compared to age and sex matched controls, which has been the norm in prior studies [28]. This is attributed to improved disease-modifying anti-rheumatic drugs and biological remedies in conjunction with early treatment leading to better control of disease activity.

Behcet's Disease

Behcet's disease is a systemic necrotizing vasculitis with a predilection for affecting the retinal circulation. The classic triad present for the clinical diagnosis of this disease is recurrent aphthous oral ulcers, genital ulcers, and uveitis. Other criteria for diagnosis include skin lesions such as erythema nodosum, pseudofolliculitis, papular or acneiform lesions, and pathergy (delayed pustule formation at a needle stick site). In a large study by Ideguchi et al., 412 patients were evaluated for the evolution of clinical manifestations of disease [29]. They found that the time from initial symptom (most commonly oral ulcer) to diagnosis was 8.6±10.1 years. Genital ulcer, eye, or skin involvement appeared 1–2 years before diagnosis. Initial manifestation of disease was deemed eye related in 14 %, with ultimately 65 % of patients developing ocular involvement.

A nongranulomatous iridocyclitis with hypopyon, posterior synechiae, and hyphema, is common. Vasculitis involving both arteries and veins can occur with associated vitritis, intraretinal hemorrhage, and retinal edema. Rapid recognition and treatment of this disease is key to limiting the damage that leads to blindness in 20–50 % of involved eyes within 5 years [30]. Colchicine, thalidomide, dapsone and pentoxyphyline are commonly used for the mucocutaneous manifestations [31]. Corticosteroids, azathioprine, cyclophosphamide, cyclosporin A, methotrexate, and chlorambucil are standard immunosuppressive drugs used [31]. Infliximab is currently reserved for refractory patients and has been found to have good effect[32•, 33–35]. Interferon alfa-2a has been used successfully to treat neuro-Behcet disease in a case report by one of these authors, and was subsequently the subject of a prospective study showing a 92 % response rate in patients with highly resistant ocular Behcet's disease [30, 36].

Treatment

The spectrum of drugs developed to treat rheumatic disease and other autoimmune diseases have often been employed to manage refractive eye disease. The benefit of therapies such as biologics is to decrease the corticosteroid burden on patients and to improve outcomes in therapy of both systemic and ocular inflammation. Widespread use is limited due to the high economic burden. Table 2 includes a list of commonly used therapies. Here, we will focus on some of the latest developments in biologics.

Corticosteroids

Corticosteroids are still the first line of therapy for the majority of patients who present with ocular vasculitis. Topical corticosteroid drops are often sufficient to treat anterior uveitis and conjunctivitis. Subtenon injections of depot corticosteroids are given to control and reduce recurrent posterior or intermediate uveitis. Intravitreal corticosteroids have a role in recalcitrant posterior and intermediate uveitis. Long-term use of corticosteroids is associated with numerous adverse effects including cataract, glaucoma and metabolic disorders. If a patient does not tolerate corticosteroids or requires a maintenance dose above 7.5–10 mg/day of prednisone equivalent, then an immunosuppressive drug should be considered [37].

Adalimumab

Multiple studies have shown the efficacy of adalimumab in treating uveitis in adults and children, primarily with diagnoses of ankylosing spondylitis and juvenile idiopathic arthritis [38, 39]. In a prospective study by Suhler et al., patients with uveitis that was resistant to at least two immunosuppressive agents were treated with adalimumab [40•]. The systemic diseases associated with the recalcitrant uveitis were: sarcoidosis (19 %), Behcet's (6 %), juvenile idiopathic arthritis (6 %), and seronegative spondyloarthropathies (6 %), and tubulointerstitial nephritis (3 %). Some 68 % responded to therapy by week 10, with 39 % success at 50 weeks. In a retrospective study by Dobner et al., they found an 82 % response to adalimumab, with 78 % continuing therapy at last follow-up (average of 88 weeks) [41]. In this group, the distribution of systemic disease was slightly different which may account for the increased response: spondyloarthropathies (35 %), juvenile idiopathic arthritis (28 %), rheumatoid arthritis (8 %), psoriatic arthritis (7 %), and Behcet's (3 %). Intravitreal injections of adalimumab have been demonstrated to be safe and well tolerated, but to date fail to show improvement in macular edema with studies ongoing to evaluate efficacy in controlling uveitic exacerbations [42].

Table 2 Treatment options in ocular vasculitis

Medical management of ocular vasculitis
• **Antibiotics**: *disease-specific*
○ Oral (ex. Tuberculosis)
○ Intravitreal (ex. Associated bacterial endophthalmitis)
○ Intravenous (ex. Lyme disease)
○ Intramuscular (ex. Syphilis)
• **Corticosteroids**: *mainstay of therapy to control inflammatory damage*
○ Oral
○ Topical
○ Sub-tenons
○ Intra-vitreal
▪ Dexamethasone (Ozurdex implant; Allergan, Irvine, CA, USA)
▪ Fluocinolone acetonide (Retisert implant; Bausch & Lomb, Rochester, NY, USA)
▪ Triamcinolone acetonide
• **Immunosuppressive**: *collaboration with Rheumatology recommended*
○ Azathioprine
○ Cyclophosphamide
○ Cyclosporine
○ Interferon-α
○ Methotrexate
○ Mycophenoloate mofetil
○ Rituximab
○ TNF-α antagonists
▪ Adalimumab
▪ Etanercept
▪ Infliximab
• **Antivascular endothelial growth factor agents**: *improve macular edema but not inflammation*
○ Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA)
○ Ranibizumab (Lucentis; Genentech)

Etanercept

A prospective study of etanercept in GPA released in 2005 revealed that there were no differences in the rates of remission with significant increased incidence of solid cancers [24]. There is further evidence that etanercept is not effective in granulomatous inflammation such as in sarcoidosis or Crohn's disease [43•, 44] While follow-up studies demonstrate that the increased risk of cancer does not persist and may also be associated to the common use of cyclophosphamide, the tumor necrosis factor inhibitors are generally avoided in the care of ANCA-associated vasculitides [45]. There has been some benefit shown in patients with Behcet's disease; however, infliximab is typically the superior choice [46].

Infliximab

The response of refractory ocular inflammatory disease to the addition of infliximab has been shown to be very high, with success rates of 77–86 % initial response, and 50–90 % at 50 weeks [33–35]. Systemic vasculitic diseases treated successfully with infliximab include perinuclear antineutrophil cytoplasmic antibody-positive systemic vasculitis with renal involvement, juvenile idiopathic arthritis, mild seronegative polyarthropathy, rheumatoid arthritis, ankylosis spondylitis, relapsing polychondritis, Crohn's disease, sarcoidosis, and Behcet's disease. Of note, the study by Sobrin et al. found 100 % response in patients with scleritis, which may represent a subset of patients most responsive to infliximab therapy [34]. Adverse reactions have been reported to most commonly include lupus-like syndrome; however, one study did experience a higher number of adverse effects including pulmonary embolus, congestive heart failure, and vitreous hemorrhage in addition to lupus-like reaction [33, 34]. Intravitreal injection of infliximab has been performed in actively inflamed eyes with Behcet's disease to good effect in a pilot study of 15 patients by Markomichelakis et al. in 2012 [32•]. Nevertheless, because of reports of secondary uveitis development in eyes injected with infliximab to treat non-vasculitic macular edema, a moratorium was recommended in 2010 on the clinical use of intravitreal infliximab outside well-designed trials [47•].

Rituximab

Rituximab has developed a role in the treatment of refractory vasculitis diseases such as rheumatoid arthritis and ANCA-associated vasculitides. Rheumatoid arthritis-associated scleritis has had a good response to rituximab in a series of case reports [48, 49]. In a study of systemic refractory granulomatosis with polyangiitis by Holle et al., a positive response was considered stabilization of disease or improvement [23]. This was achieved in 61.3 % of patients with granulomatosis with polyangiitis, with a range of responses from 0 % of orbital granulomatous inflammation to 89 % of patients with glomerulonephritis. The most common adverse event was infection in 29 % of patients, followed by 2 % infusion reaction and 3 % death (one of which was due to severe infection). The Rituximab for ANCA-associated Vasculitis (RAVE) trial presented data that supported the use of rituximab as an alternative to cyclophosphamide as the second agent following glucocorticoids, proving non-inferiority [50]. Intravitreal rituximab has been used for primary vitreoretinal lymphoma with encouraging efficacy, but has yet to be reported as a treatment in ocular vasculitis [51, 52].

Conclusions

Vasculitis is a challenging area of ophthalmology and rheumatology. Continued efforts to understand and treat the underlying causes are necessary. Efforts to establish a diagnosis that is as specific as possible in a timely fashion is critical in minimizing the visual impairment of these patients. A

multidisciplinary approach is also crucial to reducing all morbidity and mortality associated with these systemic diseases. With the advent of biological therapies, the scales have been tipped in our favor. Nevertheless, we must be well versed in adverse effects and cost-effective methods of treatment in order to provide the best care.

Compliance with Ethics Guidelines

Conflict of Interest Gabriela M. Espinoza, Ankit Desai, and Levent Akduman 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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