SMGroup

Treatment of Retinal Vasculitis

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INTRODUCTION

Retinal vasculitis is a potentially blinding condition. The vision loss in retinal vasculitis may be secondary to macular ischemia, macular edema, and neovascularization leading to vitreous hemorrhage and traction retinal detachment or secondary glaucoma [1-3]. Retinal vasculitis may be either idiopathic or secondary to infection, neoplasia, or a systemic inflammatory disease [4-6]. Therefore, the clinical significance of retinal vasculitis lies not only in being sight threatening, but more importantly, in being the presenting or even the very first manifestation of potentially lethal systemic diseases.

The ocular manifestations of retinal vasculitis are usually non-specific, or even asymptomatic. The peripheral retinal vascular changes might be asymptomatic unless it affects the vitreous and leads to symptoms of floaters. The retinal vasculitis involving posterior retinal vessels is more likely causing vision decrease and floaters. On examination, retinal vasculitis is characterized with vitreous cells and sheathing or cuffing of blood vessels. Occlusive retinal vasculitis may cause cotton-wool spots, retinal edema and intraregional hemorrhage. Optic disc edema is a common sign of retinal vasculitis, which is considered as a nonspecific finding related to intraocular inflammation. Fluorescein angiography showing leakage of the dye due to breakdown of the inner blood-retinal barrier, and staining of the blood vessel wall with fluorescein is of diagnostic value. Optical coherence tomography is a very sensitive and specific tool to detect macular edema, which often presents in retinal vasculitis [1-6].

The systemic manifestations associated with retinal vasculitis vary with the associated systemic diseases. Based on the history and systemic manifestations, searching for an underlying etiology, particularly differentiation of infectious or non-infectious etiologies is essential for determining appropriate treatment.

INFECTIOUS RETINAL VASCULITIS

Tuberculosis

The most common manifestation of ocular tuberculosis is choroiditis. However, retinal vasculitis can present in up to 54% of tubercular uveitis [7]. Although mycobacterium tuberculosis might infect the choroid directly, retinal vasculitis is most likely caused by indirect hypersensitivity to mycobacterial antigens, which might manifest as an obliterative periphlebitis, leading to retinal neovascularization and causing recurrent vitreous hemorrhage and traction retinal detachment. A definitive diagnosis of intraocular tuberculosis requires the identification of mycobacterium tuberculosis organisms in ocular tissues or fluids, which is usually difficult and might induce damage to the eye [8,9]. A presumptive diagnosis of tuberous choroiditis or retinal vasculitis can be made based on multifocal choroiditis, choroidal granuloma and retinal vasculitis, the history of contact tuberculosis or living in endemic area, proofs of extraocular (most likely pulmonary) tuberculosis, and exclusion of other causes of choroiditis [7]. Polymerase chain reaction is a very sensitive and specific diagnostic tool to detect the mycobacterium tuberculosis DNA in intraocular fluid samples from patients with tubercular retinal vasculitis [8,9]. The systemic examinations to diagnose tuberculosis and exclude other choroiditis causes included, blood examinations such as routine tests of blood (count and differentiation of blood cells), urine and stool, immunological tests for syphilis, hepatitis B and C, human immunodeficiency virus, the TORCH tests (Toxoplasmosis, Other Etymology: including Rubella, Cytomegalovirus, and Herpes), rheumatoid factor, erythrocyte sedimentation rate, concentrations of C-reactive protein, anti-nuclear antibody and anti-neutrophil cytoplasmic antibodies, x-ray or computed tomography of the chest, tuberculin skin testing and the interferon gamma release test [7-9]. Once a presumptive

or definitive diagnosis of intraocular tuberculosis is made, standard anti-tuberculous therapy according to the Centers for Disease Control guidelines for a minimum of 6 months should be made. This consisted of 2-months of a four-drug therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) followed by a period of 4 months with isoniazid and rifampicin. Local or systemic corticosteroids might be added after initiation of anti-tuberous therapy, decided according to the severity of ocular inflammation [7-9]. Pars plana vitrectomy is required when long last vitreous hemorrhage or traction retinal detachment happens.

Virus

The most common intraocular virus infection is caused by herpes group of viruses, mainly herpes simplex (HSV), varicella zoster (VZV) and cytomegalovirus (CMV). While CMV retinitis usually happens in patients with immunodeficiency caused by HIV infection or immunosuppressive therapy, acute retinal necrosis (ARN) caused by HSV or VZV infection can happen in normal immunity patient [10-12]. Atypical acute retinal necrosis presents with peripheral necrotizing retinitis, retinal arteritis, and a prominent inflammatory reaction in the vitreous and anterior chamber. The disease can progress rapidly with vision loss due to macular involvement, retinal detachment, or optic neuropathy. CMV retinitis typically presented as scattered yellow white areas of necrotizing retinitis with variable degrees of hemorrhage and mild vitreous inflammation (cheese with ketchup appearance), which usually progressed more slowly compared to ARN. A clinical diagnosis of ARN or CMV retinitis can be made based on typical fundus appearance. Polymerase chain reaction is a highly sensitive, specific, and rapid way of detecting viral DNA in intraocular fluid samples.

Anti-viral treatment is necessary for ARN or CMV retinitis. ARN patients are classically treated with acyclovir, typically undergo induction therapy with intravenous acyclovir 10-15mg/kg divided three times a day for one week, followed by oral acyclovir 800 mg five times a day for 3–4 months. It can also be treated with oral valacyclovir (1-2g q 8 hour) or famciclovir (0.5g q 8 hour), which have greater bioavailability than oral acyclovir. For CMV retinitis, ganciclovir or valganciclovir works better than acyclovir. In AIDS patients, it is also suggested to commence anti-retroviral treatment after two weeks of anti-CMV treatment by ganciclovir or valganciclovir. Intravitreal anti-viral treatment might be considered as supplementation to systemic anti-viral treatment. Surgical intervention is required when retinal detachment happens, which might occur up to 75% of ARN patients.

Syphilis

Syphilis might mimic different ocular disorders, causing vitritis, chorioretinitis, retinal vasculitis, venous and arterial occlusive disease, exudative retinal detachment, macular edema, neuroretinitis, optic neuritis, optic atrophy, choroidal neovascular membranes, and pseudoretinitis pigmentosa. Because of the diversity of the clinical manifestations, it was called great imitator. Therefore, syphilis needs to be excluded in all patients with retinal vasculitis [13].

The diagnosis of ocular syphilis is based on history, clinical examinations and lab work (serologic testing). It is recommended enzyme immunoassays and chemiluminescent immunoassays to detect antibodies to treponemal antigens as the best screening tests for syphilis followed by reflex testing of positive specimens with the nontreponemal test, rapid plasma reagin (RPR). Ocular syphilis with active clinical manifestations is considered a secondary syphilis and also a neurologic syphilis. It is treated in the same manner as neurosyphilis. Parenteral penicillin is the drug of choice for ocular syphilis. The recommended adult regimen is aqueous crystalline penicillin G 18–24 million units per day administered as 3–4 million units intravenously every 4h or by continuous infusion for 10–14 days. Corticosteroids can only be used adding to penicillin. Topical corticosteroids can be used liberally, but intravitreal injections of triamcinolone appear to be harmful. Oral corticosteroids and periocular steroid injections are generally not used, but could be considered for inflammatory complications such as macular edema [13].

RETINAL VASCULITIS ASSOCIATED WITH SYSTEMIC VASCULITIS OR CONNECTIVE TISSUE DISEASES

Behcet's disease

Behcet's disease (BD) is an idiopathic, multisystem, chronic, and recurrent inflammatory disease, characterized by recurrent oral and genital ulcers, skin and ocular lesions, and other manifestations including neurological, gastrointestinal, and vascular involvement. The underlying pathology of BD is an obliterative, necrotizing vasculitis that affects both the arteries and the veins. Its association with Class I MHC (HLA-B 51) is well known [14,15].

Ocular complications of BD are highly significant due to the impact to the patients and their quality of life. Eye involvement affects 60–80 % of BD patients. It is characterized by posterior or panuveitis including occlusive retinal vasculitis with or without hypopyon. Intraocular inflammation is bilateral in the majority of patients with Behcet's uveitis (63–100 %). The most widely used diagnosis criteria are the criteria of the International Study Group for Behcet's Disease from 1990 [16], which requires the presence of recurrent oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test.

Risk of eye lesion in BD is highest in young men and lowest in older women. Common symptoms and signs included blurred vision, periorbital or global pain, photophobia, lacrimation, floaters and periglobal hyperemia. The most common and typical manifestations are nongranulomatous panuveitis with recurrent, explosive inflammatory attacks. Anterior involvements, manifest as iritis, iridocyclitis (posterior synechia), hypopyon uveitis, scleritis, episcleritis, keratitis, corneal immune ring, or conjunctivitis (rare), usually have a better visual prognosis. Posterior involvement usually leading to a poor visual prognosis, which included periarteritis and periphlebitis with occlusive retinal vasculitis (BRAO and BRVO), retinitis, vitritis, vitreous hemorrhage, optic neuritis, papilledema or rarely choroiditis. Secondary complications of ocular episodes include macular edema, cataract, persistent posterior synechiae, peripheral anterior synechiae, macular

degeneration, secondary glaucoma (may be neovascular), iris deformity and/or atrophy, vitreous detachment, retinal detachment, epiretinal membrane, retinal or optic nerve atrophy, branch retinal vein occlusion, iris or retinal neovascularization, retinal tear, macular hole, vitreo-retinal hemorrhage, end-stage disease, phthisis bulbil, and rarely conjunctival ulcer and extraocular muscle paralysis.

Fundus fluorescein angiography is particularly useful for detecting retinal vasculitic lesions and reveals perivascular staining of the retina with vascular dye leakage of the dilated retinal capillaries during acute stage, inflammation, and occlusion of the retinal vessels. These signs can be detected with fundus fluorescein angiography even before ophthalmoscopic signs of detectable retinal perivasculitis clinically. In addition, early and profuse leakage from the optic nerve head during early transit and even, in advanced cases, neovascularization can be observed. Similarly, cystoid macular edema with its petalloid appearance, macular ischemia and optic disk edema as well as disk neovascularization can be identified with fluorescein angiography or more sensitively with optical coherence tomography.

Sarcoidosis

Ocular manifestations of sarcoidosis have been reported in up to half of patients with biopsy-proven sarcoidosis [17]. Although ocular sarcoidosis tends to initially present as anterior granulomatous uveitis, it can involve almost any part of the eye, leading to a wide spectrum of ocular involvement. Manifestations vary enormously and include granulomatous or nongranulomatous anterior uveitis; intermediate uveitis; retinal periphlebitis, usually nonocclusive; multifocal choroiditis; papillitis, optic nerve granuloma, or papilledema; lacrimal gland enlargement and dry eye; and orbital involvement or scleritis. Typical posterior segment findings of sarcoidosis include vitritis, retinal periphlebitis, preretinal inflammatory nodules and "candle wax drippings". Choroidal lesions have also been reported in ocular sarcoidosis. Retinal vasculitis is a characteristic feature of sarcoidosis. It is nearly always a retinal periphlebitis, and retinal arteries are only rarely involved. The involvement of vessels is discontinuous, which appears clinically as skip lesions. It may be mild and associated with peripheral retinal and focal vitreal infiltrates indistinguishable from idiopathic pars planitis. Retinal vasculitis may be the presenting sign in patients who develop sarcoidosis many years later. In the acute stage, patients might present with vitritis, retinal hemorrhage and edema. With systemic corticosteroid treatment, periphlebitis resolves, but some residual sheathing may persist. Yellow perivenous exudates, described as candle wax drippings are also sometimes seen, supportive of a clinical diagnosis of sarcoidosis [18].

The diagnosis of sarcoidosis remains a diagnosis of exclusion [17,18]. The typical ocular fundus appearance, the chest radiograph or computed tomography and a raised serum angiotensin converting enzyme (ACE) levels are helpful for making the diagnosis. Noncaseating granulomas on biopsy together with clinical features are usually considered as a proof of the diagnosis of sarcoidosis.

Sarcoid-associated anterior uveitis usually responds satisfactorily to topical corticosteroid therapy. Sarcoid uveitis frequently causes macular edema, which might lead to severe vision loss. Although there is no consensus on the optimal management of inflammatory macular edema, intravitreal steroids or anti-vascular endothelial growth factor agents are usually effective. In refractory cases, vitrectomy might be considered to control the macular edema. Systemic corticosteroid treatment is commonly used in sarcoidosis; it has been necessary in more than 50% of those with sarcoid uveitis and is used by the physician to treat various manifestations, including pulmonary sarcoidosis with significant reduction in lung function [17,18].

Systemic Lupus Erythematosus

Retinal vascular lesions, mainly arterial occlusion are the most common ophthalmic manifestations of SLE, which can cause severe visual loss in 55% of patients [19-21]. The prevalence ranges from 3% to 29% and depends on the patient population studied. Vascular occlusive retinopathy can be the primary manifestation that leads to the diagnosis of SLE. The retinopathy generally consists of cotton-wool spots with or without retinal hemorrhages. Sometimes it can also present with severe retinal vaso-occlusive disease characterized by diffuse arteriolar occlusion with extensive capillary nonperfusion. A more focal vascular disease, including retinal artery or vein occlusion, may occur. Patients with SLE and raised antiphospholipid antibodies have a higher risk of developing occlusive retinal vascular disease. The underlying pathological process is probably secondary to immune complex deposition in the vessel wall. These changes are found in all arterioles, including those of the retina and choroid. Immunological abnormalities are common and include high titers of anti-double-stranded DNA antibodies, antinuclear antibody, positive lupus erythematosus cell preparation, reduced serum complement, raised circulating immune complexes, and hypergammaglobulinemia [19-21].

On fundus fluorescent angiography, vascular occlusion can manifest as widespread arteriolar or branch retinal artery occlusion (BRAO) with severe retinal ischemia and neovascularization. Larger retinal vessels may be occluded leading to retinal and optic disc infarction that may also result in neovascularization. Central retinal artery occlusion (CRAO) and central retinal vein occlusion (CRVO), while very rarely seen in other causes of retinal vasculitis, have been reported secondary to SLE.

Wegener's Granulomatosis

Wegener's granulomatosis is a necrotizing granulomatous vasculitis with a predilection typically for the upper and lower airways and the kidneys [22]. Ocular involvement has been reported to occur in 28–58% of patients with Wegener's granulomatosis and may precede the involvement of other organs [2,22]. Ocular manifestations, which have been described, include orbital involvement secondary to invasion by paranasal granulomata, nasolacrimal duct obstruction, episcleritis, scleritis, corneal ulceration, optic nerve vasculitis, retinal artery occlusion, choroidal arterial occlusion, and retinal vasculitis. The diagnosis of Wegener's granulomatosis is based on

typical clinical findings and supporting histologic data. Typical histopathologic features include inflammation of small- and, less often, medium-sized vessels, necrosis, and granuloma formation. The classic 'cytoplasmic' staining pattern (cANCA) is seen in Wegener's granulomatosis, while the perinuclear pattern (pANCA) is associated with necrotizing and crescentic glomerulonephritis (renal vasculitis) and microscopic polyarteritis.

Ocular or orbital involvement of WG is seen in approximately 29–52% of the patients [22]. Approximately 15% of WG patients may present with ocular or orbital disease initially. Although the most common manifestation is orbital granuloma, WG can affect any ocular or periocular tissue. In the anterior segment, patients with WG may develop peripheral ulcerative keratitis, corneal granuloma, episcleritis, necrotizing scleritis, or uveitis. Retinal involvement is a relatively uncommon ophthalmic manifestation of WG (5–12%), with retinal hemorrhages in the peripheral or posterior retina being the most common finding. Both central artery and vein occlusion have been reported; the exact etiology, however, whether vasculitic, embolic, thrombotic, or a retro-orbital process, has not always been clearly defined. Retinal vasculitis in the form of arteritis or periphlebitis, is a relatively uncommon finding and may be seen with associated scleritis.

Vascular endothelial growth factor (VEGF) levels are elevated in the retina of patients with ocular inflammatory disease or infection. There are accumulating reports on the use of anti-VEGF intravitreal injections for the management of complications of RV. Intravitreal corticosteroids can help macular edema temporarily until definitive therapy is instituted. Periocular steroid delivery may be an option for unilateral macular edema. Retinal vasculitis complications may also require laser photocoagulation or vitreoretinal surgery.

The optimal management of patients with systemic vasculitis or connective tissue disease requires a multidiscipline cooperation [14-22]. The main objectives in the treatment of patients with these diseases are rapid resolution of intraocular inflammation, prevention of recurrent attacks, and achievement of complete remission with preservation of vision while minimizing the potential systemic and local side effects of selected therapeutic regimen to the patient. Corticosteroids are commonly used to control the inflammation. However, due to the potential side effect of long-term high dose corticosteroids, immunosuppressant drugs such as cyclosporine A or tacrolimus are usually used simultaneously to reduce the dose and duration of corticosteroids. The advent of the biologic therapy, such as interferon and tumor necrosis factor or interleukin antagonist, has substantially improved the visual prognosis and outcomes in traditionally blinding cases, such as Behcet's disease.

MALIGNANCY ASSOCIATED RETINAL VASCULITIS

Retinal vsculitis can happen secondary to malignancy as Para neoplastic syndromes (cancer associated retinopathy or melanoma associated retinopathy) or infiltrated by lymphoma or leukemia [23,24]. Early diagnosis and treatment of underlying malignancy is critical for preservation vision and more importantly to save the patient's life.

Cancer-associated retinopathy occurs distant from the site of the tumor, typically secondary to small-cell carcinoma of the lung followed by gynecologic and breast cancers [23]. Although autoimmunity was proposed as a mechanism of cancer associated retinopathy, circulating antibodies that recognize antigens in retinal photoreceptor, bipolar, and ganglion cells varied among individual labs. The low reproducibility and reliability of the test limits its usage in making diagnosis. Therefore, the diagnosis is mainly based on clinical characteristics and is an exclusion diagnosis. These patients usually present with "positive scotoma", photopsia accompanied with progressive night blindness, visual loss, visual field loss, and attenuated retinal arterioles. Retinal phlebitis and vitritis have also been reported. Melanoma-associated retinopathy is a visual paraneoplastic syndrome occurring in some patients with metastatic cutaneous malignant melanoma. These patients usually present with a sudden onset of night blindness. Melanoma-associated retinopathy is characterized by a negative electroretinogram, similar to the pattern seen in congenital stationary night blindness. Autoantibodies might be detected from serum of patients, showing staining rod bipolar cells in the retina. Retinal periphlebitis was reported in a patient with melanoma associated retinopathy.

Ocular lymphoma usually presents as a chronic uveitis, occurring in the elderly and responding poorly to corticosteroids [24]. Arterial and venous sheathing might be noted under fundus examination. Therefore, ocular lymphoma should be considered in the differential diagnosis of retinal vasculitis. Ultrasonography may be helpful to identify subtle chorioretinal thickening. Cerebral magnetic resonance imaging or computed tomography is helpful for excluding central nervous system lymphoma, which is commonly found in ocular lymphoma. A vitreous biopsy should be performed if the diagnosis remains unclear. Similarly leukemia infiltration might also lead to retinal perivascular sheathing.

IDIOPATHIC ISOLATED RETINAL VASCULITIS

Sometimes retinal vasculitis can happen as isolated and idiopathic without accompanied systemic diseases or etiology, such as idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN). The diagnosis of idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis (IRVAN) is based on a constellation of clinical features [25,26] Three major criteria (retinal vasculitis, aneurysmal dilations at arterial bifurcations, and neuroretinitis) and 3 minor criteria (peripheral capillary nonperfusion, retinal neovascularization, and macular exudation) are used to diagnose IRVAN. IRVAN can lead to severe visual loss due to retinal ischemia and neovascularization. Clinically, IRVAN can be classified into 5 stages based on clinical manifestation: stage 1 is characterized with macroaneurysms, exudation, neuroretinitis and retinal vasculitis; patient at stage 2 developed capillary nonperfusion, which can be shown on fluorescent angiography; stage 3 is characterized with posterior segment neovascularization of disc or elsewhere and/or vitreous hemorrhage; stage 4 is characterized with anterior segment neovascularization (rubeosis iridis); and stage 5 neovascular glaucoma. A timely pan retinal laser photocoagulation carried out at early stage is critical for preservation of vision.

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