Retinal Vasculitis: Fundamentals, Diagnostics, and Management

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ABSTRACT

Retinal vasculitis is inflammation of retinal blood vessels typically resulting from infection or immune-mediated inflammatory processes. It may present as isolated ocular inflammation or as a part of severe or potentially fatal systemic disease. Ocular complications of retinal vasculitis include cystoid macular edema, neovascularization, tractional retinal detachment, and vitreous hemorrhage, which all greatly threaten vision. Multimodal imaging and thorough systemic investigations are the main tools for making a precise diagnosis, which aids in predicting disease prognosis and visual outcome as well as preserving a patient's vision and possibly their life. This review aims to discuss the current understanding of retinal vasculitis as well as current diagnostic tools and treatments.

Keywords: Retinal vasculitis; retinal vascular inflammation; posterior uveitis (Siriraj Med J 2021; 73: 493-500)

INTRODUCTION

Retinal vasculitis (RV) is a sight-threatening condition that is characterized by inflammation of the retinal blood vessels. This condition is defined by ophthalmologists as impairment of the blood-retina barrier resulting from inflammatory processes. Diagnosis of RV can be primarily made by finding sheathed retinal vessels or perivascular exudate during dilated fundus examination. However, this condition should be evaluated by and can be confirmed with fluorescein fundus angiography. RV may be idiopathic or may be a manifestation of systemic inflammatory diseases, such as Adamantiades-Behcet's disease (ABD), granulomatosis with polyangiitis (GPA), and systemic lupus erythematosus (SLE). RV can also occur as a result of infection, such as viral acute retinal necrosis, ocular toxoplasmosis, and ocular tuberculosis. It may seldomly occur in the setting of a malignant masquerade syndrome. Multimodal imaging and a thorough systemic work up are important when trying to uncover the etiology of the inflammation as it may help to improve prognosis and visual outcome, as well as reduce secondary complications such as retinal and macular ischemia, cystoid macular edema (CME), and secondary glaucoma. These are associated with poor visual outcome.[1-3] This review focuses first on the fundamentals of retinal vascular inflammation, and then aims to further discuss newer diagnostic tools and treatments.

Epidemiology

Studies have shown RV to be found in 6-15% of patients with uveitis.[4,5] Ethnicity may be responsible for differences in the incidence and prevalence of RV worldwide. Each specific disease related to RV was also found to have a different incidence and prevalence, such as in ABD, which was found in 20-420/100,000 population in Turkey, in 80/100,000 population in Iran,

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and in 0.64/100,000 population in the United Kingdom, and among these ABD patients, uveitis presented with or without RV in 45-90%.[6] The incidence of SLE also differs among regions, ranging from 0.3 to 8.7/100,000 population/year, and the prevalence ranged from 1.1 to 534.9/100,000 population. The highest incidence of SLE was found in the USA, the Caribbean, Brazil, and Sweden.[7] The incidence of retinal involvement in SLE was 7-26%.[8] Regarding infectious etiology, ocular tuberculosis (TB) is the predominant culprit in Asia. The incidence of ocular TB in Australia was 0.77/100,000, and 11% of those patients presented with RV.[7] In India, the reported incidence of ocular TB was as high as 9.86% among all types of uveitis.[9]

Pathogenesis

The mechanisms of the development of RV are not fully understood. Type III (immune complex-mediated) hypersensitivity is generally believed to be responsible for the development of RV,[3] but humoral and cell-mediated immunity may also play an important role. Immunohistochemical analysis of enucleated eyes from ABD and sarcoidosis patients revealed T-helper lymphocytes comprise most of the involved cells. Major histocompatibility complex (MHC) I and II antigens and the cell adhesion molecules intercellular adhesion molecule-1 (ICAM-1), E-Selectin, vascular cell adhesion protein-1 (VCAM-1), lymphocyte function-associated antigen (LFA)-1a, and LFA-1b were found on vascular endothelial cells.[1] In animal models and following systemic inoculation and induction of experimental autoimmune uveitis, retinal S antigen was found to play an important role in immune-mediated uveitis and RV.[10-12] Many studies also reported a genetic predisposition to be related to retinal vascular inflammation. Previous reports described a condition called autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) as being related to the development of intraocular inflammation that results from mutations in calcium-dependent cysteine protease (Calpain 5).[13] Some mutations may associate with predisposition to specific diseases, such as three prime repair exonuclease 1 (TREX1) in SLE[14], and tumor necrosis factor alpha-induced protein 3 (TNFAIP3) in ABD-like disease.[15]

Classification

Retinal vascular inflammation can be classified as either occlusive or non-occlusive depending on the mechanisms of inflammation. When vascular occlusion develops, the affected area of the retina and/or macula may become ischemic. Neovascularization (NV) generally develops when there is a significant area of retinal ischemia, and NV may eventually lead to fibrovascular traction and/or vitreous hemorrhage. RV can also be categorized by the affected retinal blood vessels into periarteriolitis, periphlebitis, or combined arteriolitis and phlebitis. Also, a pattern of small vessel leakage affecting retina where the vasculature is not clearly visible may be considered capillaritis. The usefulness of identifying the involved retinal blood vessels is to narrow the differential diagnosis in hopes of unveiling the etiology of inflammation. Causes of RV associated with different types of retinal blood vessel involvement are shown in Table 1,[2] which can be categorized into systemic autoimmune-related RV, infectious-related RV, isolated ocular inflammation with known etiology, and idiopathic RV.[1] The etiologies of RV categorized by systemic disease association are shown in Table 2.

Clinical findings

The most common ocular symptom of patients with RV is blurred vision. Additional symptoms depend on several factors, including extension of involved retinal blood vessels, associated findings, and existing complications, such as vitritis, vitreous hemorrhage, CME, retinal or macular ischemia, and papillitis. Patients may also experience photopsia, floaters, metamorphopsia, and either focal or diffuse scotomas. The location of inflammation may be limited to the posterior segment of the eye as posterior uveitis, or as panocular inflammation in more severe cases. On dilated fundus examination, one may find perivascular infiltration, vascular cuffing, or vascular sheathing. In SLE (with or without antiphospholipid thrombosis), presentation with classic RV with perivascular infiltration was less common than presentation with features of occlusive vasculopathy.[7] Exudates that result from vascular leakage are occasionally observed. Cotton wool spots representing retinal nerve fiber layer infarction can be seen in occlusive retinal arteriolitis. Late presentations of retinal vascular occlusion include retinal telangiectasia, neovascularization, tractional retinal detachment, rubeosis iridis, neovascular glaucoma, and optic disc atrophy.[16]

Diseases mimicking retinal vasculitis

Non-inflammatory conditions, such as diabetic retinopathy and Coats' disease, can sometimes be confused with RV because of extensive vascular leakage. Significant amounts of perivascular exudates along retinal blood vessels may mislead the diagnosis. Sheathing of retinal blood vessels, which can be found in RV, can also be found in other conditions, such as retinal vein or artery occlusion due to other causes.[17-19] The presence of inflammatory signs

TABLE 1. Retinal vasculitis categorized by type of retinal blood vessel involvement.

Arteriolitis	Periphlebitis	Combined arteriolitis and periphlebitis
Acute retinal necrosis	Ocular tuberculosis	Crohn's disease
Cat-scratch	Sarcoidosis	Granulomatosis with polyangiitis
Ocular syphilis	Birdshot chorioretinopathy	Relapsing polychondritis
Ocular toxoplasmosis	Pars planitis	Multiple sclerosis
Idiopathic retinal vasculitis, aneurysm and neuroretinitis		Adamantiades-Behcet's disease
Polyarteritis nodosa		
Systemic lupus erythematosus ± antiphospholipid syndrome		

TABLE 2. Differential diagnosis of retinal vasculitis according to etiology of inflammation.

Immune-related		Infectious	Masquerade
Systemic	Ocular		
Adamantiades-Behcet's disease	Birdshot chorioretinopathy	Acute retinal necrosis	Leukemia
HLA*-B27 related/ seronegative spondyloarthropathy	Pars planitis	Cytomegalovirus retinitis	Lymphoma
Granulomatosis with polyangiitis	Idiopathic retinal vasculitis, aneurysm and neuroretinitis	Syphilis	
Multiple sclerosis		Toxoplasmosis	
Polyarteritis nodosa		Tuberculosis	
Sarcoidosis			
Systemic lupus erythematosus			

*HLA = human leukocyte antigen

and associated findings of uveitis, such as inflammatory cells and keratic precipitate, support an inflammatory origin.

Multimodal imaging

Fundus photography

Location and extension of retinal and choroidal inflammation can sometimes be documented using fundus photography, and images from each follow-up visit can be used for treatment monitoring except for the patients with subclinical RV. Ultrawide field images facilitate visualization of a wider field of peripheral retina. Fig 1 shows an ultrawide field image of cytomegalovirus retinitis with frosted branch angiitis.

Fundus fluorescein angiography (FFA)

FFA is the gold standard method for diagnosis of RV. It can also be used as a tool for treatment monitoring, for complication detection, and (in some instances) for evaluating disease prognosis. FFA can reveal non-perfusion areas of ischemic retina in patients with occlusive RV, and showcase damage induced in vital sections of retina crucial for fine vision (i.e. macula). Patients with a large area of retinal ischemia and/or macular

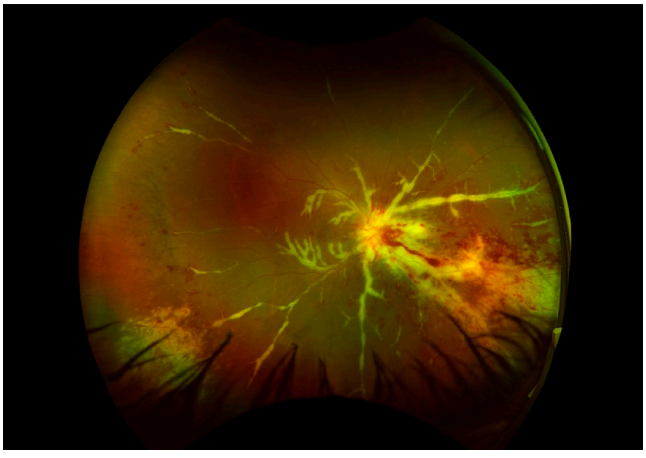

Fig 1. Ultrawide field image of cytomegalovirus retinitis.

A 27-year-old polymyositis patient presented with blurred vision. Fundus photo of the right eye shows a classic presentation of cytomegalovirus retinitis. Whitish fluffy retinal infiltrates, optic disc infiltrates, intraretinal hemorrhages, peripheral granular retinal infiltrates and perivascular infiltrates are presented.

ischemia generally have poor visual outcome.[20] FFA can also detect subclinical RV in patients thought to be otherwise clinically inactive. FFA findings in patients with RV include retinal vascular leakage/staining, optic disc leakage/staining, macular leakage, capillary drop out, vascular occlusion, and blockage.[21] Ultrawide field FFA images are preferred to conventional FFA method due to improved detection of peripheral retinal lesions.[22-24] Figs 2 & 3 show fundus photos and fundus fluorescein angiography of RV patients.

Indocyanine green angiography (ICG)

ICG is generally used to detect abnormalities in choroidal vasculature. In RV, combined FFA and ICG would be beneficial when inflammation involves both the retina and choroid, such as in Vogt-Koyanagi-Harada disease and birdshot chorioretinopathy (BSCR). Examples of choroidal abnormalities related to RV include patchy hypo-cyanescence, fuzzy choroidal vasculature, and late hyper-cyanescence of choroidal vasculature.[21]

Adaptive optics (AO) imaging

AO, which was previously developed for astronomical application, is a non-invasive and feasible imaging system. AO imaging in RV may reveal blood vessel wall thickening from inflammatory cell deposition. AO can also be used for follow-up imaging, with more defined vessel lumens indicating less inflammatory cell deposition. Other advantages of AO over FFA in addition to its non-invasive nature include its ability to detect subclinical RV earlier than detected by FFA.[25] Current challenges associated with the use of AO imaging in this setting include media opacity, peripheral RV, and pseudophakia. Also, this is not readily available in a clinical setting.

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA)

Structural abnormalities related to RV can be identified by OCT. Focal retinal thickening with loss of normal retinal lamination that suggested retinal damage has been reported.[26] Kyrieleis plaques in ocular toxoplasmosis

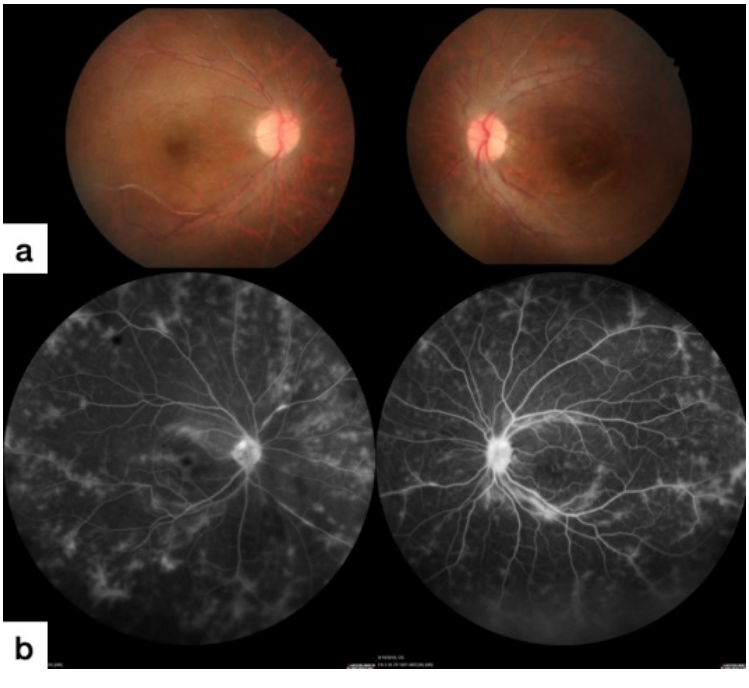

Fig 2. Fundus photo and fundus fluorescein angiography of bilateral retinal vasculitis with Behcet's disease.

Fundus photo of a 36-year-old male, Behcet's disease patient shows retinal vascular sheathing in both eyes (a). Fundus fluorescein angiogram demonstrates more obvious vascular leakage, optic disc leakage in both eyes and macular leakage in the right eye (b) compare to fundus photo.

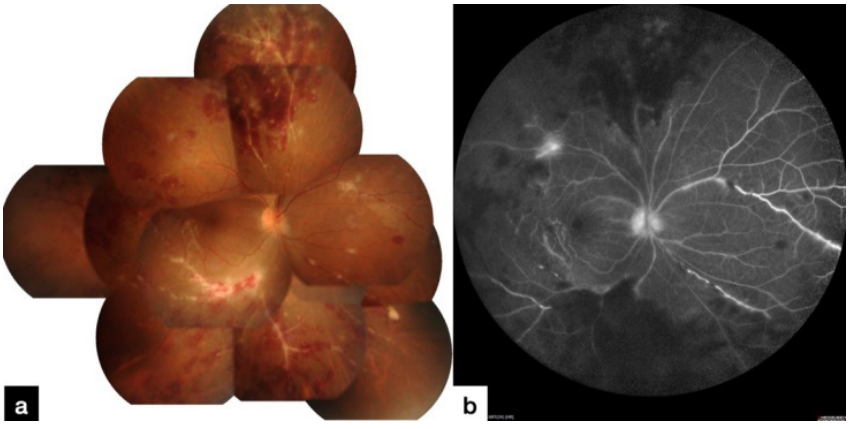

Fig 3. Fundus photo and fundus fluorescein angiography of ocular tuberculosis.

A 31-year-old male patient was diagnosed with ocular tuberculosis. Interferon gamma releasing assay was 2.1, Mantoux test was 8 mm, chest radiograph showed no pulmonary infiltration. Dilated fundus examination showed retinal periphlebitis with secondary branch vein occlusion (a). Fundus fluorescein angiogram demonstrates optic disc leakage, vascular leakage, and capillary drop-out (b).

and cytomegalovirus retinitis can be observed on OCT as hyper-reflectivity of blood vessel walls.[21] CME is clearly identified on OCT. Enhanced-depth imaging OCT yields more detail about choroidal thickness, including suprachoroidal fluid.[3] Microvascular flow of the retina and choroid can be detected by OCTA. Moreover, OCTA can identify microvascular occlusion without injection of dye. Unfortunately, the stage of inflammation (active vs. inactive) cannot be determined. Another limitation of OCT and OCTA is its limited field of view.[21]

Diagnostic testing

The causes of RV vary. Laboratory investigations and imaging should be based on clinical presentations. As such, the pattern of investigation should be based on each patient's clinical presentation and provisional diagnosis. A summary of common diagnostic studies in RV is shown in Table 3.

Treatment modalities

Treatment for RV is generally dependent on the etiology of underlying disease, if any. In infectious RV, specific antimicrobial therapy is indicated. In non-infectious RV, treatment aims to control inflammation to regain or at least stabilize vision and to prevent further complications.

Systemic corticosteroids

The initial mainstay therapy for non-infectious RV, and particularly in bilateral cases, is systemic corticosteroids due to their effectiveness and rapid response. High-dose prednisolone is generally prescribed at the initial stage. Both short term and long term unwanted and widely recognized side effects of high-dose corticosteroids are at times unavoidable, however an absolute certainty when used chronically. In patients who require long-term treatment or who suffer from serious systemic autoimmune diseases, immunomodulatory therapy (IMT) or biologics can be considered to reduce the side effects of corticosteroids and to achieve better control of inflammation.

Regional corticosteroids

Regional steroids, such as trans-septal/sub-Tenon's/intravitreal triamcinolone acetonide (TA) injection, can be considered as an adjunctive therapy for RV with or without CME. However, since the duration of TA injection treatment is short, the use of TA injection alone is not recommended. Intravitreal dexamethasone implant is thought by many to produce a slightly more sustained effect than TA[27,28] but was comparable to intravitreal triamcinolone injection at 8 weeks in terms of decreasing central subfield thickness of uveitic macular edema.[29,30] The available fluocinolone acetonide implants convey an even longer treatment duration making them more reasonable for non-infectious RV. In these therapies, systemic side effects are often avoided, while local side effects, including complicated cataract and steroid-induced glaucoma, are often still seen.[27,28,31-33]

Immunomodulatory therapy

IMT is generally required when patients become steroid-dependent, and they require long-term systemic steroids to control inflammation. Prednisolone of any duration, but particularly more than 7.5 mg/day is considered risky by many if used chronically. Studies have shown that the use of prednisone 5 mg daily for only 8 weeks in post-menopausal women was associated with the potential development of steroid-related complication, specifically decreased indices of bone formation.[34] Guidelines created by Jabs *et al.* recommend prescription of steroid-sparing agents when patients require chronic use of prednisolone greater than 10 mg/day.[35] The Ocular Immunology and Uveitis Foundation recommended to administer IMT

TABLE 3. Investigations related to retinal vasculitis.

Basic investigations	Specific investigations		Imaging
	Infection	Inflammation	
Complete blood count	Anti-HIV*	Antibody blood tests	Chest radiograph/ computerized tomography
		Antinuclear antibody	
		ANCA†	
Blood chemistries	Interferon-gamma releasing assay for tuberculosis/ T-Spot TB	Anti-cardiolipin	Brain computerized tomography/ magnetic resonance imaging
		Anti-b2 glycoprotein	
		Lupus anticoagulant	
		Anti-Smith antibody	
Blood sugar	Toxoplasma serology	Anti-SSA‡/anti-SSB§	Ultrasound
Urinalysis	Treponemal/ non-treponemal testing	Complement/immune complex studies	Gallium scan
	Mantoux test	C-reactive protein	
	Polymerase chain reaction for Herpesviridae (ocular specimen)	Erythrocyte sedimentation rate	
		HLA‖ testing	
	CSF¶ analysis		
	Vitreous biopsy		

*HIV = human immunodeficiency virus, †ANCA = antineutrophilic cytoplasmic antibody, ‡SSA = Sjogren's syndrome A antibody, §SSB = Sjogren's syndrome B antibody, ‖HLA = human leukocyte antigen, ¶CSF = cerebrospinal fluid

when corticosteroid therapy is required for longer than 3 months or a dose of more than 5 mg/day is required to control inflammation.[36] Treatment with corticosteroids alone is not recommended in certain diseases, such as ABD, GPA, and BSCR, since inflammation is generally severe and requires long-term therapy.

Favored types of IMT include antimetabolite therapy using methotrexate, azathioprine, and mycophenolate mofetil, or the interleukin-2 inhibitor cyclosporine, though the latter is seldom used as monotherapy. These are typically well tolerated and have a relatively low risk profile. Alkylating agents, such as cyclophosphamide and chlorambucil, have use, especially in more severe disease or inflammation that is recalcitrant to approaches associated with less risk, but are usually relied upon later due to their potential complications.[1,37,38]

Biologics

ABD is a good example of RV that responds well to biologics. Anti-tumor necrosis factor alpha (TNF-α) medications (i.e., infliximab and adalimumab) are recommended as a first-line therapy for active ABD with ocular inflammation by the American Uveitis Society.[39] The VISUAL I and VISUAL II clinical trials reported favorable results of adalimumab treatment in non-infectious uveitis patients.[40] Other biologics in addition to anti-TNF-α agents have been used to treat RV, including rituximab (anti-CD20), daclizumab (anti-CD25), and tocilizumab (IL-6R inhibitor).[3,20,41]

Anti-vascular endothelial growth factor (anti-VEGF)

NV and CME are two main complications found in RV that often require intravitreal anti-VEGF injection, and this treatment can be used in both infectious and non-infectious RV. When anti-VEGF is considered, it is sometimes used in combination with panretinal photocoagulation (PRP) for prevention or treatment of ischemic RV.[37] A systematic review of 4 studies comparing intravitreal triamcinolone and intravitreal bevacizumab revealed no significant difference in visual acuity at

any time point after the treatment of uveitic macular edema. One study showed significant difference in central macular thickness with potential favorable benefit with intravitreal triamcinolone.[42]

Laser photocoagulation

NV, tractional retinal detachment, and vitreous hemorrhage are more severe complications that are frequently found in occlusive RV. The mainstay therapy for managing these complications associated with widespread and irreversible retinal ischemia is PRP. Unlike ischemic central retinal vein occlusion, there is no consensus regarding the appropriate timing of PRP in occlusive RV. Rouvas *et al.* proposed PRP when there is retinal ischemia in more than 2 quadrants in idiopathic RV, aneurysm, and neuroretinitis (IRVAN).[43] Aggressive PRP may be beneficial in preventing these complications.[1,37]

Complications and prognosis

Chronic CME, macular ischemia, secondary glaucoma, and optic disc atrophy are leading causes of permanent visual damage.[2,4] Occlusive RV tends to develop complications, such as epiretinal membrane, CME, and NV, that are more likely to associate with poor visual outcome.[2,20] Smoking may associate with vascular leakage and CME, but the precise association is unknown.[44]

CONCLUSION

RV is a severe and vision threatening problem that is one of the presenting features of many specific diseases and can be very difficult to treat. Appropriate investigations and management should be tailored to the needs of each patient. Understanding of the presentation of RV and its possible systemic associations will improve diagnosis, treatment, and outcomes.

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List of abbreviations

ABD, Adamantiades-Behcet's disease
ADNIV, autosomal dominant neovascular inflammatory vitreoretinopathy
Anti-TNFa, anti-tumor necrosis factor alpha
Anti-VEGF, anti-vascular endothelial growth factor
AO, adaptive optics
BSCR, birdshot chorioretinopathy
Calpain 5, calcium-dependent cysteine protease
CME, cystoid macular edema
FFA, fundus fluorescein angiography
GPA, granulomatosis with polyangiitis
ICG, indocyanine green angiography
IMT, immunomodulatory therapy
MHC, major histocompatibility complex
NV, neovascularization
OCT, optical coherence tomography
OCTA, optical coherence tomography angiography
RV, retinal vasculitis
SLE, systemic lupus erythematosus
TA, triamcinolone acetonide
TB, tuberculosis
TNFAIP3, tumor necrosis factor alpha-induced protein 3
TREX1, three prime repair exonuclease 1

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