Original Article

Clinical features and etiology of retinal vasculitis in Northern Thailand

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Purpose: To report on the clinical features and etiology of patients with retinal vasculitis (RV). **Materials and Methods:** We reviewed medical records of 47 patients (75 affected eyes) diagnosed with RV. Clinical presentations, ocular complications, associated systemic diseases, and treatment regimens were registered. **Results:** Etiology of RV included infectious causes in 10/47, (21%) while an association with systemic and/or ocular non-infectious disorders was noted in 22/47 (47%). Eales' disease and Behcet's disease represented the most common clinical entities in non-infectious group while tuberculosis-associated RV was diagnosed in 6/10 (60%) among those with infectious disorders. RV was bilateral in 28/47 (60%) patients. Retinal veins were most commonly affected (72%, 34/47). Involvement of arteries was present in 12/47 (25%) and was associated with viral infections and Behcet's disease. Ocular complications developed in 60/75 (80%) eyes. The most common complications were elevated intraocular pressure and/or glaucoma (33/75, 44%). Retinal detachment, vitreous hemorrhage, and cystoid macular edema developed in similar percentages (15%). **Conclusions:** RV in Thailand manifested mostly in male patients, was typically bilateral and involved mostly veins. Involvement of arteries was observed in patients with viral infections and Behcet's disease. Tuberculosis was the most common infectious cause.

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Retinal vasculitis (RV) is an intraocular inflammation that predominantly affects retinal vessels of either arterial and/or venous system and can be associated with numerous infectious and non-infectious disorders though many cases remain idiopathic.[1,2] Inflammation of the retinal vasculature may occur as an isolated intraocular disorder or in association with various systemic diseases.[1,2] The list of associated systemic diseases is extensive and includes various systemic disorders such as Behcet's disease, multiple sclerosis, sarcoidosis, systemic autoimmune disease as well as infectious diseases including herpetic viral infection, toxoplasmosis, and syphilis.[1,2]

RV may lead to multiple complications including retinal ischemia, cystoids macular edema, formation of neovascularization and vitreous hemorrhages, and may cause permanent visual loss.[3] So far, there is limited information available on the causes, clinical manifestations, and outcomes of RV from Asia.[4]

In this study, we describe the clinical presentations, ocular complications, and the etiology of RV in our patients.

Materials and Methods

We retrospectively reviewed medical records of 47 (15%) new patients with RV (75 affected eyes) out of 315 new consecutive uveitis patients who had been treated in the Uveitis Clinic from June 2006 to December 2009.

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Patients were diagnosed with RV if the intraocular inflammation was located mainly in the retinal vasculature. Ocular findings included perivascular sheathing and inflammation located along the vessels associated with cotton wool spots, retinal exudates, retinal hemorrhages, ischemia or neovascularization.

All patients underwent complete ocular examination including slit lamp biomicroscopy, tonometry, and indirect ophthalmoscopy. Laboratory investigations included erythrocyte sedimentation rate, complete blood count, urine analysis, antinuclear antibody, serology for human immunodeficiency virus (HIV)-type 1, and *Treponema pallidum*. Chest x-ray (CXR) is our routine laboratory investigation for screening of RV patients. Chest computerized tomography (CT) was performed in patients who had positive of tuberculin skin test (TST) ($n = 6$) and/or abnormal CXR ($n = 5$). A measurement of angiotensin-converting-enzyme is in our institute not available. TST was performed in all patients with suspected diagnosis of ocular tuberculosis, i.e., in all patients with ocular features consistent with the diagnosis of Eales' disease ($n = 11$) and five additional patients with abnormal CXR. Due to the fact that we are in endemic area for tuberculosis and country with obligatory Bacillus Calmette-Guérin (BCG) vaccinations, we considered TST positive when the reaction was at least 15 mm in diameter.

Intraocular fluids analysis by polymerase chain reaction (PCR) for cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), and *Toxoplasma gondii* (*T. gondii*) was performed in 13/47 (28%) patients. The decision to sample intraocular fluid for PCR analysis was based on severity of clinical presentation. We included both, aqueous ($n = 9$) and vitreous ($n = 4$) assessments. Aqueous sampling was performed by anterior chamber tap according to previous techniques.[5] Vitreous sampling was principally performed in patients requiring therapeutical vitrectomy for the complications of RV. The detection of CMV, HSV, VZV

and *T. gondii* deoxyribonucleic acid (DNA) was performed as described previously.[5]

Fluorescein angiography was performed in 26 patients (55%) who had active RV and ocular media clear enough to allow photography.

Uveitis was classified according the anatomic localization recommended by the Standardization of Uveitis Nomenclature (SUN) working group.[6] Diagnosis of Eales' disease was made in the patients with no signs or symptoms of associated systemic disease and was based on the clinical features of peripheral retinal phlebitis in combination with peripheral retinal capillary non-perfusion, sometimes complicated by neovascularization with or without accompanying vitreous hemorrhages[7] and was considered a noninfectious disorder (n = 11). The patients with ocular features typical for Eales' disease, but with infectious systemic disorder present such as tuberculosis were diagnosed as infectious RV (n = 2). Diagnosis of Behcet's disease was based on the International Study Group Classification criteria for Behcet's disease.[8] Diagnosis of systemic lupus erythematosus (SLE) was based on the criteria of American College of Rheumatology.[9] Diagnosis of tuberculosis was made in patients who had CXR and/or chest CT compatible with the diagnosis of pulmonary tuberculosis and had also positive TST. In our series, positive TST solely was not sufficient to make the diagnosis of tuberculosis.

We registered clinical characteristics of RV patients including gender, age at onset, laterality, association with systemic diseases, specific ocular findings as type of affected retinal vessels, optic disc abnormalities and ocular complications as elevated intraocular pressure (IOP>25 mmHg) and/or glaucoma, cystoid macular edema (CME), vitreous hemorrhage (VH), and retinal detachment (RD). The severity of vitreous inflammation was classified according to grading system of SUN.[6]

Results

Our study included 47 patients (28; 60% males and 19; 40% females; male: female = 1.5:1). Mean age at onset was 37 years (range 9-64 years). Mean follow-up time was 29 months (range from 2 months to 42 months).

CXR's consistent with pulmonary tuberculosis were noted in 3/47 (6.4%) patients and abnormal chest CT were noted in 5/10 patients with CT performed. None of the patients was positive for HIV or syphilis serology. TST was positive in six out of 16 patients (38%). Out of the 13 patients with severe RV who underwent intraocular fluid analysis, PCR was positive in four; 31% (CMV in two and HSV in two patients).

The specific diagnoses of RV and associations with systemic disorders are given in Table 1. Infectious causes were found in 10/47; 21% patients; 6/19 (32%) patients with unilateral involvement, and in 4/28 (14%; P = 0.31) with bilateral involvement. The diagnosis of tuberculosis was made in 6/47 (13%) patients. Non-infectious origin of RV was observed in 22/47 (47%) and in 15/47 (32%) of patients remained undetermined. The common non-infectious clinical entities were Eales' and Behcet's disease and the most common cause in infectious RV was tuberculosis [Table 1].

Ocular manifestations included bilateral involvement in 28 (60%) patients. Retinal veins were most commonly affected (34/47; 72%), arteritis was present in 9/47 (19%), and involvement of both (arteries and veins) was observed in 3/47 (6%). Vitritis was noted in 44/47 (94%) of patients. Anterior chamber reaction was observed in 22/47 (47%) of patients. Optic disc abnormalities were found in 24/47 (51%) of patients and included optic disc atrophy (16/47; 34%), disc edema (6/47; 13%), and optic disc neovascularizations (2/47; 4%).

Ocular complications of RV are given in Table 2. At least one ocular complication developed in 60/75 (80%) eyes. Elevated intraocular pressure (IOP >25 mmHg) and/or glaucoma were the most common ocular complications (33/75; 44%). CME, VH, and RD developed in similar percentages (15%) [Table 2]. VH showed a borderline association with the development of RD (P = 0.0575, Fisher exact test).

Our series included 12 patients with retinal arteritis (out of whom three in combination with phlebitis). Arteritis was present in all four patients with viral etiology [Fig. 1] and 3/10 with Behcet's disease. In tuberculosis-related RV and Eales' disease, all affected patients exhibited phlebitis.

Discussion

Our study reveals that RV in our institute manifested mostly in male patients, was typically bilateral and involved predominantly veins. Tuberculosis was the most frequently identified infectious cause.

The etiology of RV was reported to vary with ethnic and geographical influences.[1] However, the diagnostic criteria and examinations of the various studies on RV were extremely variable which entirely prevents their meaningful comparison. To compare the causes of RV around the different geographical areas, the consistent use of diagnostic criteria and diagnostic procedures would be essential. For example, while Behcet's disease was the most common RV-associated systemic disease (54%) in a series of 128 patients with RV from Tunisia,[10] another study on RV from India claimed that none of 70 included RV patients had an associated systemic disease.[4] One previous study of 25 RV patients in US reported only one patient with RV-associated SLE.[11] A recent study from US[12]

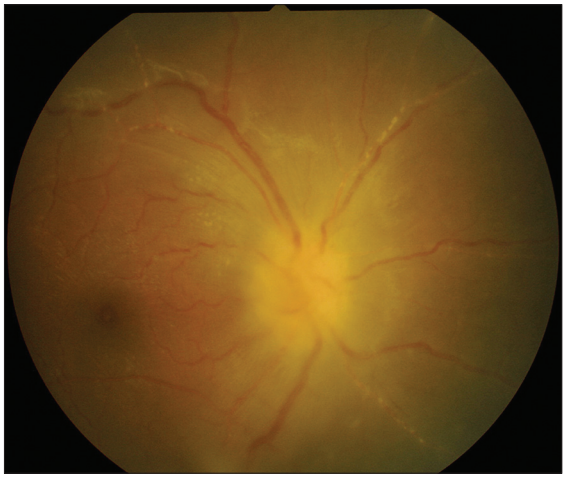

Figure 1: Fundus photograph of arteritis affecting main arteries of a patient with herpes simplex-associated vasculitis

Table 1: Causes and association with systemic disease of 47 patients with retinal vasculitis

Retinal vasculitis	Number of patients (%) *n*=47	Number of patients with arteritis (%) *n*=12
Non-infectious	22 (47)	5 (42)
Eales' disease	11 (23)	0 (0)
Behçet's disease	10 (21)	4 (40)
Systemic lupus erythematosus	1 (2)	1 (100)
Infectious	10 (21)	4 (40)
Tuberculosis	6 (13)	0 (0)
Cytomegalovirus	2 (4)	2 (100)
Herpes simplex virus	2 (4)	2 (100)
Undetermined	15 (32)	3 (20)

Table 2: Ocular complications of retinal vasculitis

Complications of retinal vasculitis (*n*=75)	Number of eyes (%)
Glaucoma	18 (24)
IOP >25 mmHg	15 (20)
Cystoid macular edema	11 (15)
Vitreous hemorrhage	11 (15)
Retinal detachment	11 (15)
Tractional	7 (9)
Rhegmatogenous	3 (4)
Exudative	1 (1)
Total number of eyes with at least one complication	60 (80%)

on 207 patients with evidence of RV (but not necessarily forming the main feature of their intraocular inflammation) documented that 7% were associated with Behcet's disease (14/207) and sarcoidosis (13/207). Tuberculosis-associated RV was diagnosed in two patients (1%).[12] In our present series of patients with RV as a principal feature of their inflammation, Behcet's disease and tuberculosis-associated RV were diagnosed in considerable percentages (21% and 13%, respectively) while the viral etiology was noted in 8.5%.

Direct proof of the presence of *Mycobacterium tuberculosis* (*M. tuberculosis*) in the ocular tissue is conclusive for establishing the diagnosis of ocular tuberculosis. Unfortunately, cultures of *M. tuberculosis*, acid-fast staining or PCR detection of mycobacterial DNA from ocular samples have low sensitivities (20-30%).[13]

The mainstay of the diagnosis of tubercular infection represents TST. TST has a low specificity due false-positive results from prior BCG vaccination and infection from atypical mycobacteria; in addition false-negative results caused by impaired cellular immunity might occur.[13] Currently, more specific diagnostic tests emerged; Interferon Gamma Release Assays (IGRA) can detect immune response to specific *M. tuberculosis* antigens and are not influenced by prior BCG vaccination or by atypical mycobacterial infection. However, IGRA's do not discriminate between latent and active tuberculosis and the results may be influenced by immunosuppressive states. Their exact diagnostic value in individuals with TST anergy has still to be determined.[14] While the positive results of IGRA tests document a (prior) infection with *M. tuberculosis*, they do not prove the etiology of ocular disease.

In the last years, with the use of IGRA tests, the latent tuberculosis was pointed out as a possible cause of RV.[15] The association of (latent) tuberculosis and hypersensitivity reaction to mycobacterial proteins in Eales' disease has been proposed by several investigators.[16-20] However, the systemic studies on the prevalence of (latent) tuberculosis in RV are lacking. In our series, IGRA tests were unfortunately not available and it is possible that the diagnosis of tuberculosis might even be more frequent if TST and/or IGRA tests were systematically used in all patients.

It is important to differentiate between infectious and not infectious RV entities since the treatment modalities are entirely different. In our series, not all patients with RV underwent the aqueous analysis and TST was only employed in patients with CXR or chest CT findings suggesting pulmonary TB or in patients with occlusive RV associated with VHs. Therefore, it is possible that the number of those with infectious RV might be underdiagnosed. Based on our results and to assess the real relationship between RV and tuberculosis, in our institution we decided to examine all patients with RV for TB and not only those with clinical features consistent with the manifestations of Eales' disease.

RV was repeatedly associated with male gender, frequent bilateral disease and involvement of retinal veins, which is in agreement with our findings.[4,10,11] Involvement of arteries was noted in all with viral causes of RV. The predominance of retinal arteritis was already previously noted in acute retinal necrosis (ARN) patients and supports the association between arteritis and viral infections.[21] In addition, arteritis was also present in Behcet's disease (3 out of 10 patients) and was also present in one patient with SLE.

In our series, the most common ocular complication consisted of elevated IOP and/or glaucoma, which was not specifically registered in other studies while retinal detachment, VH and CME were observed in similar percentages (15% each). Indian study reported VH as the most common complication with a prevalence of 30% while CME (9.7%), glaucoma (0.9%), and retinal detachment (0.9%) were less frequently found.[4] The exact cause of these differences is not known and might be in part explained by different causes of RV as well as by the availability of ophthalmologic care. Complications such as increased IOP and glaucoma could also represent the consequence of corticosteroid therapy. In addition, as all studies from tertiary centers, selection bias towards more severe cases is probable. It is possible that our patients came to our institution late in the disease process which would also explain the high prevalence of VH and RD in our series.

The limitations of our study include its retrospective design and fact that various diagnostic tests were not available in all patients. The systematic use of intraocular fluid analyses and IGRA tests might reveal more patients with infectious causes of RV and the systematic testing for anti-cytoplasmic antibody might have disclosed patients suffering from Wegener's

disease. However, Wegener's disease causes more frequently scleritis and is usually accompanied by high erythrocyte sedimentation rate and other system manifestations, and it is not likely that we would miss the diagnosis in such patients. The use of extensive diagnostic tests for diverse auto-immune disorders in all RV patients might also reveal additional diagnoses; however, the presence of solely ocular RV in patients with systemic vasculitides is not likely.

In conclusion, our study reveals that tuberculosis was the most frequently identified infectious cause of RV while the most common non-infectious causes of RV included Behcet's disease. RV in our patients was associated with male gender and a bilateral involvement of predominantly veins while arteritis was observed in viral etiology and Behcet's disease. Future systematic diagnostic assessment and use of IGRA tests might reveal additional causes of patients with RV.

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