Tubercular Retinal Vasculitis

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Introduction :

Tubercular retinal vasculitis has puzzled ophthalmologists for more than a hundred years, from a time soon after the discovery of the tubercle bacillus by Robert Koch. It has elicited more controversy in scientific meetings and medical literature, than probably any other topic in ophthalmology. Unfortunately, most of these debates are based on personal beliefs, rather than solid scientific evidence. Such lack of evidence is likely due to the inaccessibility of retinal tissues for biopsy, as well as the lack of animal models and enucleation specimens to study the pathophysiology of various stages of this disease. In this paper, we will review the possible mechanisms of tubercular retinal vasculitis and its impact on our approach to the management of this disease.

Clinical features :

Typically, this condition manifests as perivascular infiltrates along the veins, and rarely arteries [1,2]. It is often associated with vitritis, retinal hemorrhages, neuroretinitis, focal choroiditis patches (healed or active), serous retinal detachment and on fluorescein angiography, extensive closure of peripheral capillary bed [1,3]. Retinal ischemia caused by closure of peripheral capillary bed often leads to retinal neovascularization, and its sequelae - vitreous hemorrhage, and tractional retinal detachment. Though none of these clinical signs are unique to tubercular etiology, the presence of focal choroiditis patchesalong blood vessels(Figure 1), and peripheral retinal ischemia, often helps to differentiate it from other forms retinal vasculitis (in association with ancillary evidence). In a large study of 184 patients, Gupta et al found retinal vasculitis, especially when associated with focal choroiditis patches to be a statistically-proven indicator of tubercular etiology.[4]

Pathophysiology :

Much of the controversy on tubercular retinal vasculitis revolved around the pathophysiological mechanisms of this disease. The two common hypotheses suggested are:

1. Immune mediated response/hypersensitivity to tubercular antigens
2. Direct infection of ocular tissues by Mycobacterium tuberculosis

The development of immune-mediated hypothesis is rooted in our inability to isolate the organism from the eye in most of these cases. However, several factors need to be considered before we accept this hypothesis.

- The mechanism of such immune mediated reaction is not known. Type 4 hypersensitivity (cell-mediated immunity) that is commonly seen in tubercular infection never causes any vasculitic reaction. On the other hand, type 3 hypersensitivity (immune-complex deposition), that manifests as vasculitis in many parts of the body, is never seen in tuberculosis.
- There is no evidence of molecular homology between retinal antigens and mycobacterial antigens.
- Clinical studies show poor association between clinically manifest systemic tuberculosis and ocular disease. In a series of 350 patients with presumed ocular tuberculosis only 15 (4.3%) had manifest systemic tuberculosis [5]. Also, retinal, or even ocular involvement, is very rare in patients with active systemic tuberculosis. A study of 914 patients with active tuberculosis did not find a single patient with retinal periphlebitis [6]. Another study of 10,524 patients with active pulmonary tuberculosis, found only seven patients with periphlebitis and 144 patients (1.4%) with any form of presumed ocular tuberculosis [7].
- The indirect immune-mediated mechanisms also fail to explain the chronic and recurrent nature of inflammation, seen in most cases of tubercular retinal vasculitis [8]. Theoretically, persistent vasculitis could be due to host's inability to eradicate the infection or to switch off the immune response triggered by the infectious agent after it has been cleared. Since mycobacteria are known to have persistent/ dormant infection in humans, it would be logical to believe

that failure of the immune system to eradicate infection causes chronic/ recurrent inflammation in tubercular retinal vasculitis.

On the contrary, several direct and indirect evidences are available to support the mycobacterial infection hypothesis. A recent report of 42 histopathologically proven cases of ocular tuberculosis (collected over 75 years at the Armed Forces Institute of Pathology, Washington DC), showed that ocular tuberculosis is an extremely paucibacillary disease. [9] In most cases only 1-2 bacilli could be isolated from the entire sample.

Polymerase chain reaction (PCR) has been used to identify mycobacterial DNA in these tissues. However, initial studies showed the sensitivity of PCR to be as low as 33.3% in tubercular retinal vasculitis [10]. This could be attributed to the presence of inhibitory factors in the ocular fluids. Also ocular fluids may not be representative of the actual location of mycobacteria, which is more likely to be the choroid or RPE. In one series, the sensitivity of PCR could be increased to 70% by using specific clinical indicators like presence of active retinal vasculitis, snowball vitreous opacities, optic disc edema, macular edema, focal retinochoroiditis (active or healed) or serous retinal detachment [3]. Interestingly, three of 13 patients in this series had a negative tuberculin test. Newer techniques like real-time (quantitative) PCR are likely to increase the diagnostic sensitivity significantly in the future.

The beneficial effects of anti-tubercular therapy (ATT) in the management of tubercular retinal vasculitis also provide indirect evidence of the role of actively multiplying bacteria in the pathogenesis of this condition. The following case illustrates the likelihood of direct mycobacterial infection of ocular tissues in patients with tubercular retinal vasculitis. A 32 year male patient who complained of decreased vision in right eye for one month. Best corrected visual acuity was 20/40 in right eye and 20/20 in left eye. Anterior segment findings were normal in both eyes. Right fundus showed posterior vitreous cells, a dense macular pucker infero-temporal to the fovea (figure 2a) and few foci of retinal periphlebitis in the inferior periphery (not seen in figure). Left eye was normal. Systemic examination was non-contributary. Lab investigations showed a positive tuberculin test (15 mm with 5 tuberculin units, after 72 hours), but normal chest X-ray and negative tests for sarcoidosis and syphilis. Since the tuberculin test was not strongly positive, the patient was treated with a tapering course of oral corticosteroids. One month later, the patient's BCVA worsened to 20/80 in right eye. Fundus examination showed large choroiditis patch temporal to the macula, associated with multiple areas of perivenous infiltrates and retinal hemorrhages in the supero-temporal quadrant (figure 2b). Corticosteroids were stopped and the patient started on four-drug ATT (rifampicin, isoniazid, pyrazinmide and ethambutol) for three months. At two week follow-up, the choroiditis lesions and perivenous infiltrates (figure 2c). Further resolution was seen in ATT alone, during the course of follow-up (figure 2d). There was no recurrence of inflammation over next 18 months follow-up.

Diagnosis:

In the current scenario, diagnosis of tubercular retinal vasculitis is based on the following:

- Characteristic clinical signs - retinal periphlebitis associated with healed or active choroiditis patches along blood vessels and extensive areas of capillary non-perfusion on fluorescein angiography.
- Ancillary investigations like positive tuberculin test/ interferon-gamma release assay, presence of active or healed tuberculosis on chest X-ray/ computed tomography, or evidence of any other extra-pulmonary tuberculosis.
- Exclusion of other infectious and non-infectious entities that may cause similar ocular manifestations (e.g. sarcoidosis, syphilis or Behcet's disease). Another form of retinal vasculitis- Eales' disease, shares many of the features of tubercular retinal vasculitis, including a frequent association with positive tuberculin test. However, this condition is not associated with intraocular inflammation (vitritis or choroiditis lesions are not seen) and is considered to be idiopathic in origin.

Management :

Management of tubercular retinal vasculitis involves the following:

- Anti-tubercular therapy: 4-drug (rifampicin, isoniazid, ethambutol and pyrazinamide) for 2 months and 2-drug (rifampicin and isoniazid) for 4 months.
- Systemic corticosteroids
- Ancillary therapy: laser photocoagulation for retinal

neovascularisation, intra-vitreal injections (anti-VEGFs, corticosteroids) for macular edema and vitreo-retinal surgery for non-resolving vitreous hemorrhage, tractional or combined retinal detachment.

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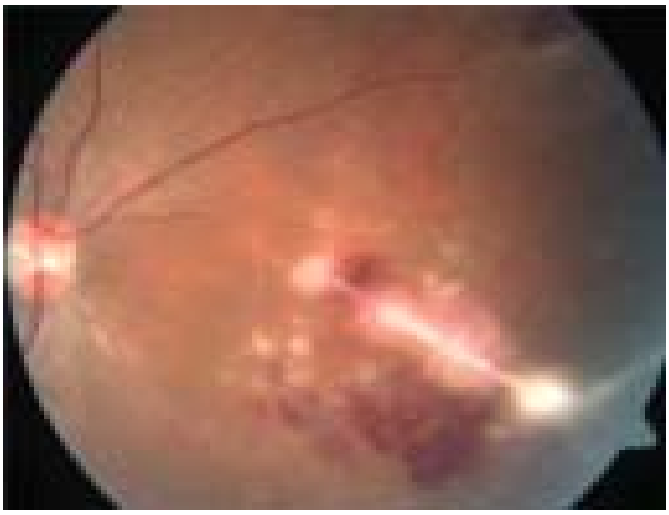

Figure 1: Active choroiditis (arrow) associated with retinal periphlebitis

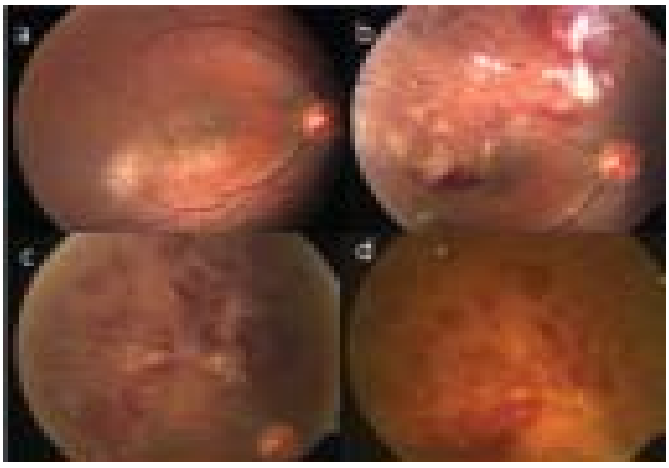

Figure2: Presumed tubercular retinal vasculitis(a) Color fundus photograph of right eye at presentation showing dense macular pucker temporal to the fovea (few foci of retinal periphlebitis were present in inferior periphery, not seen in figure) (b) Right fundus, one month after corticosteroid therapy, showing large patch of choroiditis temporal to the fovea, associated with dense perivenous infiltrates and retinal hemorrhages in the supero-temporal quadrant (c) Right fundus, two weeks after initiation of anti-tubercular therapy (ATT), showing fading of perivenous infiltrates (d) Further resolution of perivenous infiltrates, after one month of ATT