Ocular Tuberculosis Choroidal Granuloma with Unusual Recurrent Choroidal Neovascularization

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INTRODUCTION

Ocular tuberculosis is a common cause of infective uveitis among our Malaysian population as the local incidence of tuberculosis (per 100,000 people) was reported at 92 in 2018, according to the World Bank collection of development indicators, compiled from officially recognized sources.[1] Choroidal granuloma is one of the characteristic findings of ocular tuberculosis. We report a case of unilateral ocular tuberculosis with choroidal granuloma, which developed recurrent choroidal neovascularization (CNV) requiring multiple intravitreal ranibizumab injections.

PRESENTATION OF CASE

A 28-year-old healthy man presented with left eye painless blurring of vision for one-week duration. He worked as a technician with history of exposure to foreign workers at his work place. Systemic review did not show any significant history suggestive of pulmonary tuberculosis symptoms such as loss of weight, loss of appetite and fever. He had no recurrent oral ulcers, joint pains, rashes, genital ulcer or recent traveling history. There was no family history of malignancy.

Upon examination, his right vision acuity was 6/24, pin-hole 6/9, whereas his left vision acuity was 6/60, pin-hole 6/24. Anterior segments examination was unremarkable with normal intraocular pressure. Fundus examination of the left eye showed a disc size diameter hypopigmented choroidal lesion located at the centre of the fovea. Hence, uveitis work-ups to rule out systemic infection such as tuberculosis, syphilis and other systemic infections were sent. His full blood count and erythrocyte sedimentation rate were within normal range. Mantoux test showed anergy (0mm), however, his chest X-ray did not show any perihilar lymphadenopathy, lung infiltrates or cavitation. Optical coherence tomography (OCT) examination of the left eye revealed a dome-shaped choroidal elevation with hyperreflectivity at the outer retina layer and subretinal fluid. Fluorescein angiography of left eye showed leakage at the site of lesion.

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CLINICAL DIAGNOSIS

Left eye presumed ocular tuberculosis choroidal granuloma.

PATHOLOGICAL DISCUSSION

Ocular tuberculosis is a sight-threatening and treatable eye condition. It can be the primary or secondary site of *Mycobacterium tuberculosis* infection. Shahidatul-Adha, et al. (2017)[2] published a case series of 34 ocular tuberculosis patients in Hospital Universiti Sains Malaysia, majority of their patients about 58.9% had unilateral condition. The dissemination of *Mycobacterium tuberculosis* to the eye is commonly secondary to hematogenous spread to the uveal tissue.[2] Choroid is the most common ocular site being infected by *Mycobacterium tuberculosis* due to its high vascularity.[3]

Choroidal granuloma is one of the most common presentations of ocular tuberculosis. It can be unilateral or bilateral, appear as subretinal lesions with various sizes ranging from 4 to 14mm, which are greyish white to yellow in colour with indistinct border.[4] Choroidal granulomas are commonly found at the posterior pole and mid-periphery retina. It has been termed vascularized lesion in the presence of dilated, tortuous vessels overlying the granuloma. The lesion was also associated with significant exudation and leakage on angiography, and presence of subretinal fluid on OCT.[5] Patients presenting with choroidal granuloma as a primary feature usually do not have anterior segment or vitreous inflammation. Nonetheless, overlying serous detachment, retinal haemorrhages or retinal folds may be present. Once the granuloma resolves, the margin becomes distinct and more pigmented. Eventually after three to four months of treatment, the lesion heals as atrophic scar with pigmentation.[4] Our case presented in a similar manner of natural history for the disease. There was no confirmatory laboratory test to suggest or confirm a definite ocular tuberculosis. Presumed diagnosis of ocular tuberculosis was made based on the clinical findings, tuberculosis contact and positive response to anti-tubercular treatment.

Choroidal neovascularization is a sight-threatening complication of posterior uveitis.[6] The earliest mention of tuberculosis-associated choroidal neovascularization in the literature was in a 1987 case report, where subretinal neovascularization occurred 34 years after being diagnosed with tuberculosis. Treatment given was isoniazid and laser photocoagulation.[7] Tuberculosis associated with choroidal neovascularization typically occurs adjacent to the healed choroidal granuloma or choroiditis scar. Neovascular buds grow through the damaged RPE–Bruch's complex and proliferate to develop a neovascular complex. The vessels tend to leak which may lead to the accumulation of fluid in the subretinal space. The activity of choroidal neovascularization can be monitored by serial OCT based on its signs of exudation such as retinal thickening, subretinal fluid and subretinal hyperreflectivity material.[8]

The general principle of treatment for tubercular granuloma with choroidal neovascularization is to control the local infective foci and inflammation with adjunctive anti-VEGF treatment.

Other therapeutic strategies recommended for choroidal neovascularization were focal laser photocoagulation, photodynamic therapy, local corticosteroids, systemic immunosuppression, and surgery.[9] In recent years, anti-VEGF injection was also employed as the first-line treatment for choroidal neovascular membrane secondary to posterior segment inflammation. It is believed that the formation of membrane occurs from the inflammation mediated angiogenesis and also the defect in Bruch's membrane-RPE complex following inflammation.[9] Inhibition of vascular endothelial growth factor resulted in depletion of granuloma vascularity then enhances resolution of CNV.[3] The median number of intravitreal anti-VEGF injections required to achieve an inactivity in different studies is reported as 2 injections, ranging from 1-5 injections.[6] A study by Seema et al. (2011)[10] had proven that choroidal tubercular granuloma showed evidence of oxygen tension reduction with upregulation of VEGF level in the retinal pigment epithelium and photoreceptors. This had elucidated the pathogenesis of the lesion and the indication for anti-VEGF therapy.[10] Latest research by N. Singh et al. (2020)[11] showed that VEGF levels were elevated in retinal pigmented epithelium cells which were infected by *Mycobacterium tuberculosis* and vitreous samples of ocular tuberculosis patients. Photodynamic therapy (PDT) is uncommonly used currently due to its limitations in improving visual acuity and its adverse effects.[8] Furthermore, PDT may potentially upregulate the level of VEGF in the eye.

There were few case reports showing variable treatment responses in managing ocular tubercular granuloma. Oehlers, et al. (2019)[12] suggested to treat tubercular granuloma as a "bacterial tumour" with anti-VEGF. The anti-angiogenic properties reduce bacteria burden and spare host immunopathology. S. Jain, et al. (2019)[13] reported a case who had complete regression of vascularized tubercular choroidal granuloma with a single injection of intravitreal ranibizumab without combination of anti-tubercular and systemic corticosteroids. A report by Invernizzi et al. (2015),[14] suggested adjunctive anti-VEGF injection as a solution in managing a case of large optic disc tubercular granuloma in addition to conventional therapy.

DISCUSSION OF MANAGEMENT

A diagnosis of left eye presumed ocular tuberculosis was made in view of significant history of tuberculosis contact and clinical findings (Figure 1A). He was then started with anti-tubercular therapy and followed by oral prednisolone, with adjunctive intravitreal ranibizumab injection. He responded well to the treatment whereby the granuloma considerably decreased in size (Figure 1B). During his follow up, he had pre-retinal bleed and recurrent subretinal fluid which required further intravitreal injections of ranibizumab (Figure 1C). Post anti-tubercular treatment and multiple anti-VEGF injections, the lesion healed with fibrovascular tissue (Figure 1D). His vision acuity at last visit was counting fingers.

Figure 1. Serial Fundus Photos and OCT Images Showing the Progression of Patient while on Treatment for Left Eye Tubercular Choroidal Granuloma with Recurrent CNV Activity

Figure 1A. Presentation with Choroidal Granuloma

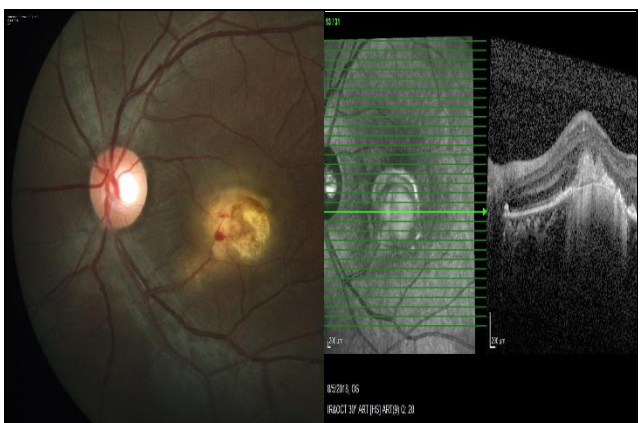

Figure 1B. After One Injection of Ranibizumab

Figure 1C. Resolution of Pre-retinal Hemorrhages after Multiple Injections of Ranibizumab

Figure 1D. Fibrovascular Scar Formation

Our case showed tubercular choroidal granuloma with recurrent CNV which required multiple anti-VEGF injections. So far there were no reports showing tubercular choroidal granuloma with recurrent CNV. This case report will be imperative to the ophthalmologists to prompt further investigation in the correlation of tuberculosis strains in different regions with regards to VEGF level in the eye.

FINAL DIAGNOSIS

Left eye presumed tubercular choroidal granuloma with recurrent CNV.

The authors wish to thank Director General of Health Malaysia for his permission to publish this article.
There are no conflicts of interest to report for any of the authors.
This case report was registered under National Medical Research Register Malaysia and informed consent was obtained from the patient.

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