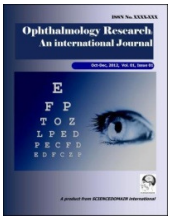

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Immune Reconstitution Inflammatory Syndrome (IRIS) Presenting as Bilateral Severe Granulomatous Sclerouveitis in a HIV-Infected Patient with Mycobacterium Tuberculosis Infection: A Case Report

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Authors' contributions

This work is carried out in collaboration of all authors. Author ELT designed the study, wrote the first draft of the manuscript and managed the literature search. Authors SOM and LSAT revised it critically for intellectual contents. Authors ELT, SOM, HH and NN were involved in the assessment and treatment of the patient. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: To report a case of tuberculosis (TB) associated immune reconstitution inflammatory syndrome (IRIS) presenting as rapid progressive bilateral severe granulomatous sclerouveitis.
Presentation of Case: A 26-year-old Human Immunodeficiency Virus (HIV) -infected male who was on antiretroviral therapy (ART) 3 months prior to presentation complained of left acute painful

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red eye with blurring of vision and floaters. There was severe granulomatous uveitis in both eyes with necrotizing scleritis in the left eye. There was also cervical lymph node that was positive for *Mycobacterium tuberculosis*. He initially responded well to antituberculosis therapy together with topical steroids and antibiotics, oral non-steroidal anti-inflammatory drugs (NSAIDS) and ART. His vision deteriorated after 6 weeks of treatment. He developed bilateral severe sclerouveitis and marked sclera thinning with self-sealed scleral perforation of the left eye. A diagnosis of IRIS was made and systemic steroid was added. Ocular inflammation was controlled, but his left vision remained poor due to perforated extensive necrotizing scleritis, seclusiopupillae and cataract.

Discussion: Intraocular TB may be presented with aggressive, rapid progression of the disease in HIV –infected patients. ART-associated TB is seen in HIV patients who developed TB after initiation of ART. Subset of ART-associated TB could be due to unmasking IRIS. Patients who were treated for opportunistic infection after ART may develop paradoxical IRIS.

Conclusion: Bilateral severe granulomatous uveitis with necrotizing scleritis is a rare manifestation of TB-related IRIS in an HIV patient. It is a potential sight threatening condition. A close monitoring for the development of IRIS during treatment of HIV is essential to minimize the morbidity.

Keywords: Immune reconstitution inflammatory syndrome; tuberculosis; granulomatous uveitis; necrotizing scleritis.

1. INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is an important complication following the management of HIV infected patients on highly active antiretroviral therapy (ART) [1-2]. IRIS is associated with various infections from bacteria, virus and fungi; autoimmune disease and malignancies [1-3]. It could be presented as “unmasked” or “paradoxical” IRIS. Tuberculosis (TB) is commonly associated with IRIS in HIV patients. The incidence ranges from 8 to 45%and is associated with extrapulmonary involvement [2-4]. TB-associated IRIS can lead to substantial morbidity [2,4]. Involvement of central nervous system can lead to high mortality [5,6]. Ocular manifestation of IRIS is rare. Most of the reported ocular cases were immune restoration uveitis or vitritis associated with cytomegalovirus retinitis [7,8]. We report a rare case of IRIS associated with TB presenting as bilateral severe necrotizing granulomatous sclerouveitis.

2. CASE REPORT

A 26-year-old HIV infected man who was recently started at 3 months duration of antiretroviral therapy (ART), presented with sudden left painful red eye for 2 weeks. The ART included Efavirenz 600mg OD, Lamivudine/ zidovudine 150/300mg BD. The left painful red eye was associated with blurring of vision and floaters. However, there were no flashes of light. He denied any history of headache, nausea and vomiting. He had no history suggestive of tuberculosis infection prior to ART. He had recently been treated for herpes varicella infection. His latest CD4 count prior to ART was 104/UL.

On examination, the best corrected right vision was 6/9 and left eye was counting fingers. Both eyes were congested and inflamed. Anterior segment examination of both eyes showed the presence of mutton-fat keratic precipitates, extensive posterior synechiae and anterior chamber cells, which was more severe in left eye. There was active necrotizing anterior scleritis involving the inferonasal quadrant of the left eye (Fig. 1). Both lenses were clear. There was mild vitreous inflammation in right eye. Left eye vitritis was more severe causing poor visualization of fundus. Intraocular pressures were normal in both eyes. Right funduscopy showed hyperemic optic disc with the presence of choroiditis, but there was no evidence of choroidal tubercle. B scan of the left eye revealed moderate vitreous opacities. A fundus fluorescein angiogram of the right eye showed an inflamed optic disc, vasculitis, choroiditis and cystoid macular edema.

Systemic examination revealed normal lung findings. Chest radiography was performed and there was no evidence of cavitation lesion suggestive of tuberculosis infection. At presentation, there was no palpable lymph node noted. Mantoux test was negative and Erythrocyte Sedimentation Rate (ESR) was not raised. Based on the recent history of herpetic infection prior to the onset of ocular symptoms, he was initially diagnosed with bilateral

granulomatous panuveitis secondary to herpetic infection. Intravenous acyclovir was then started. Two weeks after intravenous acyclovir, there was no clinical improvement of the ocular condition. A cervical lymph node was then found and was proven positive for *Mycobacterium tuberculosis* following biopsy. Mantoux test was then performed again which was positive and the ESR was raised at 98mm/hour. The diagnosis was revised as presumed intraocular TB. Systemic antituberculous therapy was initiated together with topical steroids [guttae Dexamethasone (Maxidex) 4 hourly both eyes], topical antibiotics [guttae Moxifloxacin (Vigamox) 4 hourly both eyes] and oral NSAIDS (Tab Ibuprofen 400mg BD). ART was continued.

There was remarkable improvement in the ocular inflammation. However, upon review 6 weeks later the ocular condition had deteriorated drastically. He claimed to have maintained compliance to the treatment. His right eye vision was reduced to counting fingers and left eye was only perceptive to light. There was worsening of necrotizing scleritis with scleral thinning in both eyes. There was also intense intraocular inflammation of both eyes with the presence of fibrin in anterior chamber. There was marked scleral thinning with a self-sealed scleral perforation noted on the left eye (Fig. 2). The left eye anterior chamber was shallower with presence of seclusiopupillae. Both corneas were edematous and hazy with raised intraocular pressures, right eye 26mmHg and left eye 30mmHg. There was no view of the fundi. Systemic examination revealed a new lymph node enlargement. Biopsy was done on the new lymph node and yield negative result for *Mycobacterium tuberculosis*. Other septic workout was negative, and there was no evidence suggestive of toxicity to antituberculous therapy. CD4 at this presentation was raised to 243/UL.

In view of the paradoxical worsening of the ocular inflammation, a diagnosis of IRIS was made. Systemic steroids, oral prednisolone 1mg/kg/day, were immediately commenced together with continuation of antiretroviral, antituberculosis and topical medications. The oral prednisolone was slowly tapered based on the clinical responses. At six months of follow up, both eyes ocular inflammation has been controlled. The right eye visual acuity has improved to 6/9. However, the left vision remained hand movements even with well controlled ocular inflammation (Fig. 3). The left eye anterior chamber remained shallow with presence of seclusiopupillae. There was presence of cataractous lens in the left eye.

3. DISCUSSION

Clinical presentation of intraocular TB varies widely from anterior and posterior segment involvement even to neurophthalmic involvement [9,10]. It is often misdiagnosed due to lack of uniformity of diagnostic criteria, and difficulty in retrieving ocular samples [9,10]. It is even more challenging in HIV patient as in this case [9-11]. The presence of history of herpetic varicella infection masked the potential of intraocular TB. Lack of laboratory evidences further complicates the matters initially.

Moreover, herpetic and TB sclerouveitis are both responsible for the granulomatous type of intraocular inflammation. The differentiation of the clinical presentation was further complicated by poor fundus visualization. Patients with HIV infection may present with aggressive ocular TB infection despite previous adequate antituberculosis therapy [11]. However, in this case there was no history of previous tuberculosis infection. The negative Mantoux test is not surprising in HIV patients. It is reported smear positivity rates in HIV infected patients are poor [12-14].During the treatment of ART, the rapid restoration of the immune system leads to increase immune responses to a specific antigen that may cause positivity in Mantoux test [13,14].

This patient had developed ART associated TB 3 months post ART, which is a term used to define HIV patients who are diagnosed with TB infection after initiation of ART [4]. It is believed to be due to on-going persistent immunodeficiency or due to rapid restoration of the immune response against TB after commencement of antiretroviral therapy [4]. It is reported that it occurred most often within first 3 months of ART initiation [15,16]. A subgroup of ART-associated TB is due to “unmasked” IRIS [4,16]. The rapid aggressive presentation with paradoxical worsening of ocular inflammation after the commencement of anti-TB treatment in this present case leads to the diagnosis of IRIS. To the best of our knowledge, this is the first case of severe granulomatous uveitis and necrotisingscleritis in IRIS. IRIS is postulated to result from rapid restoration of the immune response towards the

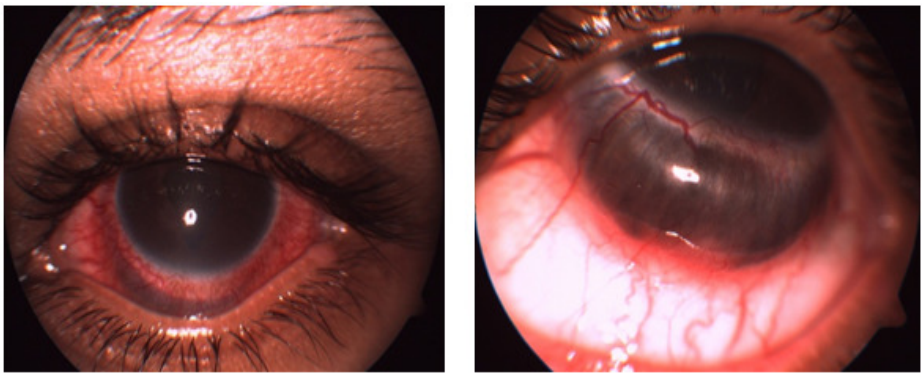

Fig. 1. Severe granulomatous sclerouveitis with inferior thinning in left eye

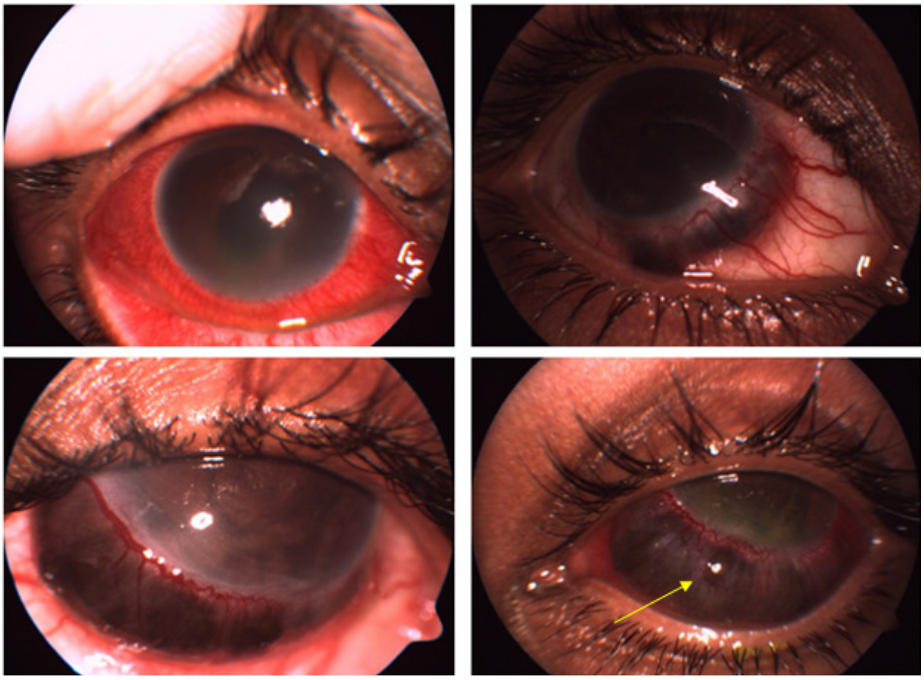

Fig. 2. Worsening of granulomatous sclerouveitis with inferior thinning of bilateral eyes. Upper panels: Right eye. Lower: Left eye with self-sealed perforation and seclusiopupillae

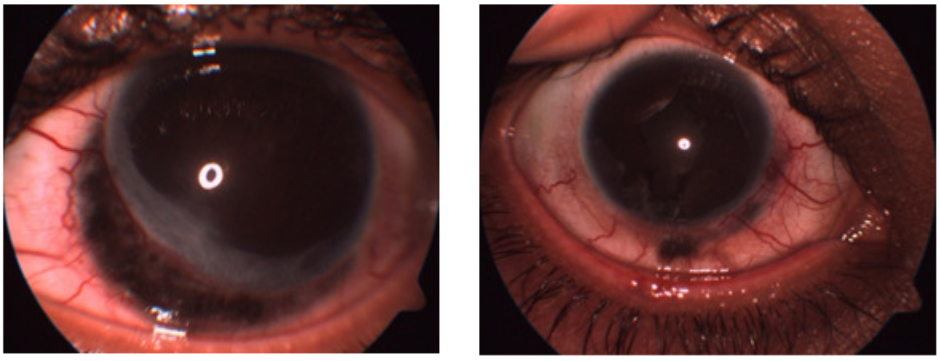

Fig. 3. Improved ocular inflammation after 6 months of follow up. Left: Left eye; Right: Right eye

pathogen and presents with a paradoxical clinical presentation [1,3,4]. It can either present as "unmasking" of an occult opportunistic infection, or "paradoxical" worsening of the symptoms, which can present at the original site or new body site [4,16-19]. Any pathogen which can provoke opportunistic infection can cause IRIS when there is recovery of pathogen specific immune responses during the course of ART [2,3].

These infections may be subclinical prior to commencement of ART and be unmasked after commencement of ART. The restored immune responses often lead to exaggerated inflammation and may be misinterpreted as opportunistic infection [3]. This immune restoration often occurs within first 3 months of ART. In this "unmasked" IRIS, viable pathogens may be isolated from the affected sites [3]. Commencement of ART in recently treated or exposed opportunistic infection can lead to paradoxical worsening of the infection. In this "paradoxical" IRIS, the immune response is against the non-viable pathogen, and cultures often yield sterile result [3]. "Unmasked" and "paradoxical" IRIS was postulated to result from different immunopathogenesis [16].

Following the recent case consensus definition, this patient was diagnosed as "unmasked" TB associated IRIS. The diagnosis of "unmasking" TB associated IRIS is suggested in patients who had not received tuberculosis treatment prior to ART and developed active TB within 3 months of ART, followed by the presence of marked inflammatory clinical manifestation or development of paradoxical responses once patient is established on tuberculosis treatment [4]. Repeated positive Mantoux test in this case supported the evidence of immune restoration as seen in unmasked IRIS in subgroup of ART associated TB [16]. There was also evidence of increment in CD4 count during the course of ART and anti-TB treatment.

The presence of tubercular lymphadenitis also increases the index of suspicious of IRIS. Extrapulmonary TB, for example tubercular lymphadenitis is reported as one of the risk factors of developing IRIS [1,2,19]. In this patient, the latest CD4 count at initiation of ART was slightly more than 100/µl. IRIS is reported to commonly develop in cases with CD4 less than 100µl [1,2,18,19]. This patient had received ART at the age of 26. Greater response to ART seen in younger age group is a recognized risk factor of IRIS [18]. In this present case, TB was diagnosed at 3 months of ART and TB therapy was then started. Early period of ART and short interval between ART and treatment of opportunistic infection as seen in these patients are another recognized risk factors for IRIS development [1,2,19].

Rapid aggressive ocular presentation with impending ocular perforation is really alarming in this patient. High index of suspicious is important to initiate appropriate treatment and arrest further morbidity for this young HIV patient. Until now, there is no prospective consensus on managing IRIS [1,2,4]. In severe cases, systemic immunosuppressive corticosteroid is recommended with continuation of treatment for opportunistic infection and HAART therapy [1,3,20]. Vision is important to improve quality of life even in HIV patients.

4. CONCLUSION

Detection and management of TB associated IRIS are challenging. The dramatic sight-threatening complications of IRIS may pose a challenge in the management of intraocular TB. High index of suspicion is warranted to minimize the morbidity and mortality due to TB associated IRIS.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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