

### Reviewer's Comments:

We have received your request for additional review of the manuscript: "Immune Reconstitution Inflammatory Syndrome (IRIS) Presenting As Bilateral Severe Granulomatous Sclerouveitis In A HIV-Infected Patient With Mycobacterium Tuberculosis Infection: A Case Report", and feel that even though authors have made changes to their work, there are still some unanswered questions and that there are still some crucial issues such as: what was the excluding criteria concerning VZV?

*Seeing that the patient had: "recently been treated for herpes varicella infection" and "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 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 (Figure 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 presence of choroiditis, but there was no evidence of choroidal tubercle. B scan of the left eye revealed moderate vitreous opacities. Fundus fluorescein angiogram of the right eye showed an inflamed optic disc, vasculitis, choroiditis and cystoid macular edema"; "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".*

So, how and why was the initial diagnosis and/ treatment abandoned and patient treated as a case of TB alone. His vision had not improved, and there were still visible signs of uveitis present which would suggest that it was VZV sclerouveitis which had then reactivated upon patient's immune recovery.

When looking at immune disorders Mantoux testing is of little relevance seeing that treatment agents themselves play a role and may provide inadequate results.

Positive findings concerning lymph nodules cannot indicate that uveitis is tuberculous in nature which is further supported by the fact that the patient's visual efficiency had not improved, it had in fact worsened. I.e. I am of the opinion that this patient had opportunistic TB cervical lymphadenopathy.

**To conclude, I am of the opinion that there are still a few issues regarding this material, and that the authors need to be a bit clearer in their understanding of uveitis, sclerouveitis, inclusion/exclusion diagnostic criteria, and IRU.**

### Author's Feedback:

Thank you for the considerate and fruitful comments.

This patient was first diagnosed with bilateral granulomatous panuveitis. This could be due to TB or VZV due to the recent infection of VZV. Based on the recent clinical history and at this point, the Mantoux test

was negative and there were no clinical symptoms or signs suggestive of TB, hence the diagnosis was tailored to herpetic origin.

However, despite treatment, there was no clinical response to the intravenous acyclovir. Based on this, we have re-investigated the patient, and at this time, he had developed cervical lymphadenopathy, which biopsy was positive for *Mycobacterium tuberculosis*, and at this time, the repeated Mantoux was positive, as well as the ESR was raised. At this point, we revised the *clinical diagnosis* to bilateral granulomatous panuveitis secondary to TB infection. In view of difficulty and inadequate sample that could be withdrawn from the ocular tissue, ocular sample was not taken for PCR. We feel that clinical diagnosis at this point is sufficient. In addition, the patient responded to the antituberculosis therapy with improvement of ocular inflammation and vision. Therefore it supported our diagnosis of presumed ocular TB leading to granulomatous uveitis. The ocular condition was severe and involved the sclera with presence of perforation. Therefore we use the term sclerouveitis in the title.

We agreed with the point that this patient had opportunistic TB cervical lymphadenopathy, which could be result from “unmasked” IRIS. We were treating the patient as opportunistic TB infection, and he responded to the treatment. However, he then developed paradoxical worsening of the ocular inflammation. At this point he was re-investigated for possibility of other infection and treatment failure but yield negative result. Due to the short duration of positive response to antituberculosis treatment and paradoxical worsening of clinical condition, following the recent case definition consensus by Meintjes et al, patient was then diagnosed with unmasked IRIS. Meintjes et al proposed the case definition of paradoxical IRIS, ART associated TB and unmasked IRIS based on clinical presentation. This is especially useful in limited resource setting. Previous definition criteria of IRIS include: confirmed HIV diagnosis, temporal association of ART, demonstration response to ART, which include CD4 count, other marker of immune recovery for example conversion of tuberculin test from negative to positive. No doubt, other immunology marker can aid in supporting the diagnosis. However, in view of limited resource, we were unable to proceed with the other immunological testing. In this patient, there was demonstration of conversion of Mantoux from negative to positive result, as well as increment of CD4 count, therefore, it supports our diagnosis of TB associated IRIS.