CASE REPORT

Immune reconstitution inflammatory syndrome in a HIV-infected patient with disseminated tuberculosis

Koh KC, Pak JW

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Authors:

Koh Kwee Choy
(Corresponding author)
MMed, MBBS
Department of Medicine, International Medical University, Jalan Rasah, 70400 Seremban, Negeri Sembilan, Malaysia.
Email: kweechoy_koh@imu.edu.my

Pak Jun Wee
MBBS
Hospital Raja Permaisuri Bainun, Jalan Hospital, 30990 Ipoh, Perak, Malaysia.
Email: joewee_12@hotmail.com

Abstract

Immune reconstitution inflammatory syndrome (IRIS) is the paradoxical worsening of pre-existing infectious processes after commencement of anti-retroviral therapy (ART) in HIV-infected patients. Its manifestations are dependent on the underlying opportunistic infections. We report a case of an HIV-infected patient with disseminated tuberculosis, who responded to anti-tuberculosis therapy but suffered from paradoxical worsening after commencement of ART.

Introduction

Immune reconstitution inflammatory syndrome (IRIS) occurs as a result of successful anti-retroviral therapy (ART), in which there is a sudden 'inflammatory flare' towards pre-existing infections that were previously subclinical due to immunosuppression.[1] The clinical features are closely linked to the type and location of the pre-existing infection. IRIS is usually self-limiting and is rarely fatal, especially if the pre-existing infection is effectively treated. Failure to recognize IRIS may lead to mismanagement and detrimental outcomes.

Case Summary

MF, a 35-year-old man, was first diagnosed in 2008 with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) co-infection acquired from intravenous drug use with a history of needle sharing. He first presented on the 3rd of May 2013 with complaints of progressively enlarging painful neck swelling for more than 3 weeks associated with fever, night sweats and productive cough. In addition, he complained of significant weight loss and poor appetite for the past 6 months.

On examination, multiple tender and immobile cervical lymph nodes measuring 1–2 cm in diameter were observed. Although his chest radiograph results were normal, sputum analyses on the 7th and 8th of May 2013 showed the presence of acid-fast bacilli (AFB). Based on this, he was diagnosed with pulmonary tuberculosis along with tuberculous lymphadenitis and underlying HIV-HCV co-infection. At this point, fine-needle aspiration cytology (FNAC) and biopsy of the enlarged neck nodes were performed.

Oral first-line anti-tuberculosis (anti-TB) therapy was commenced for the patient, consisting of isoniazid, rifampicin, pyrazinamide and ethambutol with supplementation of pyridoxine and cotrimoxazole for prophylaxis against Pneumocystis jiroveci pneumonia (PJP), on the 10th of May 2015. When the patient was discharged on the 17th of May 2015, his symptoms of cough, fever and night sweats had resolved, and the neck swelling was noticeably reduced.

He returned for a review at the infectious diseases clinic on the 31st of May 2013. The neck swelling had completely disappeared. His CD4 cell count, on the 12th of May 2013, was 444 cells/mm^3. Taking into account the poor constitution of the patient at the time, ART regime was commenced consisting of stavudine, lamivudine and efavirenz for HIV infection, and the patient was advised to continue with the anti-TB therapy. Stavudine was chosen over the usual zidovudine, as the patient had anaemia at the time (haemoglobin level of 8.5 g/dL).

On the 24th of June 2013, MF presented with complaints of progressive painful enlargement of neck swelling for approximately 1 month, associated with intermittent fever for a week. Physical examination revealed multiple enlarged, tender, erythematous matted lymph nodes at the submental, submandibular and anterior cervical chain of the lymph nodes (Figures 1 and 2). Apart from that, examination of other systems yielded unremarkable results.

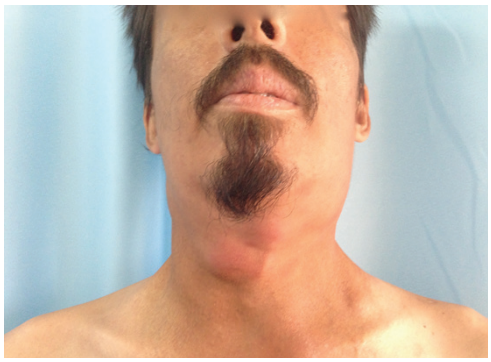

Figure 1. Anterior view of the neck swelling

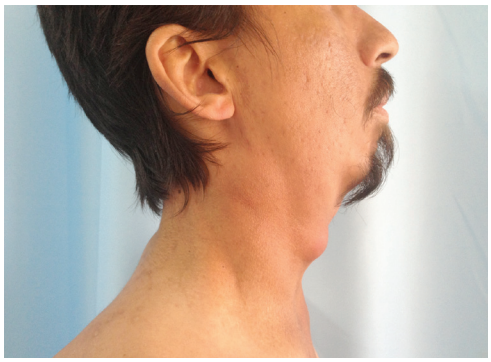

Figure 2. Lateral view of the neck swelling

Investigations showed elevated erythrocyte sedimentation rate (ESR) of 120 mm/h, C-reactive protein (CRP) level of 71.6 mg/L and lactate dehydrogenase (LDH) level of 292 U/L. Lymph node aspiration performed on the 26th of June 2013 was positive for AFB. A lymph node biopsy performed on the 27th of June 2013 was subsequently reported to show evidence of chronic granulomatous inflammatory process consistent with tuberculous lymphadenitis. However, special stains for AFB and fungal bodies were negative.

At this point, the diagnoses of drug-resistant *Mycobacterium tuberculosis*, non-tubercular *Mycobacterium* infection and IRIS were considered. Retrospective tracing of the initial sputum culture and sensitivity showed first-line anti-TB therapy–sensitive *M. tuberculosis*, ruling out the first two differential diagnoses. Careful history-taking revealed a temporal association between commencement of ART and the subsequent appearance of neck node enlargement.

A final diagnosis of IRIS was made. The same ART regimen, oral cotrimoxazole and anti-TB therapy were continued along with the addition of oral prednisolone at 50 mg daily (1 mg/kg/day). The cervical lymphadenopathy rapidly resolved in 2 weeks, with resolution of fever. The patient was discharged well on the 17th of June 2013, with continuation of the same ART regimen and oral cotrimoxazole; his anti-TB therapy regimen was converted to maintenance phase consisting of oral isoniazid and rifampicin.

Discussion

The incidence of IRIS in patients in whom ART is started varies with the pre-existing illness. Studies have reported IRIS in 63% of HIV-infected patients with cytomegalovirus retinitis, 30%–34% of those with inactive cryptococcus, and 30% of those with *M. tuberculosis* infection.[1,2]

Major risk factors for the development of IRIS include a CD4 cell count <100 cells/mm^3 (although IRIS may occur at any CD4 cell count), a heavy pathogen burden before ART initiation, and a short duration between treatment of the infection and commencement of ART.[3-8] IRIS usually presents within the first 4–8 weeks after the initiation of ART, although IRIS has been reported to occur as early as 3 days and up to several years after ART initiation.[5,9]

The immunopathology of IRIS is largely determined by the provoking pathogen.[10] In M. tuberculosis and other mycobacterial infections, granulomatous inflammation usually predominates,[2,10] as was the case in this patient. The IRIS phenomenon is presumed to be the result of partial reconstitution of the host immune response and a transient increase in inflammation.[11]

Although, no universally accepted diagnostic criteria for IRIS exist, a diagnosis of IRIS should be considered when all or most of the following features are present: HIV infection with low pretreatment CD4 count (one important exception to this rule is tuberculosis, in which IRIS can occur at any CD4 count), positive virological and immunological responses to ART, clinical features of inflammatory response, and a temporal association between the commencement of ART and the onset of clinical features of the illness.[12]

In tuberculosis-associated IRIS (TB-IRIS), manifestations include worsening of pulmonary symptoms or chest radiograph findings suggestive of worsening tuberculosis, enlarging lymph nodes, and meningeal symptoms.[5] TB-IRIS may develop as early as 10 days after initiation of ART to as long as 180 days, but usually occurs within 2 months of ART initiation.[13,14] Our patient had

cervical lymphadenopathy that resolved following anti-TB therapy only to recur and worsen after commencement of ART. This is known as *paradoxical worsening*, which is defined as the exacerbation or recurrence of symptoms from a previously known or treated disease after initiation of ART.[1]

The risk of IRIS is higher among patients in whom ART is initiated at earlier points than later within the course of TB treatment.[15,16] Increasing the duration of time between the treatment of known tuberculosis and the initiation of ART has been shown to decrease the incidence of IRIS.[17] Nevertheless, the benefits of early initiation of ART in these patients far outweigh the risks of morbidity associated with TB-IRIS. Although the recommended timing for initiation of ART in HIV-infected patients with tuberculosis and a CD4 cell count >350 cells/mm^3 is after the completion of anti-TB treatment, the decision to initiate ART earlier in this patient was taken on account of his severely malnourished state on presentation.[18,19]

Differential diagnoses that must be considered in such patients include anti-TB resistance, non-adherence to medication, drug hypersensitivity reaction and development of new occult infection. Effort must be made to rule these out before considering IRIS as the final diagnosis.

Patients should be treated for the underlying infection as soon as possible. Except in severe cases, ART should not be interrupted during the management of IRIS. Several case series have described the efficacy of corticosteroids in reducing the inflammatory response associated with IRIS.[10] Oral prednisolone at 1–2 mg/kg/day can be prescribed for 1–2 weeks followed by a taper. The potential benefits of corticosteroid therapy should be weighed against its risks, including worsening glycaemic control, hypertension, altered mental status, acute flare of infections and predisposition to new infections.

Conclusion

The clinician should be alerted to the possibility of IRIS after initiation of ART in HIV-infected patients treated with anti-TB therapy. Prevention of complications associated with IRIS requires careful monitoring, particularly in patients with low CD4 cell counts and a history of co-infections.

In cases of paradoxical worsening, treatment of the underlying infection should be continued to suppress replication of the provoking pathogen and reduce antigen load.[10] ART should only be ceased if the disease is life-threatening. Corticosteroids may be useful in reducing the inflammatory response associated with IRIS.[12]

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Conflict of interest

None.

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