Tuberculosis and human immunodeficiency virus coinfection complicated by immune reconstitution inflammatory syndrome

To The Editor,

A 28-year-young man presented with 1-month history of a progressively enlarging swelling on both sides of the neck [Figure 1a] along with persistent fever. On examination, the neck swellings were soft and nontender. Computed tomographic (CT) scan of the neck showed necrotic conglomerated bilateral cervical, axillary, and mediastinal lymphadenopathy. Fine-needle aspirate (FNA) sent for nucleic acid amplification test was positive for *Mycobacterium tuberculosis* (TB). Human immunodeficiency virus (HIV) serology was also positive with very low CD4 (20 cells/mm^3) count. Antitubercular therapy (ATT) comprising rifampin, isoniazid, pyrazinamide, and ethambutol was initiated along with daily trimethoprim/sulfamethoxazole and weekly azithromycin for prophylaxis for PCP pneumonia and nontubercular mycobacteria, respectively, as per the Indian national guidelines. After 14 days of ATT therapy, he was started with antiretroviral therapy (ART) consisting of tenofovir, lamivudine, and efavirenz.

After 6 weeks of starting ART, the patient developed severe watery diarrhea, high-grade fever with increase in the size of lymph node swelling. There was no bleeding in stools, nor any abdominal pain. Stool was negative for any ova or cyst. Cultures from blood, stool, and urine were normal. Both upper and lower gastrointestinal endoscopy, including biopsy revealed normal study. CT abdomen was also reported normal. There was no response to metronidazole and trimethoprim/sulfamethoxazole. The CD4 count had increased to 200 cells/mm^3. A repeat FNA of the lymph node did not reveal any drug resistance to ATT by line probe assay and culture. The patient's treatment of ATT was reviewed and found to be adequate in terms of dosage of drugs and compliance to therapy. Subsequently, he was started with corticosteroids keeping the possibility of paradoxical immune reconstitution inflammatory syndrome (IRIS) and showed dramatic response within 3 days. With steroid tapering over 2 weeks and continuation of ATT and ART, he is presently at follow-up and doing well at 3 months of therapy [Figure 1b].

IRIS is a clinical entity characterized by an excessive inflammatory response to a preexisting antigen or pathogen and a paradoxical deterioration in clinical status after initiation of ART.[1] IRIS can be present two different types: "paradoxical" worsening of symptoms of a known disease, either at a new body site or at the original body site; and the "unmasking" of an occult opportunistic infection (OI), in which disease that was not clinically apparent prior to ART manifests during ART.[2]

The pathophysiology of IRIS is probably related to the dysregulated immune response to an antigen, leading to exaggerated inflammatory features within a milieu of proinflammatory cytokines as it has been seen more commonly in ART naïve. A shift from T-helper 1 to T-helper 2 response has been suggested.[3] The diagnosis of IRIS traditionally as per French *et al*. require two major or one major with two minor criteria. Major criteria include atypical OI or tumor responding to ART; and a viral RNA fall by 1 $\log_{10}$ copies/mL. Minor criteria include increased specific immune response, increased CD4 count, and spontaneous resolution.

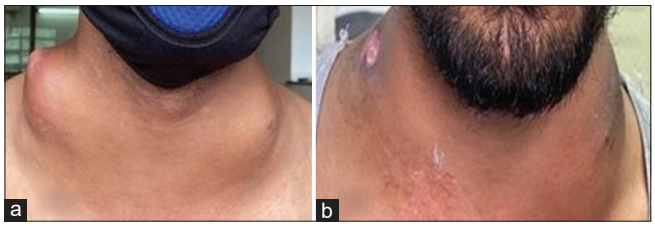

Figure 1: Bilateral enlarged cervical lymphadenopathy (a) with clinical resolution at 3 months of therapy (b)

However, due to the paucity of viral RNA level testing in developing countries like India, the national authorities in India have devised a simple working criterion-new OI in 6 weeks to 6 months of starting ART, associated with increase in CD4 count which our patient fulfilled.[4] There are no consensus guidelines on the management of IRIS, and the key aim is the treatment of the underlying infection, with possible adjunctive therapy to reduce inflammation. Anti-inflammatory agents including nonsteroidal anti-inflammatory drugs and corticosteroids are options, but the data supporting their use are largely limited. There has been only one randomized trial, comparing prednisone (at a daily dose of 1.5 mg/kg for 14 days and then 0.75 mg/kg daily for an additional 14 days) with best supportive care in the management of IRIS in patients with TB showing the benefit of steroids, probably due to suppression effects on proinflammatory cytokines, for example, interleukin (IL)-6, IL-10, tumor necrosis factor-α, interferon-gamma (IFN-Y), and IFN-Y induced protein 10. Discontinuation of ART is generally not advisable given the risk of HIV disease progression and development of antiretroviral drug resistance, with the possibility of IRIS recurrence when it is later recommenced.[5]

IRIS is more common in HIV with initial high viral load and low CD4 levels. However, in view of being a diagnosis of exclusion, low level of awareness, underdiagnosis, varied presentations, varied diagnostic criteria, and underreporting, the prevalence of IRIS is unknown. Various studies have documented the prevalence of IRIS to be around 8%–43%.[2] Paradoxical IRIS is more common than unmasking IRIS. Nearly one-fourth of cases of IRIS in a study from South Africa were due to TB preceded only by mucocutaneous manifestations. Among TB, the most common imaging finding in IRIS due to TB is lymph node enlargement.[6] This often leads to a diagnostic dilemma and often necessitates the evaluation of treatment compliance and ruling out resistant forms of TB before considering a diagnosis of IRIS.

To conclude, IRIS is a heterogeneous condition with varied manifestations. However, treating physicians must maintain a high index of suspicion for its early diagnosis and treatment, especially when there is paradoxical worsening in clinical status of a patient with HIV infection who has poor baseline immune function and shows worsening or new symptoms after starting ART.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Lipman M, Breen R. Immune reconstitution inflammatory syndrome in HIV. Curr Opin Infect Dis 2006;19:20-5.
2. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, *et al.* Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8:516-23.
3. Martin-Blondel G, Mars LT, Liblau RS. Pathogenesis of the immune reconstitution inflammatory syndrome in HIV-infected patients. Curr Opin Infect Dis 2012;25:312-20.
4. Ish P, Nischal N. HIV in ICU. In: Soneja M, Khanna P, editors. Infectious Diseases in the Intensive Care Unit. Singapore: Springer; 2020. [doi: 10.1007/978-981-15-4039-4_17].
5. Meintjes G, Wilkinson RJ, Morroni C, Pepper DJ, Rebe K, Rangaka MX, *et al.* Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 2010;24:2381-90.
6. Valentin L, Dinardo A, Chiao E, Woc-Colburn L, Nachiappan A. Tuberculosis IRIS: A mediastinal problem. F1000Res 2013;2:54.

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