CASE REPORT

Immune Reconstitution Inflammatory Syndrome: A Rare Cause of Pleural Effusion in Rifampicin Resistance Non-HIV TB Lymphadenitis Patient

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Abstract

The initiation of anti-tubercular treatment can trigger a pathological hyper-inflammatory response to viable or dead *Mycobacterium* tuberculosis, known as tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS). Tuberculosis immune reconstitution inflammatory syndrome has been extensively studied in HIV patients and is very rare in non-HIV patients. However, it can occur following corticosteroid withdrawal, discontinuation of anti-TNF therapy, or recovery from neutropenia in non-HIV patients. In non-HIV TB patients, TB-IRIS is particularly rare. The most common manifestation of TB-IRIS in cases of TB lymphadenitis is the development of new lymphadenopathy or the enlargement of pre-existing lymph nodes. Here, we report cases of rifampicin-resistant tubercular lymphadenitis with IRIS presenting with pleural effusion, which completely resolved following steroid therapy.

Keywords: Case report, Immune reconstitution inflammatory syndrome, Rifampicin resistance, TB immune reconstitution inflammatory syndrome, TB lymphadenitis.

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Abbreviations used in this Article

ART = Antiretroviral therapy; ATT = Anti-tuberculosis treatment; TB-IRIS = TB-immune reconstitution inflammatory syndrome.

Introduction

A paradoxical worsening or recurrence of existing tuberculous lesions, or an emergence of new lesions, in patients getting appropriate anti-tuberculosis drugs is commonly referred to as TB-immune reconstitution inflammatory syndrome (TB-IRIS).[1] With an incidence of approximately 18%, IRIS is frequently seen in people with HIV.[2] Uncertainty surrounds the exact frequency of IRIS in non-HIV patients. However, there have been cases reported in non-HIV individuals, particularly following corticosteroid withdrawal, anti-TNF medication cessation, or neutropenia recovery. Although very rare in non-HIV TB patients, IRIS can occur in this population. Paradoxical responses are more frequently observed in patients with extrapulmonary tuberculosis.[3] The central nervous system remains the most common presentation site, affecting 50% of the patients.[3] The risk factors for IRIS are low baseline CD4 count and male gender. In people with peripheral TB lymphadenitis and without HIV, immunological reconstitution inflammatory syndrome may occur in up to one-quarter of cases.[4] The main symptom of TB-IRIS is the development of already-present lymph nodes or the development of new lymphadenopathy.[4] The association between multi drug resistant (MDR) TB and IRIS is not well studied. There are very few reported cases. There is a report of cases of MDR pulmonary tuberculosis with IRIS manifested as central nervous system granuloma.[5] To the best of our knowledge, we are reporting the first rifampicin-resistant tuberculosis lymphadenitis case presented with pleural effusion as IRIS after starting anti-tuberculosis treatment (ATT) in India.

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Case Description

A 20-year-old male student presented to pulmonary medicine out patient department (OPD) with swelling of the supraclavicular lymph node for 2 months. There was no fever, weight loss, or loss of appetite. On examination, his vitals were stable. There was no pallor, icterus, cyanosis, or clubbing. There was the enlargement of the right supraclavicular lymph node of size 2 × 3 cm, firm in consistency, not fixed to the underlying skin or overlying structure. The examination of other systems found no abnormalities, and there was no enlargement of any organs. The patient underwent a fine needle aspiration cytology of the lymph node. The whole array of baseline blood tests revealed insignificant changes; however, the erythrocyte sedimentation rate increased to 50 mm/hour.

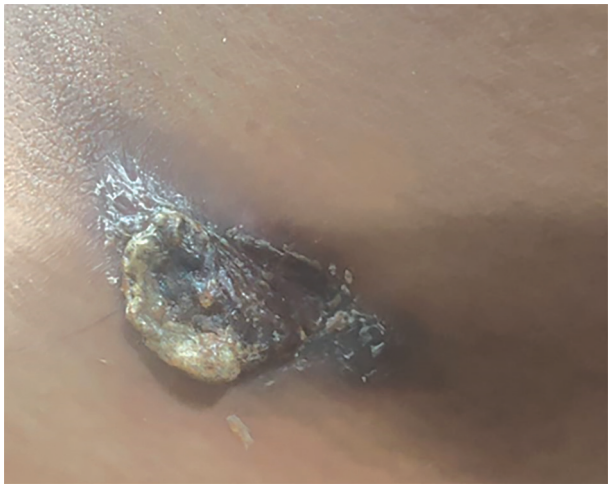

Fig. 1: Supraclavicular lymph node with discharging sinus after 1 month of ATT

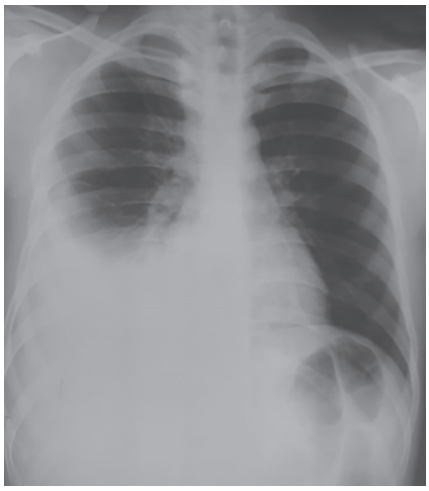

Fig. 2: Chest X-ray showing right moderate effusion

Fine needle aspiration cytology of the lymph node revealed granulomatous lymphadenitis, and the acid fast bacilli (AFB) smear from the lymph node aspirate was negative. Cartridge-based nucleic acid amplification test (CBNAAT) from the lymph node was resistant to rifampicin, and line probe assay (LPA) was negative. His chest X-ray was normal at the initiation of treatment. The patient was ultimately diagnosed with rifampicin-resistant tubercular lymphadenitis and was initiated on a bedaquiline-based, shortened MDR regimen. After four weeks of treatment, he presented to the pulmonary medicine OPD with complaints of right-sided chest pain for 1 week and a dry cough for 1 week. At the time of presentation, his lymph node size was decreased, and there was a tubular ulcer and sinus formation (Fig. 1). Patient complained about the medication. A chest X-ray was taken, showing a right moderate pleural effusion (Fig. 2). Pleural fluid was aspirated and sent for analysis. The analysis revealed no malignant cells, a total cell count of 150 cells per cubic millimeter, with negative lymphocyte findings, and a negative culture result. The ADA level was 23. The culture showed no growth. His CECT thorax was showing moderate pleural effusion with no parenchymal opacity or no thoracic lymphadenopathy. His ultrasonography of the abdomen was normal. The bronchoscopy done on that patient was normal, and BAL CBNAAT and culture were normal. As a chest X-ray was taken before starting ATT, it was normal. So we consider the diagnosis of TB-IRIS. He was diagnosed with a case of IRIS, which leads to pleural effusion. He was started on steroids at 0.5 mg/dL. After 15 days of steroids, there was a resolution of pleural effusion. After 15 days of steroids, there was a partial resolution of the effusion. After 1 month of steroids, there was a complete resolution of pleural effusion (Fig. 3).

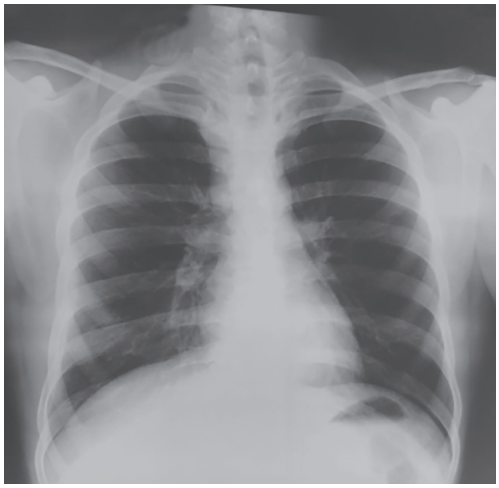

Fig. 3: Chest X-ray after 1 month of steroid treatment

Discussion

The new thing about our cases was that (i) the patient was HIV negative; (ii) there was no worsening of lymph node size as in IRIS; (iii) IRIS manifested as pleural effusion; (iv) and the patient was a rifampicin-resistant TB lymph node case. The beginning of antitubercular treatment could result in TB-IRIS, a pathological hyper-inflammatory response to live or dead *Mycobacterium* tuberculosis. The majority of studies have been conducted on TB-IRIS in HIV patients. IRIS is of two types. When a previously diagnosed tuberculosis infection responds to TB medication at first but worsens after starting antiretroviral therapy (ART), this is known as paradoxical IRIS.[6] Unmasking TB-IRIS is characterized by a scenario in which a subclinical infection stays undiagnosed until the ART-induced immune reconstitution sets off an overly inflammatory disease presentation.[6] It is predicted that approximately 2–23% of HIV-negative patients getting anti-tuberculosis drugs will develop TB-IRIS.[7] In a prospective cohort study, 2% of HIV-negative patients experienced this condition.[4]

The pathogenesis of IRIS is extensively studied in HIV patients. Its pathogenesis remains largely speculative. The immunopathology of TB-IRIS was originally characterized as an overproduction of inflammatory cytokines, in particular IFNγ, TNFα, and IL-6 (hypercytokinemia).[6] Cytokine storm (or hypercytokinemia) is still considered to be the central part of TB-IRIS immunopathology.[6]

The IRIS is the diagnosis of exclusion. Various definitions of diagnostic criteria for IRIS were developed in HIV-infected patients. The criteria for diagnosing IRIS in a non-HIV patient are as follows: (1) paradoxical deterioration of TB-related symptoms and/or radiologic findings at the primary or at new locations during or after anti-TB treatment; (2) initial improvement of TB-related symptoms and/or radiographic findings after adequate anti-TB treatment for a certain

amount of time; (3) absence of conditions that reduce the efficacy of anti-TB drugs, (e.g., poor compliance, drug malabsorption, drug side effects); (4) ruling out other potential causes of clinical deterioration.[1] Numerous diagnostic criteria have been developed to diagnose HIV patients with IRIS. The diagnostic criteria include those proposed by Shelburne et al.[8] A consensual definition for TB-associated IRIS in HIV was developed in 2008 for settings with limited resources.[9] Young people who identify as male, who are anemic, and who have low lymphocyte counts are more prone to get IRIS.[3] According to Worodria et al., TB-IRIS typically develops after a median of 2 weeks following the initiation of treatment.[10] The majority of the patients (70%) with TB-IRIS had extra-pulmonary manifestations.[10] Low hemoglobin and low CD4 count were significant predictors of TB IRIS.[10]

There is a 4.5% documented total mortality rate linked to IRIS.[11] There is no standard treatment guideline for TB-IRIS. Roughly 50% of lymph node TB-IRIS cases resolve on their own.[1] Aspiration is frequently necessary for soft-tissue abscesses or symptomatic pleural effusions. Four to six weeks of systemic corticosteroid therapy improves the result.[1] The standard suggestion is to begin with 1–2 mg/kg of prednisone (or the equivalent) for 1–2 weeks, followed by a progressive lowering of the dose over 4–6 weeks, even though there are no trials, particularly on the base dose of prescribed corticosteroids.[12]

Conclusion

An uncommon occurrence in non-HIV individuals is known as TBIRIS, which is characterized by a decline in clinical function following the initiation of ATT. It can manifest as the appearance of a new infection that was previously masked due to profound immune suppression. It is important to consider the possibility of IRIS when there is clinical worsening after initiating ATT, which can even occur in immunocompetent young adults. Before initiating treatment for IRIS, other potential causes of clinical deterioration should be ruled out. The most typical sign of TB lymphadenitis with IRIS is the growth of pre-existing lymph nodes or the onset of new lymphadenopathy. Additionally, new-onset pleural effusion can occur after starting (ATT) due to TB lymphadenitis.

Limitation of the Study

Thoracoscopy-guided pleural biopsy was not done because the patient did not give consent to the procedure.

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