Case Report

Paradoxical Reaction in Lymph Node Tuberculosis Presented as Shoulder Osteomyelitis

V. P. Lakshmi, B. Abhinandh, Akhilesh Kunoor[1], Thadi Mohan[2], Aadharsa Sugunan[3], Jerry Jose[4]

Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Departments of [1]Respiratory Medicine and [2]Orthopedics, Amrita School of Medicine, Amrita Vishwa Vidyapeetham, Kochi, [3]Lecturer, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, [4]Department of Pulmonology, Little Flower Hospital and Research Centre, Angamaly, Kerala, India

Abstract

Paradoxical reactions (PRs) can be viewed as an abnormal immune response toward the anti-tubercular treatment (ATT). It is characterized by clinical worsening of the patient's symptoms and signs following an initial improvement despite definitive treatment with ATT. Tubercular lymphadenitis is the most common extrapulmonary manifestation seen under PR. Other sites of involvement include the pleura, central nervous system, bones, and muscle. Although some paradoxical events may not require any intervention, studies have shown to have good outcomes using glucocorticoid therapy. This case reports a PR that involves tubercular lymphadenitis and osteomyelitis, which showed marked improvement of patient ailment following a 1-month course of oral steroid.

Keywords: Osteomyelitis, paradoxical reactions, prednisolone, tubercular lymphadenitis

Introduction

Tuberculosis-associated paradoxical reactions (TB-PRs) are described as worsening of the patient's condition following an initial improvement after beginning the treatment with anti-tubercular drugs. This may manifest as deterioration of the preexisting lesions or appearance of new lesions or the worsening of chest radiographs, which follows a definitive treatment.[1,2] PR results from an acute exaggerated restoration of host immunity against live or dead pathogens during treatment. This leads to an uncontrolled inflammatory response which can be misdiagnosed as anti-tubercular treatment (ATT) resistance. PR is commonly seen in HIV-infected patients who are being treated with highly active antiretroviral therapy (HAART) but is rare in HIV-negative patients, although certain studies have reported the incidence of TB-PR between 2% and 23%.[3,4] The exact mechanism behind the development of PR is unknown, however, most cases of PR have been associated with raised inflammatory markers, tuberculin conversion during the treatment course, and disseminated infections.[4,5] We aim to present a case of PR that manifested as tubercular osteomyelitis of left proximal humerus secondary to extrapulmonary tubercular lymphadenitis in an HIV-negative patient and to review literature about incidence, diagnostic criterion of PR, manifestations, and its management.

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.jpp_61_21

Case Report

A 19-year-old nursing student was presented to outpatient department in October 2019 with complaints of pain and swelling of the left shoulder of 2 months duration. She also had an irregular fever for the previous 1 month. She had a background history of lymph node TB and was on ATT for 4 months. She was previously evaluated in a peripheral institution for right supraclavicular swelling. Histopathology of excision biopsy was showing necrotizing granulomatous lymphadenitis in June 2019. She was tolerating ATT well and completed 1 month of treatment. Later, she developed an abscess formation in the right supraclavicular lymph node area. Her CB-NAAT (cartridge-based nucleic acid amplification test)

Address for correspondence: V. P. Lakshmi, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi - 682 041, Kerala, India.
E-mail: lakshmivp606@gmail.com

How to cite this article: Lakshmi VP, Abhinandh B, Kunoor A, Mohan T, Sugunan A, Jose J. Paradoxical reaction in lymph node tuberculosis presented as shoulder osteomyelitis. J Pharmacol Pharmacother 2021;12:140-3.

Received: 27-05-2021 **Revised:** 29-06-2021
Accepted: 04-08-2021 **Web Publication:** 25-11-2021

was diagnostic of *Mycobacterium tuberculosis* and sensitive to rifampicin. She was being treated with isoniazid, rifampicin, pyrazinamide, and ethambutol with 1 month extended intensive phase (a total of 3 months duration). Her regimen was changed to continuous phase - isoniazid, rifampicin, and ethambutol after this period. Despite good treatment compliance, she had worsening pus drainage from the right supraclavicular region. She also developed erythema, pain, and swelling over the left shoulder with restricted abduction. There was no sinus or abscess formation on the left shoulder. Initial X-ray of the left shoulder showed diffuse osteopenia of proximal humerus [Figure 1a]. Subsequent X-rays showed well-defined small lytic lesions in that area. Magnetic resonance image of the left shoulder revealed heterogeneously enhancing altered marrow signal intensity with mottled appearance involving the metadiaphyseal region of humerus, a well-defined peripherally enhancing collection with thick walls and internal septations in the intramuscular plane along teres minor muscle, significant synovial thickening, and enhancement, and moderate to massive joint effusion with extension into the bicipital groove and adjacent bursa. These features were suggestive of osteomyelitis of the left shoulder with shoulder effusion. She was treated with a broad-spectrum antibiotic course with no clinical improvement.

Her chest radiograph was normal. Acid-fast bacilli (AFB) smear and GeneXpert from right supraclavicular abscess sent to the intermediate reference laboratory, were positive and sensitive to rifampicin. Her initial laboratory investigations showed a white cell count of 4.0 K/μL with 13.7% lymphocytes, hemoglobin concentration of 10.9 g/dL, C-reactive protein (CRP) level of 52.38 mg/L, and an erythrocyte sedimentation rate (ESR) of 81 mm/h [Table 1].

AFB culture from pus at 6 weeks was negative. Since she had no evidence of drug resistance, the newly developed shoulder effusion and persisting pus discharge were considered as PR. She was initiated on oral prednisolone 30 mg OD and etoricoxib tablet 60 mg OD after which she started responding well. She showed healing sinus after 5 days and her lymph nodes gradually disappeared. The steroid was tapered over 1 month, and she was continued on ATT. She came for review after 7 months, with no active discharge from the right shoulder. On examination of her left shoulder, she had 3 cm × 3 cm fluctuant cystic swelling over the inner aspect of the proximal arm just above the axilla. There was no local warmth and her range of motion was complete with no deficits. The right supraclavicular region showed healing of the sinus tract from the cervical lymph node biopsy site. She had no active discharges.

On her review 1 year after ATT initiation, she had no complaints of fever, pain, or pus discharge from the right shoulder. An ultrasound study of the neck revealed subcentimetric cervical lymph nodes with no evidence of obvious collection and her chest radiograph was normal. A well-circumscribed lytic lesion was noted in the proximal humerus along with smaller such lesions adjacent to the larger osteolytic lesion in her shoulder radiograph [Figure 1b]. Her inflammatory markers were normal (CRP: 0.46, ESR: 9) and she had no evidence of active TB.

Her ATT was stopped after 1 year of treatment considering her clinical improvement. She was reviewed after 3 months of stopping ATT. The osteolytic lesions were still visible in her left shoulder radiograph but were less clearly demarcated [Figure 1c], which was considered a clinical improvement.

Discussion

The paradoxical and exaggerated response by the immune system against invading pathogens can be termed immune reconstitution inflammatory syndrome (IRIS). TB-associated IRIS (TB-IRIS) which is synonymously known as TB-PR, has been seen commonly in HIV patients who are being treated with HAART.[6] In a retrospective study conducted by an urban teaching hospital, 28% was the observed frequency of TB-IRIS in HIV-infected TB patients.[4] In HIV-negative TB patients particularly in those with extrapulmonary involvement, the frequency of TB-IRIS was shown to be ranging from 2% to 25% according to various studies.[2-6] TB-IRIS presents as transient worsening in patient symptoms during drug therapy and is commonly characterized by development or enlargement of preexisting lesions, lymph node enlargement, worsening chest infiltrates new-onset pleural effusion, or suppuration at different site.[7] It can occur at any time, ranging from a few weeks to months after the ATT initiation and hence it is difficult to differentiate PR

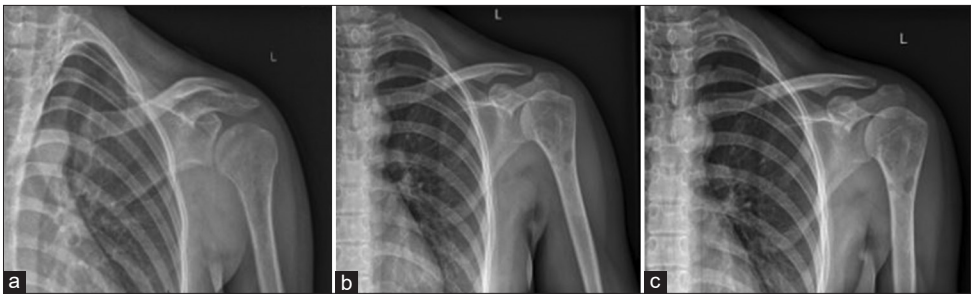

Figure 1: Comparison of shoulder radiographs (a) during initiation of oral steroid therapy, (b) after 8 months postoral steroid therapy, (c) after 1 year postoral steroid therapy

Table 1: Laboratory investigations

Laboratory parameter	Reference range	Baseline	1-month postoral steroid	6 months postoral steroid	8 months post oral steroids
CRP	0.0-1.0 (mg/L)	52.38	2.53	0.16	0.46
WBC	4.0-10.0 (k/μL)	9.98	6.16	6.68	6.96
Lymphocytes	20.0-40.0 (%)	13.7	23.2	27.1	13.2
RBC count	3.8-4.8 (m/μL)	3.34	4.47	4.72	4.41
Hemoglobin	12.0-15.0 (g/dL)	10.9	12.6	13.6	13.0
ESR	8.0-20.0 (mm/h)	81	13	8	9
Albumin	3.5-5.2 (g/dL)	3.9	4.5	-	-

CRP=C-reactive protein, WBC=White blood cell, RBC=Red blood cell, ESR=Erythrocyte sedimentation rate

from drug resistance, disease relapse, and treatment failure.[4] It is indeed necessary to diagnose PR, as a misdiagnosis may further lead to unnecessary escalation of ATT drugs or may increase the treatment duration. The diagnostic criteria for TB-IRIS include (1) paradoxical worsening of preexisting or appearance of new radiological lesions, (2) no evidence of drug resistance, (3) lack of adverse effects, noncompliance, or other factors that may dampen treatment efficacy. The risk factors that serve for the development of TB-IRIS include baseline anemia, lymphopenia, hypoalbuminemia, peripheral lymph node involvement, and a marked change in lymphocyte counts.[2,5,8] TB-IRIS can involve lungs, lymph nodes, brain, pleura, bone, and muscle. In a single-center study that involved HIV-negative patients with TB, 25% of the patients had PR, out of which lymphadenitis was the most common extrapulmonary manifestation.[2] In our case, the patient presented with newly developed shoulder effusion, persistent pus discharge, and recent skeletal involvement, despite good compliance and negative cultures, which was indicative of a PR. Although the pathogenesis of TB-IRIS in HIV-negative patients is unclear, it has been widely linked to immune reconstitution to the dying pathogens during the treatment. Dying mycobacteria releases toxins, tubercular proteins, and cell wall components to which hypersensitive reactions are elicited by the host immune system.[9] Other postulates also support immune reconstitution of T-helper 1 CD4+ driven responses in both HIV-infected and negative patients with TB.[3]

The treatment of TB-IRIS has no definite guidelines, but data from studies states that most cases of paradoxical events resolve by themselves with ATT alone. Nonetheless, evidence from other sources has also suggested drainage or aspiration of soft-tissue abscess and pleural effusion.[3] Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids have also been used to treat many known cases of paradoxical exacerbations, and are known to significantly reduce morbidity of the patients.[1,3] In a randomized placebo-controlled trial performed at a secondary care hospital, a 4-week course of glucocorticoid was shown to reduce the days of hospitalization and therapeutic procedures as well as rapid recovery from symptoms and improved quality of life. The study had no evidence of adverse reactions toward the corticosteroid, although the patients who received steroids experienced minor infections (such as oral candidiasis and herpes simplex).[1] Here, the patient was anemic with a baseline hemoglobin level of 10.9 g/dL. Her white blood cell counts were slightly higher, she had low baseline lymphocytes (13.7%) and marked elevation of CRP (52.38 mg/L), which are common features of PR. She had worsening of her primary lesion and appearance of a new distant lesion (shoulder osteomyelitis) despite definitive treatment led to a suspicion of TB-IRIS. As a previous line probe assay had ruled out drug resistance, she was initiated on steroid therapy and responded well to a 4-week course of oral prednisolone.

Conclusion

The case presented here describes a rare PR in the form of shoulder osteomyelitis along with the deterioration of primary lesion, to which the patient responded well to a short course (4 weeks) of oral steroid and NSAID. Although difficult to diagnose, the few determinants that cause such events, such as the absence of drug resistance, baseline anemia, and lymphopenia, and elevated inflammatory markers do aid in the diagnosis of TB-PR.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. 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.
2. Geri G, Passeron A, Heym B, Arlet JB, Pouchot J, Capron L, *et al.* Paradoxical reactions during treatment of tuberculosis with extrapulmonary manifestations in HIV-negative patients. Infection 2013;41:537-43.
3. Lanzafame M, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. J Clin Tuberc Other Mycobact Dis 2016;3:6-9.

4. Breen RA, Smith CJ, Bettinson H, Dart S, Bannister B, Johnson MA, *et al.* Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004;59:704-7.
5. Cheng SL, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. Int J Tuberc Lung Dis 2007;11:1290-5.
6. Pornsuriyasak P, Suwatanapongched T. Thoracic manifestations of paradoxical immune reconstitution inflammatory syndrome during or after antituberculous therapy in HIV-negative patients. Diagn Interv Radiol 2015;21:134-9.
7. Sarfaraz S, Iftikhar S, Salahuddin N. Frequency, clinical characteristics, risks, and outcomes of paradoxical upgrading reactions during anti-tuberculosis treatment in tuberculous lymphadenitis. Pak J Med Sci 2020;36:S27-32.
8. Kunoor A, Suseela RP, Raj M, Thankappan RC, James PT. Treatment outcomes of patients on non-Revised National Tuberculosis Control Programme (private) anti-tuberculosis regimen from a tertiary-care centre in Kerala, India. Egypt J Chest Dis Tuberc 2019;68:24-7.
9. Kabra MN, Kunapareddy T. Paradoxical upgradation response in non-HIV tuberculosis: Report of two cases. Indian J Med Microbiol 2019;37:450-3.