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IP International Journal of Orthopaedic Rheumatology

Journal homepage: https://www.ijor.org/

Case Report

Disseminated histoplasmosis in a patient with rheumatoid arthritis receiving tofacitinib therapy in India: A case report

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Abstract

Tofacitinib, a Janus kinase (JAK) inhibitor, is increasingly prescribed for autoimmune disorders such as rheumatoid arthritis (RA). By targeting JAK1 and JAK3, it modulates cytokine-mediated immune responses, thereby suppressing lymphocyte activity. Although effective in controlling inflammation, tofacitinib may heighten the risk of opportunistic infections. Histoplasma capsulatum, a thermally dimorphic fungus, causes histoplasmosis, a disease typically rare in India but now more frequently observed, especially among individuals with compromised immunity, such as those with HIV or receiving immunosuppressive therapies. This report describes a rare case of disseminated histoplasmosis in a 58-year-old patient with rheumatoid arthritis receiving tofacitinib. Tofacitinib was promptly discontinued, and the patient was treated with oral itraconazole (200 mg twice daily), leading to complete resolution of the lesion. This case underscores the importance of considering systemic fungal infections in immunosuppressed patients on JAK inhibitors and highlights the effectiveness of early antifungal intervention and modification of immunosuppressive therapy.

Keywords: Histoplasmosis, Tofacitinib, Janus Kinase inhibitor, Rheumatoid arthritis, Immunocompromised patients.

Received: 01-07-2025; **Accepted:** 27-10-2025; **Available Online**: 10-12-2025

1. Introduction

Histoplasma capsulatum is a dimorphic fungus that thrives in soil enriched with bird or bat droppings. Although historically associated with the Ohio and Mississippi River valleys in the United States, its presence has been increasingly documented in parts of India, particularly across the Gangetic plains, including regions such as West Bengal, Uttar Pradesh, Delhi, Rajasthan and Haryana.[1,2] In individuals with intact immune systems, the infection is often mild or subclinical. However, in immunosuppressed patients like those with HIV and patients on immunosuppressive therapies,[1] the organism can disseminate beyond the lungs to involve multiple organs. Dissemination is facilitated by the fungus's intracellular survival in macrophages, which transport it through the reticuloendothelial system.

Clinical manifestations of disseminated histoplasmosis may include persistent fever, weight loss, hepatosplenomegaly, and haematological abnormalities.[3] Risk factors for widespread or severe disease include very young or older age, male sex, Caucasian ethnicity, high-level exposure to the organism, and most significantly, immunosuppression.[4]

JAK inhibitors, including tofacitinib, have become standard therapeutic options for autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Tofacitinib acts by inhibiting the JAK-STAT pathway, a key intracellular signalling mechanism involved in cytokine-mediated inflammation.[5,6] While this downregulation is beneficial for autoimmune disease control, it also impairs host defenses, predisposing patients to a range of infections,

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https://doi.org/10.18231/j.ijor.12110.1763374073

including tuberculosis, herpesviruses, and systemic fungal infections.

Although histoplasmosis linked to JAK inhibitors has rarely been reported, two cases have been described with disseminated disease in patients receiving ruxolitinib.[7,8] Here, we present a rare case of disseminated histoplasmosis in an Indian patient receiving tofacitinib, highlighting the emerging relevance of fungal infections in patients treated with JAK inhibitors, especially in geographic areas with increasing endemicity.

Disseminated histoplasmosis associated with tofacitinib therapy has been rarely documented. Waheed et al. (2016) reported one of the earliest such cases in a rheumatoid arthritis patient on tofacitinib who developed disseminated histoplasmosis involving the lungs and lymphatic system, underscoring the double-edged nature of immunomodulatory therapy, effective disease control at the cost of heightened infection susceptibility.[9] In this context, our case adds to the limited global literature by documenting disseminated histoplasmosis in a rheumatoid arthritis patient on tofacitinib from India, where histoplasmosis is increasingly being recognized as an emerging endemic mycosis. This report emphasizes the need for clinical vigilance, early recognition of atypical cutaneous lesions, and prompt antifungal management in immunosuppressed patients receiving JAK inhibitors, especially in developing regions with evolving fungal epidemiology.

2. Case Presentation

A 58-year-old male from Haryana with a 12-year history of inflammatory arthritis involving large joints presented to our clinic. He had been previously diagnosed with rheumatoid arthritis, supported by positive serological markers including anti-CCP (145 U/mL; reference <20 U/mL), ANA (1:160, speckled pattern), and Ro52 antibodies (index value 2.8; reference <1.0). His disease had been managed with methotrexate (15 mg weekly) and hydroxychloroquine (200 mg daily) for the past three years.

Over time, the patient began experiencing recurrent flares, indicating suboptimal disease control. Following a thorough infectious disease workup, including screening for tuberculosis, hepatitis B, and hepatitis C, all of which returned negative. Tofacitinib was introduced six months prior to presentation to achieve better disease modulation. The patient responded well, achieving clinical remission.

He later reported to the outpatient rheumatology department with one-month history of a painless, progressively enlarging soft tissue swelling over the right thigh, which subsequently ulcerated. There was no associated history of trauma, fever, weight loss, or appetite loss. The patient had been administered a course of amoxicillin-clavulanate and cefepime by a physician with no symptom relief.

On physical examination, he was alert, afebrile, and hemodynamically stable. There was no peripheral lymphadenopathy. Local examination revealed a 3 × 4 cm ulcerated swelling with serous discharge on the anterior aspect of the right mid-thigh. Systemic examination was unremarkable. **Figure 1** shows the clinical photograph of the ulcerated swelling.

Laboratory parameters showed a normal complete blood count and inflammatory markers (C-reactive protein: 5 mg/dL; erythrocyte sedimentation rate: 20 mm/hr). Magnetic resonance imaging (MRI) of the right thigh revealed a lobulated soft tissue lesion located in the subcutaneous plane of the mid-thigh.

Given the unusual presentation and persistence of the lesion, a broad differential diagnosis was considered. Serological testing for tuberculosis, HIV, hepatitis B, and hepatitis C were again negative. A whole-body positron emission tomography-computed tomography (PET-CT) scan was performed, which showed subcentimetric mediastinal and hilar lymph nodes, likely reactive in nature.

The patient was referred to the surgical team for incision and drainage of the lesion. Intraoperatively, a deep ulcer with undermined edges was noted. Tissue was sent for histopathological evaluation.

Figure 1: A 3 × 4 cm ulcerated swelling with serous discharge on the anterior aspect of the right mid-thigh

Histopathology revealed a dense inflammatory infiltrate in the lower dermis and subcutis, composed predominantly of foamy histiocytes, mixed inflammatory cells, neutrophilic microabscesses, and areas of granulation tissue. Numerous small, uniform fungal yeast forms, consistent with Histoplasma capsulatum, were identified within histiocytes, surrounded by clear halos suggestive of pseudocapsules. Fungal stains confirmed the diagnosis. Urine antigen testing for Histoplasma was negative. **Figure 2** presents the histopathological slides of the lesion.

Tofacitinib was promptly discontinued, and the patient was initiated on oral itraconazole 200 mg twice daily by the infectious diseases team. Over subsequent weeks, he demonstrated marked clinical improvement, with complete healing of the thigh ulcer. He continues to do well on methotrexate and hydroxychloroquine.

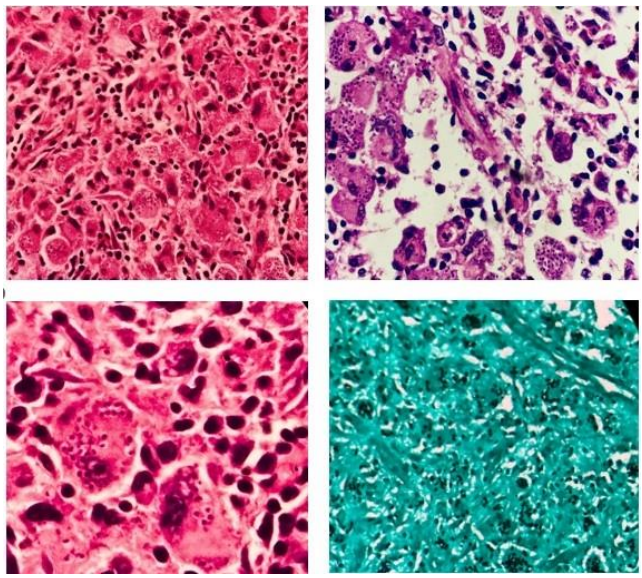

Figure 2: Microscopic examination of soft tissue of right thigh shows diffuse and dense inflammatory infiltrate composed of sheets of foamy histiocytes, mixed inflammatory cells, neutrophilic mircoabscesses and some granulation tissue. Numerous small, uniform fungal yeast forms, compatible with histoplasmosis, surrounded by clear spaces (pseudo capsule) are noted within the histiocytes (confirmed by fungal stains).

3. Discussion

Although histoplasmosis has not been classically endemic to India, a rising number of cases have been reported in recent years, particularly in the Gangetic plains and parts of central India.[2] This increase may reflect not only evolving epidemiology but also improved diagnostic tools and heightened clinical awareness. Infection typically occurs through the inhalation of fungal microconidia present in contaminated soil, often associated with bird or bat droppings. Once inhaled, the spores convert to the yeast form in the lungs and are phagocytosed by alveolar macrophages. These infected macrophages facilitate hematogenous dissemination, especially in individuals with compromised immune systems.[10]

In immunocompetent hosts, histoplasmosis is often subclinical or limited to pulmonary involvement. However, in immunosuppressed individuals, such as those receiving JAK inhibitors, dissemination can occur, leading to involvement of extrapulmonary sites. In this case, the patient presented with an isolated cutaneous lesion, which later revealed a fungal infection.

Tofacitinib suppresses immune responses by interfering with the JAK-STAT signalling pathway, thereby impairing cytokine activity essential for intracellular pathogen clearance. While tuberculosis remains the most frequently encountered opportunistic infection in Indian patients on tofacitinib, the risk of invasive fungal infections such as histoplasmosis must also be considered in the differential diagnosis, especially when patients present with atypical lesions or systemic signs without a clear aetiology.

Diagnosis of disseminated histoplasmosis requires a high index of suspicion and the integration of clinical, radiological, and pathological findings. In this patient, definitive diagnosis was made via histopathological examination of the skin lesion, which revealed numerous intracellular yeast forms characteristic of Histoplasma capsulatum. These organisms were seen within clusters of foamy histiocytes, accompanied by microabscesses and granulomatous inflammation.[11]

Effective management of disseminated histoplasmosis involves prompt antifungal therapy along with modification of immunosuppressive treatment. Multidisciplinary approach, engaging rheumatologists, infectious disease specialists, surgeons, and pathologists, is often necessary. While liposomal amphotericin B is typically used in severe or acute cases, oral itraconazole remains the mainstay for step-down and maintenance therapy.[12] In this case, early diagnosis, timely withdrawal of tofacitinib and the initiation of oral antifungals treatment resulted in favourable clinical resolution.

4. Conclusion

This case underscores the need for heightened clinical vigilance regarding opportunistic infections such as disseminated histoplasmosis in patients receiving JAK inhibitors like tofacitinib. As the use of these agents becomes more widespread in India, particularly in areas with emerging endemicity, physicians should be alert to atypical presentations. Prompt recognition and initiation of appropriate antifungal therapy are essential to prevent complications and ensure optimal patient outcomes.

5. Source of Funding

None.

6. Conflict of Interest

None.

7. Acknowledgement

None.

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Cite this article: Rawat S, Chaturvedi VP, Malik VK, Gogia A, Rao S, Shanmugam H. Disseminated histoplasmosis in a patient with rheumatoid arthritis receiving tofacitinib therapy in India: A case report. *IP Int J Orthop Rheumatol*. 2025;11(2):102-105.