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Case Report

An atypical mycobacterial infection while on Janus kinase inhibitor therapy

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Abstract

Janus kinase inhibitors are immunomodulatory drugs increasingly used to treat a broad range of inflammatory dermatologic conditions. Although effective, they carry a risk of serious adverse effects, including opportunistic infections. We present a patient who developed an atypical mycobacterial infection while on the Janus kinase 1 and Janus kinase 3 inhibitors, tofacitinib.

A 76-year-old man was started on tofacitinib for a severe ulcerative colitis flare. Six weeks after starting therapy, he developed an erythematous papule on his right forearm that progressed into an ulcerating nodule. Initial biopsies suggested subcutaneous pyoderma gangrenosum. However, after failing multiple treatments, repeat biopsies and cultures were performed. An acid-fast bacilli stain was positive and specialized tissue cultures identified Mycobacterium chelonae. The lesions resolved after 6 weeks of clarithromycin therapy.

This case highlights the immunosuppressive effects of Janus kinase inhibitors, which can lead to atypical infections including nontuberculous mycobacteria. Additionally, this case highlights the diagnostic challenges associated with these infections, which often require multiple biopsies and specialized microbiological techniques to diagnose.

As the use of Janus kinase inhibitors expands, clinicians must maintain a high suspicion for atypical infections, particularly in patients with unusual dermatologic symptoms. Prompt diagnosis and intervention are essential to prevent complications.

Introduction

Janus kinase (JAK) inhibitors are a class of immunomodulatory drugs used to treat a wide variety of inflammatory diseases. The Janus kinase enzymes, JAK1, JAK2, JAK3, and tyrosine kinase 2, are a class of intracellular tyrosine kinases that act as signal transducers responsible for the expression of various proinflammatory cytokines.[1] Tofacitinib is an oral JAK inhibitor, preferentially inhibiting JAK1 and JAK3, approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis (UC), and polyarticular juvenile arthritis in patients who failed or were intolerant of tumor necrosis factor blockers. Patients taking JAK inhibitors have an increased risk of serious bacterial, fungal, and viral infections.[1,2] Other adverse effects of tofacitinib include increased risk of malignancy, thrombosis, and major adverse cardiovascular events in patients with at least one cardiovascular risk factor.[3]

As JAK inhibitors continue to gain approval for additional dermatologic conditions, including recent approvals for atopic dermatitis and alopecia areata, it is crucial for dermatologists to recognize and manage potential adverse effects.[2,4] Herein, we present a patient who developed an atypical infection and ulcerative nodules while on tofacitinib.

Case Synopsis

A 76-year-old man with a past medical history significant for bladder cancer (in remission), UC, hypertension, hyperlipidemia, benign prostatic hyperplasia, and psoriasis presented to an outside clinic in August of 2020 for treatment of a severe UC flare. Previous UC flares had been successfully managed with mesalamine and his psoriasis was well controlled by the use of topical corticosteroids. The patient was started on tofacitinib XR for treatment of his UC flare. However, approximately 6 weeks later,

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Figure 1. *Patient on initial presentation to our clinic, showing grouped, ulcerating, fluctuant nodules tracking up the right extensor forearm in a sporotrichoid pattern.*

the patient developed an erythematous welt localized to his right forearm after pressure-washing his driveway. He did not recall trauma. The nodule progressively spread up his arm, became fluctuant, and ulcerated over the next few weeks.

In October 2020, the patient underwent two sets of skin biopsies for hematoxylin and eosin (H&E) and tissue cultures. Histology showed perivascular and granulomatous dermatitis with neutrophilic infiltrate. Tissue cultures and polymerase chain reaction were negative for bacteria, fungus, and atypical mycobacteria. Given the prominent neutrophils on H&E, negative infectious workup, and concomitant UC, he was given a working diagnosis of subcutaneous pyoderma gangrenosum. Treatment with oral corticosteroids and intralesional triamcinolone injections resulted in minimal improvement.

In January 2021, additional punch biopsies were obtained for H&E and microbiology when more fluctuant lesions developed. Histology showed acute and chronic granulomatous inflammation, and acid-fast bacteria (AFB) stain was positive for few polymorphous bacilli. The patient was treated with courses of minocycline and amoxicillin/clavulanate with minimal improvement.

In June 2021, the patient presented to our clinic seeking a second opinion as he continued to have ulcerating, fluctuant nodules tracking up the right extensor forearm in a sporotrichoid pattern **(Figure 1)**.

Additional punch biopsies were repeated for H&E and microbiology. Histology showed suppurative granulomatous inflammation with overlying pseudoepitheliomatous hyperplasia. Notably, no organisms could be seen on routine staining (ie, periodic acid-Schiff, Grocott methenamine silver stain, Fite acid-fast stain, AFB, and negative AFB) **(Figure 2)**.

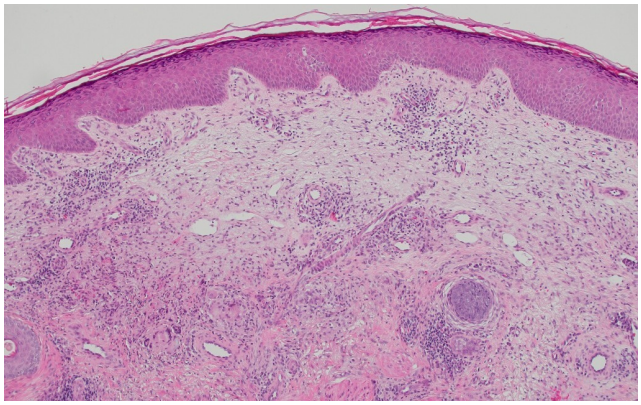


Figure 2. *Hematoxylin and eosin at 10× magnification showing suppurative granulomatous inflammation with overlying pseudoepitheliomatous hyperplasia.*



Figure 3. *Resolution of ulcerative nodules with residual postinflammatory hyperpigmentation after treatment with clarithromycin.*

Given the previous positive AFB stain, tissue culture was sent to a specialized lab for atypical mycobacterial culture and the patient was started on itraconazole 100mg daily and clarithromycin 500mg twice per day. Four weeks later, tissue culture showed preliminary growth of AFB. Speciation later revealed Mycobacterium chelonae, resistant to minocycline but susceptible to clarithromycin. After 6 weeks of clarithromycin therapy, the lesions fully resolved **(Figure 3)**.

Case Discussion

Janus kinase inhibitors are currently under investigation for a variety of autoimmune and inflammatory diseases, including many dermatologic conditions.[1] These drugs carry several adverse effects including serious opportunistic infections.[1,2] As demonstrated in this case, atypical mycobacterial infections may require several biopsies and an experienced microbiology lab to identify the culprit pathogen. Prior literature suggests only 30% of Mycobacterium chelonae samples are positive on a single AFB smear. Routine gram stains and cultures are not sensitive, as detection often requires culture media such as Lowenstein-Jensen and lower temperatures between 28-30° C.[5] A review of the literature revealed one case report of disseminated cutaneous Mycobacterium chelonae infection during treatment with tofacitinib for seronegative rheumatoid arthritis. The lesions resolved after treatment with tobramycin and azithromycin.[6]

Atypical infections, such as those caused by Mycobacterium chelonae, Nocardia, Aspergillus, Cryptococcus, and Sporothrix schenckii, can clinically resemble pyoderma gangrenosum.[5-7] These infections frequently present as chronic, ulcerative cutaneous nodules and plaques that are often initially misdiagnosed owing to overlapping clinical features and their relative rarity. In this case, the standard treatment for pyoderma gangrenosum, including the use of systemic and intralesional corticosteroids, resulted in minimal improvement in the patient's presentation. This lack of response underscores the need for vigilance in therapy-refractory cases, in which atypical infections should remain high in the differential diagnosis. In such scenarios where typical treatment fails, it is essential to perform repeat biopsies and cultures, alongside specialized tests such as acid-fast stains and mycobacterial cultures, to ensure accurate diagnosis and guide appropriate treatment.

The JAK enzymes are a class of intracellular tyrosine kinases responsible for the expression of various proinflammatory cytokines.[1] JAK3 is primarily expressed in hematopoietic and immune cells, whereas other JAK pathways are ubiquitously expressed.[4] JAK3 is the only JAK protein that associates with a single receptor, exclusive to cytokines critical for the development and function of T and B cells.[4,8] Mutations in JAK3 can present as severe combined immunodeficiency syndrome, underlying its role in immune function.[1] Although tofacitinib was initially thought to be a specific JAK3 inhibitor, it was found to have additional activity against JAK1 and, to a lesser extent, JAK2.[9] Given that JAK2 plays a critical role in myelopoiesis and erythropoiesis and JAK3 is essential for lymphocyte proliferation, recent studies have theorized more selective JAK1 inhibition may offer similar clinical efficacy with an improved safety profile owing to less activity against JAK2 and JAK3.[4] However, cytokine receptors often use a combination of JAKs for signal transduction and randomized control trials have indicated considerable overlap in the safety profile of JAK inhibitors, regardless of selectivity.[1,10] There is no certainty that more selective JAK1 medications would not predispose to atypical infections, as seen in this case.

In January 2022, the selective JAK1 inhibitors upadacitinib and abrocitinib became the first oral immunomodulatory agents approved for the treatment of moderate to severe atopic dermatitis in the United States. In phase III trials of abrocitinib, the most common treatment-emergent adverse events were headache, nausea, diarrhea, upper respiratory infection, acne, and atopic dermatitis. Serious adverse events included a few cases of pneumonia, herpangina, staphylococcal infection, herpes zoster, and eczema herpeticum.[2] The most common treatment-emergent adverse effects reported in phase III trials for upadacitinib included acne, upper respiratory infection, and worsening atopic dermatitis with reported opportunistic infections including eczema herpeticum and herpes zoster.[11] No atypical mycobacterial infections were reported. In June 2022, the JAK1 and JAK2 inhibitor baricitinib became the latest oral JAK inhibitor approved for a dermatologic condition-severe alopecia areata. The additional activity of baricitinib against JAK2-dependent cytokines such as granulocyte colony-stimulating factor and granulocyte-macrophage stimulating factor may increase the risk of infection and adverse events even more so when compared to the selective JAK1 inhibitors.[4]

Conclusion

JAK inhibitors show promise in treating many inflammatory and autoimmune dermatologic conditions, with evidence suggesting they could be effective for psoriasis, dermatomyositis, hidradenitis suppurativa, lichen planus, and vitiligo.[1] This case report illustrates the consequences of JAK-related immunosuppression and the challenges in diagnosing atypical mycobacterial skin infections. As these agents become more widely available and prescribed, dermatologists should continue to be suspicious of atypical infections in patients taking immunomodulatory agents who present with new cutaneous nodules.

Potential conflicts of interest

The authors declare no conflicts of interest.

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