Disseminated nocardiosis in a patient on infliximab and methylprednisolone for treatment-resistant sweet's syndrome

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ABSTRACT

A 62-year-old white man with a 10-year history of treatment-refractory Sweet's syndrome was admitted to the hospital with the onset of purpuric lesions. Methylprednisolone and infliximab were administered. Our patient developed disseminated *Nocardia* infection and eventually succumbed. Opportunistic infections such as *Nocardia* have been associated with infliximab and other tumour necrosis factor (TNF)-α inhibitors. The astute clinician should be aware of the risk of rare opportunistic infections, particularly in patients on TNF-α inhibitors and systemic corticosteroids.

Key words: Infliximab, nocardiosis, Sweet's syndrome

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INTRODUCTION

The risk of opportunistic infections in patients on TNF-α inhibitors has become well recognized. This risk must also be considered for patients who are using these medications for off-label inflammatory skin conditions. We present the first patient with treatment-refractory Sweet's syndrome who developed disseminated *Nocardia brasilienses* whilst on methylprednisolone and infliximab.

CASE REPORT

A 62-year-old white male with a 10-year history of treatment-refractory Sweet's syndrome was admitted to the hospital with purpuric skin lesions. The patient had myelodysplastic disease that was under treatment with intravenous immunoglobulin (IVIg) infusions, and also diabetes mellitus, peripheral neuropathy, chronic corticosteroid-induced adrenal suppression. As Sweet's syndrome proved refractory to dapsone, methotrexate, etanercept, lenalidomide, rituximab, cyclosporine, mycophenolate mofetil, and cyclophosphamide, methylprednisolone and infliximab infusions were administered. After the second infusion of infliximab, he presented with new purpuric, painful lesions, and subjective fever. On examination, a 6 cm indurated erythematous and purpuric plaque with overlying pustules was noted on the left flank of abdomen, with similar smaller plaques located distally over both lower extremities [Figure 1]. Wound culture revealed *Nocardia brasiliensis*, and infliximab was discontinued. Histopathologic examination showed branching, filamentous organisms consistent with *Nocardia* [Figure 2]. Subsequently, the patient developed pulmonary involvement and was diagnosed with disseminated *Nocardia* infection. During the course of his prolonged hospitalization, trimethoprim–sulfamethoxazole (TMP-SMX), imipenem, minocycline, and amikacin were administered for *Nocardia* infection. Seven months later, after mistakenly receiving infliximab during a scheduled IVIg infusion, the patient experienced a recurrence of *Nocardia* infection with both cutaneous and systemic involvement. The patient was hospitalized for over 5 months in three separate hospitals and was transferred to our care with widely disseminated *Nocardia*. Multiple antibiotics were administered during his treatment, but the patient eventually succumbed to respiratory failure.

DISCUSSION

As more patients are being treated with immunosuppressive medications such as TNF-α

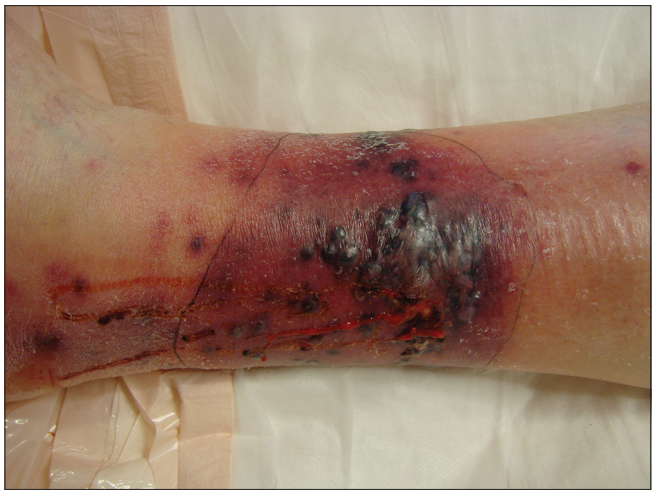

Figure 1: Indurated, erythematous, and purpuric plaque on the distal lower extremity

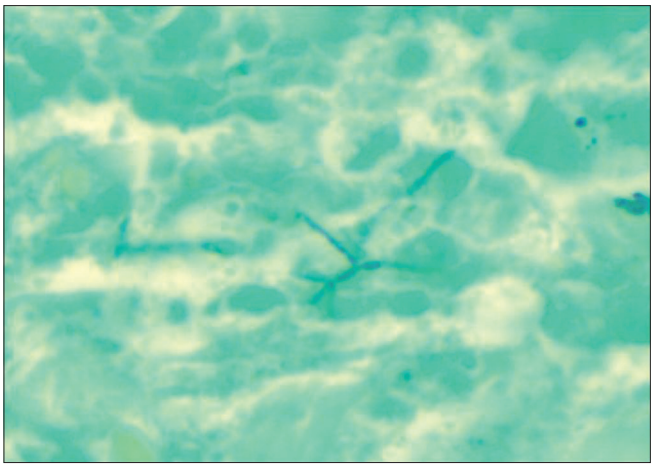

Figure 2: Branching, filamentous organism on Gomori methenamine silver stain consistent with Nocardia, ×40

inhibitors, the rates of infectious complications, especially with atypical pathogens, are increasing. In the literature, most cases of TNF-α inhibitor-related *Nocardia* infections have been reported in patients with psoriasis, rheumatoid arthritis, or inflammatory bowel disease.[1] The risk of opportunistic infections such as *Nocardia* is well recognized in these patients. However, patients being treated with TNF-α inhibitors for off-label inflammatory skin disorders are also at risk. To our knowledge, this case represents the only *Nocardia* infection reported in a patient being treated with a TNF-α inhibitor for Sweet's syndrome.

Nocardia is a ubiquitous, opportunistic gram-positive filamentous bacteria.[2] It causes cutaneous or disseminated disease most commonly in immunosuppressed patients. *Nocardia asteroides* causes most cases of disseminated nocardiosis with skin involvement; however, most cutaneous nocardiosis is caused by *N. brasiliensis*.[3] Clinically, cutaneous nocardiosis may present as nodules, pustules, ulcerative lesions, bullae, or abscesses.[3] Disseminated infection can occur rarely from primary cutaneous infection but more commonly causes secondary skin involvement.[2,3] Mortality rate for patients with central nervous system or disseminated nocardiosis has been estimated to be as high as 50%.[1]

Culture is the gold-standard for diagnosis of *Nocardia*, but it may also be identified on histologic evaluation as characteristic filamentous organisms.[4,5] Firstline treatment includes TMP-SMX for 6–12 months. Other antimicrobial agents that have been used successfully alone or in combination with TMP-SMX include amikacin, imipenem, minocycline, tetracycline, dapsone, streptomycin, linezolid, cycloserine, amoxicillin–clavulanate, macrolides, and fluoroquinolones.[3,6]

Several TNF-α inhibitors, including infliximab, have been reported to be associated with nontuberculosis opportunistic infections, such as *Nocardia*.[4,6,7] It is hypothesized that infliximab's high peak drug levels, high-affinity TNF-α binding, as well as macrophage and T-cell death lead to more significant immunosuppression when compared with other TNF-α inhibitors.[6] A French RATIO study demonstrated higher rates of opportunistic infection in patients on monoclonal-type TNF-α inhibitors, such as infliximab, versus the soluble-type TNF inhibitor, etanercept.[7] This study also found that one-third of these opportunistic infections were caused by bacterial pathogens, such as *Nocardia*.[7] Infliximab binds both soluble and transmembrane TNF-α, thereby inducing apoptosis of macrophages and T cells, which are essential for cell-mediated immunity. This impairment of cell-mediated immunity is implicated in the susceptibility to granulomatous infections, such as nocardiosis.

In all patients on TNF-α inhibitors, including patients being treated for inflammatory skin disorders, such as Sweet's syndrome, the slow-growing types of bacteria should be considered in the differential diagnosis when presenting with signs of cutaneous or systemic infection. Cultures must be maintained for at least 2–3 weeks to detect the presence of such bacteria.[3,6] It is important for dermatologists to adequately inform patients on TNF-α inhibitors about the risk of opportunistic infections and to maintain a higher index of suspicion while culturing such patients.

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