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Disseminated Nocardiosis Associated with Treatment with Infliximab in a Patient with Ulcerative Colitis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 57
Final Diagnosis: Disseminated nocardiosis
Symptoms: Chills • cough • fever • shortness of breath
Medication: Infliximab
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease

Background: Opportunistic infections may occur when patients with inflammatory bowel disease (IBD) are treated with tumor necrosis factor (TNF)-alpha inhibitors. With the increasing use of new immunosuppressant drugs, the incidence of opportunistic or atypical infections is also increasing, including with *Nocardia* spp. A high level of awareness of atypical infections is warranted in immunosuppressed patients.

Case Report: A 57-year-old female African American, with a past medical history of ulcerative colitis (UC) and arthritis, was treated with infliximab and prednisone. She presented to the emergency department with acute onset of chest pain, shortness of breath, and a two-week history of a productive cough. Examination showed hypoxia, tachypnea, decreased and coarse bilateral breath sounds, and fluctuant, tender, erythematous masses on her trunk and groin. Laboratory investigations showed a leukocytosis with a left shift. She was initially treated for presumed community-acquired pneumonia (CAP). However, blood cultures grew *Nocardia farcinica* and treatment with trimethoprim-sulfamethoxazole (TMP-SMX) was begun, which was complicated by severe symptomatic hyponatremia. Following recovery from infection and resolution of the hyponatremia, the patient was discharged to a senior care facility, but with continued treatment with TMP-SMX.

Conclusions: To our knowledge, this is the first case of disseminated nocardiosis associated with infliximab treatment in a patient with ulcerative colitis. As with other forms of immunosuppressive therapy, patients who are treated with infliximab should be followed closely due to the increased risk of atypical infections. When initiating antibiotic therapy, careful monitoring of possible side effects should be done.

MeSH Keywords: Colitis, Ulcerative • Hyponatremia • Immunosuppression • Immunosuppressive Agents • Nocardia Infections • Trimethoprim-Sulfamethoxazole Combination

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/906391

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Background

Nocardiosis is a disease caused by a Gram-positive, partially acid-fast, methenamine silver-positive, aerobic actinomycetes that can cause pulmonary, skin, or disseminated manifestations in immunosuppressed patients, with the most common organisms being *Nocardia asteroides* and *Nocardia brasiliensis* [1]. Nocardiosis has been typically described in immunosuppressed patients, including those with human immunodeficiency virus (HIV) infection, organ transplant recipients, and patients on chronic steroid therapy; infections may occur when patients with inflammatory bowel disease (IBD) are treated with immunosuppressive therapy, including tumor necrosis factor (TNF)-alpha inhibitors such as infliximab [2].

TNF is a pro-inflammatory cytokine secreted by macrophages and by activated T cells, which is where TNF-alpha inhibitors exert their mechanism of action. Infliximab is a humanized monoclonal antibody that is comprised of a human immunoglobulin G constant region that binds to TNF [3]. TNF-alpha inhibitors have become more commonplace in the medical treatment of moderate-to-severe ulcerative colitis (UC) (Figure 1). The use of TNF-alpha inhibitors, such as infliximab, reduces the activity of the disease, induces remission, mucosal healing, and has a corticosteroid-sparing effect [4,5]. Patients who are treated with TNF-alpha inhibitors are at risk for reactivation of *Mycobacterium tuberculosis* (TB), infection with other Mycobacteria, infection with atypical fungal organism such as *Pneumocystis jirovecii (carinii)*, Candida, and Aspergillus, as well as various parasitic and viral pathogens including Leishmania, Toxoplasma, herpes simplex virus (HSV), and Epstein-Barr virus (EBV) infection [6].

Case Report

A 57-year-old female African American had a past medical history of moderate ulcerative colitis (UC), which was in remission, and had been diagnosed 11 years previously, was treated with infliximab at 5mg/kg every eight weeks for fourteen years, due to a failed clinical response to sulfasalazine therapy, and oral prednisone 10 mg daily. She presented to the emergency department complaining of sudden onset of chest pain, concomitant shortness of breath, and a two-week history of a productive cough.

On examination, she had an oxygen saturation of 88% on room air, a temperature of 37°C, and a respiratory rate of 24 breaths per minute. On pulmonary auscultation, there were bilateral diminished breath sounds with superimposed crackles. Multiple abscesses were noted on examination of the skin of her chest, back, and groin area (Figure 2). Initial laboratory tests showed a white blood cell (WBC) count of 31,980×10^9/L. Chest computed tomography (CT) and chest X-ray showed consolidation of the upper lobes, and a right-sided pleural effusion (Figures 3, 4).

The patient was admitted to hospital with a presumptive diagnosis of community-acquired pneumonia (CAP) and multiple skin abscesses, and she was treated empirically with levofloxacin and vancomycin. Common pathogens causing CAP were considered to be most likely causes, including *Streptococcus pneumoniae* and *Staphylococcus aureus*, but fungal causes, including Coccidioidomycosis and Aspergillosis, were considered in the differential diagnosis, as the patient lived in the southwestern USA. The skin lesions were incised and drained, and blood, sputum, and wound cultures were examined using Gram's staining and other microbial histochemical stains. *Nocardia farcinica* (Figure 5) sensitive to trimethoprim-sulfamethoxazole (TMP-SMX) was identified only in blood cultures and treatment with intravenous (IV) TMP-SMX commenced at 500 mg every 8 hours.

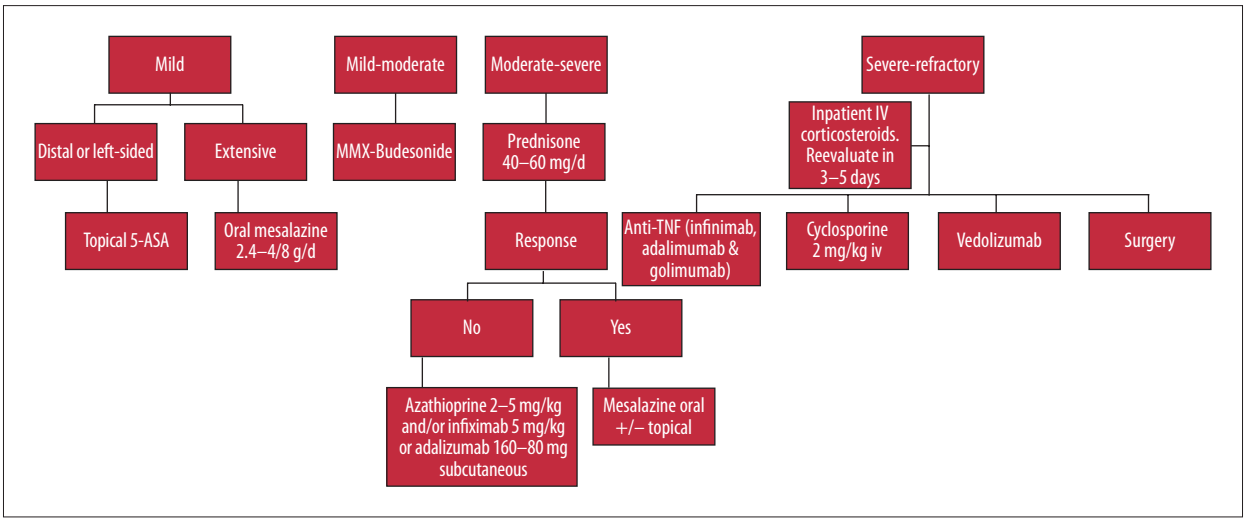

Figure 1. Treatment algorithm for ulcerative colitis 5-ASA – 5-aminosalicylates; MMX – multimatrix.

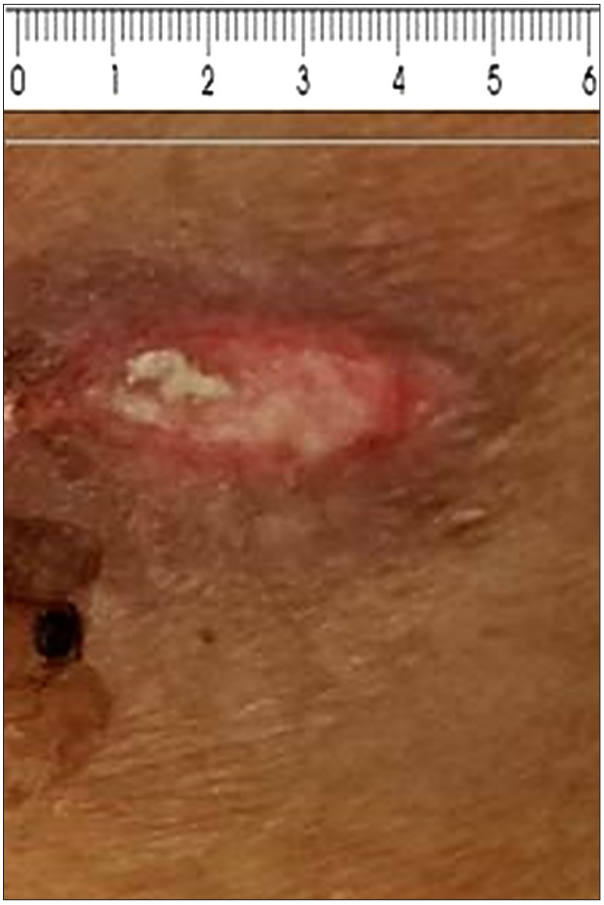

Figure 2. Skin abscess in a patient with disseminated nocardiosis.

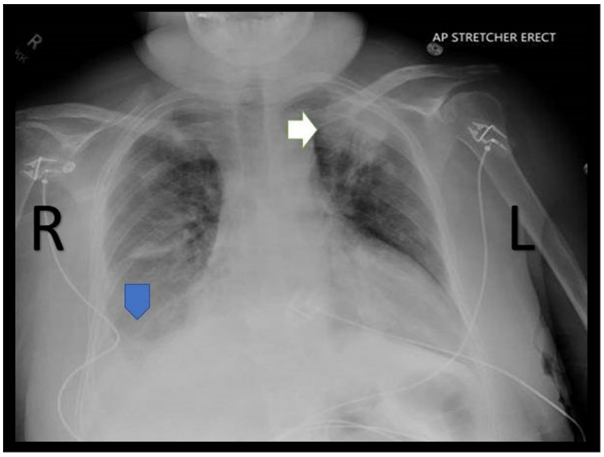

Figure 3. Chest X-ray in a patient with disseminated nocardiosis. The chest X-ray shows right lobe consolidation (arrow) and right-sided pleural effusion (arrow head).

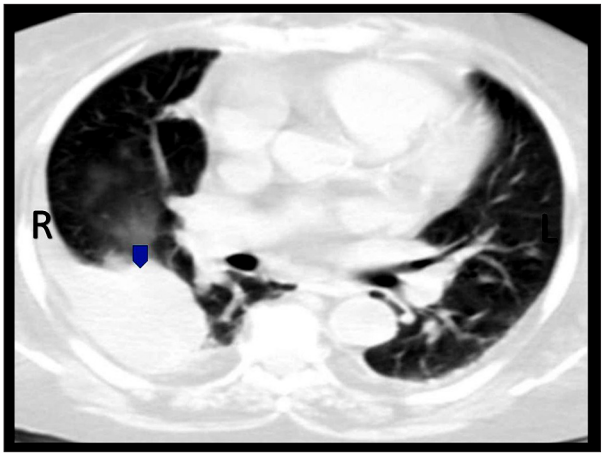

Figure 4. Computed tomography (CT) imaging of the chest in a patient with disseminated nocardiosis. The computed tomography (CT) image of the chest shows a right-sided pleural effusion (arrowhead).

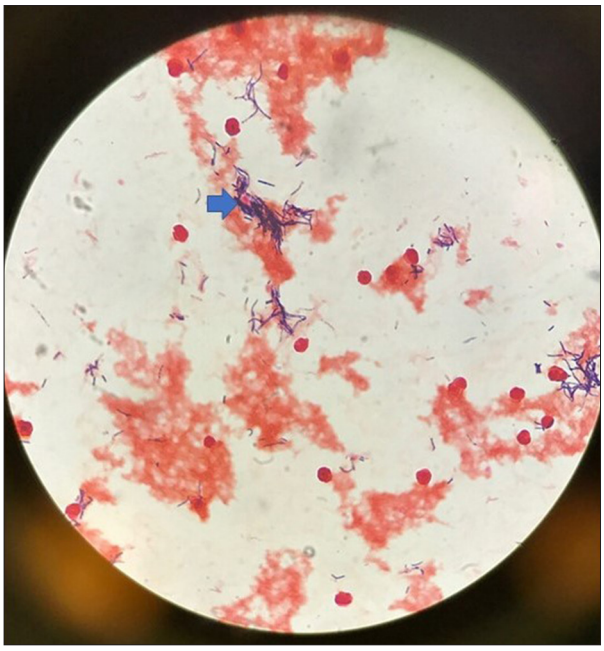

Figure 5. Photomicrograph of the light microscopic appearance of a Gram's stained blood culture sample in a patient with disseminated nocardiosis. Gram's stain from the blood culture sample shows *Nocardia farcinica* (arrow), which are Gram-positive, rod-shaped bacteria.

The patient's clinical course in the hospital was complicated by tonic-clonic seizures due to hyponatremia that was exacerbated by TMP-SMX treatment. The patient developed acute hypoxic respiratory failure due to pulmonary edema, requiring endotracheal intubation, and mechanical ventilation. When her respiratory status had improved, she was transferred to the medical unit still on IV antibiotic therapy.

When the patient was clinically stable, she was discharged to a senior care facility and was treated with oral TMP-SMX 500 mg every 8 hours, with the recommendation to maintain lifelong treatment with TMP-SMX, with the measurement of serial sulfonamide

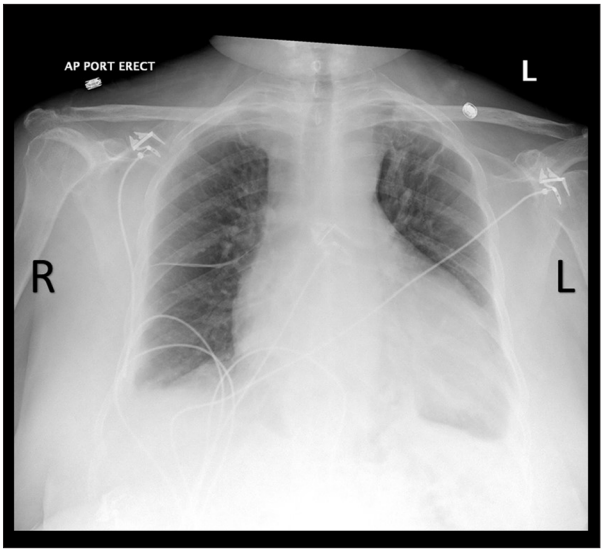

Figure 6. Chest X-ray following treatment with trimethoprim-sulfamethoxazole (TMP-SMX).

levels, and with close follow-up by an infectious disease specialist. The patient was switched to vedolizumab for maintenance therapy of her UC and associated arthritis, as the patient had refused surgical treatment options of her UC. Currently, the patient remains asymptomatic with a chest X-ray (Figure 6) at three months showing improvement from her initial presentation.

Discussion

A rare case has been presented of disseminated *Nocardia farcinica* detected in the blood cultures of a patient with ulcerative colitis (UC) and associated arthritis, treated with infliximab and steroids, whose infection was successfully treated with trimethoprim-sulfamethoxazole (TMP-SMX). To our knowledge, this is the first case report of a patient with UC treated with infliximab who developed disseminated nocardiosis [2].

The diagnosis of *Nocardia* spp. infection can be made by on positive microbial cultures but histological and histochemical identification of the pathogen can be used. In this case, the source of infection could have been either the lung or the skin, as she presented with pulmonary symptoms and skin lesions. However, only the blood cultures were positive for *Nocardia farcinica*. Following first-line antimicrobial treatment with TMP-SMX, the patient's pneumonia and skin abscesses resolved [7].

On treatment with high-dose TMP-SMX, the patient developed hyponatremia, a recognized complication, caused by blocking of the sodium channels in the distal nephron [8]. It has been reported that non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy may be treated with other antibiotics, including amikacin and ciprofloxacin for patients with sulfa allergies or *Nocardia spp* infections that are resistant to TMP-SMX, but fortunately, resistance to TMP-SMX can be as low as 0.5% [9].

Infliximab may have a greater immunosuppressive effect when compared with other TNF-alpha inhibitors, due to its high TNF-alpha binding capacity, and studies have shown that monoclonal antibody TNF inhibitors (infliximab, adalimumab) are associated with an increased risk of opportunistic infections when compared with other forms of TNF-alpha inhibitors [10,11]. In this case, the patient was also receiving steroids as part of her treatment, which can potentially increase the risk of infections by atypical organisms, therefore a high suspicion for infection with *Nocardia* spp. is warranted when assessing patient receiving this form of immunosuppressive therapy [12].

TNF-alpha is an important inflammatory mediator in the formation of granulomas and is involved in the immune response against infection from *Nocardia* spp. infection, which means that the increased use of TNF-alpha inhibitors favors an increased incidence of reported cases nocardiosis [12]. Nocardia is a microorganism that is usually found in soil and is contracted by inhalation, and there has been an association with this infection in different climatic areas of the southwest US, a place where this patient has resided for most of her life [13].

In addition to increasing the risk of opportunistic infections, treatment with anti-TNF agents can have other adverse effects, such as local injection site reactions, serum sickness-like reactions, vasculitis, drug-induced lupus, and some reports of skin cancer. Because this patient developed a complication from her infliximab therapy, a monoclonal antibody that targets $\alpha 4\beta 7$ integrin and prevents infiltration of leukocytes to the intestinal mucosa, vedolizumab, was chosen to manage the patient's UC, since vedolizumab is more gut-selective and poses less of a risk for the development of opportunistic infection [14,15].

Conclusions

Clinicians should be aware of the possibility of *Nocardia* spp. infections in patients receiving infliximab and steroid therapy for ulcerative colitis. Early recognition of atypical infection, appropriate diagnosis with microbial cultures, and timely treatment with the most effective antibiotic can lead to a better clinical outcome in these patients. This case report is notable as it describes a case of opportunistic infection, disseminated nocardiosis due to *Nocardia farcinica*, in a patient treated with the anti-TNF-alpha monoclonal antibody, infliximab, and hyponatremia due to antimicrobial treatment with high-dose TMP-SMX.

Conflicts of interest

None.

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