Infections in Oncology

DISSEMINATED NOCARDIA BRASILIENSIS INFECTION IN AN IMMUNOCOMPROMISED PATIENT

John S. Sarzier, MD; John N. Greene, MD; Ramon L. Sandin, MD, MS; Alexander S.D. Spiers, MD, PhD; Patricia J. Emmanuel, MD; Robin F. Valder, MT (ASCP); Myles E. Gombert, MD; and Albert L. Vincent, PhD
H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla

Introduction

A novel therapeutic approach for Nocardioid infections is presented. We report the successful treatment of lymphocutaneous nocardiosis with a three-drug combination in an immunocompromised patient with in vitro susceptibility testing used to guide therapy. New therapeutic options are required in some patients due to their failure to respond to the treatment of choice, trimethoprim-sulfamethoxazole (TMP-SMX). Success with combination therapy for the treatment of lymphocutaneous nocardiosis with newer antibiotics is being reported more frequently. As the availability of in vitro susceptibility testing increases, directed treatment of susceptible isolates can be implemented.

Case Report

A 72-year-old man presented with a history of non-Hodgkin’s lymphoma (well-differentiated lymphocytic, low grade, stage 1) confined to the mediastinum. Radiation therapy to the mediastinum and left chest resulted in a good response with an apparent remission. The clinical course was complicated by radiation pneumonitis and a pure red-cell aplasia, both requiring corticosteroid therapy. He received 40 mg of prednisone per day for approximately one year, which produced corticosteroid-induced noninsulin-dependent diabetes mellitus. Several months after his presentation with lymphoma, while using corticosteroids, the patient complained of ataxia, headache, and tremulous hands, but no fever or cough. A lumbar puncture revealed a cryptococcal antigen titer of 1:512 in cerebral spinal fluid (CSF) and 1:256 in serum. He was treated for cryptococcal meningitis with amphotericin B for one week. Because of renal insufficiency, 400 mg of fluconazole per day was substituted. After seven months of therapy, CSF became negative for cryptococcal antigen and culture; fluconazole was then discontinued. After doing well for approximately one year, a painful raised nodule appeared above the right eyebrow over a period of a few days. The nodule was accompanied by painful swelling of the left forearm and wrist, which limited the range of motion in his left elbow and wrist. He denied fever, chills, cough, headache, or change in vision. At this point, he was frequently tilled the soil in his backyard plot but denied recent trauma or puncture wounds.

Examination revealed a 2-cm pusular nodule above the right eyebrow. The flexor surface of the left forearm was diffusely indurated with extension to the wrist. A Gram stain of aspirate from the forehead lesion revealed many white cells but no organisms. India ink stain was negative. A computed tomography-guided aspirate of the forearm swelling (Fig 1) revealed Gram-positive, beaded, filamentous, branching rods (Fig 2) that stained modified acid-fast positive. They were negative by the Kinyoun acid-fast stain. Culture on Sabouraud’s dextrose agar, Lowenstein-Jensen media, and chocolate agar in two days grew Nocardia sp, further identified as Nocardia brasiliensis. Five days after admission, several painful erythematous nodules appeared on the patient’s upper back that covered 4 to 5 cm, and the left anterior axilla developed yet another nodule. Resection of the axillary lesion revealed necrotic adipose tissue with acute suppurative inflammation. A Fite stain for Nocardia sp failed to reveal the organism, yet Nocardia sp was grown from this specimen within two to three days. After five days, the forehead aspirate grew Nocardia sp on chocolate agar as well. A chest radiograph revealed changes consistent with radiation pneumonitis without focal lesions. The serum cryptococcal antigen was 1:128, but the CSF analysis was negative. Culture, cell count, modified acid-fast stain, and chemistry of the CSF were all unremarkable. The patient was treated for disseminated nocardiosis with intravenous TMP-SMX, imipenem/cilastatin, and amikacin. The axillary nodule and forearm abscesses were debrided and drained. Corticosteroid use was tapered off over the next several weeks, and high-dose intravenous gammaglobulin was given to maintain a corticosteroid-induced remission of the red-cell aplasia. Susceptibility testing was performed on this isolate using agar dilution methodology.1 Minimal inhibitory concentrations were established for five antimicrobial agents: ceftaxidine (1 µg/mL), amikacin (0.5 µg/mL), imipenem (8 µg/mL), minocycline (1 µg/mL), and TMP-SMX (0.5 µg/mL). By the third week of treatment, the forehead lesion had resolved, and the forearm swelling and axillary nodules had reduced in size. The arm was less painful and more mobile. Outpatient treatment consisted of oral TMP-SMX, two double-strength tablets four times a day, which led to complete resolution of all lesions after six weeks of therapy. Having completed six months of oral TMP-SMX, one double-strength tablet twice a day, he now remains asymptomatic with no evidence of infection or malignancy.
Discussion

*Nocardia* spp are cosmopolitan aerobic actinomycetes of the soil, but there are occasional causes of opportunistic infection. These organisms are Gram positive, partially acid-fast, and true branching filamentous bacteria. They may produce either localized skin infections or disseminated involvement. *Nocardia asteroides* causes 90% of all reported cases of systemic nocardiosis, with 60% to 80% of these being lung infections in immunocompromised individuals. Systemic infections involve the central nervous system in 20% to 40% of cases. Hematogenous dissemination leads to cutaneous lesions in only approximately 5% of cases. Nocardiosis usually follows an indolent course of one to three weeks before being recognized, but immunocompromised patients may suffer rapid progression of disease within days.

Primary cutaneous disease typically follows traumatic implantation of *Nocardia brasiliensis* into subcutaneous tissue, although all *Nocardia* sp can cause cutaneous disease. Cutaneous nocardiosis typically occurs in otherwise healthy individuals and may present clinically in any of three manifestations: a mycetoma, a lymphocutaneous type (often resembling sporotrichosis), and a localized superficial skin infection such as a granuloma, an abscess, cellulitis, or ulceration.

Primary cutaneous *Nocardia* infections first appear as small, firm, painless subcutaneous nodules. Sinus tracts develop as the lesion grows. Granules are absent in the sinus discharge of *Nocardia brasiliensis* lesions, distinguishing them from other causes of mycetoma. Cutaneous foci may spread along fascial planes or lymphatics or occasionally via the blood. The disease may invade bone, blood vessels, and lymphatic vessels, paving the way for secondary bacterial infections at any of these sites.

The incidence of nocardiosis in the United States is estimated to be 500 to 1,000 cases each year. The preponderance of *Nocardia brasiliensis* cases arise in the Southern and Southwestern United States. Sixty-three percent of cases have been reported from Texas, North Carolina, California, Oklahoma, and Florida. Men are affected two or three times more often than women. This gender susceptibility has been confirmed in animal models and may be related to hormonal effects on *Nocardia* growth and virulence.

Disorders predisposing to systemic *Nocardia* infections include pulmonary alveolar proteinosis, mycosis fungoides, leukemia, lymphoma, dysgammaglobulinemia, chronic granulomatous disease of childhood, Cushing’s syndrome, corticosteroid therapy, and solid organ transplantation. Other chronic illnesses associated with *Nocardia* infections are chronic obstructive pulmonary disease, alcoholism, tuberculosis, rheumatoid arthritis, mixed connective tissue disease, inflammatory bowel disease, diabetes and, more recently, AIDS. Nocardia infections have occurred in pregnancy, but pregnancy does not lead to a more protracted course of infection.

It is believed that neutrophils initially inhibit the growth of *Nocardia* sp until macrophages can be fully activated. These immune defenses are compromised in patients with neutropenia and also in patients whose macrophages are affected by corticosteroid therapy, as in our case. Overall, 50% of all *Nocardia* infections occur in patients with compromised cell-mediated immunity. In a study by Wilson et al., 86% of cases that specified immunosuppressive agents reported the use of prednisone and azathiopeprine. They also noted that a frequent opportunistic coinfection associated with nocardiosis is cryptococcal meningitis, as well as bacterial infections, pneumocystis pneumonia, aspergillosis, and candidemia. Likewise, our patient developed cryptococcal meningitis prior to his nocardiosis. In addition to his non-Hodgkin’s lymphoma, prednisone and cyclophosphamide therapy probably predisposed our patient to this *Nocardia* infection.

The suggested therapy for nocardiosis involves treatment with TMP-SMX for six months or longer. Some suggest that therapy be continued for up to one year to prevent relapse. Resistance to TMP-SMX has been noted recently, but antimicrobial therapy for these infections continues to evolve. While sulfonamides have been the mainstay of treatment for many years, novel approaches now utilize quinolones, amikacin, and *N*-formimidoyl thienamycin. Clinical applications of nonsulfonamide treatment for *Nocardia* sp are varied and include those infections caused by resistant organisms, intolerance to sulfa agents (in three HIV-infected patients), and failure of primary therapy.

A combination of TMP-SMX, imipenem, and amikacin produced a prompt response in our patient and may benefit others with a similar clinical presentation. After initially obtaining a significant clinical response with an intensive intravenous regimen, oral therapy may be adopted. However, the best chance of cure without subsequent relapse remains tapering off immunosuppressive therapy, as in our case, or resolving the underlying condition. When prolonged immunosuppression is expected in a patient with nocardiosis, intensive intravenous antibiotics should be considered based on in vitro sensitivity, if available, followed by chronic suppressive oral TMP-SMX or minocycline.

Appreciation is expressed to Catherine Hearn for her assistance in the preparation of the manuscript.

References