

Epididymo-Orchitis and Central Nervous System Nocardiosis in a Bone Marrow Transplant Recipient for Acute Lymphoblastic Leukemia

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Abstract

Objectives: We report a case of epididymo-orchitis and central nervous system nocardiosis in a 22-year-old man with T-cell acute lymphoblastic leukemia; he was an allogeneic marrow recipient with acute and chronic graft-versus-host disease.

Materials and Methods: He had microscopic hematuria and cytomegalovirus antigenemia. He deteriorated subsequently while on cyclosporine and steroids, requiring hospital admission owing to fever and swelling of the left testis and generalized tonic-clonic convulsions.

Results: Brain magnetic resonance imaging showed abnormal signal area in right parietal and left parieto-occipital lobes. The lesions had mass effect, edema, and ring enhancement. Findings were indicative of a brain abscess. A testicular biopsy from the lower pole of the left testis was done. A white-to-yellowish discharge was seen and subsequently, *Nocardia* grew in culture.

Conclusions: Trimethoprim-sulfamethoxazole was prescribed, and significant improvement was seen after 2 weeks. The patient was discharged. He was subsequently referred after 3 weeks due to graft-versus-host disease and died of pancytopenia.

Key words: *Nocardia*, Stem cell transplant, Testicular involvement, Brain abscess, Immunocompromised

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The genus *Nocardia* is a weakly gram-positive, filamentous bacteria, found worldwide in soil. Human disease from this microorganism was first described by Eppinger, in 1890, after bovine disease was described by Nocard in 1888. Pathogenic *Nocardia* is a member of the Nocardaceae family, the aerobic actinomycetes (1). Nocardiosis is usually acquired by inhalation of spores, which results in pulmonary involvement in 90% of cases (2). Because of the high tendency of hematogenous dissemination, brain, kidney, joints, bones, and eyes are nonpulmonary sites of manifestation (3).

The incidence of *Nocardia* infection for geographically defined populations is reported up to 0.3-0.4 per 100 000 per year. However, immunocompromised individuals (such as transplant recipients) have an elevated incidence of Nocardiosis—up to 340 times compared with geographically defined populations—which points out that the immunosuppression is the main risk factor (4). Further risk factors are human immunodeficiency virus and *Cytomegalovirus* infection, long-term corticosteroid treatment, and lymphoreticular malignancies. The infection is also more common among men (2-3:1), and in individuals aged younger than 10 years and older than 40 years (5).

Nocardiosis is an extremely rare cause of epididymo-orchitis. Clinically, the infection presents as a painful enlargement of the testicle with few inflammatory signs. Mortality is high, and treatment includes long-term sulfonamide therapy, combined with orchiectomy (6).

Case Report

The patient was a 22-year-old man, a known case of T-cell acute lymphoblastic leukemia for 1 year. He had received allogeneic stem cell transplant from his fully matched HLA sibling, with the conditioning regimen

of cyclophosphamide and busulfan. Then, the patient developed grade II gastrointestinal graft-versus-host disease. Cyclosporin and methotrexate were started before stem cell transplant for prophylaxis of graft-versus-host disease, and methylprednisolone was started after graft-versus-host disease. He developed hemorrhagic cystitis. Due to *Cytomegalovirus* antigenemia (PP65 positive with a titer of 4/50000), we started ganciclovir as pre-emptive therapy, and continued it for 14 days. However, the patient became pancytopenic, and bone marrow aspiration showed hypocellularity, so we discontinued ganciclovir. He subsequently developed a fever of higher than 38°C, hematuria, and swelling of left testis.

He was admitted again after 3 days with the impression of epididymo-orchitis and treated with ceftriaxone (1 g every 12 h IV). After a few days, he developed a generalized convulsion. We checked his cyclosporine level (which was high [800 mg/dL]), so with the possibility of cyclosporine toxicity, cyclosporine was discontinued. A brain computed tomography scan was done, showing multiple, hypodense areas, in the parietal and temporal lobes. He also had a high-grade fever (39.5°C), focal seizures, a decreased level of consciousness, and left upper and lower extremity weakness.

Brain magnetic resonance imaging showed an abnormal signal area in right parietal and left parieto-occipital lobes. The lesions had mass effect, edema, and ring enhancement (Figure 1). Findings were indicative of a brain abscess. A testicular biopsy from the lower pole of the left testis was done. Grossly, white-to-yellowish discharge was seen. Culture and pathology revealed necrosis with focal fibrosis and acute and chronic inflammation, but no fungal element was visible. The result of culture by Thayer-Martin media

was positive for *Nocardia*. Acid-fast stain also was weakly positive.

Trimethoprim-sulfamethoxazole (TMP-SMX) (1 double-strength tablet, bid, po) was started, and after receiving this treatment for 2 weeks, significant improvement in level of consciousness and testicular involvement was seen. Also, after 2 weeks of antibiotic therapy, testicular discharge was decreased, and convulsions stopped with anti-convulsant drugs. The patient was discharged thereafter with medications including cotrimoxazole. He was hospitalized again after 2 weeks with aggravation of the underlying disease due to graft-versus-host disease. He died of pancytopenia and graft-versus-host disease, and there was no chance for new brain imaging.

Discussion

Nocardiosis is a localized or disseminated infection caused by soilborne, aerobic actinomycetes (7). Infection is commonly introduced through the respiratory tract, and pulmonary disease is the most common presentation. Approximately 45% of patients with systemic nocardiosis have central nervous system infections (5).

As previously mentioned, the lung is the most commonly involved organ (2), and hematogenous dissemination can lead to involvement of other organs. Brain, kidney, joints, bones, and eyes are the most commonly involved organs (3). Nocardial involvement of the testes, particularly concomitant testicular and brain involvement, has rarely been reported. This case is being reported for the rare manifestation of a simultaneous involvement of the brain and the testicles by *Nocardia* species.

Nocardiosis is also a rare cause of epididymo-orchitis. A 78-year-old man presented to the Mayo Clinic with fever and weight loss after being treated with cyclophosphamide and prednisone for an immune-mediated vasculitis. He was found to have a testicular abscess, and an orchiectomy was performed. *Nocardia asteroides* complex was identified on the wound cultures (8). A case of epididymo-orchitis due to *Nocardia asteroides* in a liver transplant recipient, and 4 other cases have been reported. All patients were immunocompromised, and other organs were affected simultaneously. Clinically, the infection presents as a painful enlargement of the testicle with few inflammatory signs. Mortality is high (3/5), and in the

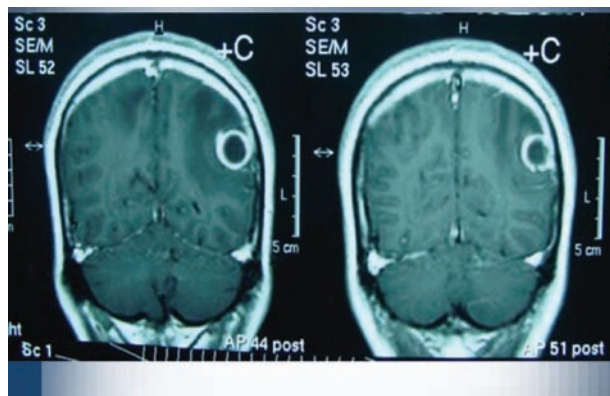


Figure 1. Brain nocardiosis in a bone marrow transplant recipient.

2 survivors, long-term sulfonamide therapy was combined with orchiectomy (6). Wheeler and associates also reported a case of epididymitis that evolved into testicular nocardiosis after cardiac transplant (9). Thus, nocardiosis should be considered in the diagnosis of epididymo-orchitis in the immunocompromised host.

Six cases of systemic *Nocardia* infections were reported among 302 allogeneic bone marrow transplant recipients. All patients had been treated previously for acute graft-versus-host disease. At the time of diagnosis of systemic *Nocardia* infection, a median of 198 days after transplant (range, 148-1121), all patients had extensive, chronic, graft-versus-host disease, and were taking 2 to 3 immunosuppressive medications. Before the diagnosis of *Nocardia* infection, the patients had experienced multiple, opportunistic infections including *Mycobacterium avium-intracellulare*, *Pneumocystis carinii*, and *Cytomegalovirus* antigenemia. Treatment with TMP-SMX, ceftriaxone, or carbapenem antibiotics results in a median survival of 219 days, from the time of diagnosis to an actual 1-year survival of 40%. All patients who had received more than 2 weeks of therapy were cured of their infections. Notably, 5 of 6 patients in this cohort were unable to take TMP-SMX owing to myelosuppression (10).

The diagnosis of *Nocardia* is difficult and time-consuming, and consists of isolation of *Nocardia* species from blood, urine, airway-samples, and biopsies. It can take days to weeks to confirm the suspicion (8). Trimethoprim-sulfamethoxazole is the drug of choice in the acute and chronic treatment of nocardiosis, achieving high tissue concentrations in lung, brain, skin, and bone (11). Initially, carbapenems can be added to TMP/SMX for patients with pulmonary and cerebral manifestations. The final choice of antibiotic treatment, however, depends on the susceptibility testing, because some strains of *Nocardia* (eg, *N. nova*, *N. otitidiscaviarum*, and especially, *N. farcinica*) may have high-grade resistance to sulfamethoxazole (12). In case of sulfamethoxazole resistance, linezolid is the agent of choice, because it is effective against all species of *Nocardia* including *N. farcinica* (13). Prolonged linezolid treatment can, however, be limited by serious myelosuppression, including neutropenia, thrombocytopenia, and anemia (14).

In the literature, the duration of treatment of nocardiosis is not well-defined, and recommendations are empirical. However, all transplant recipients

should be treated for at least 12 months. Facing the tendency of nocardial infections to relapse, a lifelong treatment is recommended (11). Patients with brain abscess have to be followed up very closely, because the mortality rate is reported to be up to 90%. In cases of nonresponsiveness to antibiotics, surgical removal of brain abscesses is indicated (15).

Nocardiosis should be considered in the diagnosis of epididymo-orchitis and also, ring-enhancing brain lesions in the immunocompromised hosts. Morbidity and mortality are high (from fulminant nocardiosis). A high index of suspicion, followed by a rapid diagnosis and treatment, is warranted.

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