Femoral Osteomyelitis Due to *Aspergillus nidulans* in a Patient with Chronic Granulomatous Disease

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**Abstract**

13 cases of osteomyelitis caused by *Aspergillus nidulans* have been previously reported in patients with chronic granulomatous disease (CGD). All of them have been associated with simultaneous pulmonary infection and have had an extremely poor outcome. We report an unusual case of femoral osteomyelitis due to *A. nidulans* in a 16-year-old male with CGD, without pulmonary involvement. Treatment with liposomal amphotericin B and granulocyte colony-stimulating factor as well as extensive surgical debridement followed by prolonged treatment with itraconazole resulted in an excellent clinical response.

**Introduction**

Chronic granulomatous disease (CGD) is a rare inherited disorder of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in which neutrophils and monocytes fail to generate reactive oxidants such as superoxide anion and hydrogen peroxide, key elements in host defense against a variety of pathogens [1]. Patients with CGD are therefore susceptible to recurrent, life-threatening bacterial and fungal infections. Invasive aspergillosis frequently occurs in these patients [2]. While *Aspergillus fumigatus* is the most common fungal pathogen, *Aspergillus nidulans* can also cause invasive aspergillosis with excessive morbidity and increased mortality [3, 4]. 13 cases of osteomyelitis due to *A. nidulans* have previously been reported in patients with CGD [3, 5–13]. All of them have been associated with simultaneous pulmonary infection and have had an extremely poor outcome. We report a very unusual case in which *A. nidulans* caused osteomyelitis unrelated to pulmonary infection and had a favorable outcome.

**Case Report**

The patient was a 16-year-old male with X-linked CGD who was admitted to the hospital for osteomyelitis in the left femur. The diagnosis of CGD had been established 7 years earlier, when his older brother was first diagnosed with CGD. Prophylaxis with liposomal amphotericin B and granulocyte colony-stimulating factor as well as extensive surgical debridement followed by prolonged treatment with itraconazole resulted in an excellent clinical response.

Figure 1. Roentgenogram of the lower part of left femur and the knee showing an osteolytic lesion of the distal metaphysis of the femur. Arrow indicates the site of the lesion.
The patient presented with pain at the distal end of the left thigh for approximately 2 weeks and a low-grade fever 3 days before admission to the hospital. Physical examination at admission revealed a temperature of 37.5 °C and a painful knee without other signs of local infection. Laboratory findings included leukocyte count 7,400/μl with 65% neutrophils, C-reactive protein (CRP) 44.5 mg/l and erythrocyte sedimentation rate (ESR) 64 mm/h.

A roentgenogram of the painful area (Figure 1) revealed an osteolytic lesion of the distal metaphysis of the femur, whereas sonographic examination of the left knee was normal. Magnetic resonance imaging (MRI) was suggestive of osteomyelitis without participation of the surrounding soft tissues (Figure 2a). Aspiration of the osteolytic lesion revealed no pathogen by histology or microbiological culture. Therapy with cloxacillin (2 g every 6 h, iv) was initiated. One week later the patient’s condition had not been improved, his temperature ranged from 37–38.5 °C and swelling, warmth and redness were observed along with pain. On the 10th day of hospitalization, laboratory findings consisted of mild leukocytosis (WBC 10,700/μl with 65% neutrophils), ESR 100 mm/h and CRP 54.3 mg/l. On the 60th day of hospitalization, a second MRI showed increased bone destruction compared to the previous examination (Figure 2b). At this time, an extensive surgical debridement was performed and the culture again yielded A. nidulans. The dose of liposomal amphotericin B was increased to 6.25 mg/kg per day and granulocyte colony-stimulating factor (400 μg daily, sc) was added to his regimen. After 6 additional weeks, hematological examination showed hemoglobin 7.7 g/dl (400 µg daily, sc) was added to his regimen. After 6 additional weeks, hematological examination showed hemoglobin 7.7 g/dl and recombinant erythropoietin (4,000 mU sc) together with folic acid (5 mg three times a week po) were added.

After 8 weeks of treatment with a total of approximately 21 g of liposomal amphotericin B, the patient’s condition had improved. A new roentgenogram showed no further progress of the femoral damage; in addition, the laboratory values were significantly improved (WBC 7,800/μl, ESR 57 mm/h, CRP 10 mg/l). The patient was free of pain and started to walk with assistance. Liposomal amphotericin B, G-CSF, erythropoietin and folic acid were discontinued. The antifungal treatment was switched to oral itraconazole solution (400 mg per day). Serum levels of itraconazole measured by a bioassay ranged within 0.9 –1.05 mg/l.

After 7 months, the patient was again able to walk and no symptoms and signs of local infection were apparent. Additionally, the radiological findings have improved. The patient continues to receive IFN-γ and itraconazole as long-term prophylaxis.

Discussion

We present this case because it is the first reported episode of a long bone osteomyelitis due to A. nidulans that occurred in a CGD patient without simultaneous pulmonary infection. Surveillance sputum cultures were negative for A. nidulans and clinical examination as well as chest roentgenogram did not reveal any evidence of lung disease.