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CARE REPORT

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Aspergillus osteoarthritis in acute lymphoblastic leukemia

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Abstract We report an unusual case of arthritis of the right wrist due to *Aspergillus fumigatus* without evidence for a generalized infection, following chemotherapy for acute lymphoblastic leukemia. The diagnosis was made by surgical biopsy. Amphotericin-B (Am-B) was not tolerated by the patient. Liposomal preparations of Am-B penetrate poorly into bone and cartilage. Therefore, oral itraconazole was given; the arthritis improved and chemotherapy was continued without infectious complications. Two weeks after complete hematopoietic recovery, an intracranial hemorrhage from a mycotic aneurysm of a brain vessel occurred, although the patient was still receiving itraconazole. We emphasize the importance of prompt and thorough efforts to identify the causative agent in immunocompromised patients with a joint infection. Itraconazole is effective in *Aspergillus* osteoarthritis but, due to its poor penetration into the brain, the combination with a liposomal formulation of Am-B is recommended.

Key words *Aspergillus fumigatus* · Osteoarthritis · Itraconazole · Leukemia

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Introduction

Aspergillus species can cause life-threatening infections in immunocompromised patients. Infections are most commonly acquired through inhalation of *Aspergillus* spores, and the lung and the brain are predominantly affected. *Aspergillus* osteoarthritis occurs infrequently through hematogenous dissemination, by direct spread from an overlying focus, open wounds, or surgical procedures. The location most commonly affected is the spine. The clinical signs are often nonspecific. The diagnosis is based on microscopic examination and on cultures of biopsy material. Here, we present the case of a patient with acute lymphoblastic leukemia (ALL) who acquired an *Aspergillus fumigatus* osteoarthritis of the right wrist, where no primary focus was found. The diagnostic procedures and the fatal outcome despite effective treatment of the osteoarthritis with itraconazole are outlined.

Case report

A 59-year-old Caucasian man was admitted in May 1997 with ALL (common ALL). Following chemotherapy with vincristine, daunorubicin, l-asparaginase, and prednisone, a complete remission was achieved and the patient was discharged. Prophylactic CNS irradiation was administered in the outpatient setting. Two weeks later, he presented with painful swelling of the right wrist. Physical examination revealed erythema, warmness, induration, and impaired mobility. No other clinical abnormalities were detected at that time. The patient was afebrile. His white blood cell count was normal (9.4 G/l), with 85% segmented neutrophils. CRP was 2.63 mg/dl, fibrinogen 803 mg/dl. Serum electrolytes, creatinine, and liver enzymes were within the normal values.

An MRI scan of the right wrist showed a diffuse inflammation of the os scaphoideum, os lunatum, joint capsula, and the periarticular soft tissue. A surgical joint biopsy was performed. Histological examination revealed inflammatory tissue with lymphocytes, plasma cells, and histiocytes. *Aspergillus fumigatus* was grown in cultures from biopsy material. Repeated blood cultures remained sterile. A CT scan of the thorax was normal. Therapy with amphotericin-B (Am-B) was begun at a dose of 1 mg/kg body wt. but discontinued 3 days later due to toxicity (fever, rise

in serum creatinine to 300 mmol/l). Because itraconazole (ITRA) is effective in *Aspergillus* osteomyelitis, and liposomal formulations of Am-B penetrate poorly into bone and cartilaginous tissues, and because the combination of ITRA and Am-B may be antagonistic, ITRA was administered as a single agent with a starting dose of 400 mg/day and a subsequent escalation up to 900 mg/day [1, 2]. The arthritis improved and an MRI scan performed after 2 weeks of treatment showed regression of the inflammation. The next chemotherapy cycle was administered while ITRA was continued. No infectious complications occurred during the period of granulocytopenia. ITRA serum levels were between 0.4 and 4 μg/ml. Two weeks after hematopoietic reconstitution, while he was still receiving ITRA, the patient presented with headache and aphasia. A CT scan of the brain showed a subdural hematoma of the left parietal region. An MRI scan revealed an aneurysm of the left arteria cerebri media, 6 mm in diameter, and no signs of cerebral aspergillosis. The patient's condition worsened rapidly, with fever and a rise in CRP up to 54 mg/dl. A chest X-ray and a thoracic CT scan showed a diffuse infiltrate in the right upper lobe of the lung. Repeated blood cultures were positive for *Staphylococcus aureus*. The patient died 4 weeks after hematological reconstitution, being in complete remission. The autopsy revealed bilateral pneumonia, and *S. aureus* was grown from tissue cultures. There was no histological or microbiological evidence of pulmonary aspergillosis. The aneurysm of the arteria cerebri media was confirmed and the histological examination of the aneurysm showed mycotic hyphae consistent with *Aspergillus fumigatus*. Histological examination of the right wrist revealed no inflammation and no fungi. A total dose of 25.4 g ITRA over 7 weeks had been administered when the intracranial bleeding occurred.

Discussion

Invasive aspergillosis causes substantial morbidity and mortality in patients undergoing aggressive chemotherapy for malignant disease. Chemotherapy including treatment with steroids put our patient at risk for invasive aspergillosis. Standard treatment of *Aspergillus* osteomyelitis includes therapy with Am-B and surgical débridment of affected tissues [3]. For patients who do not tolerate Am-B, ITRA can be effective in the treatment of *Aspergillus* arthritis [1]. After single 200-mg doses, concentrations of the drug in bone, liver, and muscles are two to three times higher than the corresponding serum concentrations. In contrast, low to negligible amounts are found in cerebrospinal fluid [4]. The wrist arthritis caused by *Aspergillus fumigatus* in our patient responded well to the treatment with ITRA. Unfortunately, despite a total dose of 25.4 g ITRA delivered over 7 weeks, mycotic damage of a brain vessel with intracranial bleeding occurred, probably due to insufficient brain levels of ITRA. The new antifungal voriconazole, currently available only in clinical trials, has been effective in a patient with cerebral aspergillosis, suggesting a sufficient penetration into the CNS [5].

This report emphasizes the importance of prompt and thorough efforts to identify the causative agent in immunocompromised patients with a joint infection. Treatment with ITRA is effective in *Aspergillus fumigatus* arthritis. In such patients, spread to the brain should be considered, and repeated MRI studies might therefore be beneficial. For patients who do not tolerate Am-B, we recommend a combination therapy with ITRA and a liposomal formulation of Am-B, which crosses the blood-brain barrier.

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