Candida tropicalis arthritis of the knee in a patient with acute lymphoblastic leukaemia: successful treatment with caspofungin

Candida arthritis in patients with a haematological malignancy is rare. We report a case of Candida tropicalis arthritis of the knee that occurred in a patient with acute lymphoblastic leukaemia during the recovery phase of post-chemotherapy neutropenia. Although the Candida tropicalis isolates from synovial fluid and synovial tissue were sensitive to fluconazole in vitro, a 6-week course of oral treatment failed to produce clinical improvement. The arthritis resolved after 7 weeks of combination therapy with caspofungin, a new echinocandin class of antifungal agent that acts primarily on the cell wall. Eleven other reports of Candida arthritis in patients with a haematological malignancy were reviewed.

Introduction

Candida arthritis in patients with a haematological malignancy is rare despite the considerably increased incidence of disseminated candidiasis over the past decade.1,2 We report a patient with acute lymphoblastic leukaemia who developed Candida tropicalis arthritis of the knee during a course of chemotherapy. An initial suboptimal response to treatment with fluconazole and intolerance of amphotericin B led to the prescription of a new class of antifungal agent, caspofungin. Successful control of Candida arthritis allowed chemotherapy to be continued.

Case report

A 53-year-old Chinese man, previously in good health, was diagnosed with precursor B-cell acute lymphoblastic leukaemia with negative BCR-ABL gene rearrangement in July 2002. Complete remission was achieved upon completion of phase I induction chemotherapy (daunorubicin, vincristine, prednisolone, and intrathecal methotrexate). Phase II induction chemotherapy (cyclophosphamide, cytarabine, 6-mercaptopurine,
and intrathecal methotrexate), and consolidation chemotherapy were then commenced. Treatment was administered via a Hickman catheter and trimethoprim-sulphamethoxazole prescribed to prevent *Pneumocystis carinii* infection.

Shortly after phase I consolidation in November 2002, the patient developed a neutropenic fever that responded to empiric 14-day treatment with vancomycin and carbepenam. Despite supporting treatment with granulocyte-colony stimulating factor, absolute neutrophil count remained at 0.5 x 10⁹ /L or less for 10 days before starting to rise. At a neutrophil count of 12 x 10⁹ /L, the patient experienced recurrent fever accompanied by the development of arthritis in the right knee. Arthrocentesis of the swollen, red, hot, and tender knee joint yielded 50 mL of purulent fluid containing 28 800 cells/mm³ (>90% polymorphs) but no crystals. Gram stain for micro-organisms and the Ziehl-Neelsen stain for acid-fast bacilli were negative. Arthroscopic lavage and synovectomy were also performed. Empiric treatment for pyogenic arthritis with the broad-spectrum antibiotic cefepime was commenced. Anti-leukaemic chemotherapy was withheld in view of the persistent knee joint infection. The symptoms and signs of arthritis and fever persisted despite a 10-day course of cefepime.

Culture of the synovial fluid and the synovial tissue later grew *C. tropicalis* that was sensitive to fluconazole (minimal inhibitory concentration, 2 µg/mL). All other culture specimens—blood, urine, and sputum—were negative. Histology of the synovial biopsy revealed necrotising granulomatous inflammation with reactive lymphoid infiltrates, neutrophils, epitheloid histiocytes, and multinucleated giant cells. The Ziehl-Neelsen and the Wade Fite stains for acid-fast bacilli were negative. Arthroscopic lavage and synovectomy were also performed. Empiric treatment for pyogenic arthritis with the broad-spectrum antibiotic cefepime was commenced. Anti-leukaemic chemotherapy was withheld in view of the persistent knee joint infection. The symptoms and signs of arthritis and fever persisted despite a 10-day course of cefepime.

Magnetic resonance imaging of the affected knee demonstrated gross joint effusion, mild synovial thickening, and diffuse high T2-weighted signal with contrast enhancement in the femoral and proximal tibial subarticular region signifying inflammatory/infective changes (Fig). Abdominal computed tomography showed no evidence of hepatosplenic candidiasis.

The patient’s response to fluconazole remained suboptimal after 6 weeks of treatment (400 mg/d orally for 2 weeks, 600 mg/d intravenously for 4 weeks), so intravenous caspofungin was added (70 mg stat, then 50 mg/d). Fluconazole was continued but administered orally at a dose of 600 mg/d. Knee symptoms began to improve and walking with aid was possible towards the end of the second week of combination therapy. Therapy was well tolerated with no adverse effects. Serial blood cell counts, electrolytes, and hepatic enzymes remained normal. After 7 weeks of combination therapy, symptoms and signs of arthritis had almost completely subsided.

Bone marrow examination in April 2003 confirmed that the patient remained in remission. Phase II consolidation chemotherapy was resumed and followed by re-induction chemotherapy and phases III and IV
consolidation chemotherapy. No relapse of fungal arthritis occurred during prophylactic oral fluconazole therapy. Unfortunately his leukaemia relapsed in October 2003 and was refractory to salvage chemotherapy. At the time of his death in January 2004, there was no apparent recurrence of Candida arthritis.

Discussion

This case demonstrated the key host factors that predispose a patient to Candida arthritis: intensive chemotherapy, profound post-chemotherapy neutropenia, and prolonged use of broad-spectrum antibiotics. Although the exact pathogenesis of Candida arthritis was unclear, it appeared to have originated endogenously from the host’s altered microbial flora and to have spread haematogenously. Cytotoxic agents damaged the gastro-intestinal mucosa and antibiotics eliminated the normal bacterial flora allowing colonisation by commensal organisms, such as Candida albicans and C tropicalis. These are common isolates from patients with Candida fungaemia and arthritis is one of the systems involved in disseminated candidiasis.1,2 No evidence of disseminated candidiasis was present in this patient but a transient C tropicalis fungaemia cannot be ruled out. This type of arthritis differs to that produced by direct injury where Candida guilliermondi and Candida parapsilosis are usually implicated.3

A review of the literature revealed no more than 11 cases of Candida arthritis in patients with haematological malignancy (Table).4-11 The spectrum of haematological disease ranged from acute leukaemia, blastic phase of chronic myeloid leukaemia, and smouldering leukaemia to chronic lymphocytic leukaemia and small lymphocytic lymphoma. Candida albicans4,6,9,11 and C tropicalis4,6,7,10 species accounted for five and six cases of Candida arthritis, respectively in this series of 12 patients (including ours). Candida krusei4 species, an emerging pathogen ascribed partly to triazole use, caused arthritis in one patient. The knee was the sole joint affected among these patients and the reason for which remains unclear.

The C tropicalis isolates from our patient were sensitive to fluconazole in vitro. Although fever resolved and joint fluid was sterile, joint swelling and pain persisted. An inadequate intra-articular level of fluconazole might have accounted for this. Alternatively, clinical response might lag behind microbial response. Amphotericin B, the mainstay antifungal agent used since the 1970s and to which most Candida isolates are sensitive, was stopped in this patient because of renal toxicity. The addition of

<table>
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<td>M/53</td>
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<td>Fluconazole and caspofungin</td>
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</tbody>
</table>

* ALL denotes acute lymphoblastic leukaemia, AML acute myeloid leukaemia, CML-BC chronic myeloid leukaemia in blastic crisis, SLL small lymphocytic lymphoma, and CLL chronic lymphocytic leukaemia
† iv denotes intravenously, and ia intra-articularly
‡ Present case
caspofungin cured the arthritis. Four clinical trials support the efficacy of caspofungin in the treatment of oropharyngeal/oesophageal candidiasis.12-15 Adverse effects reported to date include fever, thrombophlebitis, headache, and raised liver enzyme levels. There are no known contra-indications to caspofungin use except in those with a history of hypersensitivity to the drug. Caution should be exercised if prescribed alongside cyclosporine because of potential drug-drug interactions. The clinical efficacy of caspofungin in the treatment of Candida arthritis has not been previously reported. Because of its unique mechanism of action, there is no cross-resistance with polyenes and azoles, both of which act on the cell membrane. As such, it offers a valuable alternative for resistant Candida infections.

References