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

急性淋巴細胞白血病患者成功以卡泊芬淨治療熱帶念珠菌膝關節炎

***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.**

血癌病人極少會患上念珠菌關節炎。本文報告一名急性淋巴細胞白血病者在化療後嗜中性白血球減少症康復期間，患上熱帶念珠菌膝關節炎。雖然從滑膜液和滑液組織分隔出來的熱帶念珠菌證實氟康唑對此有療效，但病人口服該藥6星期後，病情沒有任何進展。病者改用卡泊芬淨混合療法，7星期後關節炎治癒。卡泊芬淨是一種新的刺白菌素抗真菌藥，主要在細胞壁上產生作用。本文亦回顧11個血癌病人患上念珠菌性關節炎的病例報告。

Key words:
Antifungal agents;
Arthritis, infectious;
Candidiasis;
Knee joint;
Leukemia, lymphocyte, acute

關鍵詞：
抗真菌藥；
關節炎，感染性；
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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 10^9 /L or less for 10 days before starting to rise. At a neutrophil count of 12 x 10^9 /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/mm^3 (>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.

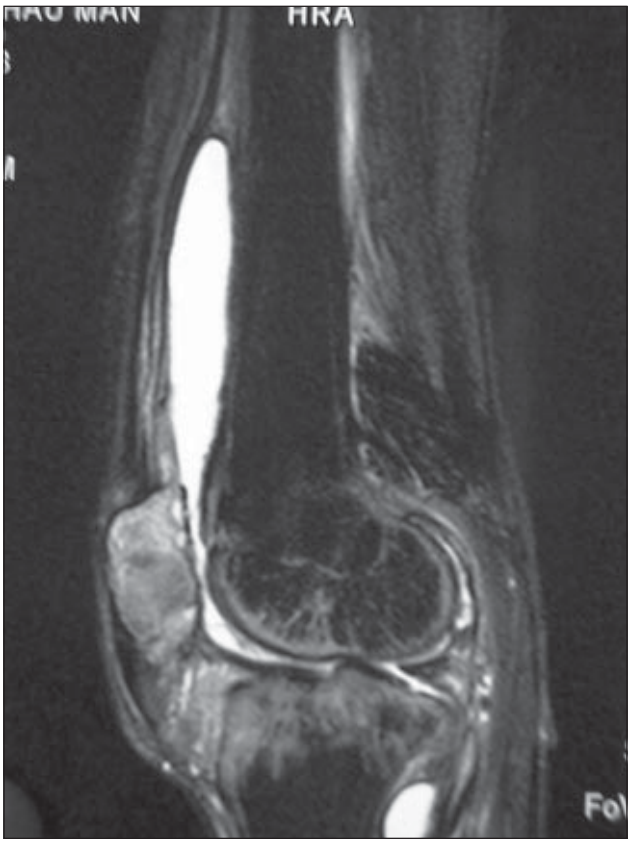

Fig. T2-weighted magnetic resonance image with fat suppression of right knee showing gross effusion

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, epithelioid histiocytes, and multinucleated giant cells. The Ziehl-Neelsen and the Wade Fite stains for acid-fast bacilli were negative, so was the Grocott stain for fungus. Immunohistochemical study of the lymphoid infiltrate showed presence of almost exclusively T cells (CD3+, CD20-, and CD79a-). There was no evidence of leukaemic infiltration. Oral fluconazole at a dose of 400 mg/d was added. The fever gradually resolved, although joint swelling persisted with severe pain. An increased dose (600 mg/d) of fluconazole was commenced intravenously with the addition of intravenous amphotericin B. The latter was discontinued after a few days because of renal toxicity. Arthrocentesis was repeated several times: turbid aspirate continued to show abundant polymorphs, although bacterial and fungal cultures remained negative.

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

Table. Summary of clinical features of *Candida* arthritis in patients with haematological malignancy

Sex/Age (years)	Underlying disease*	*Candida* species	Affected joint	Therapy†	Outcome
F/11	ALL[4]	*C tropicalis*	Knee	Amphotericin B (iv, ia)	Resolved
M/12	ALL[5]	*C albicans*	Knee	5-Flucytosine and amphotericin B (ia)	Resolved
M/59	AML[6]	*C tropicalis*	Knee	Amphotericin B (iv) Miconazole	Intolerance Resolved
M/67	CML-BC[6]	*C tropicalis*	Knee	Ketoconazole	Resolved
F/62	CML-BC[6]	*C albicans*	Knee	Amphotericin B (iv, ia)	Early death
M/68	Smoldering leukaemia[6]	*C albicans*	Knee	Ketoconazole Miconazole Amphotericin B (iv, ia)	Ineffective Ineffective Resolved
F/66	SLL[7]	*C tropicalis*	Knee	Amphotericin B (iv) Miconazole	Intolerance Resolved
M/41	AML[8]	*C krusei*	Knee	Amphotericin B (iv)	Resolved
M/67	CLL[9]	*C albicans*	Knee	Fluconazole	Resolved
F/77	AML[10]	*C tropicalis*	Knee	Fluconazole	Resolved
F/59	CML-BC[11]	*C albicans*	Knee	Fluconazole Liposomal amphotericin B	Ineffective Resolved
M/53‡	ALL	*C tropicalis*	Knee	Fluconazole Fluconazole and caspofungin	Ineffective Resolved

* 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

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 smoldering leukaemia to chronic lymphocytic leukaemia and small lymphocytic lymphoma. *Candida albicans*[5,6,9,11] and *C tropicalis*[4,6,7,10] species accounted for five and six cases of *Candida* arthritis, respectively in this series of 12 patients (including ours). *Candida krusei*[8] 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

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.

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