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Case report

Septic arthritis due to *Histoplasma capsulatum* in a leukaemic patient

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SUMMARY A case of septic, histoplasmal monoarthritis of the knee in a leukaemic patient is described. Ketoconazole therapy failed to eliminate the infection, but after histoplasmosis was diagnosed prolonged therapy with amphotericin B was curative.

Key words: fungi, histoplasmosis, leukaemia, myeloproliferative disorders, antifungal agents.

A 29-year-old man with acute myelogenous leukaemia refractory to chemotherapy was admitted to the hospital with fever, diarrhoea, and neutropenia on 23 September 1983. On physical examination the patient's temperature was 38·5°C. His pulse was 120/min, blood pressure, 150/60 mmHg, and respiratory rate 18/min. He had severe mucositis of the oropharynx. There were no other significant physical findings. His white blood cell count on admission was $4{\cdot}3 \times 10^9$/l with 86% blasts, 12% neutrophils, and 2% lymphocytes. His haemoglobin was 9·1 g/dl, and his platelet count 22×10^9/l. Stool cultures for enteric pathogens were negative. Blood cultures, held for one week, were negative.

On 26 September 1983 he developed a right knee effusion. 15 ml of thick, yellow, cloudy synovial fluid was aspirated. The fluid contained $1{\cdot}2 \times 10^9$/l white blood cells, with 99% mononuclear cells and 4×10^9/l red blood cells. The protein content was 1·9 g/dl, (19 g/l), and an examination for crystals was negative. Gram's stain of the fluid revealed Gram-positive cocci, but bacterial cultures were subsequently negative.

After failure to respond to broad-spectrum antibiotics, including vancomycin, clindamycin, tobramycin, and trimethoprim-sulphamethoxazole, the patient was given amphotericin B empirically, resulting in prompt defervescence. A total dose of 180 mg of pamphotericin B was given over five days. Broad-spectrum antibiotics were given for 22 days because of the possibility of bacterial infection. Chest roentgenograms during this period showed an infiltrate in the lower left lung. The patient was discharged on 15 October 1983, receiving trimethoprim-sulphamethoxazole, one double-strength tablet twice a day, and ketoconazole, 200 mg twice a day.

On 17 October 1983, two days after discharge, he was readmitted with a fever of 39°C, chills, and weakness. On examination an effusion of the right knee was noted. There were no other significant physical findings. His peripheral white blood cell count was $8{\cdot}2 \times 10^9$/l, with 56% blasts, 22% neutrophils, 6% lymphocytes, and 16% monocytes. His haemoglobin was 11·2 g/dl, and his platelet count 30×10^9/l. At this time a small, budding yeast was isolated from the synovial fluid cultures obtained 26 September 1983. The yeast was subsequently identified as *Histoplasma capsulatum*, the identification being based on the microscopic morphology, conversion to mould phase at room temperature, and the production of characteristic tuberculate macroconidia. Roentgenograms of the right knee did not show changes of osteomyelitis.

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Serum liver function tests were within normal limits except for a mildly elevated alkaline phosphatase. On his third day in hospital amphotericin B was administered; complete defervescence occurred within 24 hours. A total dose of 880 mg of amphotericin B was given over the next month. A chest roentgenogram while the patient was in hospital was negative, and the knee effusion disappeared. Sputum and urine cultures were negative for fungus. Complement fixation testing for serum antibodies to histoplasma yeast antigen was negative on 21 October 1983.

On 6 December 1983 the patient died of his underlying disease. Necropsy revealed no microscopic or cultural evidence of histoplasmosis. Retrospectively, stored serum samples from 13 September 1983 and 11 October 1983 both showed a 1:8 titre for antibodies to histoplasma yeast antigen, by means of complement fixation. Stored serum from 15 November 1983 and 6 December 1983 were negative when tested for antibodies to histoplasma antigen.

Discussion

Histoplasma capsulatum rarely invades synovial membranes or bone. However, there have been a few reported cases of histoplasmal septic arthritis, which probably resulted from haematogenous seeding of the joints.[1–4] A reactive polyarthritis has also been described in a patient with histoplasmosis which was thought to be immunologically mediated.[5] Although disseminated histoplasmosis frequently occurs in immunocompromised patients and often involves the bone marrow, infection of joints or bone has not been described in these patients.[6–8] In contrast, disseminated histoplasmosis due to the African strain, *Histoplasma duboisii,* commonly invades bone.[9]

Retrospective serological testing for antihistoplasmal antibodies showed the presence of antibodies on two occasions when the patient was actively infected. A previous review concluded that serological testing in immunocompromised patients with proved histoplasmosis infection is unhelpful because serologic titres are often low and serial titres are often not available.[7] In spite of these difficulties, a positive serological titre may suggest the diagnosis of histoplasmosis and prompt further diagnostic tests, especially in a geographic area where histoplasmosis is not endemic.

Our patient relapsed after a five-day course of intravenous amphotericin B followed by oral ketoconazole, before the diagnosis was known. When histoplasmosis was diagnosed, prolonged therapy with amphotericin B was curative. Others have reported a poor response to ketoconazole therapy in immunocompromised patients with histoplasmosis.[8] Amphotericin B remains the therapy of choice for immunocompromised patients with disseminated histoplasmosis.

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