Amphotericin B responsive *Scedosporium apiospermum* infection in a patient with acute myeloid leukaemia

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Abstract

A 71 year old man with newly diagnosed acute myelomonocytic leukaemia developed a soft tissue infection of his foot during his first course of chemotherapy. *Scedosporium apiospermum* was isolated from the lesion, which resolved rapidly on treatment with intravenous amphotericin B despite being resistant in vitro to this agent. This observation suggests that sensitivity testing of *S apiospermum* should be interpreted with caution and that clinical response may be a better indicator of outcome.

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Case report

A 71 year old man was admitted under the care of the geriatric services following an anterior myocardial infarction. He made an uneventful recovery from this, but was noted to have hepatosplenomegaly and a total leucocyte count of 45×10^9/l, with a blood film suggestive of acute myelomonocytic leukaemia (AML). This was confirmed on examination of a bone marrow aspirate and a trephine biopsy specimen. The patient was enrolled on the Medical Research Council AML 11 trial, and randomised to receive DAT (daunorubicin, cytosine arabinoside, tuioguanine) 3 + 10. He was commenced on prophylactic ciprofloxacin 250 mg and fluconazole 50 mg, both twice daily, when he became neutropenic. His initial course was uneventful apart from a pyrexial episode six days after his initial chemotherapy which responded promptly to piperacillin and gentamicin. No bacterial or fungal pathogens were isolated. On day 13, while still profoundly neutropenic, the patient complained of pain in his right foot. On examination, there was tenderness over the metatarsal heads, no erythema and the overlying skin was intact. Over the next 48 hours, the foot became increasingly painful, swollen and erythematous. A necrotic ulcer developed between the fourth and fifth toes. Bacterial culture of a swab from this ulcer and blood cultures were negative. He was commenced empirically on teicoplanin 400 mg once daily and the fluconazole was increased to 100 mg twice daily.

Six days after the onset of symptoms, there was no improvement and a grey mould was isolated from swabs of the ulcerated area. Growth was observed after two days on Sabouraud dextrose agar supplemented with 0·1 g/l chloramphenicol, incubated at 30°C in 5% CO_2. This was subsequently identified as *Scedosporium apiospermum* by the Public Health Laboratory Service Mycology Reference Laboratory in Bristol. When the mould was first isolated, the patient was started on amphotericin B intravenously at a dose of 1 mg/kg daily; ceftazidime and flucloxacillin were also given. After seven days, the pain and swelling had begun to resolve, the amphotericin B dose was reduced to 1 mg/kg on alternate days and the antibacterial agents discontinued. After one month, amphotericin B was discontinued because of hyponatraemia and a rise in serum creatinine concentration from 75 μmol/l to 106 μmol/l. Treatment was continued with itraconazole capsules, initially at 300 mg twice daily, tapering to 100 mg twice daily. By this time the minimal inhibitory concentrations (MICs) of amphotericin B and itraconazole were available: amphotericin B MIC 8 mg/l, reported as resistant, and itraconazole MIC 4 mg/l, reported as intermediate sensitivity. The MICs were assayed using an agar incorporation method in Sabouraud agar. Serum itraconazole concentrations were not measured. The lesion gradually resolved despite continued neutropenia; bony destruction was not evident on *x* ray. He was discharged home 10 weeks after admission. The patient's leukaemia did not remit after the first course of chemotherapy and after the subsequent course, his marrow became severely hypoplastic with failure to regenerate. The patient remained red cell and platelet dependent and had further episodes of bacterial septicaemia. His neutrophil count never recovered following his second course of chemotherapy. He was maintained on itraconazole 100 mg twice daily and there was no recurrence of infection in his foot. The patient died of cerebral haemorrhage four months after diagnosis and three months from the first appearance of the foot lesion.

Discussion

Scedosporium apiospermum is the anamorphic (asexual) form of the fungus *Pseudallescheria boydii*. It is this form which is isolated from clinical specimens. *S apiospermum* is ubiquitous in soil and rotting vegetation and may cause human infection after traumatic subcutaneous implantation or inhalation.[1] The commonest infection associated with this organism is soft tissue mycetoma leading to sinus formation and eventual osteomyelitis. Fungal soft tissue

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infections are common in developing countries where fungal elements in soil and vegetation may become implanted under the skin, particularly where farmers work barefoot. Sporadic cases occur in temperate countries, again with reports in agricultural workers.[2] The case reported here was a keen gardener, but he did not report any penetrating injuries to the foot. In immunocompetent patients the initial lesion is usually a hard, tender subcutaneous nodule which eventually softens and ulcerates. The classic description is of sinus formation, discharging tiny white grains composed of fungal elements. It spreads slowly through the soft tissues and if left untreated, will eventually invade bone.[1 3] Bronchopulmonary infection usually involves colonisation of bronchi or preexisting cavities, though pneumonia with abscess formation has been reported.[4] In neutropenic patients rapid spread may occur, to local lymph nodes or even haematogenously.[5] The initial treatment of serious fungal infection in neutropenic patients is usually intravenous amphotericin B. This remains the treatment of choice for aspergillus, the most common cause of fatal fungal infection, and is also highly active against candida species.[6] Most strains of *S apiospermum* are resistant in vitro to amphotericin B and itraconazole is now regarded as the treatment of choice.[7] Surgical drainage of collections remains important; before the development of effective antifungal agents, amputation was sometimes necessary.[8] Sensitivity testing of fungi is difficult and is most reliably done by a reference laboratory. The correlation between serum and tissue concentrations and the MIC of amphotericin B for most fungi has not been established, consequently the predictive value of sensitivity tests is limited.[9]

In conclusion, we have reported a rare but well described fungal infection which responded to conventional blind amphotericin B treatment despite resistance in vitro. This case reinforces the need to interpret laboratory results in conjunction with clinical findings.

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