Aspergillus flavus Endocarditis in a Child with Neuroblastoma

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We report a case of Aspergillus flavus endocarditis in a 6-year-old boy with stage IV neuroblastoma with no pre-existing cardiac disease. The infection was successfully treated with high-dose liposomal amphotericin (AmBisome) once daily. Recurrence was prevented with itraconazole oral solution once daily as maintenance therapy. Adjunctive surgery was not required. The patient’s cardiac function was uncompromised, but subsequent death from progressive neuroblastoma prevented long-term follow-up.

Introduction

Endocarditis caused by Aspergillus species in immunocompromised adult and paediatric patients without underlying cardiac defects is uncommon.1,2 Blood cultures are rarely positive3 and diagnosis is most often achieved by histology and by microbiological culture of surgically resected vegetations. Echocardiography can be useful for visualization of vegetations.4 Fungal precipitin tests and antibody titres may be helpful in diagnosis and in monitoring the progress of infection. Mortality from Aspergillus endocarditis is high. A combined approach of surgery and aggressive antifungal chemotherapy is usually the best option for treatment.5 Here we report a case of A. flavus endocarditis in a paediatric patient who was being treated for neuroblastoma.

Case Report

A previously fit 6-year-old boy presented with a 4-month history of septic skin spots followed by coughing, weight loss, anorexia and lethargy. He developed difficulty in walking and pain in his hip approximately 1 month prior to admission to hospital. Full blood count showed moderate normochromic normocytic anaemia with a normal white cell count, low platelets and a leucoerythroblastic blood film (Hb: 8.5 g/dl, RBC: 3.22 x 1012/l, WBC: 5.8 x 109/l, neutrophils: 2.6 x 109/l, lymphocytes: 47.0%, monocytes: 5.0%, platelets: 71 x 109/l). His ESR was elevated at 65 mm/h. Urinary catecholamines were increased. Abdominal ultrasound and computed tomography (CT) scan revealed a left suprarenal mass. Bone scan and skeletal survey suggested extensive bony metastatic disease. Examination of a bone marrow aspirate revealed infiltration with neuroblastoma cells, which was confirmed on trephine biopsy and tumour markers. Biopsy of the primary mass also confirmed neuroblastoma.

Chemotherapy consisting of vincristine, cyclophosphamide, etoposide and alternating carboplatin and cisplatin was started. As an alternative to adjunctive surgery, antifungal therapy was changed to high-dose (5 mg/kg) liposomal amphotericin (AmBisome) once daily. After 3 weeks of AmBisome therapy there was no evidence of fungal lesions on echocardiography. After a total of 6 weeks of AmBisome, antifungal therapy was changed to long-term maintenance with itraconazole oral solution (5 mg/kg once daily). Serum itraconazole levels were monitored by HPLC on a regular basis to ensure that absorption from the gastrointestinal tract was satisfactory. Over a period of 14 weeks, the average pre-dose count was 2.6 x 109/l. Prior to this he had been neutropenic for approximately 2 weeks (less than 0.5 x 109/l neutrophils for 6 days and between 0.5 and 1.0 x 109/l neutrophils for the remainder). Blood from the Hickman line was taken for culture, and vancomycin therapy was started for a suspected bacterial line infection. Aspergillus flavus was isolated from blood culture after 2 days’ incubation. One set of repeat blood cultures grew the same organism. The minimum inhibitory concentration (MIC) of amphotericin against the A. flavus isolate (determined according to the method of Warnock6) was 1.0 mg/l. Daily amphotericin therapy (1 mg/kg) was started. Chest X-ray and abdominal ultrasound performed after the first positive blood culture showed no evidence of infection. Echocardiography revealed the patient’s Hickman line apparently passing through the tricuspid valve and into the right ventricle, but no evidence of infection. One week later, repeat echocardiography revealed a fungal vegetation on the wall of the right ventricle with involvement of the chordae. The dimensions of this echogenic mass were 6 mm by 8 mm. The patient’s C-reactive protein level on the date of first positive blood culture was 46 mg/l. Throughout the following week, C-reactive protein levels were monitored daily and increased to 147 mg/l. Five days after the first positive blood culture, tests for Aspergillus precipitins were positive by CIE (titre 1:8). Aspergillus antigen tests (Pastorex Aspergillus latex agglutination test) were negative. Culture of routine screening swabs, including Hickman line site swabs, revealed no evidence of Aspergillus species.

The patient’s Hickman line was removed and amphotericin therapy continued via a peripheral line fed into the left median cephalic vein. Culture of the Hickman line tip revealed a fungal vegetation of echogenic appearance with evidence of involvement of the chordae. The dimensions of this fungal vegetation were 6 mm by 8 mm. The patient’s C-reactive protein level on the date of first positive blood culture was 46 mg/l. Throughout the following week, C-reactive protein levels were monitored daily and increased to 147 mg/l. Five days after the first positive blood culture, tests for Aspergillus precipitins were positive by CIE (titre 1:8). Aspergillus antigen tests (Pastorex Aspergillus latex agglutination test) were negative. Culture of routine screening swabs, including Hickman line site swabs, revealed no evidence of Aspergillus species. The patient’s Hickman line was removed and amphotericin therapy continued via a peripheral line fed into the left median cephalic vein. Culture of the Hickman line tip was negative. One week later a soft systolic murmur was detected and echocardiography revealed that the initial fungal vegetation had increased in size and that an additional echogenic mass was present, also in the right ventricle, on the wall opposing the primary lesion. As an alternative to adjunctive surgery, antifungal therapy was changed to high-dose (5 mg/kg) liposomal amphotericin (AmBisome) once daily. After 3 weeks of AmBisome therapy there was no evidence of fungal lesions on echocardiography. After a total of 6 weeks of AmBisome, antifungal therapy was changed to long-term maintenance with itraconazole oral solution (5 mg/kg once daily). Serum itraconazole levels were monitored by HPLC on a regular basis to ensure that absorption from the gastrointestinal tract was satisfactory. Over a period of 14 weeks, the average pre-dose

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level was 0.61 mg/l (range: 0.03–1.23 mg/l) and the average post-dose level was 0.88 mg/l (range: 0.06–1.48 mg/l). Serology for Aspergillus species, performed on a weekly basis, demonstrated positive precipitin results (titres of 1:8–1:64) for a period of 13 weeks. Aspergillus antigen tests remained negative throughout. The patient’s cardiac status was not compromised; however, as a result of the fungal endocarditis it was necessary to interrupt his treatment for neuroblastoma. After a delay of 4 weeks, anti-cancer chemotherapy was recommenced and was tolerated; however, it proved impossible to clear bone marrow infiltration with neuroblastoma. The patient died of progressive malignant disease 8 months after diagnosis of Aspergillus endocarditis. Throughout this period there was no recurrence of fungal infection.

Discussion

Aspergillus endocarditis most commonly occurs after cardiac surgery or as a result of disseminated fungal infection in an immunocompromised patient. The prognosis is generally poor and definitive diagnosis ante-mortem is difficult. Blood cultures are generally negative. Surgery is often required in cases of suspected Aspergillus endocarditis to confirm the diagnosis, and is generally indicated as an adjunct to antifungal therapy in valve replacement for proven infection. There are, however, rare exceptions where medical management alone has been effective. The portal of entry for Aspergillus conidia is most commonly the respiratory tract. However, the use of central venous lines can be associated with cutaneous aspergillosis and subsequent systemic infection.

Our patient’s A. flavus endocarditis was possibly line-associated in spite of negative culture results from the line tip. Culture of A. flavus from two blood specimens from the Hickman line, the position of the mural vegetation relative to the line tip, and the lack of evidence of invasive fungal disease at any other site suggest this.

Invasive fungal infection is generally more common in patients with acute leukaemia than in those with solid tumours. The cytotoxic chemotherapy for the former group is more intensive, producing longer periods of more profound neutropenia, predisposing them to invasive fungal infection. First-line antifungal therapy for endocarditis remains amphotericin; however, in our case treatment with the conventional preparation of this drug did not prevent the increase in size of the original vegetation nor the appearance of a second echogenic lesion. As liposomal amphotericin (Ambisome) is significantly less toxic than conventional amphotericin, it can be administered at higher doses. At a dose of 5 mg/kg per day it proved to be an effective treatment for this case. The usual sequence of clinical events in Aspergillus endocarditis entails rapid progression of fungal disease, requiring adjunctive surgery to remove infected tissue.

Itraconazole oral solution, used for maintenance therapy in this case, was well tolerated and was successful in preventing recurrence of fungal infection. Assay of serum concentrations of itraconazole monitored its absorption from the gastrointestinal tract. Studies to date suggest that serum concentrations of itraconazole of greater than 0.25 mg/l are adequate for antifungal prophylaxis. Our patient’s serum itraconazole concentrations, both pre- and post-dose, exceeded this level for eight of the 10 serum specimens analysed.

In conclusion, this report details a case of Aspergillus endocarditis in a patient with neuroblastoma, without pre-existing cardiac disease and with no evidence of invasive fungal infection at any other site. Adjunctive surgery of the mural fungal lesions was not required, as antifungal therapy alone produced resolution of infection. High-dose Ambisome may well be an effective treatment in such cases and the oral solution formulation of itraconazole a satisfactory antifungal maintenance therapy.

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References