Two cases of aspergillus endocarditis in non neutropenic children on chemotherapy for acute lymphoblastic leukaemia

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Abstract

Fungal endocarditis (FE) is a rare complication in immunocompromised patients which is difficult to diagnose and has been characterized by excessive mortality (>50%) and morbidity, regardless of treatment. The lack of clinical trials due to the small number of cases contributes further to a poor outcome. In our two cases of aspergillus endocarditis we reviewed the clinical features, echocardiographic findings, microbiologic data, treatment, and outcome of these 2 cases and provide a current characterization of the syndrome. In this paper we have demonstrated the diversity of presentation of a critical fungal infection in immunocompromised but non neutropenic paediatric patients. The prompt diagnosis and initiation of treatment is crucial for a favourable outcome along with the use of double antifungal treatment with liposomal amphotericin and voriconazole initially which could be later switched to oral voriconazole with a good tissue penetration. Histological samples as well as radiological evidence and echocardiograms should be reviewed by experienced clinicians in order to aid diagnosis and promptly initiate treatment for these patients in order to achieve a favourable outcome.

Introduction

Fungal endocarditis (FE) is an uncommon occurrence. Previously published series reported fungi as causes of infective endocarditis in 1.3-6% of cases. FE has been characterized by excessive mortality (>50%) and morbidity, regardless of treatment. A combined medical-surgical approach seems to offer an improved outcome. However, there are no clinical trials to support or refute this opinion, largely because of the rarity of the syndrome. Advances in medical and surgical therapies, including reconstructive cardiovascular surgery, implantation of intracardiac prosthetic devices, prolonged use of IV catheters, exposure to broad-spectrum antibiotics, and immunosuppression, have been implicated as causes of the increase in the number of cases of fungemia and FE seen. Establishing a definitive diagnosis of infective endocarditis is frequently a problem.1,2 Aspergilli are widespread molds populating virtually every site of organic debris. More than 200 different species of Aspergillus are known, but only a few are consistently pathogenic. A. fumigatus and A. flavus are the most frequently isolated species.3

Case #1

A 2 years old girl was diagnosed with pre B-ALL with a total white cell count of 43.000/dL and started treatment on the UKALL2003 trial. During intensification block where patients receive Vincristine along with anthracyclines she was admitted with ongoing pyrexia, tachycardia, rigors and a blanching rash on the left thigh. The full blood count showed a WBC:3.000/dL N:1.800/dL and a high C-reactive protein. As there was no obvious focus of infection and had a Hickman line she was started on broad spectrum antibiotics for presumed line infection according to the regional protocol (meropenem and vancomycin) for immunocompromised patients which was switched to second line antibiotics 48 hours later due to persistent pyrexia. Simultaneously blood cultures were positive for aspergillus fumigatus. Clinical examination revealed a systolic murmur and bilateral crackles. The echocardiogram demonstrated a right atrium/Superior Vena Cava echogenic lesion representing a vegetation. The biopsy of the lesion confirmed the presence of aspergillus fumigatus. The patient underwent a high resolution chest CT scan which didn’t reveal any evidence of fungal infection. Hickman line was removed and a temporary neck line was inserted for antifungal treatment. Chemotherapy was withheld. She was commenced on liposomal Amphotericin 3 mg/kg along with intravenous voriconazole which was switched to oral voriconazole once adequate levels in the blood were reached. Liposomal amphotericin was discontinued after 2 weeks and she remained on oral Voriconazole throughout chemotherapy. An Echocardiogram was repeated after 4 weeks and showed no evidence of vegetations with negative blood cultures. Currently the patient is well and in remission from ALL.

Case #2

An 11 years old boy diagnosed with Acute Lymphoblastic leukaemia in March 2004. He was treated on UKALL 2003 trial. During his maintenance phase he was admitted to hospital with pyrexia and shortness of breath suggestive of pneumonia. The full blood count showed WBC:12000/dL N:8.400/dL and a high C-reactive protein. Chest X-ray was normal. He was started on intravenous meropenem as guided by the regional protocol for immunocompromised patients and four days later his temperature was settled as well as his symptoms and in the absence of positive blood cultures he was discharged from hospital on oral clarithromycin. However 5 days later the patient was readmitted with pyrexia, productive cough and the chest X-ray showed right middle lobe consolidation. He was started on intravenous ceftuoxime and Azithromycin with minimal improvement. Sputum samples were sent for microscopy and cultures. Two days later he developed a systolic murmur and the antibiotics were changed to benzylpenicillin and gentamycin for presumed endocarditis despite the lack of positive blood cultures. In addition to this Aspergillus fumigatus was grown from the sputum cultures. He had a high resolution CT scan of the chest which showed a cavitiation on the right middle lobe representing an aspergilloma. Treatment with intravenous Ambisone was initiated along with intravenous voriconazole which was switched to oral voriconazole once adequate levels in the blood were reached. Liposomal amphotericin was discontinued after 2 weeks and she remained on oral Voriconazole throughout chemotherapy. An Echocardiogram was repeated after 4 weeks and showed no evidence of vegetations with negative blood cultures. Currently the patient is well and in remission from ALL.

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Key words: Aspergillus endocarditis, leukaemia, liposomal amphotericin, voriconazole.

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cal sections there were numerous PAS positive hyphae representing Aspergillus. Cultures confirmed the presence of Aspergillus fumigatus. Post operatively he became hypotensive and required inotropic support in the paediatric intensive care unit. Liposomal Amphotericin was discontinued after 17 days and he was continued on oral voriconazole for three months. He had a follow up high resolution CT scan and an ECHO which confirmed complete resolution of the aspergillomas.

Discussion

Systemic aspergillus endocarditis occurs mainly in severely immunocompromised patients and in most cases in the literature includes a pulmonary focus and the survival was frequently poor. Review of the British literature showed five patients with fungal endocarditis in the setting of bone marrow transplantation and revealed the same difficulties in diagnosis and poor outcome. Amphotericin B, as exemplified in the current literature review, remains the mainstay of medical therapy. Mortality caused by Aspergillus endocarditis is unique, since most of the cases reported to date included severe pulmonary disease. Despite the lack of clinical and pathological signs of a pulmonary port of entry, infection through the respiratory tract cannot be ruled out, since the respiratory tract is considered the usual port of entry for these organisms although the presence of the central line in our first case favours its use as the main site for Aspergillus entry and hence it was removed rapidly. In our second case, no venous access device had been in place during the onset of fever, and preceding bacterial sepsis with pneumonia might have caused pulmonary tissue damage, facilitating aspergillus entry along with the use of broad spectrum antibiotics. According to the international literature the strongest risk factor for disseminated aspergillosis is prolonged granulocytopenia in the context of immunosuppressive chemotherapy. In our patients aspergillus endocarditis presented in complete remission from leukaemia, and the neutrophil count was normal at the onset of infection.

In conclusion these two cases of Aspergillus endocarditis showed the diversity of presentation of a critical fungal infection in immunocompromised non neutropenic paediatric patients. The prompt diagnosis and initiation of treatment is crucial for a favourable outcome along with the use of double antifungal treatment with liposomal amphotericin and voriconazol which could be later switched to oral voriconazole with a good tissue penetration.

References