MEDICAL MANAGEMENT OF ASPERGILLUS FLAVUS ENDOCARDITIS

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An 11-year-old boy underwent a matched unrelated bone marrow transplant for refractory acute myeloid leukemia. He developed invasive aspergillus pneumonia and endocarditis post-transplant. The fungal endocarditis was successfully eradicated with liposomal amphotericin at the dose of 10 mg/kg/day. Surgical intervention was not required and no serious side effects of liposomal amphotericin were observed at this dose.

Keywords. Aspergillus flavus, bone marrow transplant, endocarditis, liposomal amphotericin

Even with the use of filtered laminar flow rooms, about 5% of bone marrow transplant (BMT) recipients develop invasive aspergillosis [1]. The mortality rate due to invasive aspergillosis in these children approaches 90% [2] and a combined approach of surgery with antifungal therapy is considered to be the best treatment option [3]. However, surgery may not be feasible in a sick child. Published information about alternative approaches in such a condition is minimal. We describe a child with fungal endocarditis, post BMT treated successfully using a high dose of liposomal amphotericin.

CASE REPORT

An 11-year-old boy with refractory acute myeloid leukemia (AML) (FABM2) failed to achieve remission on the Medical Research Council AML-12 induction protocol [4] and subsequently also on the FLAG protocol [5]. Remission was finally achieved with CLASP (cytarabine and L-asparaginase) chemotherapy and sustained with 3 pulses of high-dose cytarabine-based chemotherapy (MIDAC, MACE, and CLASP) [4]. A matched unrelated T-cell-depleted bone marrow transplant was performed in remission. Oral itraconazole and acyclovir were given as antifungal and antiviral prophylaxis, respectively, pre- and post-transplant. Total body irradiation, cyclophosphamide, and Campath-H were used for conditioning. Methotrexate and cyclosporin were used as prophylaxis for graft versus host disease.
On day 7 post-transplant, the boy became pyrexial and developed a small necrotic lesion on the tip of his nose. Ceftriaxone and gentamicin were commenced along with granulocyte colony stimulating factor (G-CSF). The lesion progressively increased in size and required debridement on day 13. Liposomal amphotericin at the dose of 5 mg/kg/day was started the same day. Histological examination of the debrided tissue showed fungal hyphae and Aspergillus flavus was subsequently isolated on tissue culture. Although the child improved clinically, fever persisted. An echocardiogram (ECHO) on day 27 showed vegetations on the right ventricular wall and near the mitral and tricuspid valve leaflets. The vegetations were sized as between 9 × 8 mm and 12 × 10 mm. The next day the boy developed respiratory failure and required ventilation. A chest X-ray (CXR) showed generalized opacification, and a high-resolution computerized tomography (CT) scan of the chest showed bilateral hazy infiltrates and nodularity suggestive of invasive pulmonary aspergillosis. A bronchoalveolar lavage performed at the same time failed to isolate any pathogenic organisms. The dose of liposomal amphotericin was then increased to 10 mg/kg day⁻¹. The boy’s clinical condition improved steadily and he was extubated 6 days after increasing the dose of liposomal amphotericin. He required no further respiratory support, including oxygen. An ECHO performed on day 42 (2 weeks later) and on day 60 showed normally functioning cardiac valves with no evidence of vegetations. Repeat CXR and CT scan of the chest also showed marked resolution of the parenchymal disease.

**DISCUSSION**

Invasive nasal aspergillosis is an unusual presentation of systemic aspergillus infection in the immunosuppressed patient. Although isolation of Aspergillus species on nasal screening is thought to be predictive of invasive multisystem disease, this is not thought to be beneficial for patients managed in filtered laminar flow settings [6]. Our patient developed invasive cutaneous disease even though he was managed in a HEPA-filtered cubicle. The finding of Aspergillus flavus on nasal cultures together with the CT features of invasive pulmonary aspergillosis and vegetations on the ventricular wall, unusual in bacterial endocarditis, favor a diagnosis of fungal endocarditis. In this case itraconazole prophylaxis failed, which may reflect the wide inter- and intraindividual variability of the drug when administered orally to neutropenic patients [7]. In this case, progressive pulmonary disease with endocardial involvement developed while the patient was on standard recommended doses of liposomal amphotericin. Recommendations for management in such cases are varied and usually include surgical resection of the vegetations. Since this was not feasible in this boy’s condition, we elected to increase the dose of liposomal amphotericin to 10 mg/kg day⁻¹. This
proved effective, and he quickly became better with marked improvement in the respiratory condition and disappearance of cardiac vegetations.

Toxicity observed at this dose was persistent hypokalemia and a transient increase in urea and creatinine on day 30. Hypokalemia was successfully managed with potassium supplements and amiloride, a potassium-sparing diuretic. The rise in urea and creatinine levels was less than 2-fold and coincided with the time when the patient was unwell and in need of intensive treatment, which could have aggravated the rise in these compounds. We did not note any other adverse effects. Serum potassium and creatinine normalized with the withdrawal of high-dose liposomal amphotericin.

Because of the attendant renal toxicity of amphotericin and the fact that doses cannot be escalated without causing severe adverse effects, it is now the standard practice in our unit to use liposomal amphotericin instead of amphotericin. We have now used this high dose of liposomal amphotericin in other patients with suspected/proven disseminated fungal disease with no significant toxicity. To our knowledge there is only one other previous report of nonsurgical treatment of fungal endocarditis [8]. In that case, a child with neuroblastoma and aspergillus endocarditis was successfully treated with liposomal amphotericin at a dose of 5 mg/kg day\(^{-1}\). In our case, disease progressed on this dose and the clinical condition improved only when the dose was increased to 10 mg/kg day\(^{-1}\). Where surgical debridement of invasive aspergillosis is not feasible, particularly in the BMT setting, liposomal amphotericin alone at a dose of 10 mg/kg day\(^{-1}\) can be used effectively with little toxicity.

**REFERENCES**