Invasive Aspergillosis in Paediatric Oncology Patients

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SUMMARY

Invasive aspergillosis predominantly occurs in immunocompromised patients and is often resistant to different therapeutically strategies. However, mortality significantly increases if the central nervous system is affected. In this report we describe two cases of invasive aspergilosis, one with kidney involvement with a successful treatment while the other with pulmonary and cerebral involvement with a grave outcome.

KEY WORDS:
Aspergillosis, Oncology, Pulmonary, Nephritis

INTRODUCTION

Invasive aspergillosis (IA) is a serious life threatening complication in immunocompromised children. The average incidence of IA is estimated to be 5-25% in patients with acute leukaemia, 5-10% after allogeneic bone marrow transplants, and 0.5-5% following autologous bone marrow transplants[1]. Although recognised as the most common fungal infection in cancer patients, its true incidence is probably underestimated because of the low sensitivity of diagnostic tests. In neutropenic patients, mortality rates range from 50%-90%[2]. Clinical features of different types of IA depend on the organ of localization. We report two cases of IA to illustrate the aggressive nature of this disease.

CASE 1

A 5 year-old Indian boy was diagnosed to have acute lymphoblastic leukaemia. He developed febrile neutropenia and was receiving broad spectrum antibiotics as well as Amphotericin B at a dose of 1mg/kg/day. He complained of right sided abdominal pain associated with loose stool. An ultrasound done showed bilateral enlarged kidneys and distended gallbladder. Serial blood cultures and fungal antigen were all negatives. As the fever and pain persisted, the possibilities of typhilitis, pyelonephritis and pseudomembranous colitis were considered at this point. CT scan was done (Figure 1) which showed a necrotising pyelonephritis.

His condition subsequently deteriorated. He was then subjected to exploratory laparotomy. At laparotomy, a necrotic right kidney was found and nephrectomy was performed. Histopathology confirmed renal aspergillosis. Following laparotomy, his condition improved. He was treated with liposomal Amphotericin B for six weeks. He is currently on oral itraconazole and is receiving maintenance chemotherapy.

CASE 2

A 10 year-old Malay girl, diagnosed to have acute myeloid leukaemia developed febrile neutropenia after chemotherapy. She was also treated with broad spectrum antibiotics and amphotericin B at a dose of 1mg/kg/day. The fever persisted and she developed respiratory distress. A chest radiograph and CT scan of the thorax (Figure 2) revealed three fungal balls.

She underwent thoracotomy and two of the fungal balls were removed. Histopathology confirmed aspergillomas. She was treated with liposomal Amphotericin B (2.5mg/kg/day) for six weeks and concomitant caspofungin (25mg/day) for one month. Despite this, she presented with headache and seizures. A CT scan of the brain showed hydrocephalus with a well circumscribed lesion in the frontal horn of the left lateral ventricle suggestive of a fungal ball and cerebrospinal fluid PCR was positive for Aspergillosis. A ventriculo-peritoneal shunt was inserted, unfortunately her condition deteriorated and she died.

DISCUSSION

We have described two children with leukaemia who developed IA during periods of febrile neutropenia. Both children had already received conventional Amphotericin B. Liposomal Amphotericin B is recommended in patients with refractory disease (as in both our patients) or in patients who develop nephrotoxicity. The major limiting factor, particularly in developing countries, is the expense, which precludes the use of higher doses.

Caspofungin is a newer echinocandin drug which has been reported to have some benefit in combination with liposomal Amphotericin B[3]. Unfortunately our patient developed progressive disease despite this combination. The ideal dose of casfofungin for children has not been established. We used approximately 1 mg/kg/day which may not have been adequate. Itraconazole is recommended for patients with stable disease who are still receiving chemotherapy.

The most common form of IA is pulmonary, compromising 70-97% of all cases[4]. Symptoms and signs are usually non-specific. Haemoptysis is said to occur rarely in children; our patient never had this symptom. Surgery is an important

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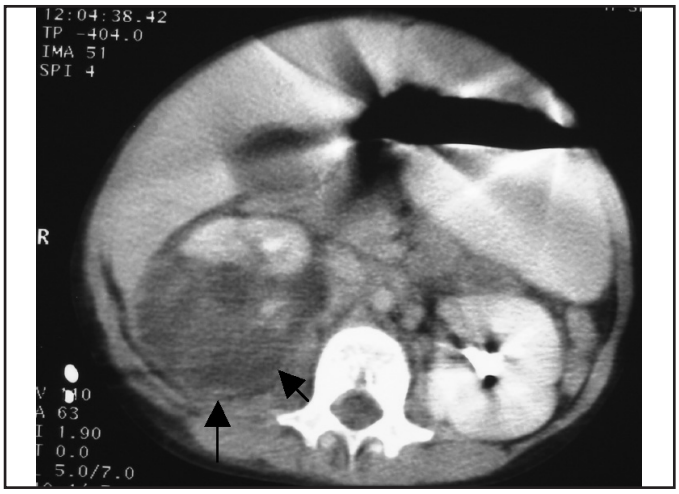

Fig. 1: Right necrotising pyelonephritis. Right kidney grossly enlarged with prominent low attenuating areas affecting most of right kidney with small residual area of normal renal parenchymal. Left kidney is normal at this level. (arrows are showing capsule of the right kidney)

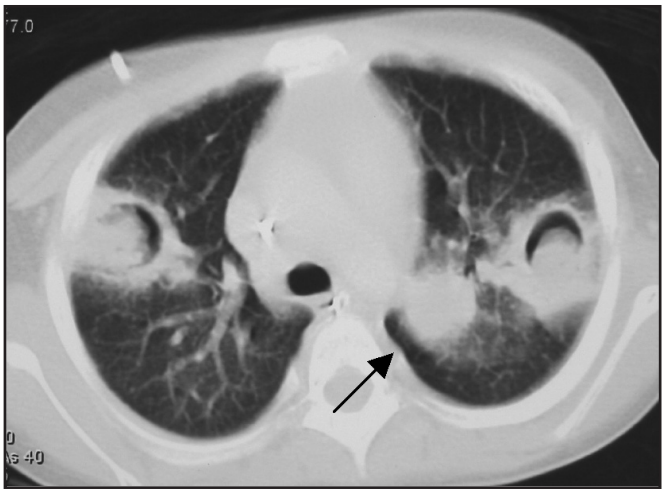

Fig. 2: Two cavitating lung nodules with "crescent sign" involving the right and left upper lobes respectively and a lung nodule in the left upper lobe medially (arrow).

adjunct in managing pulmonary aspergilloma; neutropenia has not been shown to be a contraindication[4]. Unfortunately, in our second case, one aspergilloma could not be removed due to its proximity to the hilum. This could have been a source of dissemination and the reason for her poor response to treatment.

The central nervous system (CNS) is the commonest target organ of disseminated aspergillosis. Hypodense lesions in the brain on CT scan are typical. The prognosis of CNS aspergillosis in immunocompromised patients is particularly dismal with mortality rates approaching 100%[1]. Voriconazole has been shown to penetrate the blood brain barrier well and is indicated in CNS disease. Unfortunately, at the time that these children presented, voriconazole was not available in Malaysia. The combination of caspofungin and voriconazole has been reported to be efficacious[5].

Isolated renal aspergillosis is rare. The first case reports were in leukaemic patients. It has also been reported in renal transplant recipients, the route of infection is thought to be ascending. Fungal infection was not suspected in our patient until the confirmation of histopathology results.

In conclusion, IA continues to be a scourge of paediatric oncology patients, causing considerable morbidity and mortality. The treatment is both time consuming and costly. It is hoped that availability of better and cheaper antifungal drugs in the future will improve the prognoses of these patients.

REFERENCES

1. Denning DW. Invasive aspergillosis in immunocompromised patients. Current Opinion in Infectious Diseases 1994; 7: 456–62.
2. Lin S, Schranz J, Teusch S. Aspergillosis case fatality rates: systemic review of literature. Clin Infect Dis 2001; 32: 358-66.
3. Kontoyiannis DP, Hachem R, Lewis RE, Rivero GA *et al*. Efficacy and toxicity of caspofungin in combination with liposomal Amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with hematologic malignancies. Cancer 2003; 98: 292-99.
4. Groll AH, Kurz M, Schneider W *et al*. Five year survey of invasive aspergillosis in a paediaric cancer center: epidemiology, management and long term survival. Mycoses 1999; 42: 431-42.
5. Damaj G, Ivanov V, Le Brigand B *et al*. Rapid improvement of disseminated aspergillosis with caspofungin/voriconazole combination in an adult leukaemia patient. Ann Hematol 2003; 10: 114-8.