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Invasive Aspergillosis - A Fungal Infection In An Infant Following HSCT

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Introduction

Invasive aspergillosis (IA) is one of the most frequent and serious infectious complications occurring in immunocompromised children **[1]**. Among the groups with highest incidence of IA are children severely immunocompromised due to allogeneic HSCT, those on therapy for hematologic malignancies, especially acute myeloid leukaemia and those who have primary immunodeficiencies, predominantly chronic granulomatous disease (CGD) and hyper-IgE syndrome. Other populations susceptible to IA include children undergoing solid organ transplantation (SOT), autologous HSCT, chemotherapy for solid tumour malignancy and those with advanced acquired immune deficiency syndrome or certain non-malignant hematologic disorders such as bone marrow failure syndromes or hemophagocytic lymph histiocytosis **[1]**.

Case Report

Baby R, born on 10/11/2023 is the second child born to 2nd degree consanguineous parents. His older sibling who is 2 years and 3 months of age is thus far healthy. Baby R's birthweight was 3.2 kg and after receiving the BCG vaccination was discharged from hospital at day 3 of birth. On day 6 of life the baby developed circular erythematous rash which eventually converted to generalized hyperpigmentation. A skin biopsy done revealed congenital melanosis. On day 14 of life the child developed poorly resolving pneumonia and lymphopenia. Due to severe, unusual infections he was further investigated and genetic testing confirmed the baby was having severe combined immunodeficiency (SCID) with autosomal recessive adenose deaminase (ADA) deficiency (Homozygous variant-c.703C>T p. Arg235Trp) IPT – T negative B negative type.). The baby was started on anti-tuberculosis regime at 32 days post birth. He was referred to the Bone Marrow Transplant Unit (BMTU) on 11/12/2023 for bone marrow stem cell transplantation.

On pre transplant examination he had generalized hyperpigmentation with no syndromic features, no heart murmurs and bilateral crepitations with reduced air entry of the left lung. His pre transplant investigations were as follows: full blood count WBC 6.15X 103/µL, Hb 11.8g/dL, platelets 292 X 103/µL, CRP 8mg/L, serum creatinine 25µmol/L, ALT 31 U/L, ALP 111 U/L. Viral studies revealed Hepatitis B surface antigen and Hepatitis C antigen/antibody as non-reactive, CMV PCR was negative, HIV and HHV6 were negative.

Baby R was transplanted with mismatched related allogeneic stem cells on 26/01/2024. The baby developed a febrile episode with respiratory symptoms on day 1 and his nasopharyngeal aspirate isolated *Acinetobacter* sp., while blood and urine cultures remained sterile. Viral studies done for Influenza A and B and RSV PCR were negative during that febrile episode. He was treated with intravenous (IV) piperacillin tazobactam 270mg 8 hourly for 7 days. While on IV piperacillin-tazobactam baby developed another fever spike on day 4. All cultures were negative during this episode and IV amikacin 24mg 12 hourly was started and given for 7 days. The third febrile illness appeared with accompanying diarrhoea while on IV amikacin on day 8 (03/02/2024). Stool for *Clostridium difficile* toxin A, B were negative and IV piperacillin-tazobactam 270 mg 8 hourly was re-started and given for 4 days along with oral metronidazole 25.5mg 8 hourly for 10 days. On day 11 the child developed another fever spike with negative cultures and he was treated with IV meropenem and IV teicoplanin for 10 days. Serum for aspergillus galactomannan antigen was positive with a titre of 5.51 and the baby was started on IV voriconazole on day 12. Blood for fungal culture remained negative. Due to persistent deterioration the child was started on IV cefoperazone sulbactam on day 17. The baby had developed a nappy rash which ultimately worsened by day 8 and developed into a necrotic area of the perianal region by day 13. The necrotic area was

debrided under local anaesthesia and specimens were sent to Mycology Reference Laboratory at Medical Research Institute, Colombo for fungal studies. Direct microscopy of the necrotic skin revealed septate, hyaline fungal filaments, while the culture isolated *Aspergillus fumigatus* which was sensitive to voriconazole and resistant to amphotericin B. Despite all efforts the child continued to deteriorate clinically with worsening respiratory distress and had to be intubated and transferred to the neonatal intensive care unit (NICU) on day 21 (15/02/2024). At the NICU, voriconazole was continued for a total duration of 21 days. Despite adequate medical interventions the baby succumbed to his illness, infectious and non-infectious complications followed by multi organ failure 1 month after his transplant at the age of 3 months and 17 days.

Discussion

The population-based incidence of IA in children is unknown and could vary across healthcare settings and from country to country. Despite improvements in antifungal prevention and treatment, IA is related to high mortality rates, which historically range from 52.5–85% in children with cancer, while the overall fatality rate of paediatric patients with IA who had to undergo allogeneic HSCT ranges from 45–80% in various studies **[2]**

With regard to causative species, multi centre studies and a large paediatric case series report *Aspergillus fumigatus* as the most commonly identified species, causing invasive aspergillosis accountable for about 53% of cases followed by *A. flavus* **[3,4]**. Other reported species in children include *Aspergillus niger* and *Aspergillus terreus.*

Clinical Manifestations

Lungs are the most commonly affected organ in the paediatric population which is similar to adults **[1]**. Although previous studies proposed that cutaneous IA is more common in children than adults **[5]**, more recent studies report lower rates of 14–20%. Cutaneous IA can either be primary from direct inoculation or due to nosocomial device related infection or secondary to hematogenous dissemination from another site **[6]**. *Aspergillus* can invade locally, with spread from the lung to the pleura, chest wall and heart or from the sinus to the central nervous system (CNS). Disseminated infection, is defined as disease occurring in two or more than two sites and has been reported in 10.5-38% of children with IA and can be due to hematogenous or contiguous spread **[7,8]**. Although some patients with IA present with isolated fever, the clinical manifestations vary depending on the organ system involved. Fever is common across all presentations. Manifestations of cutaneous IA can be nonspecific and include erythematous plaques, papules, nodules, pustules, blisters, ecchymosis and eschar formation, often at sites of prior trauma including intravenous catheter and tape sites **[5]**.

Diagnostic Methods

Prompt diagnosis of invasive aspergillosis is important given the high morbidity and mortality **[1]**. Culture from a sterile site and histopathologic evidence of tissue invasion remain the gold standard for diagnosis of IA but invasive procedures are necessary to obtain samples and the diagnostic yield is low **[1]**. Furthermore, *Aspergillus* is rarely recovered from blood cultures **[4,7]**. Although the yield is low, positive cultures from affected sites are valuable because the organism can be identified and can also provide antifungal susceptibilities in this era of emerging resistance even to first-line therapy **[9]**.

Other indirect diagnostics include fungal markers and radiology. Galactomannan is a polysaccharide in the *Aspergillus* cell wall that is released during fungal growth and can be measured using an enzyme immunoassay. Galactomannan testing can be performed on serum, bronchoalveolar lavage (BAL) fluid and also on cerebrospinal fluid and urine **[1]**. The sensitivity and specificity of serum galactomannan for the diagnosis of IA in children and adults is similar **[10]**.

Treatment

The 2016 IDSA guideline on the treatment of invasive aspergillosis recommends to treat cutaneous aspergillosis with voriconazole in addition to evaluating for a primary focus of infection as cutaneous lesions could reflect disseminated infection. IDSA further recommends surgical intervention as an adjunct to antifungal therapy **[11]**.

Take home message

IA is a life-threatening serious complication in immunodeficient children. Prompt diagnosis and treatment is necessary due to the high morbidity and mortality associated with the infection.

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