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Difficult diagnosis of invasive fungal infection predominantly involving the lower gastrointestinal tract in acute lymphoblastic leukaemia

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ABSTRACT

Invasive fungal infections are most commonly seen in immunocompromised patients and usually affect the respiratory system. Gastrointestinal system involvement of mucormycosis and invasive aspergillosis is rarely reported in childhood. Here we describe a 5 year old boy with acute lymphoblastic leukaemia who developed invasive fungal infection particularly affecting the lower gastrointestinal system to emphasise the difficulties in diagnosis and management of invasive fungal infections in immunocompromised patients.

1. Introduction

Invasive aspergillosis (IA) is a life-threatening opportunistic infection that usually affects immunocompromised patients [1]. Immunsuppressive therapies, high-dose corticosteroids, severe and prolonged neutropenia are the factors that facilitate the infection. Majority of the cases are caused by *Aspergillus fumigatus*, followed by *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* [2]. IA most commonly involves the respiratory tract, lung or sinus but the central nervous system, cardiovascular system, and other tissues may be infected as a result of hematogenous spread [3]. Gastrointestinal (GI) aspergillosis, which is associated with high mortality, is a rarely seen form of extra-pulmonary aspergillosis and is most often described in the setting of disseminated disease [3]. GI involvement is rarely seen in mucormycosis, and most reported cases are associated with malignant haematological diseases [4].

Here, we describe a child with acute lymphoblastic leukaemia (ALL) who developed probable invasive aspergillosis and diagnosed with GI mucormycosis by histopathologic examination simultaneously. He survived with aggressive antifungal therapy and surgery.

2. Case

A 5-year-old boy was diagnosed with CALLA (+), pre-B cell ALL in July 2013. He was put on Standard risk arm of ALL BFM 2000 Protocol at day −30. The patient was referred to our intensive care unit because of clinical deterioration and severe lower gastrointestinal system bleeding. At the admission day, at day 0, the patient's general condition was poor, with tachycardia and respiratory distress present. His body temperature was 38.5 °C, and jaundice, abdominal distension and mucositis were also observed. Laboratory test results showed a white blood count of 48/mm^3, an absolute neutrophil count of 6/mm^3, haemoglobin of 6.9 g/dL, a thrombocyte count of 35,000/mm^{3}and C-reactive protein of 11.7 mg/dL (N:0–0.5 mg/dL). The prothrombin time and activated partial thromboplastin time were prolonged, with a high international normalised ratio. The patient's biochemical values revealed a total bilirubin of 7.3 mg/dL, with direct bilirubin

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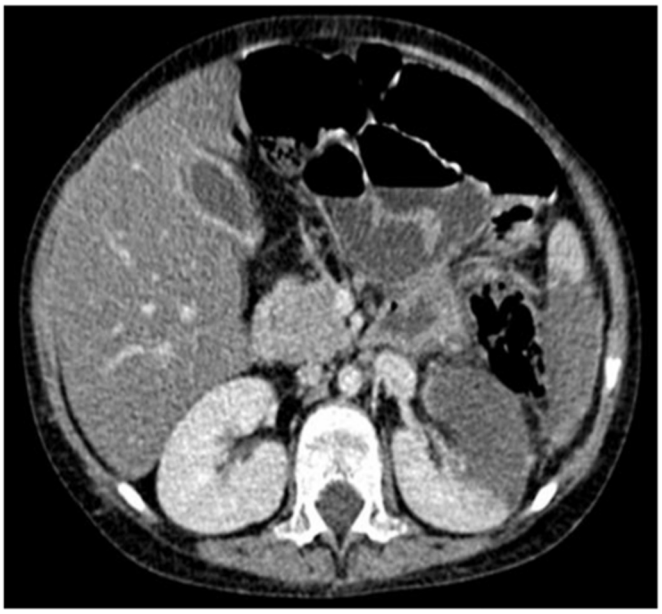

Fig. 1. CT scan showed colonic mural thickening in the splenic flexure, infarct formation in the kidney and spleen which were suggestive of IA on the 8th day.

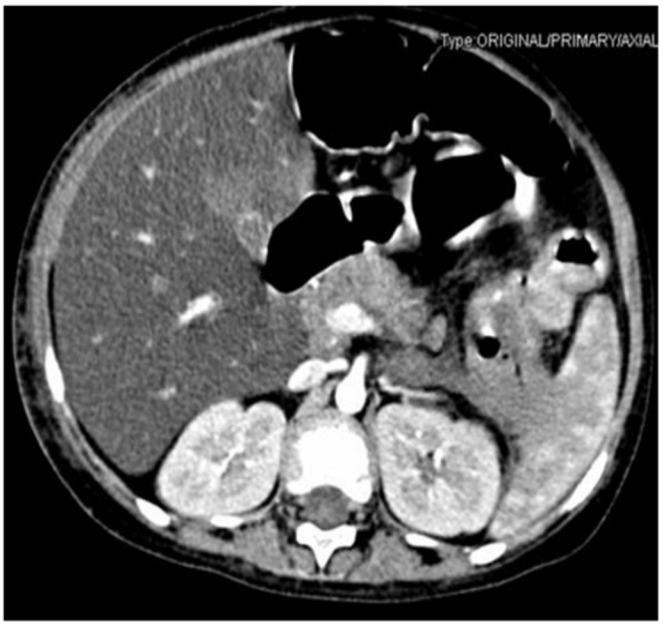

Fig. 2. CT scan showed progression in fungallesions, peripheral invasion, a covered perforation in the splenic flexure and a new hypodense lesion in the liver suspecting an aspergilloma on the 16th day.

dominance, hypokalaemia and hypocalcaemia. He was intubated and required sedation, mechanical ventilation and haemodynamic support. Erythrocytes, platelet suspension and fresh frozen plasma were administered for continuing upper and lower GI bleeding. Broad-spectrum antibiotics (piperacillin–tazobactam, amikacin and vancomycin) were started initially. At day +4, the antibiotics were changed to teicoplanin and meropenem because of the ongoing fever, and caspofungin was added after yeast (*Candida krusei*) growth in a blood culture at day +6. Abdominal ultrasonography revealed nothing of note, except hepatomegaly and minimal abdominal plastering fluid. At day +8, the patient was still febrile but he was no longer neutropenic. Gancyclovir treatment was started following a positive result of a polymerase chain reaction (PCR) analysis for cytomegalovirus, and voriconazole was added following the detection of mould in a nasopharyngeal swab. At this time, a thoraco-abdominal computed tomography (CT) scan showed colonic mural thickening in the splenic flexure and infarct formation in the kidney and spleen that were suggestive of IA. Nodular lesions compatible with IA were detected in the lung (Fig. 1). Serum galactomannan antigen was positive (> 4.73), and fungal cultures of sputum, tracheal aspirate were positive for *A. flavus*. At day +14, he was afebrile, and teicoplanin and meropenem were stopped. As no further bleeding had occurred over the previous 48 h, he was taken to the haematology department. Despite an initial improvement (reduced GI symptoms and haemorrhage) with the voriconazole treatment, the patient developed massive abdominal distension at day +16. A new abdominal CT revealed progression of the fungal lesions and peripheral invasion, with a covered perforation in the splenic flexure and a new hypodense lesion in the liver that resembled an aspergilloma (Fig. 2). The patient underwent an immediate bowel resection and splenectomy. After the surgery, he was taken to the paediatric intensive care department. Metronidazole was added to the treatment, caspofungin was stopped, and intravenous liposomal amphotericin B (AmB) (5 mg/kg/day) was started. The patient showed a clinical improvement after the surgery, with resolution of the abdominal distension and rectal bleeding. However, at day +20, he was febrile again, and teicoplanin was added due to the growth of coagulase-negative staphylococci in a blood culture. At day +22, he was reintubated because of increased respiratory distress,

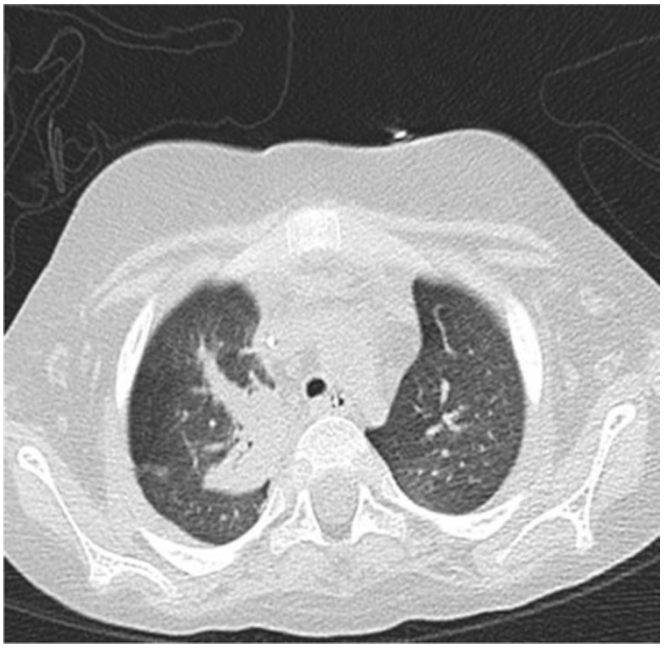

Fig. 3. CT scan revealed lesions compatible with IA.

and a repeat CT scan showed no change in the lesions, which were compatible with aspergillus. At this point, inhaled AmB (25 mg twice weekly) was added (Fig. 3.). At day +29, a histopathological analysis of resected specimens of the bowel and spleen showed ulceration, with intense inflammation, and non-septate, thick, variable in diameter fungal hyphae, which were compatible with mucormycosis (Fig. 4). Culture or PCR for pathogenic fungi from resected material could not be performed. The dose of liposomal AmB was increased to 10 mg/kg/day, posaconazole was started, and voriconazole was stopped. At day +34, bone marrow aspiration was performed and resulted in haematological remission. At day +37, a tracheostomy was performed due to prolonged ventilator dependence. His lower GI symptoms did not show persistence with this therapy. A galactomannan test positivity showed