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Case Report

Invasive Fungal Coinfection by Mucormycosis and Pulmonary Aspergillosis in An Immunocompromised Child

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Abstract

Mucormycosis and Aspergillosis are potentially lethal invasive fungal infections that mainly affect immunocompromised and diabetic patients, being exceptional in the paediatric population. The diagnosis is microbiological, and it is essential to have a strong clinical suspicion. The treatment is based on the combination of antifungal drugs (liposomal amphotericin B with voriconazole) and surgical debridement. Invasive fungal coinfection by *Mucor* and *Aspergillus* in children has never been reported. We present the case of a 4-year-old girl with coinfection by invasive Mucormycosis and pulmonary Aspergillosis as a consequence of ALL-L2 treatment. The patient received chemotherapy (cytostatics and steroids) for ALL-L2 resulting in neutropenia and hyperglycemia, well known risk factors for this type of infections. Two weeks later, she developed invasive cutaneous mucormycosis that required debridement of the right upper limb. She continued to have fever and a bronchoalveolar lavage (BAL) showed *Aspergillus terreus* and cavitated pulmonary nodules were found in a Chest computed tomography (CT). She was treated initially with liposomal amphotericin B and voriconazole and micafungin was added because of torpid evolution. However, she continued to deteriorate and died 22 days after admission in Pediatric Intensive Unit Care due to multiorgan failure. We hypothesized that triple antifungal therapy (including posaconazole) and aggressive surgical management could improve the outcome of these infections and reduce the morbidity and mortality of invasive Mucormycosis and Aspergillosis coinfections.

Keywords: Mucormycosis, Aspergillosis, Acute lymphoblastic leukemia

Introduction

Mucormycosis is an invasive fungal infection caused by fungi in the order *Mucorales*, that mainly affects immunocompromised patients. Risk factors for this infection include hematological malignancies and diabetes mellitus, but a significant proportion of patients affected by Mucor are immunocompetent individuals. Cutaneous mucormycosis is the third most common clinical form of the disease, after pulmonary and rhino-cerebral [1]. Diagnosis is difficult because of the nonspecific findings of mucormycosis. Although it represents a rare disease, its consequences are devastating, since it is associated with unacceptably high mortality rates, ranging from 20–50% if localised, up to 70–90% in cases of disseminated disease [2,3]. In heavily immunocompromised patients, *Mucorales* have a tropism for angioinvasion, resulting in dissemination, tissue infarction and necrosis. Invasive aspergillosis (IA) is one of the most common and severe infectious complications occurring in immunocompromised children [4]. The incidence of IA appears to be increasing in both, children and adults. Significant advances have occurred in the diagnosis and therapy of IA in the last 15 years, and recent studies indicate that clinical outcomes have improved during this time [5]. However, outcomes and long-term survival after IA diagnosis remains suboptimal [4-7]. Invasive *Mucor* and *Aspergillus* coinfection has been rarely reported in bone marrow transplant recipients, diabetics or immunocompromised patients [8-12]. Indeed, in children it has only been reported exceptionally [13-17]. We report an invasive coinfection with *Mucor* and *Aspergillus* in a 4-year-old girl with Acute lymphoblastic Leukemia (ALL) subtype L2 under treatment with chemotherapy and glucocorticoids.

Case Presentation

We present the case of a 4-year-old girl diagnosed with ALL-L2 that underwent treatment with chemotherapy and glucocorticoids. The patient was admitted to Pediatric Intensive Unit Care (PICU) due to suspicion of tumor lysis syndrome. After resolution of the tumor lysis the patient was transferred to the Haematology ward to continue treatment of her baseline disease. 15 days after admission, the patient reported pain in the upper right limb associated to an erythematous lesion that was diagnosed as skin cellulitis, and treatment with amoxicillin-clavulanic acid was started. The lesion progressively worsened and one week later it developed swelling, paresthesia and reduced mobility despite an adequate treatment with antibiotics and analgesia. Due to lack of improvement, plastic surgery and vascular surgery were contacted. The physical examination revealed necrotic lesions, hypoperfusion and absence of distal pulses in the upper right limb, so an urgent Doppler ultrasonography was requested that showed

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no radial, ulnar, or humeral Doppler flow in the right upper limb. Doppler flow was normal at the axillary level. The patient underwent a surgical thrombectomy and was subsequently readmitted to PICU. Due to the necrotic appearance of the lesions and the persistence of hyperglycemia and neutropenia, cutaneous mucormycosis was suspected so treatment with liposomal amphotericin B(L-AmB) was started. 24 hours after admission to PICU, the pain in the upper right limb reappeared and the distal pulses were difficult to palpate, so a second Doppler ultrasonography was requested, revealing there was no axillary flow. A second thrombectomy was performed. Cultures taken in theatre were sent to microbiology and pathology labs and clinical suspicion of mucormycosis was confirmed (Figure 1A and 1B). Despite the second thrombectomy, blood flow in the upper right limb was not restored and the patient required resection of the right arm. After surgery, the patient remained in PICU, intubated and mechanically ventilated, with great haemodynamic inestability and need of high doses of vasoactive drugs. Throughout admission she had constant fever and high C-reactive protein levels (CRP maximum values 404.7 mg/l) and procalcitonin (PCT 144.5 ng/ml), without microbiological isolation, so she received empirical antibiotic therapy with Meropenem, Vancomycin and Amikacin. The first microbiological isolation was *Mucor*, when observing branched filamentous structures (compatible with *Mucor* type fungal structures) in the thrombotic material sent to pathology lab during the second thrombectomy (Figure 1B and 1C). Structures adhered to multiple vessels of the disarticulated limb were observed in the thrombus and in axillary and thoracic adenopathies removed in surgery, so she was diagnosed with disseminated mucormycosis. The patient continued to deteriorate with rectal bleeding and profuse diarrhoea. A head-chest-abdomen CT scan with intravenous contrast was performed and an increased size of soft tissues was observed, with hypodense lesions and peripheral enhancement in the shoulder stump, infiltration of the pectoralis major and extension to skin (Figure 2A). Periscapular tissues and muscles were also affected suggestive of myositis and infectious abscesses. Perihiliar mediastinal nodules and multiple bilateral cavitated nodules appeared in the pulmonary parenchyma. Abdominal ascites was confirmed with pancolitis, dilation and thickening of the submucosa of the colon, as well as a nodule in the upper pole of the left kidney. No intracranial lesions were observed. Microbiological solation of *Aspergillus terreus* was confirmed in bronchoalveolar lavage and Voriconazole was associated to L-AmB antifungal therapy and later, micafungin was added due to extreme clinical instability. The patient had a sustained fever up to 40° C and purulent material was drained through the surgical wound of the upper right limb. At that time, a second chest and abdomen CT scan was performed, in which findings were similar to the previous ones, as well as unfavorable radiological evolution of soft tissue abscess in the right axillary region and an increase in the number and size of the cavitated lung nodules (Figure 2B). Finally, the patient died 22 days after admission in PICU due to disseminated Mucormycosis and Aspergillosis fatal coinfection.

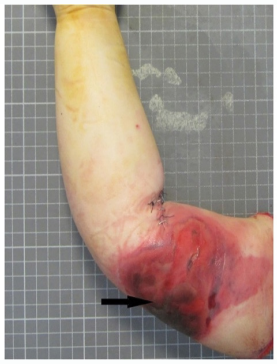

Figure 1A: Cutaneous mucormycosis with vascular invasion in upper right limb.

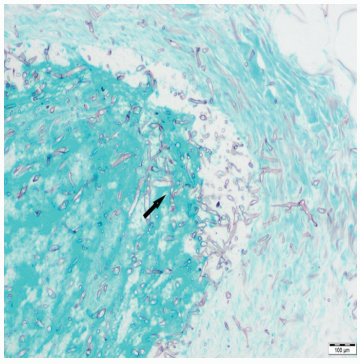

Figure 1B: Multiple septate hyphae with thin walls (arrow). Groucott stain, X 100 magnification.

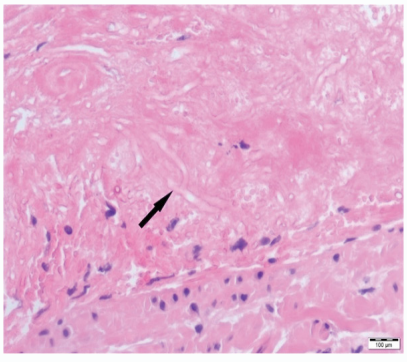

Figure 1C: Unbuttoned branched hyphae. Hematoxylin and eosin staining. X 100 magnification.

Discussion

As mentioned above, mucormycosis diagnosis is based on clinical suspicion and microbiological isolation. Although it is stated that hematogenous dissemination of cutaneous mucormycosis is rare, it is always necessary to consider it diagnosis in patients with risk factors (neutropenia and hyperglycemia in our case) who present necrotic cutaneous lesions of torpid evolution [2,6]. The antifungal treatment of choice is L-AmB without the need of combination with other antifungal drugs [18]. Over the past decade, several new antifungal drugs suitable for clinical use and novel strategies for treating invasive fungal infection have been developed. L-AmB, posaconazole and isavuconazole are currently available and show good results against mucormycosis. L-AmB has a less toxic profile compared with conventional amphotericin B (AmB) and can be safely administered at much higher doses (up to 10 mg/kg). L-AmB is the appropriate empirical antifungal for invasive mucormycosis. In cases of L-AmB treatment failure or intolerability, posaconazole or isavuconazole may serve as last resource [7,18-20]. In this case, invasive mucormycosis was complicated with invasive pulmonary aspergillosis, so voriconazole was associated to L-AmB. Due to the lack of response and the limited published literature and experience on this type of coinfection [14-17], micafungin was associated [18,19]. We described

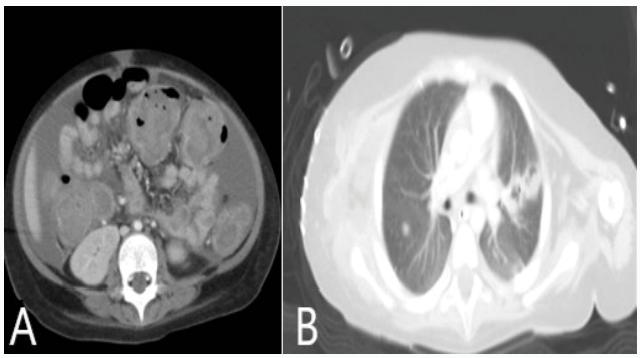

Figure 2A: First body CT scan. A. Pancolitis and dilation and thickening of the submucosa of the colon, as well as a nodule in the upper pole of the left kidney. B. Soft tissues with hypodense lesions and peripheral enhancement in the shoulder stump, infiltration of the pectoralis major and extension to soft skin. Periscapular tissues and muscles are affected with findings suggestive of myositis and multiple abscesses. Paratracheal mediastinal nodules and multiple bilateral cavitated nodules in the pulmonary parenchyma.

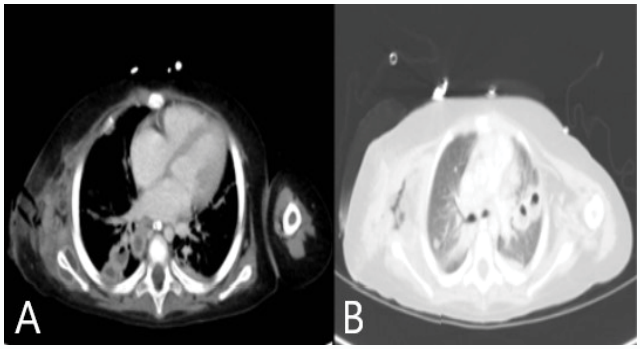

Figure 2B: Second Chest CT scan. Increase in the participation of soft tissues at the thoracic level and an increase in the number and size of the cavitated lung nodules.

this case as a rare entity in pediatric patients, so a strong suspicion is necessary, and it is essential to consider the risk factors for the development of mucormycosis. Mortality of invasive mucormycosis is high in patients with multiple risk factors such as acute myeloid leukemia, neutropenia, hyperglycemia and broad-spectrum antibiotic treatment[1]. Our case presented all these risk factors and despite an aggressive therapeutic approach, with surgical debridement and empirical invasive antifungals, the patient passed away. In conclusion, an early diagnosis and treatment of this entity might improve the outcome of this fungal invasive coinfection and reduce mortality. We hypothesized that triple antifungal therapy (including posaconazole) and aggressive surgical management could have better results reducing the morbidity and mortality of mucormycosis and aspergillosis coinfection in children.

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