A case of successful treatment of mucor pyelonephritis in a child with acute lymphoblastic leukemia

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ABSTRACT

Invasive fungal infection (IFI) is a known complication in children with malignancy. Mucormycosis is a rare cause of IFI in children receiving chemotherapy. Isolated renal involvement of mucormycosis is extremely rare and carries a grave prognosis. A high index of suspicion and early management with antifungals and surgery is essential in the treatment of mucormycosis. Here, we describe a child with mucor pyelonephritis treated successfully with antifungals and surgery with the review of literature.

Key words: *Fungal infection, Leukemia, Mucormycosis, Pediatric, Renal*

Invasive fungal infection (IFI) is a common complication in children with hematological malignancies. While *Candida* species, *Aspergillus* species, and *Cryptococcus neoformans* are responsible for the majority of IFIs, mucormycosis is the second most common invasive mold infection [1]. Mucormycosis (also called zygomycosis) is the name for the group of diseases caused by the fungi of the order Mucorales of zygomycetes class. It is considered to be an uncommon opportunistic infection that usually affects immunocompromised patients such as those suffering from hematological malignancies, patients undergoing bone marrow transplantation, and kidney transplantation.

Rhinocerebral mucor infections are commonly described in the literature. Although renal involvement is not so uncommon in disseminated mucormycosis, isolated renal involvement is extremely rare with only case reports being reported. Mucormycosis responds poorly to antifungals alone and frequently requires resection of the affected organ. Unlike other common fungal infections like *Candida*, mucormycosis has a poor prognosis, especially in immunocompromised patients. Here, we describe a child with acute lymphoblastic leukemia (ALL) who developed Mucor pyelonephritis with renal abscess and was successfully treated with antifungals and nephrectomy, followed by the review of literature.

CASE REPORT

A 7-year-old Indian girl presented with complaints of easy bruising for 1 week. She was diagnosed with Pre-B ALL after bone marrow studies. She was started on treatment as per Berlin-Frankfurt-Munster (BFM) ALL-90 protocol after securing a central line. During induction chemotherapy, she developed febrile neutropenia. Two sets of blood cultures were sterile. Urine culture grew *Escherichia coli*. She was treated with broad-spectrum antibiotics. As fever persisted, fungal workup was done.

Computed tomography (CT) of the chest and echocardiogram was normal. Invasive fungal markers like serum galactomannan were done to rule out other fungal invasive infections and were found negative. Ultrasound (USG) of the abdomen was done which showed heterogeneous hypo-echoic echogenicity with no demonstrable vascularity at the upper pole of the right kidney - suggestive of infarction or infectious etiology. CT abdomen showed well-defined non-enhancing, low attenuating focus in the upper and mid pole of the right kidney, indicating evolving abscess with pyelonephritis (Fig. 1). It also revealed a non-obstructing cast with central calcification in the right renal pelvis.

Subsequently, she underwent fine-needle aspiration cytology, which was consistent with fungal infection but speciation was not possible. Repeated blood cultures were done to rule out fungemia in the bloodstream, which was negative. In the absence of fungemia, and the fungal infection being localized to the kidney, we continued to use the central line with standard aseptic precautions. Antifungal was escalated to amphotericin B. Follow-up USG abdomen showed interval development of cystic changes at the upper pole of right kidney and right hydroureteronephrosis with echogenic content - fungal ball. CT abdomen showed interval development aneurysmal dilation of the upper interpolar hilar division of the right renal artery - likely representing mycotic aneurysm. CT chest was normal.

In view of progressive fungal infection despite antifungals, the right radical nephrectomy was done. Histopathological examination showed broad non-septate, pleomorphic hyphae

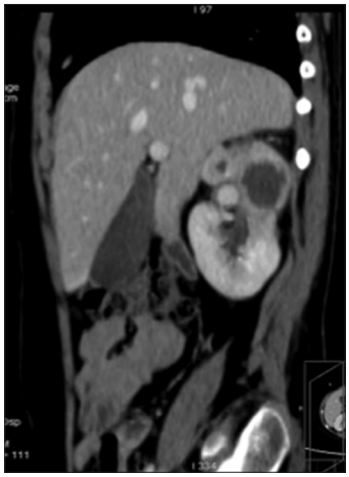

Figure 1: Computed tomography of the abdomen showing lesion in the upper pole of the right kidney

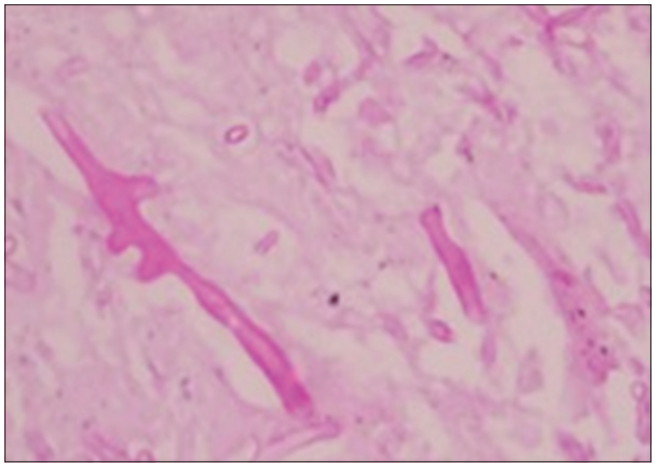

Figure 2: Histopathological examination is showing broad non-septate, pleomorphic hyphae predominantly branching at right angles

predominantly branching at right angles, which are characteristic features of mucormycosis (Fig. 2). It also showed dense lymphoplasmacytic infiltrate with granulomatous reaction and giant cell reaction. Acid-fast bacilli (AFB) stain for tuberculosis was negative. Ureter and renal vessels were unremarkable. Antifungals were given for 2 weeks postoperatively. Post-operative recovery was uneventful. Chemotherapy was continued, and she finished maintenance chemotherapy about 2 years back. Presently, she is going to school and doing well.

DISCUSSION

IFI is commonly encountered in children receiving chemotherapy. The incidence of IFI has been reported from 14% to 24 % by various investigators [2,3]. Most common fungal pathogens are candidiasis and aspergillosis. The incidence of mucormycosis is five- to ten-fold less than the other fungal infections [1]. In a review by Pagano *et al.,* two-thirds of IFI cases were attributable to molds and the rest of yeasts. Out of the infections caused by molds, zygomycetes accounted for only 4% of cases [4]. *Rhizopus*, *Mucor*, and *Lichtheimia* (formerly *Absidia*) are the most common genera that cause mucormycosis, accounting for 70–80% of all cases, whereas *Cunninghamella*, *Apophysomyces*, *Saksenaea*, *Rhizomucor*, *Cokeromyces*, *Actinomucor*, and *Syncephalastrum* are responsible for <1–5% of reported cases [5].

Mucormycosis affects all age groups from neonates to geriatric patients. The risk factors for mucormycosis are hematological malignancies, trauma, diabetes mellitus, malnutrition, severe burns, immunosuppressive therapy, etc. The major underlying conditions responsible for mucormycosis, as reported by "The global fungal infection registry" are: Malignancy (63%), diabetes (17%), and solid organ transplantation (10%) [5]. The transmission of mucormycosis is by inhalation of spores, through the gastrointestinal route or by implantation of spores at the sites of trauma [6]. The risk factors in our child were the malignancy and immunosuppressive therapy and the mode of transmission was probably inhalation. Angioinvasion is one of the characteristics of mucormycosis, which leads to vessel thrombosis, tissue necrosis, and disseminated disease [5].

Data on mucormycosis in immunocompromised children are limited. Rhinocerebral mucormycosis is the most common form of mucormycosis. Other sites such as the lungs, intestinal tract, and skin can also be affected, although isolated kidney involvement is rarely described [6]. Similarly, reports of nasal sinuses mucormycosis, intraoral mucormycosis, muscular mucormycosis, and the hepatic mucormycosis have been described by various investigators. In a review by Pagano *et al.,* in patients with hematologic malignancies, lung (64%) was the most frequent site of mucormycosis followed by orbito-sinus-facial structures (24%), while cerebral involvement and disseminated infection were observed in only 19% and 8% of the cases, respectively [4]. Dabritz *et al.* reported 12 pediatric cases of mucormycosis involving soft tissues, lungs, and rhino-cerebrum [1]. Very few reports describe an isolated renal involvement. Similar to our child, Keishin *et al.* described a 14-year-old girl with ALL who developed isolated renal abscess due to mucormycosis and was treated with antifungals and nephrectomy [6]. Yu *et al.* described another case of isolated renal zygomycosis due to *Rhizopus* oryzae, but in a patient with systemic lupus erythematosus on steroids [7].

Diagnosis of mucormycosis depends on the identification of morphological features of the etiologic agent. Characteristic features include invasion of the vessels walls and presence of fungi in the glomeruli, tubules, and interstitium [6]. Diagnosis of mucormycosis is difficult as bacteria are frequently isolated from the tissue, which may dissuade the clinician from suspecting a concomitant IFI [1]. Katragkou *et al.* also attributed the difficulty in diagnosis to tissue handling. Aggressive tissue grinding or homogenization may destroy the hyphae. Furthermore, antifungal therapy commenced before the biopsy can lead to atypical morphological features, thereby posing a diagnostic dilemma [5]. Because of the frequent presence of tissue necrosis, macrophage infiltration, langerhans cell accumulation and granuloma formation, tuberculosis is one of the differential diagnosis. The AFB stain on our child was negative thus excluding tuberculosis as the causative agent. Other differentials are renal tumors, infarction, abscesses, and angioinvasive pathogens such as *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., and *Pseudomonas aeruginosa* [5,6].

Iron plays a central role in the pathogenesis of mucormycosis and Francesco *et al.* have suggested the use of iron chelators as adjunctive therapy along with avoidance of iron supplementation and blood transfusion. They also reported a case of recurrent rhino-cerebral mucormycosis treated with antifungals, surgery, and long-term posaconazole [1]. In their review, they report that diabetic patients with rhino-oculo-cerebral mucormycosis receiving liposomal amphotericin and caspofungin had a survival advantage over those receiving a single drug [1]. Cofre *et al.* also reported that caspofungin and amphotericin B were synergistic *in vitro* [8]. There are also case reports advocating the use of hyperbaric oxygen in the treatment of mucormycosis [1].

The time of initiation of antifungal is extremely important as Chamilos *et al.* reported a two-fold increase in mortality resulting from delayed amphotericin-B (AMB) based therapy (83% vs. 49%) [5]. In another study, patients with hematologic malignancies and zygomycosis in whom AMB-based therapy against zygomycosis was delayed had higher mortality at 12 weeks than patients who had received treatment early [9]. Although surgery forms the cornerstone of treatment in mucormycosis, Mutchnick *et al.* have reported a successful outcome in invasive orbital and intracranial rhino-mucormycosis without orbital exenteration or cerebral debridement [10].

Mucormycosis has a grave prognosis, and majority of patients still die within 12 weeks of diagnosis if not managed properly [1]. In a review by Pagano *et al.,* the highest IFI-attributable mortality rate was associated with zygomycosis (64%), which was followed, by fusariosis (53%), aspergillosis (42%), and candidemia (33%) [4]. Katragkou *et al.* also opined that the invasive nature of the disease leads to overall mortality exceeding 50% [5]. Hence, early diagnosis and treatment are of utmost importance in the treatment of mucormycosis.

CONCLUSION

Mucormycosis as a cause of IFI is rarely encountered in children with ALL with isolated renal involvement being even rarer. Due to the difficulties encountered in diagnosis, a high level of suspicion is required to diagnose mucormycosis. Despite the advent of newer antifungal agents, the prognosis remains poor. Our case demonstrates that aggressive treatment with antifungals and surgery is essential to improve outcome.

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