Case Report

Disseminated fatal mucormycosis in a relapsed acute lymphoblastic leukemic child

Latha M. Sneha, Rekha Ravikumar, Julius Xavier Scott, Rajendiran Swaminathan[1]

Department of Pediatrics, Division of Pediatric Hemato Oncology, Sri Ramachandra University, [1]Department of Pathology, Sri Ramachandra University, Chennai, Tamil Nadu, India

ABSTRACT

Despite the recent advances in the pharmacotherapeutics of pediatric cancer, opportunistic invasive fungal infections still cause a significant mortality and morbidity in these immunocompromised population, being attributed to the continuous marrow suppression and aggressive chemotherapy. Mucormycosis is the third leading invasive fungal infection after candidiasis and aspergillosis. The elusive presentation and the pleiotropic clinical features of this rare, yet rapidly progressive and frequently fatal infection often cause diagnostic delays, thereby resulting in poor outcomes. A physician's early suspicion and preemptive treatment remains the important key element in the early identification, irrespective of the technological advancements. We report a case of disseminated mucormycosis in a child with relapsed acute lymphoblastic leukemia, who eventually succumbed to death despite timely intervention and appropriate treatment due to aggressive nature of the invasive fungal infection.

Key words: Child, intestinal mucormycosis, relapsed acute lymphoblastic leukemia

INTRODUCTION

Mucormycosis, a relentlessly progressive and fatal infection, is emerging as the third common opportunistic fungal infection in pediatric malignancies.[1] The extensive angioinvasion, thrombosis, tissue infarction and necrosis, and hematogenous dissemination, combined with the diagnostic delays, attribute to the grave prognosis. A high dose of liposomal amphotericin B and a radical surgical resection are the mainstay of treatment.[2] Based on the organ involved, mucormycosis causes five different clinical conditions – rhinocerebral, pulmonary, gastrointestinal (GI), cutaneous, and disseminated. Among these conditions, rhinocerebral is the most common and intestinal is the rarest form.[3]

CASE REPORT

An 8-year-old male child, a case of pre-B cell acute lymphoblastic leukemia (ALL), with central nervous system (CNS) and bone marrow relapse, was on the 2nd week of reinduction chemotherapy, on prednisolone, doxorubicin, vincristine, and L-asparaginase. He presented with complaints of fever and constipation for 4 days. There was no history of abdominal pain, abdominal distention, or bilious vomiting. On

Address for correspondence:
Dr. Latha M. Sneha, Division of Pediatric Hemato Oncology, Sri Ramachandra Medical Centre, No. 1, Ramachandra Nagar, Porur, Chennai - 600 116, Tamil Nadu, India.
E-mail: drmslatha@yahoo.com

Access this article online	
Quick Response Code:	Website: www.caijournal.com
	DOI: 10.4103/cai.cai_2_17

How to cite this article: Sneha LM, Ravikumar R, Scott JX, Swaminathan R. Disseminated fatal mucormycosis in a relapsed acute lymphoblastic leukemic child. Community Acquir Infect 2017;4:17-9.

examination, he was pale. The abdomen was soft and bowel sounds were present. There was no abnormality detected on examination of cardiovascular, respiratory, or CNS.

His hemoglobin was 7.2 g/dl, total white blood cell count was 1100/mm^3, platelet count was 23,000/mm^3, and absolute neutrophil count was 563/mm^3. His renal function test was within normal range. Serum alanine transaminase (251 U/L) and aspartate transaminase (404 U/L) enzymes were elevated. Other parameters of liver function test were normal. He was started on piperacillin/tazobactam with amikacin. Blood cultures were sterile. In view of persistent fever spikes, after 48 h of starting antibiotics, the antibiotics were upgraded to meropenem and vancomycin, and liposomal amphotericin B was added later, based on institutional febrile neutropenia guidelines. Serum galactomannan was negative. The child developed cellulitis over the right hypochondrial region and ultrasound abdomen revealed multiple poorly demarcated hypoechoic lesions in the liver and spleen. The cellulitis was progressive with extensive involvement of the abdominal wall. Contrast-enhanced computed tomography abdomen was suggestive of gastric and intestinal perforation. The child was taken for emergency laparotomy. Intraoperatively, he was found to have multiple large perforation of stomach with anterior wall necrosis, massive peritonitis, and liver and spleen infarcts with duodenal blowout. The anterior wall of stomach and part of the transverse colon were resected and sent for histopathological examination. Histopathology reports of the resected tissues showed extensive mucormycosis infection in the ischemic areas of colonic wall [Figure 1]. He had a unrelenting course with pleural, cardiac, and CNS involvement and succumbed to disseminated mucormycosis, 10 days after the diagnosis.

DISCUSSION

Children with hematological malignancies are susceptible to a number of opportunistic infections due to profound and protracted neutropenia, caused by the use of aggressive chemotherapeutic drugs and marrow suppression. Although the incidence of invasive fungal infections (4.9%–7.2%) is much less compared to bacterial and viral infections, they have a much higher mortality rate.[2] Most of these infections are caused by *Candida* species, aspergillosis, mucormycosis, histoplasmosis, and cryptococcosis.

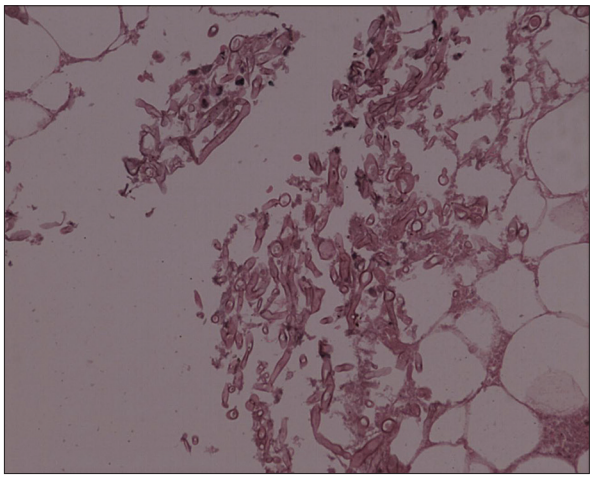

Figure 1: Broad, aseptate, and elongated microscopic organisms, characteristic of mucormycosis seen in the colonic mucosa

Mucormycosis is an angioinvasive fungal infection caused by the species of *Rhizopus*, *Mucor*, and lichteimia. Earlier, mucormycosis, a community-acquired infection in the setting of diabetic ketoacidosis, is slowly evolving into a nosocomial infection associated with iatrogenic immunosuppression. The mononuclear and polymorphonuclear phagocytes by virtue of the generation of oxidative metabolites and cationic peptide defensins are the principal host defense mechanisms against mucormycosis. This explains the increased incidence of the invasive fungal infections during the prolonged neutropenic period. Voriconazole, which has a broad spectrum of activity against *Aspergillus*, *Candida*, being used for fungal prophylaxis in relapsed and transplant patients, has literally no clinically relevant activity against mucormycosis. This has led to the selective inhibition of other fungi and colonization of mucormycosis in the susceptible population.[4]

As the fungal spores are ubiquitous in the environment, the spores easily gain access and spread infection through inhalation, ingestion, or inoculation. Commonly occurring sites of primary infection include respiratory tract, orbit, sinuses, and brain. The clinical hallmark of mucormycosis is rapid tissue necrosis as the fungi are known to invade arteries causing thrombosis, resulting in tissue infarction, necrosis, and hematogenous spread of the fungi. They rarely invade the GI system.[5] Within the GI system, stomach is most commonly affected followed by colon and small intestine. Review of literature reveals ten cases of pediatric malignancies associated with intestinal mucormycosis and 58% of them died.[1] So far, five cases of mucormycosis infection in relapsed acute leukemia have been reported, of which three were rhinocerebral and two were pulmonary.[6-8]

Challenges in establishing the diagnosis of intestinal mucormycosis are attributed to the rarity of such cases, very few signs and symptoms that are suggestive of systemic fungal infection and the GI side effects of the chemotherapeutic agents used in ALL which may cause abdominal pains and mimic the symptoms of intestinal mucormycosis, such as gastritis caused by L-asparaginase, abdominal neuropathy caused by vincristine, and pancreatitis caused by L-asparaginase.[9] The initial radiological findings of infarction in multiple organs are identical with that of aspergillosis, but the rapid clinical deterioration on voriconazole therapy should alarm a physician to identify the etiological agent.

Culturing organisms from the infected site is not reliable, as mucormycosis being ubiquitous, colonizes normal people,

and is frequently a laboratory contaminant. With no reliable serologic or polymerase chain reaction-based tests, diagnosis of mucormycosis is made by biopsy of infected tissues, showing wide, ribbon-like aseptate hyphal elements that branch at right angles.

The management of intestinal mucormycosis should include high index of suspicion, particularly when the patient presents with nausea, bloody vomiting, abdominal pain, distention, and constipation. Fever is the most common symptom found in 51% of patients.

The three key strategies in the successful management of mucormycosis are (i) rapid initiation of effective antifungal therapy combined with aggressive search for the diagnosis; (ii) extensive early surgical debridement; and (iii) rapid control of the underlying medical condition.[2] Appropriate antifungal regimen is critical for effective treatment. Liposomal amphotericin B and amphotericin B lipid complex are the first line of drugs for mucormycosis. However, combination therapy with liposomal amphotericin B and posaconazole has a more favorable outcome.[5] The characteristic features of mucormycosis – angioinvasion, thrombosis, and tissue necrosis – result in poor penetration of drugs at the site of infection, making them less effective *in vivo*.[4] Antifungal therapy alone without surgical debridement has not shown successful outcome. The premorbid status of the patient and rate of the neutrophil recovery determines the prognosis of the condition.

Delay in diagnosis of mucormycosis in immunocompromised individuals leads to life-threatening complications such as bowel wall perforation in GI mucormycosis, hard palate perforation in rhinocerebral form, and in extremely rare cases, thyroiditis in disseminated form.[10]

CONCLUSION

We would like to emphasize that it is critically important to start, initial empirical therapy with polyene antifungal, if the clinical suspicion for mucormycosis is high, as radiological findings lag behind the clinical progression. An aggressive diagnostic maneuver like endoscopic biopsy should not be delayed in case of negative imaging studies, to get an early diagnosis, as a radical surgical debridement of fungal foci would improve the outcome and survival.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Radhakrishnan N, Yadav SP, Oberoi J, Kulshreshta R, Bhalla S, Sachdeva A. Intestinal mucormycosis: A rare entity in pediatric oncology. Pediatr Hematol Oncol 2013;30:178-83.
2. Guymer C, Khurana S, Suppiah R, Hennessey I, Cooper C. Successful treatment of disseminated mucormycosis in a neutropenic patient with T-cell acute lymphoblastic leukaemia. BMJ Case Rep 2013;2013. pii: Bcr2013009577.
3. Samanta DR, Senapati SN, Sharma PK, Shruthi BS, Paty PB, Sarangi G. Hard palate perforation in acute lymphoblastic leukemia due to mucormycosis – A case report. Indian J Hematol Blood Transfus 2009;25:36-9.
4. Spellberg B, Edwards J Jr., Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556-69.
5. Pagano L, Offidani M, Fianchi L, Nosari A, Candoni A, Picardi M, *et al.* Mucormycosis in hematologic patients. Haematologica 2004;89:207-14.
6. Parkyn T, McNinch AW, Riordan T, Mott M. Zygomycosis in relapsed acute leukaemia. J Infect 2000;41:265-8.
7. Wali YA, al Lamki Z, al Kindi H, Taqi AM, Shah W, Soliman H, *et al.* Case report. Successful outcome of invasive nasal sinus zygomycosis in a child with relapsed acute lymphoblastic leukaemia due to liposomal amphotericin B. Mycoses 2001;44:195-9.
8. Grauer ME, Bokemeyer C, Welte T, Freund M, Link H. Successful treatment of mucor pneumonia in a patient with relapsed lymphoblastic leukemia after bone marrow transplantation. Bone Marrow Transplant 1993;12:421.
9. Sellappan B, Bakhshi S, Safaya R, Gupta AK, Arya LS. Invasive colonic mucormycosis in early induction therapy of childhood acute lymphoblastic leukemia. Indian J Pediatr 2005;72:77-9.
10. Irga N, Kosiak W, Jaworski R, Komarnicka J, Birkholz D. Hyperthyroidism secondary to disseminated mucormycosis in a child with acute lymphoblastic leukemia: Case report and a review of published reports. Mycopathologia 2013;175:123-7.