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Original Article

Gastrointestinal mucormycosis in the pediatric age group: an evolving disease

Nidhi Mahajan, Niyaz Ahmed Khan, Arti Khatri, Shafqat Bano, Chabbi Ranu Gupta, Mamta Sengar, Karnika Saigal, Arpita Chattopadhyay, Natasha Gupta

Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110031, India

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Abstract: Background: Mucormycosis is a devastating opportunistic fungal infection resulting in significant mortality, especially in pediatric patients with predisposing risk factors. Materials & Methods: Biopsies and surgical specimens reported and proven as Mucormycosis in children under 12 years of age were retrieved from the records for three years (January 2018 to January 2021). Complete data, predisposing factors, treatment, and clinical outcome were recorded. Results: 15 cases were identified, ranging from 9 days to 5 years. The male-female ratio was 3:1; three children were preterm. Fourteen children were diagnosed with gastrointestinal Mucormycosis (14/15), and one had palatal and sinusoidal involvement. Abdominal pain with distention was the most typical complaint. On microscopy, biopsies and surgical specimens showed extensive liquefactive necrosis with broad aseptate fungal hyphae. An intraoperative diagnosis was rendered in two cases. All neonates underwent exploratory laparotomy with surgical debridement and were administered Liposomal Amphotericin B. However, only two neonates survived out of the fifteen cases, one with disease limited to the appendix and pouch colon. The others succumbed to the disease despite antifungal therapy and surgical debridement. Thus, the overall mortality in the current study was calculated to be 86%, with neonatal mortality of 75%. Conclusion: Gastrointestinal involvement is more common in neonates and infants with a male preponderance. The diagnosis relies on direct microscopy, histopathology, and fungal culture. Intraoperative tissue may be sent in all suspected cases for direct microscopic examination for rapid diagnosis and treatment.

Keywords: Fungus, rhinocerebral, gut, KOH, antifungal, histopathology

Introduction

Mucormycosis is an invasive and lethal fungal infection caused by order Mucorales. The exact incidence or prevalence is difficult to calculate as there are few population-based studies. However, the published literature shows its annual incidence in the general population as 1.7 cases per million individuals in the United States [1]. In India, the prevalence is 0.14 cases per 1000 population, which is 80 times higher than the developed nations [2]. Immunocompromised status due to hematologic malignancies, diabetes, solid or stem cell transplants, and immunosuppressant therapy such as corticosteroids are predisposing factors for invasive Mucormycosis. However, recently there has been an appreciation for this lethal fungus in other patient groups like premature neonates, children undergoing abdominal surgeries, corrective surgery for congenital heart disease, children in pediatric intensive care units, post burns or trauma, and children with autoimmune disorders under immunomodulatory agents [3].

The interaction between the fungal hyphae and the host's immune response results in variable immune impairment, determining the final disease outcome. Clinical presentations of Mucor include sinusoidal, rhinocerebral, orbital, pulmonary, and cutaneous with relatively uncommon gut involvement [4]. Gastrointestinal involvement is predominantly seen in neonates who rapidly progress to disseminated disease and constitutes 7% of the total cases [1]. The disease shows vascular invasion by the fungal hyphae leading to thrombosis, marked tissue infarction, and necrosis, which prevents drug penetration to the affected tissue leading to

dissemination and high mortality [5]. The present case series from a tertiary care center aims to draw attention to the emerging problem of Mucormycosis in neonates, highlighting the variable disease phenotype and variable clinical presentations and providing insight into recent advances in pathogenesis and diagnostic modalities.

Materials and methods

Source of data

The study was conducted in the Department of Pathology and Pediatric surgery for three years (January 2018 to January 2021) and comprised fifteen pediatric patients. Data include demographic characteristics (age, gender), prenatal history (maturity, birth weight, vaccination history), clinical presentation, predisposing risk factors, provisional clinical diagnosis, laboratory, radiologic investigations, histopathological findings, treatment, and disease outcome were recorded.

Inclusion criteria: All the biopsies and surgical specimens reported as Mucormycosis in children from birth to 12 years of age were included in the study. Proven Mucormycosis was defined by compatible clinical or radiologic findings with histopathologic evidence of the fungus with or without microbiological identification of the organism.

Exclusion criteria: The study excluded all gastric and intestinal biopsies negative for fungus on histopathology.

Special stains

Special stains like Periodic Acid Schiff (PAS) and Gomori's methenamine silver (GMS) were performed on processed tissue to highlight the fungal hyphae.

Steps for periodic acid Schiff (PAS) staining

1. Section was deparaffinized. 2. Treated with 0.5% periodic acid reagent for 5-7 minutes. The periodic acid oxidized all the reactive glycol groups to aldehydes. 3. Then, it was rinsed in distilled water. 4. Subsequently, fresh Schiff reagent was poured (a mixture of pararosaniline and sodium metabisulfite) for 10-12 minutes. This released a pararosaniline adduct, staining the glycol-containing cellular components as magenta pink. 5. Next, the section was washed in lukewarm tap water for 5 minutes. 6. Counterstained with Harris hematoxylin for 1 minute. 7. Washed in tap water for 5 minutes. 8. Dehydrated and mounted with the help of a synthetic mounting medium.

Steps for Gomori's methenamine silver (GMS) staining

1. Section was deparaffinized and hydrated with distilled water. 2. Preheated 2% Chromic acid was added and it was allowed to stand for 5 minutes. The chromic acid oxidized the mucopolysaccharides in the fungal wall to release aldehyde groups. 3. Then, the section was washed in tap water and rinsed in distilled water. 4. 1% Sodium metabisulfite was added for 1 minute at room temperature. This step removes the last traces of chromic acid. 5. The section was washed in tap water and rinsed in distilled water three times. 6. Working silver methenamine solution was poured for one minute. The slides were agitated in the hot solution. The aldehyde groups released then reduced the silver nitrate to metallic silver, which was visible as black color. 7. Next, the section was rinsed in distilled water with two changes. 8. Section was stained with 0.5% Gold chloride for 1 minute or until grey (This caused the production of the silver-gold complex, which led to the intensification of color. This step also prevented non-specific background staining). 9. Washed in distilled water. 10. 5% Hypochlorite was put for 3 minutes, which helped remove the unreacted silver. 11. Washed in tap water and rinsed in distilled water. 12. Counterstained with working Light green solution for 1 minute. 13. Rinsed in distilled water. 14. Dehydrated, cleared, and mounted.

Results

Clinical findings

A total of 15 cases were identified. Age ranged from 9 days to 5 years. The majority of patients (8) were neonates with a mean age of presentation of 13.1 days. Four cases were between 1 month to 1 year of age, and three children presented later in life at 2, 4, and 5 years of age. The male-female ratio was 3:1. Only three children were preterm with 35-37 weeks of gesta-

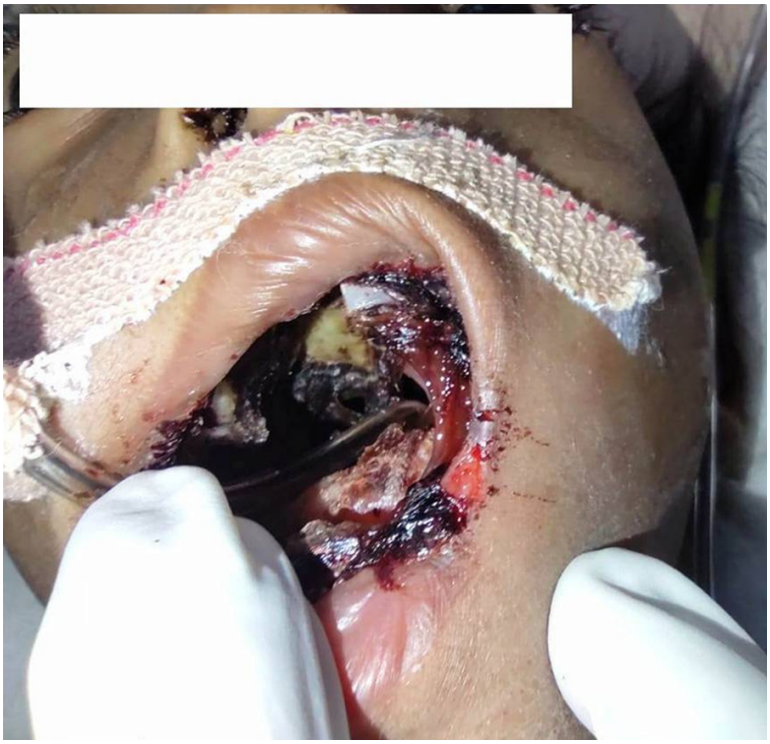

Figure 1. Clinical photograph. The palate showing black colored necrosis.

Table 1. Age-specific provisional diagnosis

Age	Provisional Diagnosis	No. of cases
< 1 month	Bowel atresia/Malrotation/Volvulus	2
	Necrotising Enterocolitis Totalis	2
	Perforation Peritonitis	1
	Hirschsprung's Disease	1
	Pouch Colon	1
	Invasive Fungal Disease	1
1 month-1 year	Perforation Peritonitis	3
	Invasive Fungal Disease	1
1-12 years	Small Bowel mass? Lymphoma	1
	Palatal Perforation? Fungal	1
	Colonic Perforation	1

tion of the eight neonates. The rest were full term at birth. The birth weight ranged between 2.2 to 2.8 kilograms. Five of them were hospital deliveries and vaccinated at birth. Fourteen children were diagnosed to have gastrointestinal Mucormycosis, and one had palatal and sinusoidal involvement. The former presented with clinical features like abdominal pain and distension, which were seen in 14 cases (93%), bilious vomiting in 10 cases (66%), diarrhea, bleeding per rectum, and an abdominal lump in one case each. One child presented with diabetic ketoacidosis and features of nasal congestion, discharge, and palatal perforation (**Figure 1**). The provisional clinical diagnoses of all cases have been summarised in **Table 1**. Of these, only three cases carried preoperative suspicion of invasive fungal disease.

Radiological findings

Basic radiological investigations such as x-ray of the abdomen were done for all cases of GI Mucormycosis once admitted to the emergency room, with all neonates showing evidence of pneumoperitoneum. CECT was available in only three cases: two were GI cases, namely bowel mass (**Figure 2**) and pouch colon, along with one patient with palatal perforation.

Predisposing factors

With respect to predisposing factors, only three neonates were preterm, and six were low birth weight. The child with palatal perforation was an insulin-dependent diabetic and had presented to us with diabetic ketoacidosis. The child with abdominal mass had severe protein-energy malnutrition. Two children showed neutropenia; the rest all had normal differential leucocyte counts. None of our patients had received any prior antifungal or corticosteroid therapy.

Histologic & microbiologic findings

The complete surgical specimen was received in only three cases. The rest of the cases were mainly received as tissue biopsies. Multiple biopsies were received in cases with widespread GI involvement. Case-wise, site distribu-

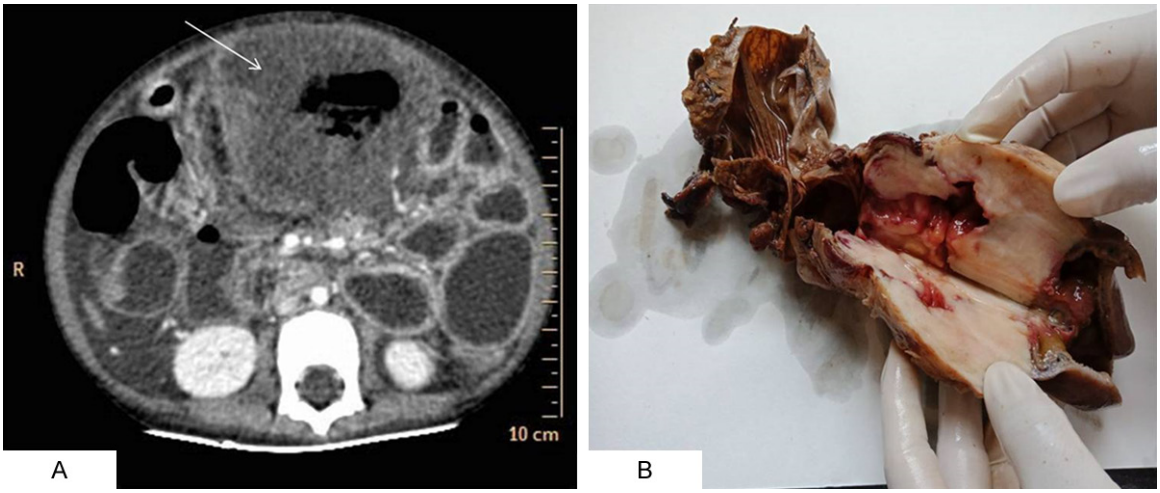

Figure 2. Radiological image & macroscopy. A. Radiological image: CECT of abdomen showing diffuse wall thickening forming a large mass in jejunum and ileum. B. Macroscopy: Gross specimen of intestine showing a grey white firm mass involving the intestinal wall circumferentially causing luminal narrowing.

Table 2. Case distribution as per site of involvement

Site of Involvement		Number of cases
Multiple sites (Stomach, small bowel, colon)		3
Small Bowel	Duodenum	1
	Jejunum	3
	Ileum	3
Large Bowel	Transverse colon, Sigmoid colon	1
	Pouch colon	1
	Appendix	1
Stomach		1
Hard Palate		1

tion is shown in **Table 2**. Intestinal specimens were gangrenous and thinned with numerous tiny perforations and grossly non-viable resected margins. A microscopic examination from both perforation sites of surgical specimens and biopsies showed extensive liquefactive tissue necrosis, and infarction with entrapped ribbon-like aseptate thin walled fungal hyphae with obtuse or right-angle branching (**Figure 3A-C**).

One of the specimens was an intestinal segment with a circumferential mass measuring 7.0 × 5.0 × 3.5 cms, which caused luminal narrowing. Microscopy from this mass revealed extensive fibroblastic and granulomatous reactions. Along with this, there was an extensive inflammatory infiltrate composed of histiocytes, eosinophils, neutrophils, plasma cells, and lymphocytes, along with giant cells showing entrapped fungal hyphae (**Figure 3B**). These hyphae were highlighted on special stains like PAS and GMS (**Figure 3D**) as magenta pink and black colored hyphae, respectively. In addition, fungal culture was positive in one case; however, speciation was not done due to unavailable resources.

Treatment and outcome

All cases with GI Mucormycosis underwent exploratory laparotomy with surgical debridement. Also, all were given liposomal Amphotericin B. However, only two neonates survived out of the fifteen cases, with disease limited to appendix and pouch colon. The others succumbed to the disease despite antifungal therapy and surgical debridement. Therefore, the overall mortality in the current study was calculated to be 86%, with neonatal mortality of 75%.

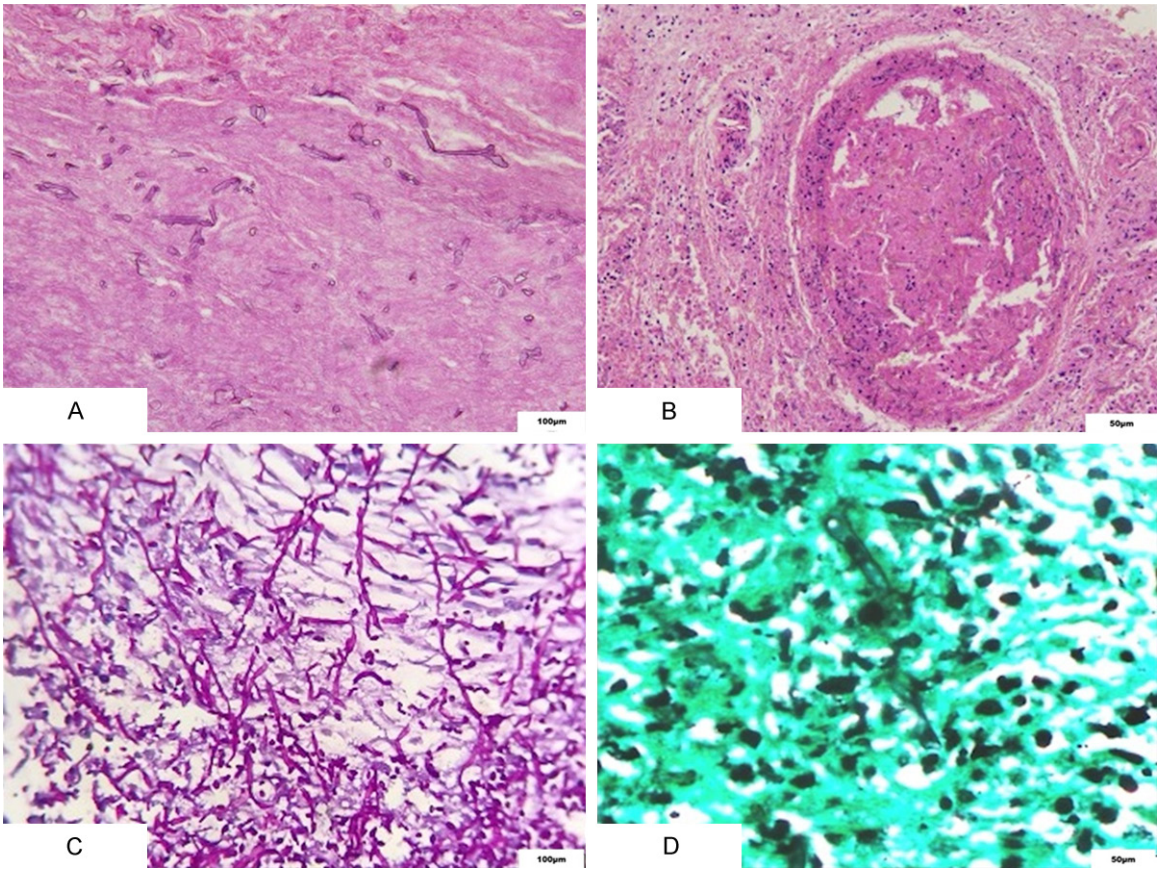

Figure 3. Microscopic examination. A. Scanner view showing heavy colonization by fungal hyphae (hematoxylin & eosin, 40X). B. Hyphae are broad and aseptate, with thin walls dispersed in a background of liquefactive necrosis (hematoxylin & eosin, 100X). C. High power view of the hyphae showing obtuse angle branching. The background shows mixed inflammatory infiltrate (hematoxylin & eosin, 400X). D. Silver Methanamine highlights the fungal elements (Gomori's Methanamine silver stain, 100X).

Discussion

Mucormycosis, fungi of the order Mucorales, causes a heterogeneous infection in both children and neonates, most cases caused by Rhizopus or Mucor species. The organism is found in decaying vegetation and soil. It proliferates, produces spores, and becomes airborne. Despite the widespread presence of the fungal spores, the infection mainly occurs in immunocompromised hosts. Risk factors for the fungal infection include diabetes mellitus, hematologic malignancies, persistent neutropenia, bone marrow or solid transplant recipients, and patients on immunosuppressant therapy like corticosteroids, treatment with deferoxamine, iron overload state, premature neonates, children undergoing abdominal surgeries, corrective surgery for congenital heart disease, children in pediatric intensive care units, post burns or trauma, severe protein-energy malnutrition and children with autoimmune disorders [3, 6]. Termos et al. [1] found Kwashiorkor, pellagra, amoebic colitis, and typhoid as additional predisposing factors in neonates with invasive Mucormycosis. Dabritz et al. [7] reported that disseminated disease and age less than one year were independent risk factors for children's high fungal load and mortality. Patra et al. [8] and Agarwal et al. [9] reported prematurity as an essential risk factor in all neonates affected in their study. The current study also showed low birth weight, protein-energy malnutrition, and diabetes as risk factors, but prematurity alone was found as a risk factor in only 20% of cases.

Infection can be sinusoidal, rhino-cerebral, orbital, pulmonary, cutaneous, renal, gastrointestinal, or disseminated. Gut involvement is

relatively uncommon and accounts for only 7% of all the reported cases [1, 6]. GI, disseminated and cutaneous diseases are more often seen in neonates than older patients. For example, Otto et al. found GI presentation in 55% of neonates, whereas in the present study, all the neonates (100%) presented with gastrointestinal disease. Patra et al. [8] and Aggarwal et al. [9] also reported predominant GI involvement in six and two neonates, respectively. In contrast, adults' Indian and western literature reveals predominant rhino-cerebral, sinusoidal, pulmonary, and orbital involvement [10-13].

Necrotizing enterocolitis in premature neonates is a clinical mimic but primarily involves the ileum and large bowel. On the contrary, premature neonates with Mucor infection can show more extensive gut involvement anywhere from the esophagus to the large bowel [14]. The present study underscores prematurity as a risk factor as the majority of the neonates were term deliveries (62%). However, their predisposition can be explained by coexistent severe malnutrition and low birth weight.

The critical factors involved in the pathogenesis of Mucor are host defense mechanisms, hyperglycemia, iron store status, and interaction of fungus with the endothelial lining of blood vessels. In immunocompetent individuals, the phagocytic cells kill fungus with the help of oxidative metabolites. Prolonged steroid use and diabetes cause hyperglycemia leading to impaired phagocytic cell function. Ketoacidosis in the latter patients may also decrease phagocytic activity. Malnutrition causes a decrease in iron-binding protein, which leads to raised serum iron levels [15].

Zinc is a trace element required for the development and function of the immune system in humans. Similarly, the fungus also requires zinc as it acts as a cofactor for various enzymes like superoxide dismutase and alcohol dehydrogenase. Both zinc deficiency and its excess can cause immune dysregulation [16]. The fungus must acquire zinc from the human host to cause infection. However, specific intracellular and extracellular mechanisms deprive the fungus of zinc metal. In humans, immune cells including neutrophils, monocytes, and dendritic cells release proteins like calprotectin and calgranulin, which bind zinc and manganese. Through these molecules, the immune cells provide antimicrobial properties. Calprotectin also explicitly limits the growth of the hyphal form of fungus. Some zinc-binding proteins like metallothionines withhold zinc from the fungus. On the other hand, fungi secrete zinc-binding proteins such as zincophores and zinc transporters for transporting zinc. However, the exact molecular mechanism of zinc transport for the survival and virulence of various fungal species in the human host is not known [16, 17].

The essence of diagnosis of Mucormycosis is the identification of host risk factors, a high index of suspicion, and expeditious clinical assessment. Abdominal distension with bilious vomiting is the most common presentation in GI Mucormycosis. Other uncommon clinical features may be an abdominal mass, pain, and bleeding per rectum. Diplopia, pain in sinuses, periorbital swelling, palatal ulcers, and features of cranial nerve palsy in a predisposed child should raise suspicion of invasive fungal disease. A Computed Tomography scan is the radiologic investigation of choice and shows multiple nodules, pleural effusion, and a reverse halo sign in pulmonary disease [18]. GI involvement in neonates and children commonly presents with perforation of intestine and pneumoperitoneum. So, there is not usually much time for radiology and the patient ends up with emergency exploratory laparotomy on simple X-rays showing gas under the diaphragm. One of the cases in our study who underwent CT abdomen presented with two masses involving jejunum and ascending colon. Positron Emission Tomography-Computed Tomography (PET/CT) with 18F-Fluorodeoxyglucose (FDG) and endobronchial ultrasound-guided fine-needle aspiration are newer emerging promising imaging diagnostic tools for Mucormycosis [19].

The linchpin of diagnosing Mucormycosis is direct microscopy, tissue histopathology, and fungal culture. Clinical specimens sent in normal saline can be directly examined in KOH or preferably using optical brighteners like Calcofluor 3. This allows rapid intraoperative or presumptive diagnosis. Fungal elements can also be appreciated well by staining a formalin-fixed specimen with hematoxylin and eosin. They are stained as non-pigmented, wide (5-20 nm), thin-walled, ribbon-like pauciseptate to aseptate hyphae with right-angled branching.

In contrast, Aspergillus or other hyaline molds are septate, 3-5 nm wide, and form acute-angled branching [15, 20]. Tissue diagnoses are of paramount importance as this is associated with neutrophilic/granulomatous inflammation, infarction, vascular and perineural invasion. Thus, the microscopic findings establish the organism's pathogenic nature rather than a cultural or sampling contaminant. The diagnosis was established in all the cases on tissue examination in the present study, with intraoperative diagnosis in two cases. Immunohistochemistry using commercially available monoclonal antibodies against Rhizopus can aid in the diagnosis when cultures are negative and has been proven helpful in differentiating Aspergillosis from Mucormycosis [20, 21].

A fungal culture is essential for genus and species identification and antifungal susceptibility testing. The organism grows well at room temperature and is easily identified on colonial and microscopic morphology. Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF) identification of cultured Mucor is a promising tool but not widely available. It is yet to be validated for all Mucorales [15, 17]. Low sensitivity and high false negativity are significant drawbacks of culture; hence molecular identification is considered the gold standard. Molecular-based assays include conventional polymerase chain reaction (PCR), restriction fragment length polymorphism analyses (RFLP), DNA sequencing, and melting curve analysis of PCR products. Molecular-based diagnosis is rapid and promising, though it has not been widely studied and lacks thorough clinical evaluation. Therefore it cannot be recommended as the standalone, single test in routine diagnostics. Fungal biomarkers such as galactomannan and 1, 3-d-glucan assays are available but are not helpful in molds as their cell walls do not contain significant amounts of these substances [4]. Emerging non-invasive methods include electronic breath testing and antigen testing, though these are still underdeveloped.

Treatment of Mucormycosis is multi-modal. It includes antifungal therapy, immune restoration, surgical debridement, and other adjunctive therapies like hyperbaric oxygen, granulocyte-macrophage colony-stimulating factor, and interferon [18, 19, 21]. The latter may enhance the immune response, but no clinical data exist so far for their use. Recently, liposomal Amphotericin B has evolved as the cornerstone of primary therapy for Mucormycosis rather than conventional Amphotericin B because it has better CNS penetration and fewer adverse effects [22]. Delay in starting Amphotericin B is an independent predictor of poor outcome, and early initiation of the same has been associated with improved survival [22]. According to Chamilos et al. [20], rapid diagnosis and initiation of antifungal therapy within six days of presentation are strongly associated with improved patient survival. Pana et al. [23] conducted an epidemiological study from two international databases and studied many cases wherein improved morality was seen with the combined antifungal therapy and surgical intervention. All the fourteen cases with GI involvement underwent surgical intervention in the present series. Fluconazole was started empirically as these patients had severe thrombocytopenia on presentation. However, they were shifted to Amphotericin B after histopathologic confirmation.

Only two of the fifteen children survived, with a mortality of 75% in neonates and 86% in children. Dabritz et al. reported an overall mortality of 64% in neonates and 56% in children [7]. The total duration of hospital stay in these children was not more than 3-4 days since most of them had rapidly progressive disease, except in the child with pouch colon involvement and appendicular Mucor. They were stable at the time of discharge after a week.

A limitation of the present study was the lack of sub-speciation of the fungus. However, beyond this limitation, the study increases awareness of this potentially fatal disease amongst pediatric physicians and surgeons; it also enriches our knowledge regarding updates on pathogenesis and management of this fungus in a pediatric setting.

To conclude, Mucormycosis is a catastrophic illness affecting the pediatric population and associated with significant mortality. Gastrointestinal involvement is more common in neonates and infants with a male preponderance. Abdominal distension and bilious vomiting may be considered red flag signs in children with underlying predisposing factors. New molecular-based methods are gaining acceptance;

however, they are expensive and unavailable in most laboratories. Hence, the diagnosis depends on direct microscopy, histopathological examination, and fungal culture. Intraoperative tissue may be sent in all suspected cases for direct microscopic examination for rapid diagnosis and early presumptive treatment, which may promise better survival chances.

Acknowledgements

The Institution Ethical Committee approved a waiver for the study in view of it being a retrospective nature. Verbal consent was also obtained from the other authors. Written consent for participation was obtained from patient's parents as the patient is less than 16 years old. Written informed consent was obtained from the patient's parents for publication of this case report, its details, and accompanying images.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Arti Khatri, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Room No. 404, Fourth Floor, Delhi 110031, India. Tel: 8700226322; E-mail: a.khatri2008@gmail.com

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