

Gastrointestinal mucormycosis — an uncommon isolated mucormycosis

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Background: Isolated mucormycosis of the gastrointestinal tract is uncommon, with only two case reports from India. **Objectives:** To study the clinicopathologic features of gastrointestinal mucormycosis in Indian patients. **Methods:** Eight cases of isolated gastrointestinal mucormycosis, seen over six years (1992-97) are reviewed. **Results:** Five of the patients were premature babies or infants, one was a 12-year-old boy, and two were middle aged. Symptomatology included vomiting, bloody diarrhea, upper gastrointestinal bleeding, abdominal lump and abdominal distention. All the neonates presented with intestinal perforation. The duration of symptoms was ten days or less in six cases. Mucormycosis was not suspected clinically in any patient. In six cases the diagnosis was established antemortem from resection or biopsy material. Only two patients received antifungal therapy and only one patient responded. **Conclusions:** Isolated gastrointestinal mucormycosis is not uncommon in India. Early diagnosis may be helpful in reducing the high mortality. [*Indian J Gastroenterol* 1998; 17: 131-133]

Key words: Large Intestine, stomach

Mucormycosis is an uncommon and frequently fatal fungal infection, which occurs more commonly in patients with an underlying immunocompromised state such as diabetes mellitus, lymphoma or leukemia, patients with chronic renal failure on peritoneal dialysis, or preterm infants.¹ One-third of the patients with zygomycosis have been infants or children,² with malnutrition and concomitant infections being the most common predisposing factors.² Depending on the anatomical site involved, there may be one of several clinical forms: rhinocerebral, pulmonary, gastrointestinal (GI), cutaneous and disseminated.^{3,4} Gastrointestinal infection is rare, the stomach and colon being the usual sites of involvement.⁵ There are only two case reports of isolated GI tract mucormycosis in the Indian literature.^{6,7} We report the clinicopathological features of 8 cases, including one reported earlier,⁷ seen at our institution over the last 5 years.

Methods

A search of the surgical pathology files for the period 1992-97 yielded eight cases of isolated GI mucormycosis. The complete clinical records of these patients were re-

trieved, and age, sex, disease presentation, any concurrent or previous disease and/or treatment (specifically of immunosuppressive drugs), subsequent treatment given and final outcome were recorded.

Histological material available was either biopsy tissue or tissue obtained at autopsy. Hematoxylin and eosin-stained sections were reviewed and fresh 4-5 mm thick sections stained with periodic acid Schiff (PAS) and silver methanamine methods were studied to confirm the diagnosis of mucormycosis.

Results

The four male and four female patients' ages ranged from 4 days to 56 years; five were less than 1 year of age (Table). The duration of symptoms varied from 3 days to 3 years but was less than 10 days in 5 patients. Five children presented with GI perforation and peritonitis. Case 3 had cystic fibrosis. Case 5 had been receiving chemotherapy for acute lymphoblastic leukemia (ALL). The other four children who were investigated revealed no immunodeficiency; HIV status was not tested. Case 8 was a 10-month-old male child who was malnourished and presented with lump in the lower abdomen.

Both the adults presented with dyspepsia and vomiting suggestive of acid-peptic disease. Case 6 presented with massive upper GI bleeding and endoscopic examination revealed a large ulcer suggestive of malignancy. Gastrectomy was done and histological examination clinched the diagnosis but the patient died before antifungal therapy could be instituted. Case 7 was diabetic; endoscopic examination in him revealed that the entire mucosa from 20 cm beyond the incisor teeth to the opening of the pylorus was nodular with superficial ulceration. HIV status was not tested in them.

Histological findings

Cases 1 and 3 were diagnosed at autopsy, whereas cases 2, 4, 5, 6 and 8 were diagnosed on histological examination of resected specimens. In case 7, endoscopic biopsy obtained from the ulcer to rule out malignancy revealed the fungus. In cases 1 through 5, sections from the large intestine showed transmural necrosis, eosinophils and chronic inflammatory cell infiltrate along with foreign-body giant cell reaction in the lamina propria, submucosa and muscle coat with marked serositis (Fig 1). Cases 1 to 4 showed transmural perforation. Special stains revealed numerous aseptate broad hyphae dividing at obtuse angles in the

Table: Clinical features of patients suffering from GI tract mucormycosis

No.	Age / sex	Signs / symptoms	Duration	Clinical diagnosis	Comment	Survival
1.	9 d/F	Abdominal distention, vomiting, constipation	3 days	Necrotizing enterocolitis	Autopsy	Died
2.	4 d/F	Constipation, abdominal distention	3 days	Hirschsprung's disease	Surgery	Died after 1 day
3.	50 d/F	Chest infection, bloody diarrhea	10 days	Cystic fibrosis	Autopsy	Died
4.	11 mo/M	Low-grade fever, cough, abdominal distention, vomiting	7 days	Necrotizing enterocolitis	Surgery	Died after 3 days
5.	12 y/M	Abdominal pain, distention, vomiting	8 days	Subacute intestinal obstruction (ALL on chemotherapy)	Surgery	Died after 7 days
6.	52 y/M	Upper GI bleeding, vomiting	10 days	Carcinoma stomach	Gastrectomy	Died after 2 days
7.	56 y/F	Dyspepsia	3 years	Peptic ulcer, diabetes mellitus	Endoscopic ulcer biopsy	Alive
8.	10 mo/M	Dysphagia, vomiting, regurgitation	8 months	Malignancy	Excision of cecal and terminal ileal lump	Died after 18 days

wall of the intestines as well as in the blood vessels (Fig 2). In cases 6 and 7 only the stomach was involved.

In cases 1 to 6 and 8, invasive mucormycosis was diagnosed, whereas in case 7, only endoscopic biopsy was done and therefore the presence of infiltration and invasiveness could not be determined.

Treatment and follow up

Cases 7 and 8 received antifungal treatment whereas the other patients died before any treatment could be started. Amphotericin B was given intravenously in a dose of 0.1 mg/Kg body weight over a period of 7 h and the dose was increased slowly up to 0.5 mg/Kg body weight. Renal functions were monitored strictly. Case 8 developed fecal fistula after a week and died 18 days after surgery. Case 7 was free of his symptoms after a month and was doing well with good diabetic control at last follow up after 2 years.

Discussion

Infections by fungus of order *Mucorales*, class *Zygomycetes*, is termed mucormycosis or zygomycosis. The mycelia of these fungi are composed of non-septate coenocytic hyphae and are seen in the infected tissue. The pathogenic genera of this order (*Mucor*, *Rhizopus* and *Absidia*) are characterized by woolly growth of mycelia on agar plates and are differentiated by three morphologic features in culture: rhizoids, apophyses and columellae. Species identification is based on morphology of the asexual phase, physiological characteristics and azygospore production.⁸ These fungi are ubiquitous saprophytic organisms that show little pathogenicity for the normal human host. Infections occur via spores; the routes of inoculation include the intestine, skin or blood stream. Regardless of the organ or tissue involved, invasion of blood vessel walls, thrombus formation, infiltration of surrounding tissue and production of black necrotic debris occur.⁸

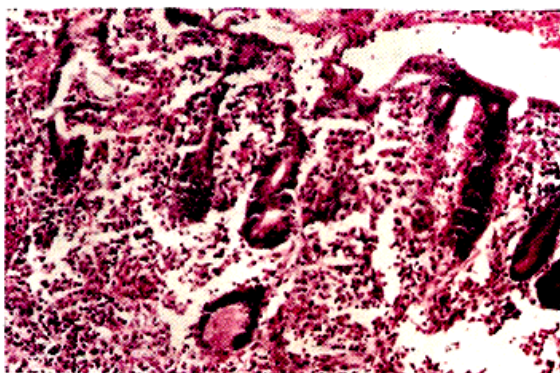


Fig 1: Photomicrograph showing mucosal ulceration, acute and chronic inflammatory cell infiltrate in lamina propria and foreign body giant cell reaction (H&E, 40X)

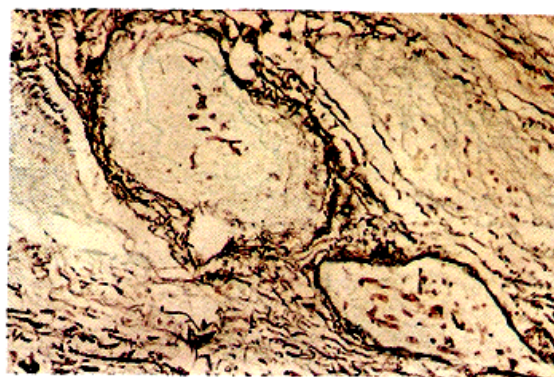


Fig 2: Photomicrograph showing blood vessel with luminal thrombus consisting of fungal hyphae. The fungus is also invading the vessel wall (PAS, 200X)

Mucormycosis accounts for 10% of all mycotic infections.⁹ Cases of GI mucormycosis have mostly been reported from Africa^{10,11} and only rarely from other areas.^{2,12} Only two cases of isolated mucormycosis of the GI tract have been reported from India;^{6,7} one of these cases is included in the present series also. Michalak *et al*² reviewed the literature till 1980 and found that one-third of the patients were children and infants. The stomach was the most common site, followed by the colon, small bowel and esophagus. Prematurity, malnutrition and gastroenteritis with dehydration were the most common predisposing factors. In contrast, six of our cases were children (possibly a referral bias); five were less than 1 year of age. Three of them were premature. One case was immunodeficient as he was on chemotherapy for ALL. Five cases of childhood GI mucormycosis presented with perforation peritonitis and one with lump in the lower abdomen. The large intestine was involved in all of them. In neonates the presentation is like necrotizing enterocolitis and may be a new form of this disease.¹²

Two of the cases were adults and the stomach was the site of involvement. Both of them had a long history of acid-peptic disease. The lone survival in our series was case 7 where the diagnosis was made antemortem by endoscopic biopsy.

Thomson *et al*¹¹ classified gastric mucormycosis into three groups: colonization, infiltrative and invasive forms. Colonization of benign ulcers occurs but does not influence the natural history of the disease. Invasive and infiltrative forms are fatal. In their series of 20 cases, all 5 patients with colonization and 6 of 7 cases with infiltrative form survived. However, only 2 of 8 patients with the invasive form survived. In the present series it is possible that the patient who survived with amphotericin treatment may have had colonization of a benign peptic ulcer.

Mucormycosis of the GI tract is associated with a high mortality. Only 4 survivors of the invasive form^{2,11,13} and 6 of the infiltrative form¹¹ are reported in the literature where diagnosis was made antemortem. Diagnosis usually depends upon evidence of tissue invasiveness as culture studies are usually negative and are hence unreliable. The presence of fungal hyphae in the tissue and angioinvasion are adequate histological proof to establish the diagnosis. Special stains like PAS and silver methanamine stain for fungi delineate morphological features clearly, but do not help in differentiating the species. Culture studies may yield better results in speciation.⁸ In doubtful cases other methods such as fluorescein-conjugated lectins or the use of cresyl violet stain which stains zygomycetale hyphae red and other mycelial fungi blue or purple can be used. Specific intradermal and complement fixation tests are available but to date have not been helpful in the diagnosis in a clinical setting.¹⁴

Since the presenting symptoms of GI tract mucormy-

cosis are nonspecific, antemortem diagnosis is rare. Signs and symptoms vary from diarrhea, bloody diarrhea and hematochezia to intestinal obstruction and perforation peritonitis. Therefore, early diagnosis needs a high index of suspicion, and coupled with aggressive surgical and antifungal therapy may help in decreasing the high mortality and morbidity associated with GI mucormycosis.² Since mucormycosis infection occurs in the presence of predisposing conditions like diabetes mellitus, malnutrition, premature infants and immunocompromised states, a high index of suspicion is required in these associated conditions. In a neonate presenting as necrotizing enterocolitis with absence of submucosal gas shadows, this condition should be suspected. For early diagnosis frozen section examination during surgery or crush preparation may be helpful.

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