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Case report

A rare case of pediatric gastrointestinal mucormycosis with a review of the literature

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ABSTRACT

This manuscript discusses a rare case of pediatric gastrointestinal mucormycosis in a hospitalized patient who presented in diabetic ketoacidosis. A review of the literature is summarized to provide an overview of mucormycosis with a discussion of the mechanisms underlying the susceptibility of diabetic patients for this condition.

Introduction

Mucormycosis is an opportunistic but devastating fungal infection caused by organisms of the order Mucorales (pin molds). The genera *Rhizopus, Mucor,* and *Lichtheimia* are the most frequently implicated in mucormycosis [1]. Mucorales are a ubiquitous group of saprobes found in agricultural and forest soils or on decomposing organic matter [2]. Microscopically, Mucorales are characterized by their broad, ribbon-like forms with wide angle branching and minimal septation [2]. These organisms enter human hosts either through inhalation of airborne sporangiospores or through direct contact with the skin or gastrointestinal mucosa [3].

Although primarily a disease of adults, mucormycosis may affect pediatric patients. In preterm neonates, the most common site of involvement is the gastrointestinal tract, usually via necrotizing enterocolitis [4–6]. The most frequent sites of mucormycosis in older children and adults are the sinuses, lungs, and skin [1,7]. Gastrointestinal and widely-disseminated mucormycosis are less common but remain an important consideration in the workup and management of severely ill patients [1,8,9]. Gastrointestinal mucormycosis can present with non-specific symptoms such as nausea, vomiting, abdominal pain, diarrhea, and abdominal distension [4]. Eventually, Mucorales cause ulceration and ischemic necrosis of bowel tissue through invasion of the underlying vasculature, and perforation may also occur [5].

Case presentation

A 13-year-old male presented to a community emergency department with several days of worsening anorexia and non-bloody, non-bilious emesis. The patient had a history of autism and behavioral concerns requiring atypical psychotics, with increased dosing of these medications approximately 6 months prior to presentation. His parents denied a history of other medical conditions, medications, or recent infections. He was found to be in diabetic ketoacidosis and was transferred to the pediatric intensive care unit. His clinical course was complicated by intermittent fevers, significant hypernatremia, coffee ground emesis, encephalopathy requiring intubation, and acute liver failure. He was started on piperacillin-tazobactam out of concern for an occult abdominal infection. A broad array of serologic, respiratory, and stool infectious studies and imaging studies were inconclusive, and he was transferred to our academic children's hospital.

Following his transfer, imaging revealed evidence of bowel perforation and he emergently underwent exploratory laparotomy, which revealed right-sided colon perforation with frank stool within the abdomen. A right hemicolectomy was performed with resection of two additional segments of dusky jejunum. The abdomen was irrigated and closed temporarily to allow for later revision.

Microscopic examination of the right hemicolectomy specimen revealed a perforated cecal ulceration with mucosal and submucosal necrosis, associated transmural inflammation, and acute serositis with purulent exudate. The proximal and distal resection margins were

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viable. Microscopic examination of the jejunal resection demonstrated patchy active inflammation, focal transmural necrosis, and diffuse acute serositis with fibrinopurulent exudate. Jejunal resection margins were partially viable with foci of mucosal and submucosal necrosis. Fungal stains were negative on representative sections from both specimens.

Two days later, the patient was brought back to the operating room for re-exploration and operative revision. The abdomen was found to contain stool which was presumed to be leaking from a pin-point perforation at the distal transverse colon, where additional ischemic tissue was identified and removed. The proximal closure at the terminal ileum was intact with viable-appearing underlying bowel. The previous arms of the jejunal resection were anastomosed, and the patient was again left in discontinuity.

Pathology exam of the colectomy specimen demonstrated focal transmural necrosis with perforation, surrounding inflammation, and diffuse serosal fibrinopurulent exudate extending to the resection margin. GMS stain revealed fungal elements morphologically compatible with Candida species (Fig. 1). AFB and Fite stains were negative for acid-fast organisms. Later that evening, blood cultures grew *Candida tropicalis* and the patient was started on micafungin.

Two days later, the patient was taken to the operating room for ileostomy placement. The viable ileal pouch was passed through a fascial defect to create the ostomy. The previous jejuno-jejunal anastomosis appeared necrotic, so it was resected to healthy bowel proximally and distally with the creation of a second anastomosis. At that time, the initially viable-appearing ileostomy had become dusky and necrotic, so the distal ileum at the ostomy site was resected to healthy bowel, concluding the procedure.

Microscopic examination of the jejunal tissue revealed marked active enteritis with mucosal ulceration and necrosis and ribbon-like fungal hyphal forms with wide angle branching, morphologically consistent with Mucormycetes species (Fig. 2). Vascular invasion and associated vascular thrombosis and ischemia were present (Fig. 3). There was a dense serosal exudate with mixed inflammation and focal yeast forms suggestive of *Candida.* Surgical margins were notable for active inflammation and ulceration overlying viable bowel wall.

The resected ileum demonstrated acute and chronic ileitis with purulent serosal exudate and focal wide-branching ribbon-like forms consistent with Mucormycetes species, as well as yeast forms consistent with *Candida* (Fig. 3). The clinical team was immediately made aware of these results, and the patient was subsequently transitioned from micafungin to liposomal amphotericin B.

Since his diagnosis of gastrointestinal mucormycosis, the patient has undergone multiple additional resections with difficulty obtaining clear surgical margins in the setting of continued small bowel necrosis and inflammation. At the time of this writing, he is awake, extubated, and being cared for on a general pediatric service.

Discussion

Incidence of mucormycosis is rising both in the United States and worldwide, likely due to an increase in at-risk populations [8,10]. Most cases of mucormycosis occur in immunocompromised patients: leading predisposing conditions include diabetes mellitus (40 % of cases), hematologic malignancy (33 % of cases), solid organ transplant (14 % of cases), and stem cell transplant (11 % of cases) [1]. In other cases, susceptibility to infection is attributable to other predisposing factors, such as corticosteroid therapy, neutropenia, recent surgery, major or minor trauma, or burn injury [1,8].

Pathogenic Mucorales organisms grow best in an iron-rich environment, and *Rhizopus* organisms use iron permeases, siderophores, and heme oxygenase homologs to re-route host iron to benefit their own growth [11]. The hyperglycemia present in uncontrolled diabetic patients exacerbates the issue, as glycosylation of transferrin and ferritin lowers their affinity for iron [12,13]. Additionally, acidic conditions can lead to conformational changes in transferrin which favors the release of chelated iron [12,14,15]. These factors help to explain the increased susceptibility of patients in uncontrolled diabetic ketoacidosis to mucormycosis—given our patient's presentation in florid diabetic ketoacidosis, he was at high risk of developing an infection with Mucorales.

Mucorales are also known to invade the host's vasculature, which promotes thrombosis and subsequent ischemic necrosis of the host tissue [11]. *Rhizopus* organisms invade endothelial cells through the binding of the endothelial cell protein GRP78 by the fungal protein CotH, which is unique to Mucorales organisms [12,16,17]. Importantly, the ketoacid β-hydroxy butyrate upregulates the surface expression of GRP78 by endothelial cells and the expression of CotH by *Rhizopus* organisms [16]. This effect does not occur in acidosis caused by lactic acid [16], furthering the vulnerability of patients in ketoacidosis to Mucorales infection. The resulting breakdown of the circulatory system limits the ability of both inflammatory cells and antimicrobial agents alike to reach the necrotic areas, highlighting the need for early surgical intervention in this condition. Extensive vascular invasion by Mucorales and associated thrombosis were identified in our patient's resection specimen, contributing to the observed tissue necrosis. The combination of the relative immunocompromise and changes in iron handling inherent to hyperglycemia with the upregulation of the endothelial cell marker GRP78 implicated in vascular invasion provide an explanation for this patient's mucormycosis infection despite the lack of formal immunosuppression.

Early diagnosis of mucormycosis is difficult given its relatively nonspecific initial symptoms [4,5]; the diagnostic dilemma is compounded by inconsistent staining patterns of Mucormycetes on commonly used fungal stains and the challenges and slow timeline of culturing mucormycosis in the routine lab setting [13,18]. If

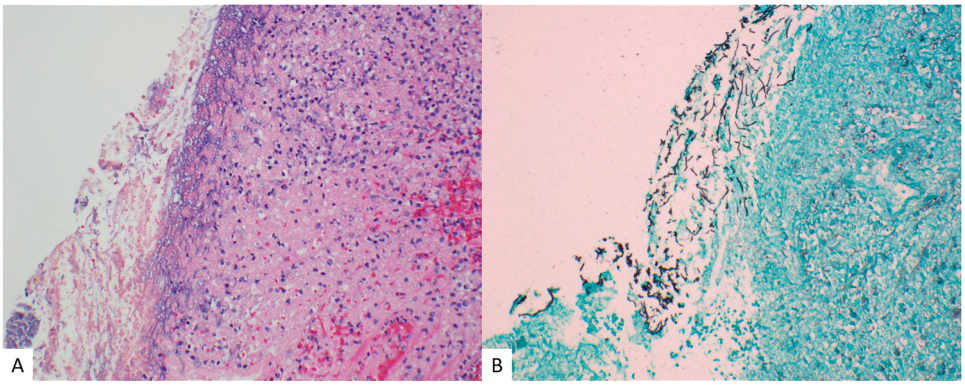

Fig. 1. Transverse colon. A) H&E, 200 ×, necrotic colon with purulent exudate. B) GMS, 200 ×, purulent exudate contains fungal elements morphologically compatible with Candida species.

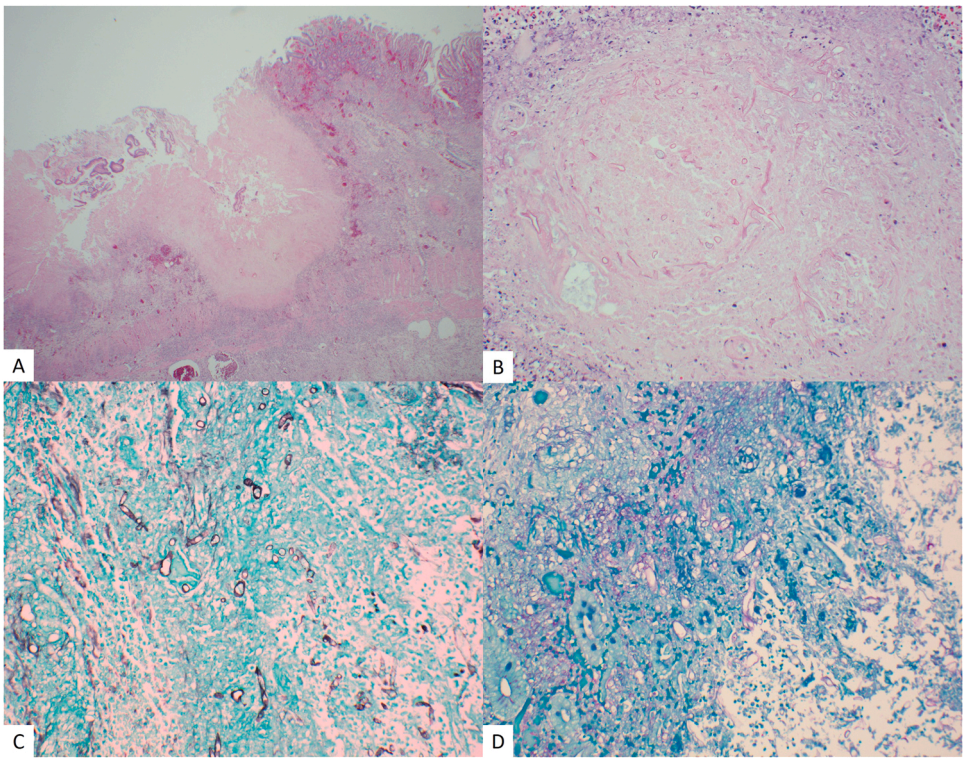

Fig. 2. Resected jejunal anastomosis A) H&E, 20 ×, marked active enteritis with mucosal ulceration and patchy necrosis. B) H&E, 200 ×, Necrotic areas demonstrate ribbon-like fungal hyphal forms with wide angle branching, morphologically consistent with Mucormycetes species. C) GMS, 200 ×, fungal hyphal forms are outlined by GMS. D) PASF, 200 ×, fungal hyphal forms are outlined by PASF.

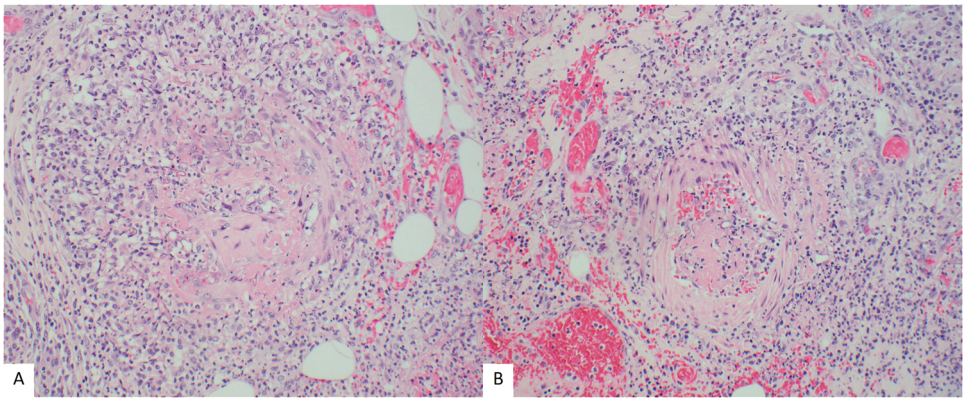

Fig. 3. Resected jejunal anastomosis A) H&E, 200 ×, vascular invasion of mucormycosis with obliteration of vasculature. B) H&E, 200 ×, tissue and vascular invasion of Mucormycetes with associated intravascular thrombosis and ischemic tissue damage.

mucormycosis is on the differential diagnosis, nucleic acid based diagnostic modalities offer high sensitivity and specificity with a much faster turn-around time: results can be available within hours of sample collection [18,19]. A wide array of samples are suitable for testing, including fresh and frozen tissue, formalin-fixed paraffin-embedded tissue, blood, urine, and bronchoalveolar lavage fluid [18,20].

Prompt recognition and treatment of mucormycosis is essential to prevent rapid progression and dissemination. Management of mucormycosis is multifactorial and should include aggressive surgical debridement, correction of predisposing factors, and antifungal therapy. Liposomal amphotericin B is the most efficacious drug in both adults and pediatric populations but carries risk of dose-related toxicity [6].

As physicians, we are responsible for ensuring the accurate and timely diagnosis of our patients, even in cases with subtle and challenging findings. The microscopic foci containing diagnostic findings of mucormycosis were few and far between and Mucorales are not always obvious on fungal stains, which only stain the outline of the organisms. Within our own pathology department, this case has served as an excellent teaching point on the importance of determining all the diagnoses in a given case and maintaining a high index of suspicion for unexpected findings – it is easy to imagine a scenario where our patient's third bowel re-resection could have been quickly signed out as acute on chronic ileitis with areas of ischemic necrosis, without identification of the pathologic Mucorales.

CRediT authorship contribution statement

Joseph Maniaci: Conceptualization, Writing – original draft, Writing – review & editing. **Thahir Sahal:** Writing – original draft, Writing – review & editing. **Christine Bookhout:** Conceptualization,

Writing – review & editing, Supervision.

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Ethical approval

Not applicable; family consent was obtained and this was a retrospective case report without research elements.

Consent

Written consent was obtained from the patient's parent and is available for review on your request.

Conflicts of interest

The authors declare no conflicts of interest.

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