Medical Mycology Case Reports 1 (2012) 52–55

Contents lists available at SciVerse ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

"We are what we eat!" Invasive intestinal mucormycosis: A case report and review of the literature

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ARTICLE INFO

Article history:
Received 27 July 2012
Received in revised form
27 July 2012
Accepted 27 July 2012

Keywords:
Gastrointestinal
Jejunum
Mucormycosis
Rhizopus

ABSTRACT

Gastrointestinal mucormycosis is an uncommon, life-threatening, angioinvasive infection with only one previous report of disease involving the jejunum. We present a case of invasive jejunal mucormycosis and review the literature, highlighting the rare clinical presentation and the value of molecular diagnostic methods. Given the global increase in patient populations at risk of mucormycosis, clinicians need to maintain a high index of suspicion and perform timely and appropriate evaluation to improve patient outcome.

1. Introduction

Fungi of the subphylum Mucoromycotina, order Mucorales cause mucormycosis—a rare, often fatal, angioinvasive infection, primarily of immunocompromised hosts [1]. *Rhizopus* species are the predominant human pathogens, commonly inhabiting soil, animal feces and decaying vegetative matter [2,3]. While any organ system may be affected, rhino-orbital-cerebral and pulmonary infections dominate the literature [2,4].

Gastrointestinal mucormycosis is the most uncommon clinical presentation being particularly rare in industrialized nations. In previous series, gastrointestinal disease has accounted for 4%–7% of all cases [2,4] with only one previous report of disease involving the jejunum [5]. Nonetheless, the incidence of gastrointestinal mucormycosis appears to be on the rise, highlighted by an increase in the number of cases indexed on PubMed—50 publications between 2000 and 2011 compared with eight between 1959 and 1989 [6].

We present a case of invasive intestinal mucormycosis in an adult male and review the literature, highlighting the rare clinical presentation and the value of molecular diagnostic methods in the management of invasive fungal infection.

2. Case

The patient, a 59 year old man who lives in rural South Australia, was retrieved to a metropolitan tertiary hospital for investigation and management of an acute abdomen in November 2011 (day 0). This occurred on the background of a past medical history significant for alcohol misuse, chronic lumbar back pain (requiring opioid analgesia) and irritable bowel syndrome. He reported longstanding alternating bowel habit and abdominal bloating with previously unremarkable upper gastrointestinal endoscopy and colonoscopy.

Importantly, 12 days prior to admission (day-12), the patient was diagnosed with *Salmonella* enteritis after developing acute diarrhea. Stool microscopy and culture confirmed growth of *S. typhimurium*.

On this occasion, the patient presented with an acute abdomen complicated by septic shock and multiorgan dysfunction. Clinical examination demonstrated peritonism with diffuse abdominal tenderness, rebound tenderness and guarding. Inflammatory markers were elevated (absolute neutrophil count 14.5×10^9/L [*N* 1.8–7.5]; C-reactive protein 150 mg/L [$N < 8.0$]). Emergency laparotomy (day 0) revealed generalized peritonitis and small bowel obstruction in the right iliac fossa secondary to acute adhesions. The proximal small bowel was reported to be "dilated and fragile" leading to perforation as it was manipulated. A 5 cm segment of macroscopically ischemic jejunum was resected.

Histological examination of the resected jejunum revealed marked edema with inflammatory cells infiltrating the wall, but not involving the serosa. Micro-abscesses and granulomata were

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2211-7539
http://dx.doi.org/10.1016/j.mmcr.2012.07.003

noted predominantly in the submucosa. Diastase treated sections stained with Periodic-acid-Schiff demonstrated focally-branching, thin-walled, infrequently septate hyphae with occasional bulbous dilatations typical of the order Mucorales (Fig. 1). On the serosal surface, there was purulent inflammation. Within the pus, using the same stain, there were small, regular hyphae consistent with *Candida* species (Fig. 2). These elements invaded the outer serosa, but were not present in the other layers of the jejunum or the lumen. There were no fissures, caseous necrosis or vascular lesions to suggest any other etiology of the jejunitis.

Unfortunately, the surgical specimen arrived in formalin and so was unsuitable for culture. A formalin-fixed, paraffin-embedded (FFPE) tissue block was sent to the mycology laboratory at the Centre for Infectious Diseases and Microbiology (Westmead Hospital, Westmead NSW) (day +2) for pan-fungal polymerase chain reaction (PCR) and internal transcribed spacer 1 (ITS1) sequencing (with the method described in Ref. [7]). Two fungi were amplified, purified and sequenced individually with identification of *Candida albicans* and a *Rhizopus* species (BLASTN sequence analysis, BioManager, ANGIS). Sequencing could not differentiate between *R. oryzae* and *R. sexualis* given their identical ITS1 sequences. Final results were available on day +25.

In the interim (day +11), the patient deteriorated with development of abdominal pain, hemodynamic instability and clinical signs of peritonism. A 2nd laparotomy revealed ileal perforation with a collection tracking from an ileal loop in the right iliac fossa to the anterior abdominal wall. "Fragile", "edematous" small bowel was again noted. A 30 cm segment of ileum was resected with creation of a functioning end-ileostomy and venting ileostomy. Histological examination of the resected ileum did not identify invasive fungal elements. Culture of the ileal tissue demonstrated growth of multi-resistant *Pseudomonas aeruginosa* (sensitive only to colistin). Fungal culture was negative at 4 weeks.

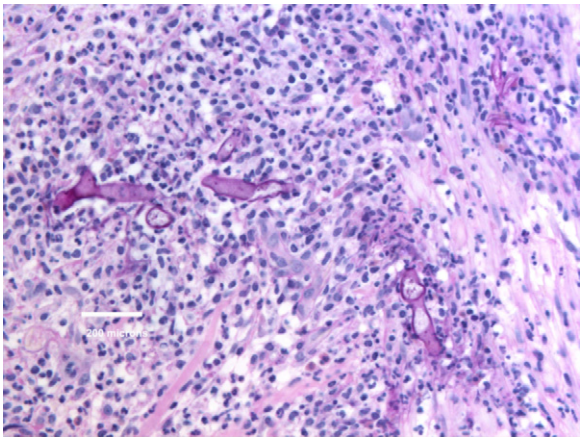

Fig. 1. Fungal elements consistent with Mucorales in the wall of the jejunum. Diastase-periodic acid-Schiff stain.

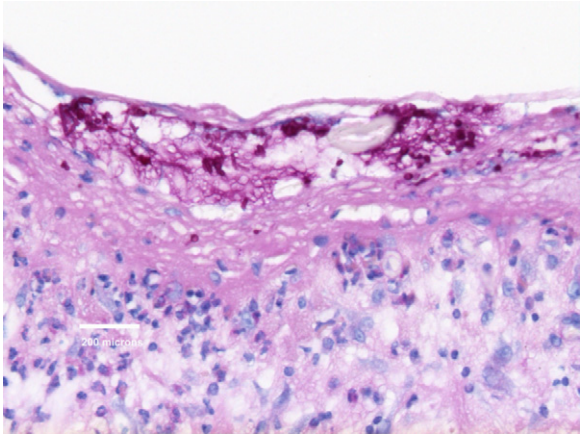

Fig. 2. Fungal elements consistent with *Candida* sp. in purulent exudate on the serosa of the jejunum. Diastase-periodic acid-Schiff stain.

After the initial laparotomy and receipt of histological findings, antifungal therapy was commenced with voriconazole (day +1). In the setting of clinical deterioration, this was substituted for intravenous liposomal amphotericin B (LAmB) 5 mg/kg daily (day +11). The patient tolerated 5 weeks of LAmB before developing acute kidney injury. Salvage therapy was commenced with oral posaconazole 200 mg four times per day (day +49). Given concerns regarding absorption, therapeutic drug monitoring was undertaken. The patient achieved appropriate posaconazole levels of 1.8–1.9 mg/L.

The patient was assessed for clinical risk factors associated with mucormycosis. Malnutrition related to alcohol misuse and recent *S. typhimurium* enteritis were the only risk factors identified. Although he brewed his own beer, he was unable to quantify his daily intake. No corticosteroid or immunosuppressive therapy had been administered. Investigations for occult malignancy, diabetes mellitus and human immunodeficiency virus were negative. There was no evidence of iron overload.

At day +224, the patient remains on posaconazole. Antifungal therapy will continue for a minimum of 12 months. There is no evidence of relapse or recurrence with resolution of abdominal symptoms, normal stomal output and normal inflammatory markers.

3. Discussion

Gastrointestinal mucormycosis is an uncommon, life-threatening infection with only one previous report of disease involving the jejunum [5]. In the largest series to date by Roden et al., 66 cases (66/929 [7%]) were gastrointestinal; there was frequent dissemination to non-contiguous organs (25/66 [38%]); and mortality was high (56/66 [85%]) related to bowel perforation and upper gastrointestinal hemorrhage [2]. A recent retrospective review by Lanternier et al. of 101 cases (60 proven, 41 probable) of mucormycosis in France between 2005 and 2007 revealed four gastrointestinal and one hepatic infection [4]. Gastrointestinal infection may be more common in the pediatric population with the only large series by Zaoutis et al. documenting 157 cases of mucormycosis with 21% involving the gastrointestinal system; mortality was 100% [8]. All parts of the alimentary tract may be affected. In a series of 87 cases, the stomach (50 cases) and colon (28 cases) were the most frequently involved sites; duodenal (two cases) and jejunal (one case) infection were very rare [5]. To the best of our knowledge, this is the second case of jejunal infection in the literature.

The diagnosis of gastrointestinal mucormycosis is often delayed because of the non-specific presentation; abdominal pain, distention and vomiting are the most common presenting symptoms [3]. Infection may present with an abdominal mass (appendiceal, cecal or ileal) mistakenly thought to be an intra-abdominal abscess [3]. Individual patient populations present with specific disease phenotypes; premature neonates develop necrotizing enterocolitis while neutropenic hosts may present with masses, febrile neutropenia, typhlitis or hematochezia [3]. Gastrointestinal mucormycosis can also involve the liver, spleen and pancreas. The pathologic hallmark of mucormycosis is infarction of host tissue resulting from angioinvasion by hyphae. This gives rise to necrotic ulcers with resultant acute abdominal pain, hematemesis, perforation and