CASE REPORT
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Unusual manifestation of gastric mucormycosis in a patient with rheumatoid arthritis

Neobična manifestacija gastričnog tipa mukormikoze kod bolesnice sa reumatoidnim artritisom

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Abstract

Introduction. Mucormycosis is a life-threatening opportunistic infection whose incidence has significantly risen during the last two decades. The gastrointestinal form is very rare, with the stomach as the most common site of infection, followed by the colon and ileum. Risk factors include uncontrolled diabetes mellitus, corticosteroid use, and organ transplantation. We report a patient with a history of rheumatoid arthritis who has developed gastrointestinal mucormycosis. To the best of our knowledge, this is the first such case reported in the literature. **Case report.** A 53-year-old female patient with a prior medical history of rheumatoid arthritis was admitted to the hospital due to persisting diarrhea. Physical examination revealed diffuse abdominal tenderness to palpation without meteorism and peritoneal signs. Laboratory results demonstrated systemic inflammation, so antibiotic therapy was administered. Abdominal computed tomography findings revealed inflammation of the rectum and the left colon. Colonoscopy findings were indicative of Crohn's disease. Additionally, the patient had developed profuse rectal bleeding and consequently underwent emergency surgery. Subtotal colectomy with ileostomy and partial gastrectomy was performed. The patient's condition rapidly worsened after the operation, and she died due to multiorgan failure. Histologic findings of resection specimens discovered chronic active colitis and extensive gastric necrosis associated with dense mixed inflammatory infiltration and numerous non-septate and 90-degree branching *hyphae*. Diagnosis of invasive gastric mucormycosis was obtained, but unfortunately, several days after the patient's death. **Conclusion.** It is very important to obtain high awareness among clinicians of this deadly infection to achieve a prompt diagnosis and effective therapy.

Key words:
arthritis, rheumatoid; diagnosis; diagnosis, differential; digestive system; histological techniques; mucormycosis.

Apstrakt

Uvod. Mukormikoza je oportunistička infekcija koja ugrožava život, čija je incidenca u značajnom porastu u poslednje dve decenije. Gastrointestinalni tip ove infekcije se javlja veoma retko, i u njemu je želudac najčešće mesto infekcije, a slede ga kolon i ileum. Faktori rizika su nekontrolisani dijabetes melitus, upotreba kortikosteroida i transplantacija organa. Prikazujemo bolesnicu sa istorijom reumatoidnog artritisa koja je dobila gastrointestinalnu formu mukormikoze. Prema našim podacima, ovo je prvi takav slučaj opisan u literaturi. **Prikaz bolesnika.** Bolesnica sa reumatoidnim artritisom, stara 53 godine, primljena je u bolnicu zbog perzistentne dijareje. Fizičkim pregledom ustanovljena je difuzna osetljivost stomaka na palpaciju, bez znakova meteorizma i peritonitisa. Labaratorijski nalazi su ukazali na sistemsku inflamaciju, tako da je uključena antibiotska terapija. Snimanjem kompjuterizovanom tomografijom nađeni su znaci inflamacije rektuma i levog kolona. Kolonoskopija je ukazivala na Kronovu bolest. Pored toga, bolesnica je razvila profuzno krvarenje iz rektuma i ubrzo je podvrgnuta hitnoj hirurškoj intervenciji. Izvršena je subtotalna kolektomija sa ileostomom i parcijalna gastrektomija. Nakon operacije, stanje bolesnice se naglo pogoršalo i umrla je od multiorganske disfunkcije. Patohistološkom analizom hirurškog materijala otkriven je hronični aktivni kolitis i opsežna nekroza želuca sa infiltracijom gustim mešovitim inflamatornim infiltratom i brojnim hifama, neseptiranim i razgranatim pod pravim uglom. Ustanovljena je

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mukormikoza, ali, na žalost, tek nekoliko dana nakon smrti bolesnice. **Zaključak.** Veoma je značajno skrenuti pažnju na ovu smrtonosnu infekciju, kako bi se postigla brza dijagnoza i uspešna terapija.

Ključne reči:
artritis, reumatoidni; dijagnoza; dijagnoza, diferencijalna; digestivni sistem; histološke tehnike; mukormikoza.

Introduction

Mucormycosis is a life-threatening opportunistic infection whose incidence has significantly risen during the last two decades [1–3]. Usually, it is caused by *Rhizopus oryzae* from the order Mucorales, which belongs to the Mucormycetes class [4]. Mucorales fungi are thermotolerant molds that are ubiquitous and widely found in forms of infective spores in organic substrates, such as bread, fruits, fermented milk, vegetable matter, alcoholic drinks, soil, and animal excreta [5, 6]. The infection is acquired by inhalation, ingestion, or inoculation of spores onto disrupted skin and mucosa. Spores invade previously damaged epithelium and penetrate through endothelial cells, causing thrombosis and massive tissue necrosis [7]. Therefore, invasive mucormycosis is classified as rhinocerebral syndrome, pulmonary, cutaneous, gastrointestinal, disseminated, and uncommon presentations [5].

The gastrointestinal form is very rare, with the stomach as the most common site of infection, followed by the colon and ileum [8]. Risk factors include uncontrolled diabetes mellitus, defects in phagocyte function, corticosteroid use, organ or stem cell transplantation, administration of deferoxamine in patients receiving hemodialysis, and iron overload [4, 9]. Trauma, burns, and surgery can be predisposing factors in immunocompetent hosts, as well [10].

We report a patient with a history of rheumatoid arthritis who has developed gastrointestinal mucormycosis. To the best of our knowledge, this is the first such case reported in the literature.

Case report

A 53-year-old female patient with a prior medical history of rheumatoid arthritis was admitted to the hospital due to persisting diarrhea presenting as 5 to 6 watery stools per day, which had lasted for 7 days, accompanied by dysuria. Her previous medical therapy included 20 mg prednisone per day and 10 mg methotrexate per week. The patient appeared pale, dehydrated, and lethargic. She did not have a fever. Her blood pressure was 95/50 mmHg with a heart rate of 95 beats per minute. Physical examination revealed diffuse abdominal tenderness to palpation without meteorism and peritoneal signs. The following laboratory results demonstrated systemic inflammation, leukopenia, hypoglycemia, hypoalbuminemia, and kidney dysfunction: C-reactive protein 229.6 mg/L (normal range 0–5 mg/L); procalcitonin 43.09 ng/L (normal < 0.05 ng/mL); white blood cells count 1.03×10^9/L (normal range 3.40–9.70 × 10^9/L); glucose 3.1 mmol/L (normal range 3.9–6.1 mmol/L); albumin 21 g/L (normal range 35–52 g/L); urea 13.9 mmol/L (normal range 2.5–6.7 mmol/L); creatinine 260 μmol/L (normal range 58–96 μmol/L); total protein 42 g/L (normal range 64–83 g/L). Other laboratory test results were unremarkable. Soon afterward, there was an overall impairment of general physical condition. The patient became hemodynamically unstable and developed acute respiratory failure, so she was intubated and put on mechanical ventilation along with inotropic support. Antibiotic therapy, including ciprofloxacin, metronidazole, then meropenem, vancomycin, and colistin, was administered intravenously (iv). Due to leukopenia, thrombocytopenia, and anemia [white blood cell count 1.9×10^9/L; platelets 16×10^9/L (normal range 150–400 × 10^9/L); hemoglobin 74 g/L (normal range 120–160 g/L)], filgrastim, units of platelet concentrate and units of reticulocyte were given. Blood culture was positive for *Pseudomonas aeruginosa*. Chest radiography findings indicated progression to respiratory distress syndrome and, therefore, intravenous methylprednisolone was initiated. Significant improvement in the patient's overall condition resulted in the withdrawal of the mechanical ventilation on day 14. During further examination, abdominal computed tomography findings revealed presacral abscess, inflammation of the rectum and the left colon, and free intraperitoneal fluid. Hence, colonoscopy was indicated, and it discovered multiple small ulcers in the rectum, edematous, erythematous mucosa in the colon, with multiple, partially fused erosions, serpiginous ulcers, and individual pseudopolyps. Mucosa had a cobblestone appearance, and the ileocecal valve was distorted. Therefore, these endoscopic findings were indicative of Crohn's disease. Several biopsies were taken, and pathohistological features correlated with acute colitis and were not conclusive for Crohn's disease. Stool samples were negative for *Salmonella spp*, *Shigella spp*, *Campylobacter spp*, *Yersinia enterocolitica*, and *Clostridium difficile* toxin. Urine culture showed 100,000,000 colony forming units (CFU) *per* mL of urine and positivity for *Pseudomonas spp*. Antibiotic, corticosteroid, and supportive therapy was continued. Nevertheless, there was an exacerbation of the patient's condition with loss of consciousness, seizures, and respiratory failure, so mechanical ventilation was initiated again. Additionally, the patient had developed profuse rectal bleeding and consequently underwent emergency surgery. Intraoperative findings revealed necrosis of the transverse colon and posterior wall of the stomach with clear ascitic fluid. For that reason, subtotal colectomy with ileostomy and partial gastrectomy was performed. However, even with the aggressive surgical and medical approach, the patient's condition rapidly worsened after the operation, and she passed away due to multi-organ failure on the 57th day of hospitalization. Histologic findings

of resection specimens discovered chronic active colitis and extensive gastric necrosis associated with dense mixed inflammatory infiltration and numerous non-septate and 90-degree branching *hyphae* (Figures 1–4). Diagnosis of invasive gastric mucormycosis was obtained, but unfortunately, several days after the patient's death. An autopsy was not performed.

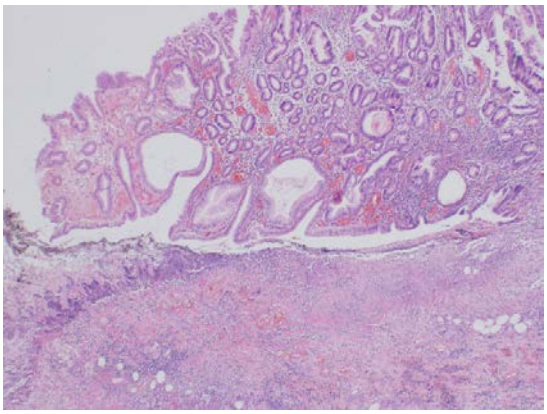


Fig. 1 – Ulceration of the gastric mucosa (hematoxylin and eosin, ×4).

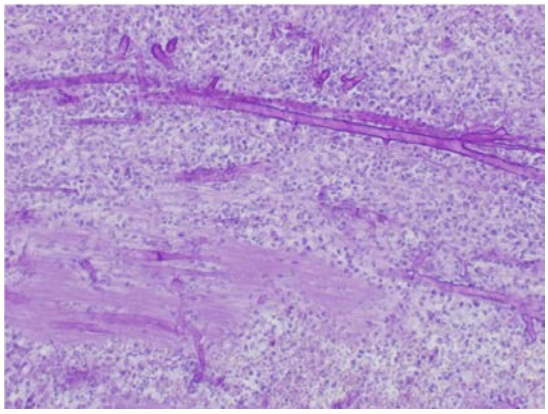


Fig. 2 – Broad non-septate *hyphae* with branching (periodic acid-Schiff, ×20).

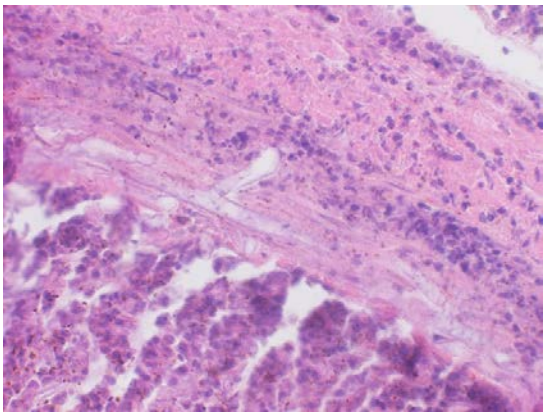


Fig. 3 – Angioinvasion by *hyphae* (hematoxylin and eosin, ×40).

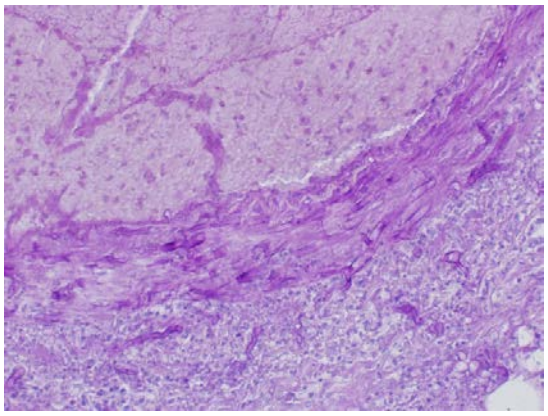


Fig. 4 – Angioinvasion by *hyphae* (periodic acid-Schiff, ×20).

Discussion

Mucormycosis is the second most frequent fungal infection in immunocompromised patients, but recently it has also been detected in immunocompetent hosts [5]. Our patient was on corticosteroid and immunomodulatory therapy (prednisone and methotrexate), which is not unusual for the development of fungal infection. However, to the best of our knowledge, she is the first patient who had developed gastrointestinal mucormycosis on the background of rheumatoid arthritis. Symptoms of gastrointestinal mucormycosis could be unspecific and vague, and they include nonspecific abdominal pain, intraabdominal abscess, distention associated with nausea and vomiting, fever, and hematochezia [11]. Our patient had severe diarrhea with watery and bloody stools, which led clinicians to suspect colitis and perform a colonoscopy. Nausea, vomiting, or other stomach-related symptoms were absent, so gastroscopy was not carried out. The endoscopic appearance of colonic mucosa had been consistent with Crohn's disease, although histopathological diagnosis did not confirm Crohn's colitis. There are few reported cases of this rare infection misdiagnosed as inflammatory bowel diseases (IBD) [12, 13]. Further differential diagnosis includes tumor, appendicitis, and typhlitis [14–17]. Gastric mucormycosis is often represented as ulceration with or without perforation and is much less common as a plaque-like lesion or exophytic ulcerated mass [18–20].

Therefore, with unspecific symptoms and unusual presentation, diagnosis is very difficult to achieve, and it requires a high rate of clinical suspicion and early multiple biopsies or surgical resection of the infected organ. Histopathological analysis of biopsied material is based on hematoxylin and eosin-stained tissue sections showing characteristic broad aseptate *hyphae*, which frequently have irregular and 90 degrees branching [5]. In our case, histpathological examination of the colonic biopsy specimens showed signs of acute inflammation. Mucormycosis was detected only in the surgical specimen of the resected stomach. An autopsy was not performed, so we did not establish disseminated mucormycosis.

Disseminated mucormycosis is documented in only 3% of cases [21]. Usually, hematogenous spreading occurs from the lungs and is less common from the alimentary tract, sinuses, and cutaneous lesions. Clinical presentation is unspecific and includes a wide range of symptoms (cerebral infection, kidney failure, hepatosplenomegaly, paralytic ileus).

The mortality rate is very high, over 90%, and diagnosis is often made on autopsy [22].

In the case of gastrointestinal mucormycosis, serial targeted biopsies from the rectum, colon, terminal ileum, and stomach are necessary. However, diagnosis is often delayed. There are no specific serologic markers, and microbiological tests are unreliable, with positive cultures in only 50% of cases [15]. Polymerase chain reaction (PCR) methods are still in the research phase, and their benefit is only in confirmation of histopathological diagnosis [5].

Despite aggressive medical treatment, the mortality of gastrointestinal mucormycosis is very high, approximately 85%, due to delayed diagnosis [21].

Only 25% of cases of gastrointestinal mucormycosis are diagnosed antemortem [21], so a high level of clinical suspicion and prompt diagnosis is crucial for reducing mortality.

The best therapeutic approach for mucormycosis (in general and especially for gastrointestinal mucormycosis) is a combination of antifungal therapy and extensive surgery. According to recommendations of the European Society of Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology (ESCMID), the treatment of choice is *iv* administration of liposomal amphotericin B at a dose of at least 5 mg/kg daily [23, 24]. Amphotericin is the medicine that has the best penetration through tissue and the least side effects. For patients who are not responding to amphotericin, posaconazole and other broad-spectrum azole are advised [5]. Extensive surgical removal of all necrotic tissue is also required. Frozen sections are often recommended for clear resection margins. And finally, it is necessary to withdraw or reduce immunosuppressive drugs and deferoxamine and to regulate hyperglycemia and acidosis in diabetic patients [8].

Additionally, the ESCMID recommends prophylactic administration of fluconazole in any patient with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages, considering these conditions create a great risk for developing invasive candidiasis, which can be a life-threatening fungal infection as well as mucormycosis [25, 26].

Conclusion

Bearing in mind the high mortality of gastrointestinal mucormycosis, it is very important to obtain high awareness among clinicians of this deadly infection to achieve a prompt diagnosis and effective therapy. Furthermore, considering that diagnosis is dependent on biopsy, it is necessary to develop new noninvasive rapid tests to establish mucormycosis as urgently as possible and to avoid the worst outcome.

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