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Abstract

Introduction: Mucormycosis is an opportunistic life-threatening infection whose incidence has significantly risen during the last two decades. 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, 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. An 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. Patient’s condition rapidly worsened after operation and she died due to multi-organ failure. Histologic findings of resection specimens discovered chronic active colitis and extensive gastric necrosis associated with dense mixed inflammatory infiltration and numerous nonseptate 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: Gastric mucormycosis, Morbus Crohn, rheumatoid arthritis
Apstrakt

Uvod. Mukormikoza je oportunistička, životno ugrožavajuća infekcija čija je incidenca u značajnom porastu u poslednje dve decenije. Gastrointestinalni tip se javlja veoma retko. Želudac je najčešće mesto infekcije, a zatim kolon i ileum. Faktori rizika su nekontrolisani dijabetes melitus, upotreba kortikosteroida, transplantacija organa. Mi smo prikazali pacijentkinju sa istorijom reumatoidnog artritisa koja je dobila gastrointestinalnu formu mukormikoze. Prema našim podacima, ovo je prvi takav slučaj opisan u literaturi. Prikaz slučaja. Pacijentkinja stara 53 godine koja boluje od reumatoidnog artritisa je primljena u bolnicu zbog perzistentne dijareje. Fizičkim pregledom je ustanovljena difuzna osetljivost stomaka na palpaciju, bez znakova meteorizma i peritonitisa. Labaratorijski nalazi su ukazali na sistemsku inflamaciju, tako da je uključena antibiotska terapija. Na kompjuterizovanoj tomografiji su nađeni znaci inflamacije rektuma i levog kolona, a kolonoskopija je ukazivala na Kronovu bolest. Pored toga, pacijentkinja je razvila profuzno krvarenje iz rektuma i ubrzo podvrgnuta hitnoj hirurškoj intervenciji. Izvršena je subtotalna kolektomija sa ileostomom i parcijalna gastrektomija. Nakon operacije, stanje pacijentkinje se naglo pogoršava i ona umire od multiorganske disfunkcije. Patohistološkom analizom hirurškog materijala je otkriven hronični aktivni kolitis i opsežna nekroza želuca infiltrisana gustim mešovitim infilmatormnim infiltratom i brojnim neseptiranim i pod pravim uglom razgranatih hifa. Ustanovljena je mukormikoza, ali na žalost, tek nekoliko dana nakon smrti pacijentkinje. Zaključak. Veoma je značajno skrenuti pažnju na ovu smrtonosnu infekciju, kako bi se postigla brza dijagnoza i uspešna terapija.

Ključne reči: gastrična mukormikoza, Kronova bolest, reumatoidni artritis.
Introduction

Mucormycosis is an opportunistic life-threatening infection whose incidence has significantly risen during the last two decades. Usually, it is caused by *Rhizopus oryzae* from the order Mucorales which belongs to the Mucormycetes class. 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. 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. Therefore, invasive mucormycosis is classified as (1) rhinocerebral syndrome, (2) pulmonary, (3) cutaneous, (4) gastrointestinal, (5) disseminated, and (6) uncommon presentations.

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, defects in phagocyte function, corticosteroid use, organ or stem cell transplantation, administration of deferoxamine in patients receiving hemodialysis, and iron overload. Trauma, burns, and surgery can be predisposing factors in immunocompetent hosts, as well.

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 didn’t 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 (normal range 0-5) mg/L; procalcitonin 43.09 (normal <0.05) ng/ml; white blood cells count 1.03 (normal range 3.40-9.70)x10^9/L; glucose 3.1 (normal range 3.9-6.1) mmol/L; albumin 21 (normal range 35-52) g/L; urea 13.9 (normal range 2.5-6.7) mmol/L; creatinine 260 (normal range 58-96) µmol/L; total protein 42 (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. Due to leukopenia, thrombocytopenia, and anemia [white blood cell count 1.9x10^9/L; platelets 16 (normal range 150-400)x10^9/L; hemoglobin 74 (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 of the patient’s overall condition resulted in withdrawal of the mechanical ventilation on day 14. During further examination, an abdominal computed tomography findings revealed presacral abscess, inflammation of the rectum, and the left colon and free intraperitoneal fluid. So, colonoscopy was indicated and 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 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 disease. Stool samples were negative for Salmonella spp, Shigella spp, Campylobacter spp, Yersinia enterocolitica, and Clostridium Difficile toxin. Urine culture showed 100,000,000 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. So, subtotal colectomy with ileostomy and partial gastrectomy was performed. But, 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 nonseptate and 90-degree branching hyphae (Figure 1 H&E stained sections 4x – ulceration of the gastric mucosa, Figure 2 PAS stained sections 20x – broad non septate hyphae with branching, Figure 3 H&E stained sections 40x - angioinvasion by hyphae, Figure 4 PAS stained sections 20x – angioinvasion by hyphae). Diagnosis of invasive gastrointestinal mucormycosis was obtained, but unfortunately, several days after the patient’s death. An autopsy was not performed.

Discussion
Mucormycosis is the second most frequent fungal infection in immunocompromised patients, but recently it is also detected in immunocompetent hosts. 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. 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 wasn’t carried out. The endoscopic appearance of colonic mucosa had been consistent with Crohn’s disease, although pathohistological diagnosis didn’t confirm Crohn’s colitis. There are few reported cases of this rare infection misdiagnosed as IBD. Further differential diagnosis includes tumor, appendicitis, and typhlitis. Gastric mucormycosis is often represented as ulceration with or without perforation, and much less common, as a plaque-like lesion or exophytic ulcerated mass.
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. Pathohistological 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. In our case, pathohistologic 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 didn’t establish disseminated mucormycosis.

Disseminated mucormycosis is documented in only 3% of cases. Usually, hematogenous spreading occurs from the lungs, and less common from the alimentary tract, sinuses, and cutaneous lesion. 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.

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

Only 25% of cases of gastrointestinal mucormycosis are diagnosed antemortem, 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 disease and European confederation of medical mycology, the treatment of choice is intravenous administration of liposomal amphotericin B at a dose at least 5 mg/kg daily. 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. 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.
Additionally, the European society of clinical microbiology and infectious disease 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.\(^{26,27}\)

**Conclusion**

Despite aggressive medical treatment, the mortality of gastrointestinal mucormycosis is very high, approximately 85%, due to delayed diagnosis\(^{21}\), so 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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Fig. 1 – H&E stained sections 4x – ulceration of the gastric mucosa
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