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Clinical Features of Fungal Peritonitis with *Candida Albicans* Infection after Gastric and Duodenal Perforation

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Abstract

Background: Acute fungal peritonitis due to gastric and duodenal perforation has been rarely reported.

Methods: In this study, we retrospectively analyzed 15 cases with acute fungal peritonitis infected with *Candida* after gastric and duodenal perforation.

Results: Gastric ulcer perforation was diagnosed in 5 cases and perforation of the duodenum was diagnosed in 10 cases. The medical background of patients included tuberculosis (TB) and long-term anti-TB therapy (5 cases), hypertension (4 cases), Type 2 diabetes (3 cases), rheumatoid arthritis (3 cases), hypoproteinemia (5 cases), and moderate anemia (7 cases). Two patients had a long-term history of drug abuse. All patients underwent surgery to repair the hole and suture the omentum over the perforation. All fungal peritonitis cases were caused by *Candida*, including *C. albicans* in 10 cases, *C. tropicalis* in 2 cases, *C. Parapsilosis* in 2 cases, and *C. kefyr* in 1 case. Fluconazole (400 mg for first day, then 200 mg/day for 7-14 days) was effective as anti-fungal treatment. The average length of hospital stay was 15.5 ± 4.1 days. Ten patients fully recovered. Incision infection was found in 3 patients. Two patients died due to multiple organ failure.

Conclusion: Our study suggests that fungal culture is necessary for patients with gastrointestinal ulcer perforation, *C. albicans* is the most common fungal infection, and anti-fungal therapy is effective for acute fungal peritonitis due to *Candida* infection.

Keywords: Gastric ulcer perforation; Fungal peritonitis; *C. albicans*; *Candida*.

Introduction

Peritonitis is a particular complication among surgical patients with hollow viscus perforation or those with intra-abdominal surgical drains [1]. Overall, fungal peritonitis accounts for approximately 3% - 12% of all cases of peritonitis in adults, but the rate varies largely between different centers [2,3] . The most common cause of fungal peritonitis is *Candida*, with the most common species of *Candida* in abdominal infection being *C. albicans* [4,5]. Without effective treatment, *Candida* peritonitis can lead to systemic infection, multiorgan failure, and death. The mortality of *Candida* peritonitis is very high, ranging from 20% - 70% [1].

Perforation of gastrointestinal ulcers is a common cause of acute peritonitis. Generally, bacteria begin to grow and gradually develop into bacterial peritonitis 6-8 hours after perforation. The most common pathogen is *E. coli*. Acute fungal peritonitis after perforation of gastrointestinal ulcer is a rare event and its etiology, treatments, and prognosis have not been well analyzed due to the limited number of cases. In this study, we retrospectively analyzed the clinical characteristics and treatment options for 15 patients with acute fungal peritonitis after gastric ulcer perforation.

Materials and Methods

Study design

A retrospective clinical study was performed at the Department of GeriatricSurgery, Second Xiangya Hospital, Central South University from March 2008 to July 2012. This study was pre-approved by The Ethics Committee for Human Research of Central South University.

Subjects

15 patients (9 males, 6 females) aged 47 to 87 years (mean age = 65 years old) with acute fungal peritonitis caused by perforation of the gastrointestinal tract were included in this study. Each patient with a positive culture of yeast or mold in their abdominal fluid sample was evaluated according to the following characteristics: age, gender, perforation location, medical background, fungal and bacterial identifications, antimicrobial treatments, and outcomes.

Microbiologic methods

Abdominal fluid was extracted from all patients and cultured. For the cultures, 50 ml of ascites were centrifuged and the pellet was cultured on specific media for both bacteria and fungi. Gram staining was performed directly on the pellet. For bacterial culture, plates were incubated for 3 days under aerobic and anaerobic conditions [6]. For

fungal culture, the plates were incubated for 7 days. If dimorphic fungi were expected, the culture period was extended to 8 weeks [7]. Fungi and bacteria were identified using standard laboratory methods.

Results

General demographic and clinical characteristics

All patients had no previous history of ulcers. Among the 15 cases, perforated gastric ulcer was diagnosed in 5 cases, perforated anterior duodenal ulcer was diagnosed in 9 cases, and perforated duodenal bulb wall was diagnosed in 1 case. The average onset time was 24 hours with a range from 8 to 36 hours. Five patients had active tuberculosis and underwent long-term anti-TB therapy with four medications — isoniazid, rifampin, ethambutol, and pyrazinamide. Four patients had hypertension with other diseases and were treated with metoprolol, iosartan, or amlodipine. Three patients had Type 2 diabetes and underwent insulin therapy and therapy with diabetes medications, such as etformin, sulfonylureas, and thiazolidinediones. Three patients had rheumatoid arthritis with other diseases and these patients were treated with immunosuppressive drugs and Chinese medicine. Five patients had hypoproteinemia and 7 patients had moderate anemia without treatment. Two patients had a history of drug abuse without HIV infection. 11 patients had 2-3 concurrent diseases.

Clinical manifestations and laboratory tests

All patients showed signs of abdominal tenderness and rebound tenderness, mainly located at the upper abdomen, and shrinking liver and dullness on percussion. Other mainly clinical symptoms included high fever, rigors, and diaphoresis. The upright abdominal X-ray showed free gas under the diaphragm. Laboratory tests showed that white blood cell count is ≥ 10 × 109/L with a neutrophil ratio > 90%. There was no correlation between white blood cell counts and inflammation. Among the 5 patients with hypoproteinemia, albumin was lower than 22.3 ± 1.2 g/L. Among the 7 patients with anemia, hemoglobin was lower than 8 g/dL. Abdominal paracentesis showed cloudy ascites. Gram staining was performed directly on the pellet of ascites and 6 patients were suspected to have *Candida* sepsis. The culture for fungi showed that all cases of fungal peritonitis were caused by *Candida*, including *C. albicans* in 10 cases, *C. tropicalis* in 2 cases, *C. Parapsilosis* in 2 cases, and *C. kefyr* in 1 case.

Surgical and supportive treatments

All patients underwent surgery to repair the hole and suture the omentum over the perforation. During the surgery, the ascites were drained and abdominal cavity was repeatedly washed with 0.9% saline. Patients with severe hypoproteinemia were treated for hypoproteinemia using standard therapy. Patients were given parenteral nutrition, including amino acids and glucose injection, the day after surgery. Enema was given two days post operation to promote intestinal peristalsis. In the event that patients did not release flatulence by the third day, they were given saline enema to promote intestinal peristalsis. After patients released flatulence, they were given liquid food and gradually moved on to solid food.

Anti-bacterial and anti-fungal treatment

Four Hundred mg of fluconazole was administered to patients by intraperitoneal injection on the first day, and then 200 mg/day for 7-14 days. Fluconazole treatment is effective in controlling infection. Due to bacterial culture requiring 3 days, patients were given broad-spectrum anti-bacterial therapy until fungal culture came out. However, these anti-bacterial treatments showed no efficacy on inflammatory symptoms.

Prognosis

The average length of hospital stay was 15.5 ± 4.1 days. Ten patients fully recovered. Incision infection was found in 3 patients. Dressing, drainage, and second suture were given to these 3 patients, and they were discharged after recovery. Two patients died due to multiple organ failure including lung, liver, kidney, heart dysfunction, etc.

Discussion

Candida spp. has become predominant pathogens in invasive fungal infection including fungal peritonitis [8]. It is estimated that 70%-90% of fungal peritonitis are caused by the *Candida* species and 80%-100% of fungal peritonitis in the pediatric population are caused by the Candida species [9]. *C. albicans* has also been reported to be more common than non-*Candida albicans* species, but a reverse tendency has been reported recently. In our case series, 100% of fungal peritonitis was caused by *Candida* with *C. albicans* in 10 cases, *C. tropicalis* in 2 cases, *C. Parapsilosis* in 2 cases, and *C. kefyr* in 1 case. The high rate of *Candida* in fungal peritonitis might be associated with the immunosupression of patients due to the concurrent chronic diseases, malnutrition, use of immunosuppressive drugs, or old age of the patients in our study, with ages ranging from 47 to 87 years with an average age of 65 years old.

Fungal peritonitis can be difficult to diagnose because the clinical signs and symptoms are indistinguishable from that of bacterial sepsis, especially before verifying the culture. In this study, nonspecific symptoms include fever, abdominal pain, rebound tenderness, rigors, diaphoresis, cloudy ascites, and white blood cell count is ≥ 10 × 109/L with a neutrophil ratio > 90%. Ultimately, patients were diagnosed with *Candida* peritonitis because 1) Anti-bacterial treatment for 3 days showed no efficacy on inflammatory symptoms; 2) Gram staining of the centrifuged pellet of peritoneal fluid showed that 40% of samples were Candida positive; and 3) The culture for fungi showed that 100% of samples were *Candida* positive. Therefore, this study suggests that the fungal infection should be highly suspected when symptoms of sepsis persist despite anti-bacterial therapy. In addition, culture for fungi should be considered in older patients with chronic disease when peritonitis is caused by gastrointestinal ulcer perforation.

The natural flora of the gastrointestinal tract is mainly gram-negative and anaerobic bacteria. However, *Candida* spp. are well-established gut commensals. Under certain conditions, *Candida* can heavily colonize in the digestive tract [10]. Immunodeficiency and prolonged exposure to antibiotics are widely thought to be two typical predisposing risk factors [8]. Currently, *C. albicans* peritonitis due to perforation of the upper gastrointestinal tract has been rarely reported. In this study, only 5 patients (33.3%) had a history of long-term anti-TB drug use due to active tuberculosis. Prolonged exposure to antibiotics is still a main risk factor in our case series, but 66.7% of fungal peritonitis was not associated with prolonged exposure to antibiotics. Of these patients, more than one patient suffered from hypertension, Type 2 diabetes, rheumatoid arthritis, hypoproteinemia, and moderate anemia. In addition, 73.3% of patients had 2 to 3 concurrent diseases. Notably, 2 patients had a long-term use of addiction drugs. Although immune function was not measured in

these patients, tuberculosis, Type 2 diabetes, and long-term use of addiction drugs can significantly damage immune function. Also, in this study, 5 patients had hypoproteinemia and 7 patients had moderate anemia. Malnutrition can also lead to breaks in GI tract and damage local immune function. Moreover, most patients in this study were old with an average age of 65 years. Old age, malnutrition, and chronic disease may cause immunosupression and subsequently increase the growth of *Candida* in the digestive tract. Upon perforation of the ulcer, *Candida* can enter the abdominal cavity and cause fungal peritonitis.

In the clinic, the therapy of *Candida* peritonitis includes conservative, medical, and surgical treatments [1]. Conservative treatments include removal of all foreign bodies in the abodominal cavity. The antifungal agents for *Candida* peritonitis include polyenes, azoles, echinocandins, and flucytosine [1]. The azoles are fungistatic against most *Candida* spp., whereas the polyenes and echinocandins are fungicidal [11]. Fluconazole is recommended for patients without prior azole exposure, and not at high risk, such as elderly, diabetic, and cancer patients [12,13]. In this study, the conservative treatments included draining ascites and washing the abdominal cavity, giving parenteral nutrition, and treatments for hypoproteinemia. Due to perforation, all patients underwent surgery to repair the hole. However, the main treatment is the use of antifungal agents. In this study, fluconazole was given intraperitoneally because it has good penetration in the peritoneum. Fluconazole regimen consisted of 400 mg for first day, and then 200 mg/day for 7-14 days, which showed high anti-*Candida* efficacy.

The prognosis of *Candida* peritonitis is very poor in critically ill surgical patients with a mortality rate between 52% and 75% [4]. However, reports from different centers are variable. A previous study demonstrated that candidemia and *Candida* peritonitis account for 37% of mortality in surgical patients [14]. Overall, the mortality rate in patients with *Candida* peritonitis is high despite treatment with antifungal agents [15]. The risk factors associated with increased mortality in *Candida* peritonitis include: extremes of age, upper GI tract infection as well as patient comorbidities, such as cardiac insufficiency, cirrhosis, diabetes mellitus, renal failure, and multiorgan failure [16]. In this study, 2 patients died with a mortality of 13.3% due to multiorgan failure. The average length of hospital stay was 15.5 ± 4.1 days. The low mortality rate in this study may be associated with early treatment with fluconazole injection intraperitoneally.

In conclusion, fungal culture is necessary for patients with gastrointestinal ulcer perforation, *C. albicans* is the most common fungal infection, and intraperitoneal fluconazole injection is effective for acute *Candida* peritonitis due to gastric and duodenal perforation.

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