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Case report

Invasive candidiasis leading to gastric perforation in an immunocompromised patient

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ABSTRACT

Invasive candidiasis remains an important cause of mortality and morbidity in patients with underlying diseases. Here, we report a case of gastric perforation due to *Candia glabrata* infection in a 74-year-old-male with Paroxysmal nocturnal hemoglobinuria (PNH) who received long-term corticosteroid treatment of hemophagocytic syndrome associated with acute cholecystitis. Total gastrectomy was performed, and he was treated liposomal amphotericin B. The patient was extubated successfully on the 2nd postoperative day, but the patient died of *Pneumocystis jirovecii* pneumonia (PJP). An autopsy revealed that there was a small amount of the cystic form of *Pneumocystic jirovecii*, but there was not the presence of *Candida spp*. Concerning the prophylaxis of invasive candidiasis, there is no strong evidence-based data in clinical practice in immunocompromised patients, such as those receiving long-term immunomodulatory therapy or corticosteroids. Our present case suggests the importance of fungal management and may indicate the need for a new approach to the fungal prophylaxis in such patients.

Introduction

Candida spp. are a major constituent of the normal commensal flora of the gastrointestinal tract, but *Candida* infections of the gastrointestinal tract are rare and gastric perforation caused by *Candida* infections is extremely rare. Invasive candidiasis can occur as a result of a compromised immune status and is associated with high morbidity and mortality [1]. Treatment of invasive candidiasis is frequently very difficult and the fungal prophylaxis is increasingly being used in patients at high risk of fungal infection, such as neutropenic patients with hematological malignancies and recipients of hematopoietic stem cell transplantation. Goodman et al. demonstrated that fluconazole prophylaxis reduced the incidence of fungal infections in severely immunocompromised patients undergoing bone marrow transplantation [2]. On the other hand, in less severely immunocompromised patients, such as those receiving long-term corticosteroids, studies on the clinical efficacy and cost-effectiveness of the fungal prophylaxis have not been conducted.

Herein, we present a rare case of invasive gastric candidiasis combined with gastric perforation in a patients with paroxysmal nocturnal hemoglobinuria who received long-term corticosteroid treatment for the complications and discuss the management of fungal infections.

Case report

A 74-year-old man was diagnosed with Paroxysmal nocturnal hemoglobinuria (PNH) in 2002. He was treated with cyclosporine A (CyA) (200 mg/day) and methenolone acetate (15 mg/day), and the pancytopenia gradually improved. In August 2017, he developed a fever, chills, and palpitation for five days prior to admission to our hospital. The physical examination findings revealed a body temperature of 40.0°C and anemic conjunctiva, and he had slightly right upper quadrant abdominal tenderness. The laboratory findings showed severe anemia and thrombocytopenia, and a marked elevation of hepatobiliary enzymes. Abdominal Computed tomography (CT) revealed swelling and wall thickening of the gallbladder and large gallstones (15 mm). On other laboratory findings, the level of ferritin and soluble IL-2R were elevated to 1505.0 ng/ml and 4490 U/mL, respectively. A bone marrow study showed hypocellular marrow and hemophagocytic histiocytes with few blast features. Based on these findings, he was diagnosed with PNH-associated hemolysis and hemophagocytic syndrome

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associated with acute cholecystitis. He received cefoperazone/sulbactam (CPZ/SBT) antibiotic therapy and steroid therapy with 80 mg/day (1 mg/Kg/day) prednisolone (PSL). Fever disappeared and his Hb level and hepatobiliary enzymes level improved. However, the platelet count recovery was incomplete and repeated bone marrow aspiration showed residual hemophagocytosis. PSL was gradually reduced and was administered over 1 month. His hemoglobin A1c was elevated to 8.5%, indicating the onset of steroid-induced diabetes mellitus (DM)

The patient had a fever again about 1 month after PSL treatment and chest CT showed ground-glass attenuation with halo sign. Serum β-D-glucan level was not elevated, but the galactomannan antigen was positive. The diagnosis of invasive pulmonary aspergillosis (IPA) was made based on these observations, and voriconazole (VRCZ) administration resulted in the elimination of fever. However, he began to experience progressive dyspnea with a dry cough one week after VRCZ treatment. Chest X-ray showed an interstitial pattern on both sides and chest CT showed ground-glass opacification (GGO) on both sides of the lung. Serum β-D-glucan level was not elevated and serum Krebs von den Lungen-6 (KL-6) was 768U/ml (normal range:<500 U/ml). The diagnosis was drug-induced lung injury by VRCZ. Methylprednisolone pulse therapy (500 mg/day x 3days) was started and liposomal amphotericin B (L-AmB) was administered to IPA instead of VRCZ. His respiratory condition was improved.

After 6 days of methylprednisolone treatment, he suddenly developed sever epigastric pain to all abdominal quadrants. Chest X-ray and abdominal CT revealed gastric perforation. His clinical course up to gastric perforation is shown in Fig. 1. Methylprednisolone was discontinued and an emergency laparotomy was performed that revealed turbid bilious fluid and perforation of the lesser curvature of the stomach with black large ulcer (8.5 cm x 5.5 cm) (Fig. 2). The peritoneal fluid culture was positive for *Candida glabrata*. Pathological examination revealed necrotic tissues associated with inflammation, a large number of budding yeasts, and some of them inside blood vessels (Fig. 3). Fungal organisms were identified on Periodic acid-Schiff (PAS) and Grocott staining. These were immunohistochemically positive for Candida (Fig. 4) (negative for Aspergillus: data not shown, for mucormycosis: not tested). The patient was extubated successfully on the 2nd postoperative (PT) day and we continued to use L-AmB for the treatment of IPA and *Candida glabrata* peritonitis. However, his respiratory condition worsened on the 7th PT day. In chest CT, GGO was observed on both sides of the lung, and β-D-glucan increased to 78.1 pg/ml. *Pneumocystis jirovecii* pneumonia (PJP) was diagnosed and the anti-PJP agent was started. However, his respiratory condition did not improve, and he died on the 12th PT day. An autopsy revealed many lesions of bronchopneumonitis caused by gram-positive cocci, and a small amount of the cystic form of *Pneumocystic jirovecii*. On the other hand, *Candida spp*. and *Aspergillus* were not present in the lung.

Discussion

Although generally rare, the prevalence of *Candida* infection of the gastrointestinal tract has significantly increased over the past 20 years due to advances in supportive care and intensive chemotherapy. The term "immunocompromised" is mainly related to underlying diseases such as acquired immune deficiency syndrome, solid organ transplantation, and hematopoietic stem cell transplantation. However, many other forms of immunocompromised patients are also susceptible to fungal infections, including patients on long-term immunomodulatory therapy or corticosteroids, and patients with malnutrition or chronic debilitating disease [3–5]. This report seems to be highly suggestive in that it shows the importance of management of fungal infections in less severely immunocompromised patients

Invasive candidiasis remains an important problem of mortality and morbidity in patients with underlying diseases. Despite the availability of some antifungal agents, the outcome of invasive candidiasis is poor and the mortality rate of 42% has recently been reported [6]. The identification of patients at risk is extremely important for the management of candidiasis. Previous reports indicated that risk factors for candidiasis included the use of broad-spectrum antibiotics, diabetes mellitus, neutropenia, impairing of T cell immunity by corticosteroid or CyA [7–12]. Recently candida infections in elderly people (over the age of 65 years) are important and expanding clinical problems [13]. Our patient was 74-years-old and received an antibiotic, CyA and corticosteroid. In addition, he had risk factors to promote invasive candidiasis because he suffered from diabetes mellitus in the course of corticosteroid treatment to hemophagocytic syndrome and drug-induced lung injury. These risk factors were likely to explain the ease of invasion of candida and the progress of invasive candidiasis. Concerning the prophylaxis of invasive candidiasis, that with new antifungal drugs has been improved and carried out, especially in patients

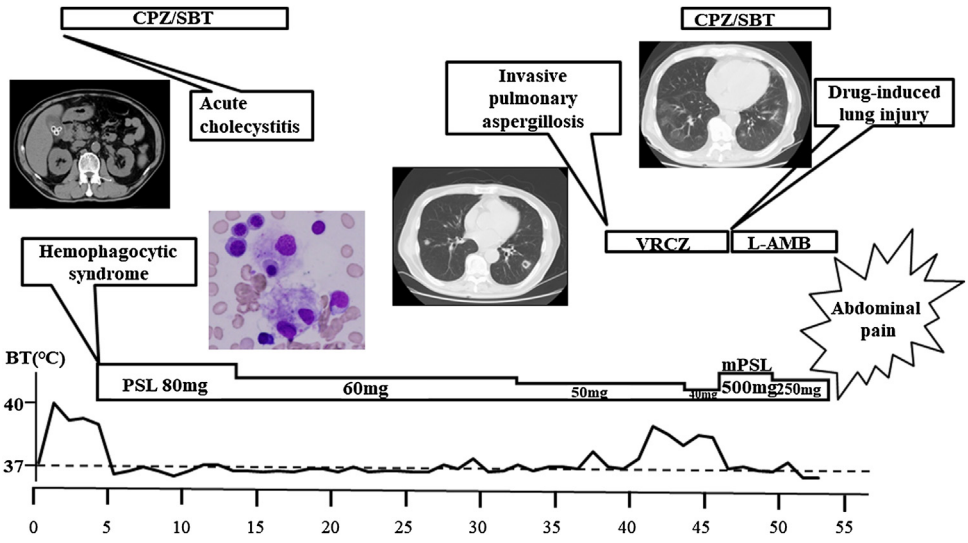

Fig. 1. The clinical course course up to the gastric perforation. CPZ/SBT: cefoperazone/sulbactam, VRCZ: voriconazole, L-AmB: Liposomal Amphotericin B, PSL: prednisolone.

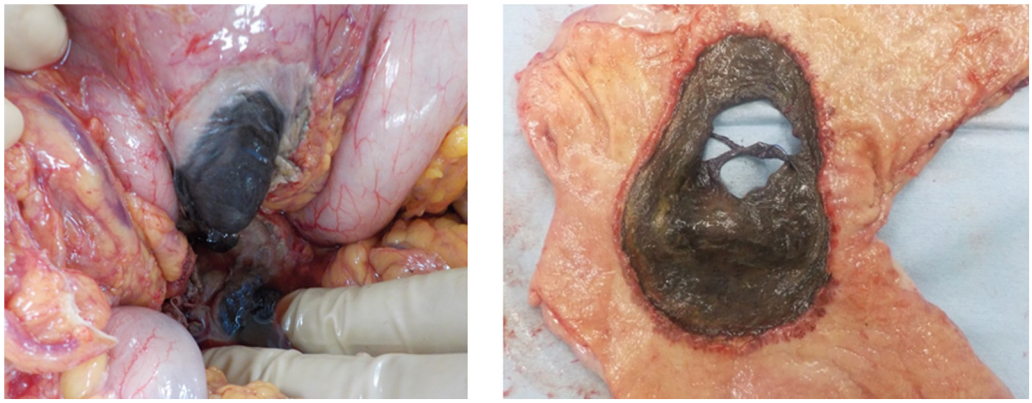

Fig. 2. The macroscopic appearance of transmural gastric necrosis and perforation of the lesser curvature of the stomach.

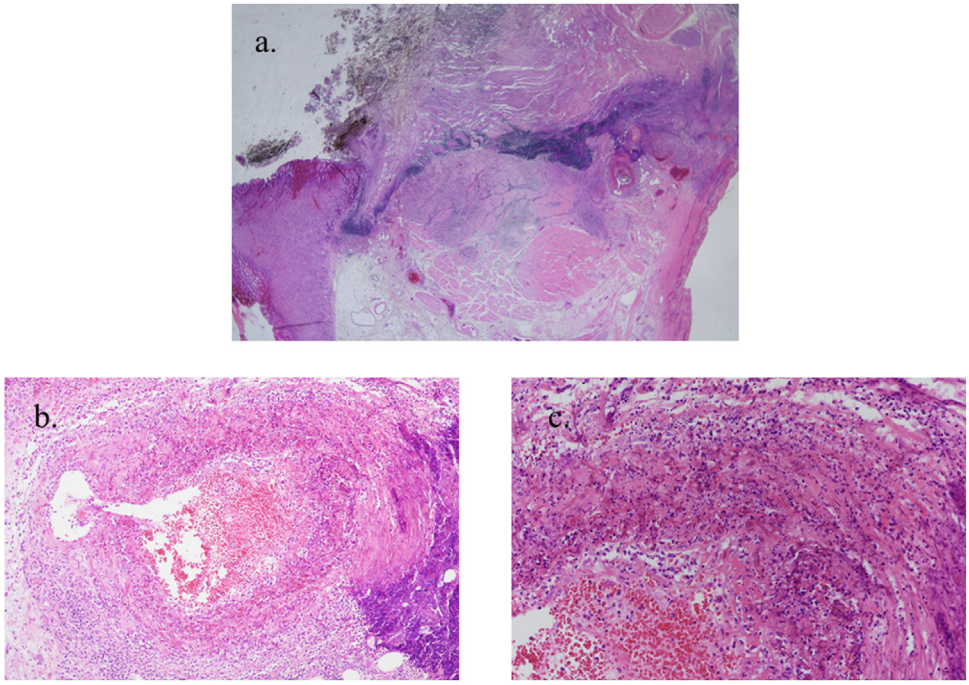

Fig. 3. The histological appearance in the ulcer part showing (a) necrosis with acute inflammation (H-E stain, x10), (b) a large number of budding yeasts (H-E stain, x40) and (c) some of yeasts inside blood vessels (H-E stain, x100). H-E: hematoxylin and eosin.

undergoing intensive chemotherapy for acute leukemia or hematopoietic stem cell transplantation [14,15]. On the other hand, in less severely immunocompromised patients, such as those receiving high-dose and long-term corticosteroids, there are some problems for determining fungal prophylaxis in clinical practice because there are not strong evidence-based data for prophylaxis and the benefit. However, since severe fungal infection as a complication is related to poor prognosis, identification of patients at risk is crucial. Therefore, it may be important to propose a scoring system combining the above risk factors and determine the clinical benefits, including cost-effectiveness in such patients.

A comprehensive review suggested that the gut is the primary source of invasive candidiasis [16]. Oral and intestinal Candida colonization has been reported to be associated with a significantly higher incidence of invasive candidiasis [17,18]. Marr at al. demonstrated that oral Candida colonization contributes to a 3-fold increase in the risk of candidemia in allogeneic stem cell transplantation patients [19]. Thus, identification of oral colonization is of great interest in the selection of patients at risk for subsequent invasive candidiasis, as well as for the implementation of prophylaxis strategies. In immunocompromised patients, oral monitoring culture from mouth-wash samples may be useful for reducing the incidence of invasive candidiasis.

The patients with PNH are frequently characterized by intravascular hemolysis and thrombosis leading to high mortality. In our patient, the autopsy revealed that there was not an appearance of thrombosis, therefore, the perforation was thought to be not caused by PNH-induced thrombosis, but the influence of invasive candidiasis. The finding of no appearance of thrombosis is consistent with the previous report by Nishimura et al. showed a lower incidence of thrombosis in Japanese patients than white patients [20]. The gastric perforation by *Candida glabrata* in our case occurred during the treatment of antifungal agents. Unfortunately, we could not conduct the antifungal susceptibility test of the isolated *Candida glabrata*, but it was not considered to be multidrug-resistant because no antifungal agents were

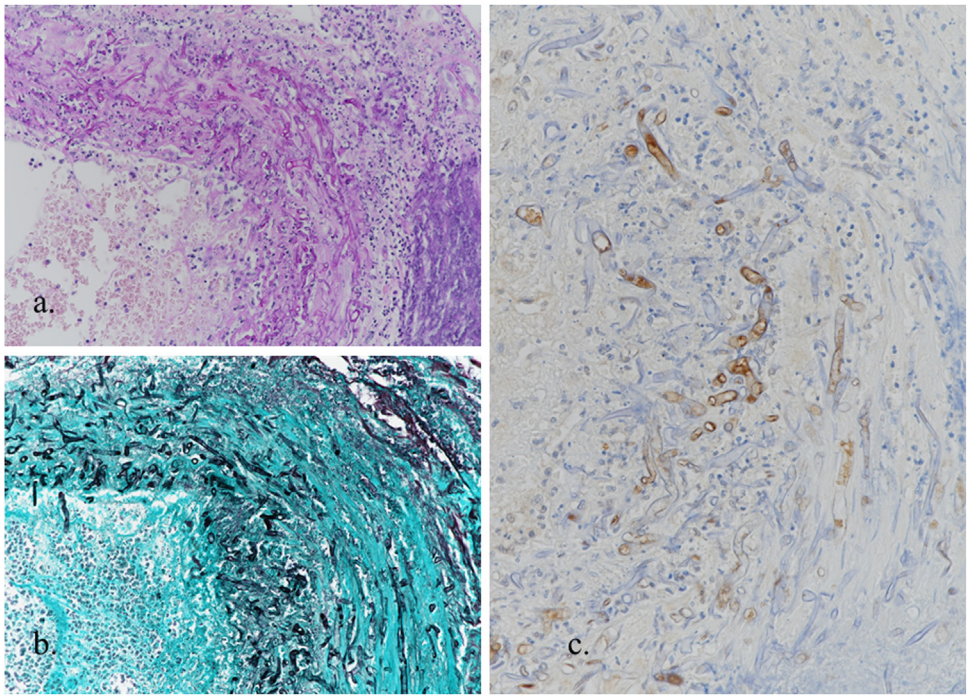

Fig. 4. The histochemical stain. (a) Periodic acid-Schiff stain, (b) Grocott stain and (c) immunohistochemical stain for Candida (x100).

administered to our patient until IPA occurred. It remains unclear why the perforation by *Candida* infection occurred. The short-term treatment was likely to explain its occurrence.

In conclusion, our present case suggests the importance of fungal management and may demonstrate the need for new approaches to the fungal prophylaxis in immunocompromised patients.

Author statement

The Authors state that the views expressed in the submitted article are their own and not official position of the institution or funder.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

[1] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:409–17.
[2] Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992;326:845–51.
[3] Parize P, Rammaert B, Lortholary O. Emerging invasive fungal diseases in transplantation. Curr Infect Dis Rep 2012;14:668–75.
[4] Schwesinger G, Junghans D, Schröder G, Bernhardt H, Knoke M. Candidosis and aspergillosis as autopsy findings from 1994 to 2003. Mycoses 2005;48:176–80.
[5] Bitar D, Van Cauteren D, Lanternier F, Dannaoui E, Che D, Dromer F, et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997-2006. Emerg Infect Dis 2009;15:1395–401.
[6] Bassetti Matteo, Giacobbe Daniele R, Vena Antonio, Trucchi Cecilia, Ansaldi Filippo, Antonelli Massimo, et al. Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project. Crit Care 2019;23:219–25.
[7] Soysa NS, Samaranayake LP, Ellepola AN. Diabetes mellitus as a contributory factor in oral candidosis. Diabet Med 2006;23:455–9.
[8] Sano T, Ozaki K, Terayama Y, Kodama Y, Matsuura T. A novel diabetic murine model of Candida albicans-induced mucosal inflammation and proliferation. J Diabetes Res 2014509325.
[9] Taieb F, Méchaï F, Lefort A, Lanternier F, Bougnoux ME, Lortholary O. Management of candidemia and invasive candidiasi. Rev Med Interne 2011;32:173–80.
[10] Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med 2009;206:299–311.
[11] Mansueto P, Pisciotta G, Tomasello G, Cabibi D, Seidita A, D'Alcamo A, et al. Malignant tumor-like gastric lesion due to Candida albicans in a diabetic patient treated with cyclosporin: a case report and review of the literature. Clin Exp Med 2012;12:201–5.
[12] Leenders NH, Oosterheert JJ, Ekkelenkamp MB, De Lange DW, Hoepelman AI, Peters EJ. Candidemic complications in patients with intravascular catheters colonized with Candida species: an indication for preemptive antifungal therapy? Int J Infect Dis 2011;15:e453–8.
[13] Barchiesi F, Orsetti E, Mazzanti S, Trave F, Salvi A, Nitti C, et al. Candidemia in the elderly: What does it change? PLoS One 2017;12:e0176576.
[14] Marr KA, Crippa F, Leisenring W, Hoyle M, Boeckh M, Balajee SA, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood 2004;103:1527–33.
[15] Ananda-Rajah MR, Grigg A, Downey MT, Bajel A, Spelman T, Cheng A, et al. Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. Haematologica 2012;97:459–63.
[16] Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? Clin Infect Dis 2001;33:1959–67.
[17] Martino P, Girmenia C, Micozzi A, De Bernardis F, Boccanera M, Cassone A. Prospective study of Candida colonization, use of empiric amphotericin B and development of invasive mycosis in neutropenic patients. Eur J Clin Microbiol Infect Dis 1994;13:797–804.
[18] Zollner-Schwetz I, Auner HW, Paulitsch A, Buzina W, Staber PB, Ofner-Kopeinig P, et al. Oral and intestinal Candida colonization in patients undergoing hematopoietic stem-cell transplantation. J Infect Dis 2008;198:150–3.
[19] Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 2000;181:309–16.
[20] Nishimura J, Kanakura Y, Ware RE, Shichishima T, Nakakuma H, Ninomiya H, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. Medicine (Baltimore) 2004;83:193–207.