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Case Report

Clostridioides difficile-related toxic megacolon after *Cryptococcus neoformans* cellulitis: A complex of two rare infections in an immunocompromised host

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ABSTRACT

A 76-year-old Japanese woman was admitted due to uncontrolled cellulitis of the right lower leg. She had deep vein thrombosis on the right limb. Moreover, she had a long history of rheumatoid arthritis treated with corticosteroids. Skin biopsy and lumbar puncture were performed to diagnose disseminated cryptococcosis. She was administered antifungal agents (liposomal amphotericin B and 5-fluorocytosine). On treatment day 14, debridement was performed, and cryptococcosis was controlled. However, she developed toxic megacolon due to *Clostridioides difficile* infection (CDI). On day 32, she was transferred to the intensive care unit due to severe acidosis and acute kidney injury secondary to CDI-related toxic megacolon. Vancomycin, metronidazole, and tigecycline were administered for treatment of CDI.

After several weeks of intensive care, toxic megacolon was improved, but renal replacement therapy was discontinued according to the patient's will. On day 73, she died of renal failure.

We experienced a complex of rare diseases, *Cryptococcus neoformans* cellulitis and *Clostridioides difficile*-related toxic megacolon. Both diseases were presumed to be the result of corticosteroid and methotrexate use. Hence, careful monitoring is required when treating immunocompromised hosts to reduce the risk of developing complications.

1. Introduction

Cryptococcus neoformans infection is an opportunistic disease that occurs in individuals with clearly identified underlying diseases [1]. As most patients are severely immunocompromised, they sometimes develop other opportunistic infections.

Clostridioides difficile infection (CDI) is another complex disease, which is common in patients with complicated medical conditions. In particular, toxic megacolon can be a fatal complication of CDI.

We report a case of cutaneous cryptococcosis, which later developed into cytomegalovirus infection and CDI-related toxic megacolon (CDI-TM). This complex of rare diseases suggests the importance of evaluating patient's immune status and prompt intervention in immunocompromised host.

2. Case report

A-76-year old Japanese woman was admitted in our hospital due to uncontrolled cellulitis. She had a 40-year history of

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rheumatoid arthritis (RA) and was treated with prednisolone, methotrexate, and celecoxib.

She also had a history of deep vein thrombosis in the right femoral vein accompanied by lower limb edema, which was controlled with warfarin for a year.

Three months earlier, the dose of prednisolone was increased from 5 mg to 30 mg/day to manage subacute flares of RA-related nonspecific interstitial pneumonia. Subsequently, a coin-shaped ulcer appeared in the right lower leg. Redness and swelling developed around the ulcer, and the patient was admitted for treatment of uncontrolled cellulitis.

Upon admission, she had low-grade fever and tachycardia. Wheezes were audible, but there was absence of hypoxia (SpO2: 96% at ambient air). She had no complaints of headache, nausea, or vomiting. She was neurologically normal, and meningism was absent. She had bilateral leg edema, and a discrete ulcer was noted on her right leg. This refractory ulcer was approximately 4 cm in diameter, and a few blisters were noted (Fig. 1a). At this time, no specific pathogens were cultured from the ulcer bottom and edges.

The clinical course is shown in Fig. 2.

Meropenem and vancomycin were initiated empirically, but were ineffective. After 7 days, a biopsy of the epidermis and subcutaneous tissues was performed (Fig. 3a–c). No major abnormalities were observed in the epidermis. In the subcutaneous tissue, stasis dermatitis was noted with diffuse infiltration of periodic acid-Schiff-positive, Grocott-positive round fungi. *Cryptococcus neoformans* was grown from subcutaneous tissue cultures.

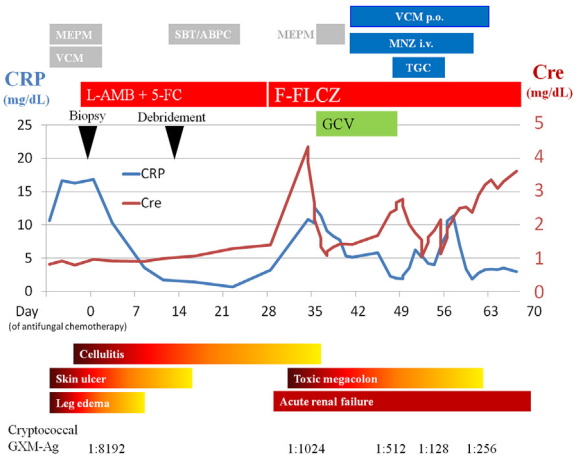

Fig. 2. Clinical course. Cre, creatinine; CRP, C-reactive protein; F-FLCZ, fosfluconazole; GCV, ganciclovir; GXM-Ag, glucuronoxylomannan antigen; i.v.,administered intravenously; L-AMB, lipospmal amphotericin B; MNZ, metronidazole; p.o., administered per os; SBT/ABPC, sulbactam/ampicillin; TGC, tigecycline; VCM, vancomycin; 5-FC, 5-fluorocytosine.

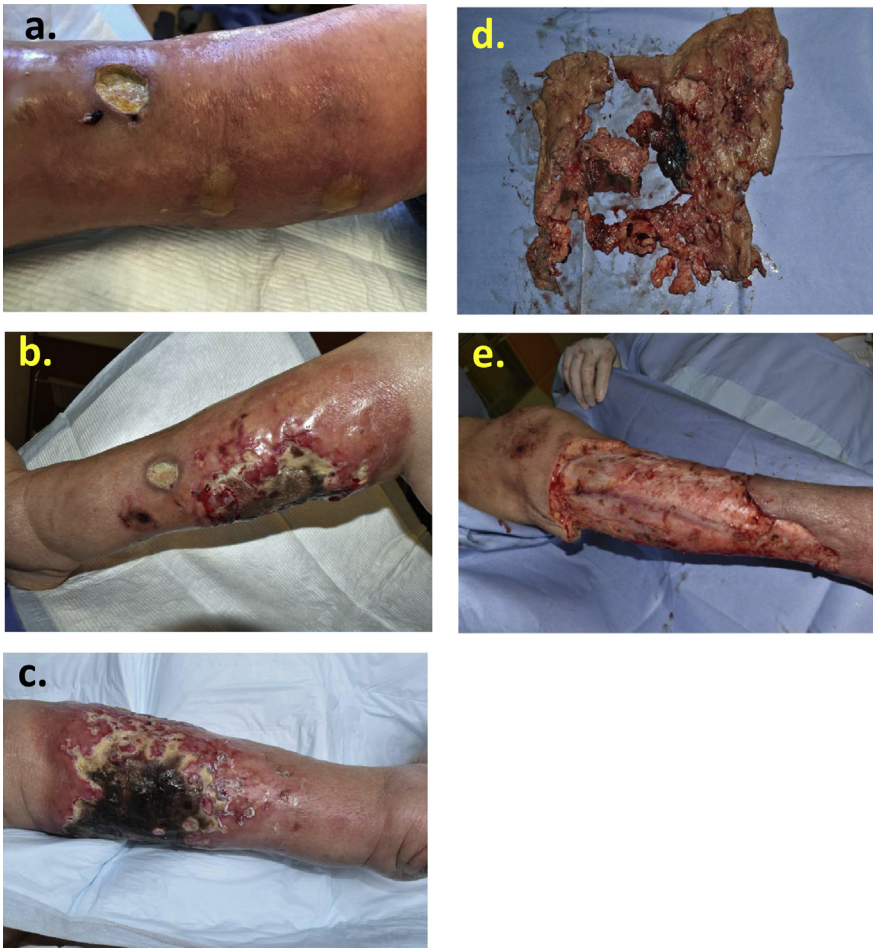

Fig. 1. Cutaneous lesions in the right lower limb; a) View from medial surface (on admission): a discrete ulcer and blisters are surrounded by edematous skin.b) View from medial surface (on day 10 of treatment): ulcer still remained and severe necrosis has developed. c) View from posterior surface (on day 10 of treatment): severe necrosis has developed. d) Resected tissue in the debridement (on day 14 of treatment).e) Right lower limb after debridement (on day 17 of treatment); necrotic tissues were all removed.

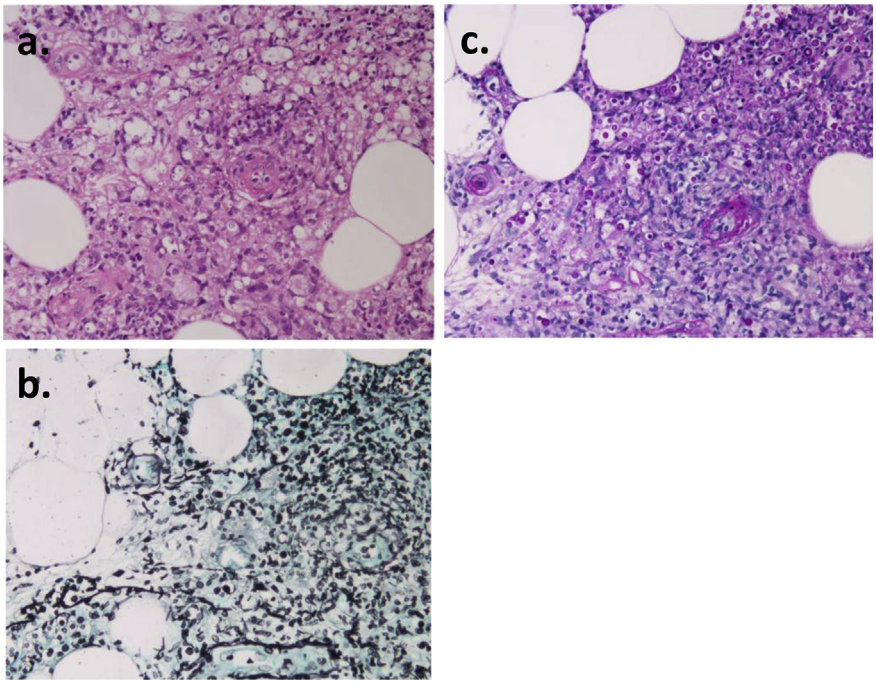

Fig. 3. Pathological findings from subcutaneous tissue biopsy a) Hematoxylin-eosin stain, 200 × ; lymphocyte and plasma cell infiltration is seen in the subcutaneous tissue. Granulomatous change and also round pathogens with capsule are seen.b) Grocott stain, 200 × ; Grocott positive round pathogens are detected. c) Periodic Acid-Schiff (PAS) stain, 200 × ; PAS positive round pathogens are detected.

Lumbar puncture yielded the following results: opening pressure, 13 cmH_2O; 6 cells/mm^3: glucose, 81 mg/dL; protein, 66 mg/dL; and *Cryptococcus* antigen, 1:4.

The serum *Cryptococcus* antigen dilution was 1:8192. No lung lesions characteristic of cryptococcosis were noted in computer tomography. Instead, slight reticular shadow and ground glass opacity compatible with rheumatic lung were observed.

Liposomal amphotericin B (L-AMB) 5 mg/kg/day and 5-fluorocytosine (5-FC) 100 mg/kg/day were administered as treatment for disseminated cryptococcosis.

On day 14 (of antifungal chemotherapy), however, skin ulcer further expanded (Fig. 1b and c). Debridement was performed (Fig. 1d) and negative pressure wound therapy (NPWT) was initiated. On day 28, treatment was switched to fosfluconazole 7.4 mg/kg/day and the dose was adjusted as patient's renal function was impaired. On day 29, she complained of mild epigastralgia. There was gradual deterioration of patient's level of consciousness. On day 32, she developed shock and was moved to the intensive care unit. Laboratory findings showed acute kidney injury (serum creatinine: 4.34 mg/dL; blood urea nitrogen: 102 mg/dL) with severe acidosis (pH of 6.993 in arterial blood gas analysis) and inflammation (CRP: 10.9 mg/dL). The patient had no complaints of diarrhea throughout the course of her admission; rather, she was constipated for more than a week. On day 32, abdominal radiography showed marked dilatation of the transverse and ascending colon, which fulfilled the diagnostic criteria of toxic megacolon (Fig. 4a). Computed tomography revealed thickening of the sigmoid colon (Fig. 4b) and eventually progressed to marked dilatation (Fig. 4d) on day 37. Meanwhile, the patient was tested for cytomegalovirus (CMV) pp65 antigenemia (C7-horse radish protein) and the results were positive (114/50,000 cells). CMV-related hemophagocytosis was confirmed by bone marrow aspiration. Ganciclovir was initiated on day 35, and prompt improvements in the symptoms of CMV disease were noted. However, toxic megacolon was still persistent on day 40 (Fig. 3c and e). On day 41, fecal *C. difficile* antigen test yielded positive result. As treatment for CDI-TM, intravenous metronidazole (MNZ) 500 mg administered every 8 hours and intraluminal vancomycin (VCM) 500 mg administered every 6 hours via nasogastric tube were initiated immediately after detection. From day 47, intravenous tigecycline (TGC) 100 mg was administered for 8 days. Elevation of lactate and creatinine kinase was not documented throughout the course, which suggests that severe intestinal necrosis will not likely occur. Besides, the patient was highly immunocompromised, and surgery was not considered. After 2 weeks of CDI treatment, toxic megacolon gradually improved and fecal *C. difficile* antigen test revealed negative results. Cutaneous lesions were controlled with debridement and NPWT (Fig. 1e), but severe renal failure remained. The best supportive care was selected according to the patient's own will. Renal replacement therapy was discontinued. On day 73, she died of renal failure.

3. Discussion

Cryptococcosis is one of the opportunistic infections with poor prognosis. In addition to acquired immunodeficiency syndrome (AIDS) or organ transplantation, various underlying diseases have been associated with the development of cryptococcosis. In non-HIV, non-transplant (NHNT) cases, most of the patients who developed disseminated cryptococcosis had history of prolonged treatment with corticosteroids, advanced malignancy, diabetes mellitus, liver cirrhosis, and autoimmune diseases [3].

The skin is the third most common site of *Cryptococcus* infection after lung and central nervous system (CNS) and is commonly affected in 10%–20% of patients with cryptococcosis [4]. Although primary cutaneous cryptococcal infections can occur in immunocompetent hosts [5], cutaneous lesion is usually a hallmark of disseminated cryptococcal infection. There is a tendency that cutaneous lesion will occur more frequently in organ transplant recipients than in AIDS or NHNT cryptococcal infection patients [3]. This is probably because the routine use of calcineurin inhibitors in

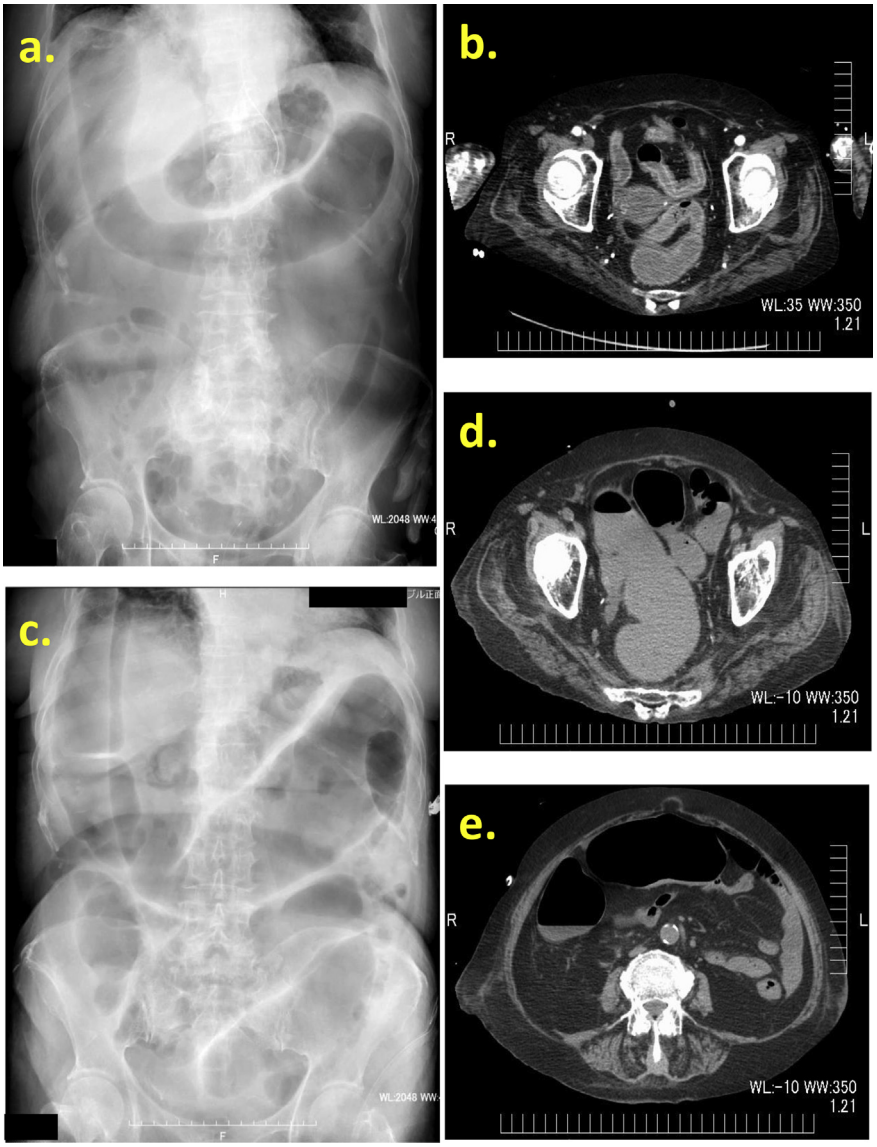

Fig. 4. Radiographic findings. a) Abdominal radiography at day 32: marked dilatation of ascending, transverse colon are detected. b) Abdominal computed tomography at day 32 (with contrast enhancement): the wall thickening of sigmoid colon are detected. c) Abdominal radiography at day 37: dilatation of ascending, transverse, and sigmoid colon was markedly worsened. d, e) Abdominal computed tomography (plain) at day 40: marked dilatation of sigmoid colon (d) and transverse colon (e) are detected.

organ transplant patients suppresses the ability of *Cryptococcus* to grow in an environment with a temperature of 37 °C, thus allowing the fungus to grow at the sites with a lower temperature, such as the limbs [6]. Our patient was an NHNT patient who was under corticosteroid and methotrexate therapy, but she developed cutaneous lesions. In this case, the occurrence of deep venous thrombosis and leg edema probably triggered the development of cutaneous cryptococcosis. Generally, cryptococcal skin infection develops almost all types of cutaneous lesions, making it difficult to provide an accurate diagnosis [4,7–12]. Although the ulcer can appear as a papule or maculopapule, it can sometimes mimic molluscum contagiosum, acne vulgaris, squamous carcinoma, or basal cell carcinoma. Of note, in severely immunocompromised host, cutaneous lesions can present as a cellulitis or an acute onset abscess mimicking bacterial infection [4,11,12]. In our case, the skin ulcer initially appeared and rapidly progressed to cellulitis after prednisolone dose escalation. At first, the cultures for *Cryptococcus* from ulcer edge or exudates were negative, which delayed the diagnosis. This finding indicated that the results of skin tissue culture for deep cutaneous fungal infection are sometimes discordant with those of histopathology. In a retrospective study conducted in a single institution, 8 of 33 (24%) patients had negative skin cultures but were histopathologically positive for fungal elements [13].

In our case, the treatment for cryptococcosis was administered according to the Infectious Diseases Society of America guidelines [14]. The guidelines clearly indicated that nonmeningeal, nonpulmonary cryptococcosis represents the consequence of dissemination even if the clinical syndrome is confined to a single anatomical site. Our patient was diagnosed with disseminated disease because of meningeal involvement and high cryptococcal antigen titer ($\geq$1:5120). Thus, the patient's treatment was similar to those of individuals with CNS disease. In addition, massive debridement was performed as patient's cutaneous lesions were not fully controlled after administering antifungal agents, probably due to severe immunodeficiency.

The patient developed toxic megacolon, a serious event caused by *C. difficile* infection. It is a severe complication caused by inflammatory bowel diseases (IBD) or infectious diseases. The consistent feature of toxic megacolon is the radiographic evidence of total or segmental colonic distension of more than 6 cm in diameter [15–17]. The pathogenesis of toxic megacolon can be explained by massive release of inflammatory mediators inhibiting colonic motility. The severe inflammation reaching the muscularis propria leads to the release of nitric oxide (NO), one of the key non-adrenergic, non-cholinergic neurotransmitters. NO then induces relaxation of the colonic smooth muscles, which leads to excessive dilatation of the colonic wall [18,19]. Classically, toxic megacolon has been reported in patients with IBD, such as ulcerative colitis or, less commonly, Crohn's disease [20]. In recent years, while the number of individuals who developed toxic megacolon due to IBD has decreased, infection-related toxic megacolon has been reported more often, with reports describing that *C. difficile*, *Salmonella*, *Campylobacter*, *Entamoeba*, cytomegalovirus, or other organisms could cause toxic megacolon [15–17]. CDI is often considered because of its frequency [21–25] and its severity. The mortality rate of CDI-TM was estimated to be 38%–80%, and its incidence continued to increase [2].

The management for toxic megacolon should aim to circumvent further complications, especially perforation. At least, bowel rest is usually necessary to attenuate the symptoms of colonic atony. Close monitoring and supportive care are imperative, and a timely decision should be made whether to perform colectomy or not [2]. In addition to standard treatments, the administration of parenteral MNZ and/or vancomycin enema, if needed, should be considered for the management of CDI-TM. Our patient was treated with MNZ administered intravenously and VCM administered via nasogastric tube. Tigecycline was also administered for 8 days, in order to increase the intestinal concentration of tigecycline [26].

For the early diagnosis of CDI-TM, two points should be considered: 1) diarrhea does not always occur, and 2) corticosteroids or analgesics mask the abdominal pain at the early stage [16]. In our case, however, the patient was diagnosed with toxic megacolon almost 10 days after presumed onset. Because the abdominal pain was ambiguous and diarrhea was absent, radiological evaluation was deferred. Probably, oral corticosteroid might have masked the pain. Corticosteroid compromises not only cellular immunity, which triggers the occurrence of *Cryptococcus* and cytomegalovirus infection, but also humoral immunity, which can be the reason for CDI [27]. Previous case reports suggested that certain immunodeficiency disorders can be predisposing factors for severe CDI-TM [28–30]. Those findings warrant the importance of evaluating patient's background. Severe immunosuppression, which can precipitate the development of cryptococcosis, can be an underlying cause of severe CDI-TM or CMV disease. In that sense, careful monitoring is required when managing immunocompromised hosts to reduce the risk of developing complications.

In conclusion, we report a rare combination of cutaneous cryptococcal infection and CDI-TM. Our case report provides the following implications in the clinical practice. First, note that the development of culture-negative cutaneous lesions in immunocompromised hosts can be a sign of cryptococcosis. Hence, histopathological diagnosis should be promptly made. Second, in patients with severe immunodeficiency, complexes of opportunistic infections can develop. Immunocompromised patients must be carefully monitored for possible complications. Lastly, sudden changes in the level of consciousness, renal insufficiency, and abdominal fullness suggest the possibility of CDI-TM. Patients who develop this disease may not experience diarrhea. Hence, it is important to not overlook the complications of severe immunodeficiency.

Authorship statement

All authors meet the ICMJE authorship criteria.

Ethics approval and consent for publication

Informed consent was obtained from the patient following provision of verbal and written information. All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest

None of the authors have financial relationships with any commercial entity with an interest in the subject of this manuscript.

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