【 CASE REPORT 】

Behçet's Disease with Bilateral Renal Infarction Due to Mucormycosis

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Abstract:

We herein report a case of Behçet's disease with renal infarction due to mucormycosis. A 76-year-old man with entero-Behçet's disease had been treated with glucocorticoid and tumor necrosis factor (TNF) inhibitors. His entero-Behçet's disease was refractory to these treatments, and ileocecal resection was performed. After the operation, renal infarction that was unresponsive to anticoagulation therapy developed. He ultimately died of renal failure due to renal infarction. At the autopsy, histopathology of abundant hyphae in the renal vessel wall revealed mucormycosis. Renal mucormycosis is an important cause of renal failure with renal infarction in immunocompromised patients.

Key words: immunocompromised hosts, renal infarction, mucormycosis

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Introduction

Infections are common complications in immunocompromised patients and are considered a significant threat to the patient's survival. Mucormycosis is a serious but rare fungal infection associated with immunosuppressive therapy. We herein report a case of refractory Behçet's disease with renal infarction due to mucormycosis.

Case Report

A 63-year-old man presenting with recurrent painful oral aphtha, erythema nodosum folliculiti, arthritis of the right ankle and knee, ileocecal ulcers with elevated levels of C-reactive protein (CRP; 9.24 mg/dL) and HLA-A26 was diagnosed with Behçet's disease. A colonoscopic examination revealed ileocolonic volcano-type ulcers. There was a punched-out ulcer and no other-segmental distribution of le-sions, including longitudinal ulcers, cobblestone appearance. A histological examination of the biopsied specimens demonstrated non-caseating epithelioid granuloma and crypt abscesses that were negative for cytomegalovirus (CMV) and acid-fast bacilli. There were no features characteristic of myelodysplastic syndrome (MDS) with chromosomal abnormalities, such as trisomy 8, on bone marrow examinations.

Based on these findings, he was diagnosed with entero-Behçet's disease and treated with glucocorticoid, tumor necrosis factor (TNF) blockers (infliximab and adalimumab), colchicine, mesalazine, mizoribine, and leukocytapheresis. When he was 76-year-old, his entero-Behçet's disease showed a poor therapeutic response to these treatments, and limited ileocecal resection was performed (Fig. 1). A histological examination of the specimens showed erosion with infusion of neutrophils, and non-caseating epithelioid granuloma as well as crypt abscesses, which were negative for CMV and acid-fast bacilli.

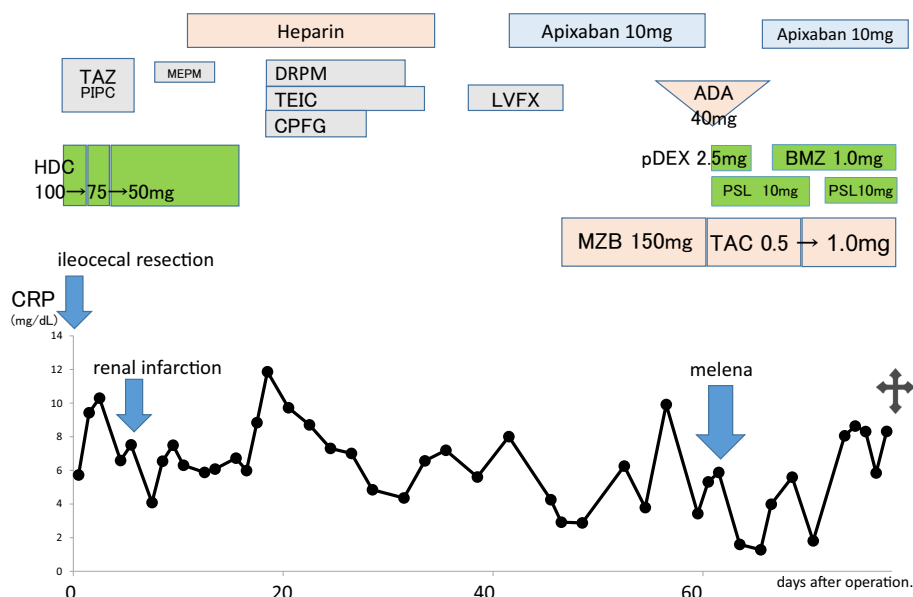Ten days after the operation, he developed left flank pain,

Figure 1. Clinical course. ADA: adalimumab, BMZ: betamethasone, CPFG: caspofungin, DRPM: doripenem, HDC: hydrocortisone, LVFX: levofloxacin, MEPM: meropenem, MZB: mizoribine, pDEX: dexamethasone palmitate, TAC: tacrolimus, TAZ/PIPC: tazobactam/piperacillin, TEIC: teicoplanin
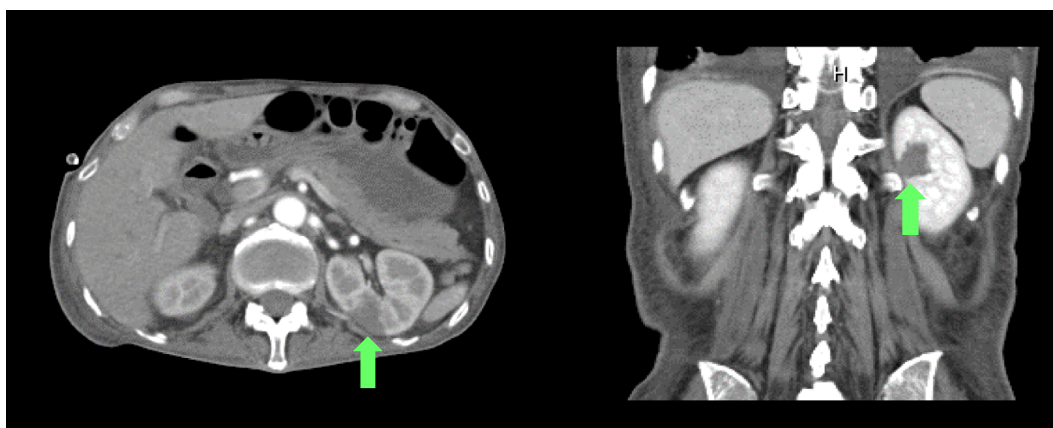

Figure 2. Findings nine days after ileocecal resection. Abdominal CT showed a hypo-dense lesion (arrow) in the left kidney upper pole that was diagnosed as renal infarction.

fever (38.0°C), pyuria, microhematuria (red blood cells: 13-1,000/high-power field, isomorphic). A physical examination was unremarkable, except for severe emaciation (body mass index 12.8 kg/m²) and mild tenderness in the left flank area. Laboratory data showed elevated levels of CRP (6.55 mg/dL), a normal renal profile, and normal levels of serum electrolytes and glucose. HIV serology was non-reactive, and the serum immunoglobulin level was within normal limits. β-D glucan and procalcitonin were negative. The urine and blood cultures were negative for bacteria, tuberculosis, and fungal growth. Abdominal computed tomography (CT) showed a hypo-dense lesion in the left kidney, which was diagnosed as renal infarction (Fig. 2). Percutaneous drainage and needle biopsy of the kidney were performed under CT scan guidance, but only minimal amount of brownish fluid

came out, and the culture was negative. Heparin sodium injection (14,000 U/day), meropenem, and caspofungin were started; however, his fever continued despite these treatments. CT showed enlargement of the bilateral renal infarction.

Sixty days after the operation, he developed massive gastrointestinal bleeding with hemorrhagic shock. Abdominal CT and lower gastrointestinal endoscopy showed aphthoid lesions due to entero-Behçet's disease and bleeding at the oral side of the surgical anastomosis. Endoscopic clipping of the bleeding lesion was performed. CMV antigenemia was negative. Dexamethasone palmitate 2.5 mg/day (3 days), prednisolone 10 mg/day, adalimumab 40 mg/2 weeks were started, and the gastrointestinal bleeding was improved.

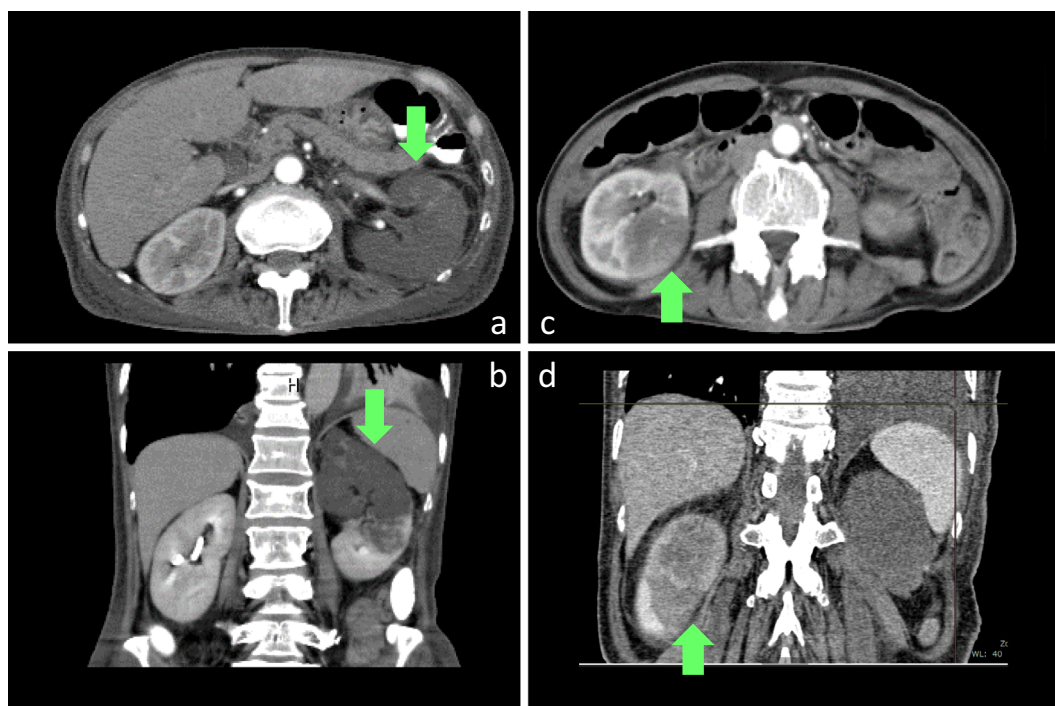Nephrectomy was recommended for the renal lesion, but

Figure 3. Abdominal CT findings 73 days after ileocecal resection. (a, b) Enlargement of the left kidney and renal infarction. (c, d) Another hypodense lesion in the right kidney.

his condition rendered him unsuitable for the operation, including severe emaciation, malnutrition, a poor general condition with refractory entero-Behçet's disease, and an immunodeficient state due to the immunosuppressive therapy.

Seventy-three days after the operation, gross hematuria and pyuria, elevation of the levels of serum creatine (0.43→1.00 mg/dL) and CRP (1.81→8.06 mg/dL), enlargement of the left renal infarction (Fig. 3a, b), and another hypo-dense lesion in the right kidney (Fig. 3c, d) appeared. He ultimately died of renal failure 75 days after the operation.

At the autopsy, the bilateral kidneys were enlarged (right 340 g, left 370 g) and showed a variegated appearance with large infarcts, ischemic cortical necrosis (well-defined necrotic yellow mass), hemorrhaging, and exudate on the surface (Fig. 4a). The renal artery showed occlusion of the lumina by thrombi (Fig. 4b). The urinary bladder showed petechial hemorrhaging over the mucosa (Fig. 4c). Myocardium showed liner infarcts and ischemic cortical necrosis (Fig. 4d) in the interventricular septum. The intestines did not show any ischemic changes or ulcers.

A microscopic examination of the renal artery showed abscesses with a necrotic center containing septate hyphae of mucor with a right-angled branching pattern and invasion of the blood vessels in the adjoining vessel wall (Fig. 5a, b). The mycelium was positive for anti-Rhizomucor (Fig. 6a) antibody and anti-Rhizopusantibody (Fig. 6b) but negative for anti-Aspergillus antibody (Figure not shown). Mucor hyphae were present in the blood vessels, glomeruli and tubules, urinary bladder (Fig. 5c), and cardiomuscle tissue (Fig. 6d). There were no mucormycotic lesion in the lungs, paranasal sinuses, or gastrointestinal tract. Our case was thus concluded to have died of renal failure due to bilateral renal infarction induced by disseminated mucormycosis.

Discussion

Awareness of invasive fungal infection has increased in clinical practice among patients with an immunocompromised state (1, 2). Mucormycosis is a serious but rare fungal infection caused by a group of molds called mucormycetes. Mucormycosis is an opportunistic fungal infection that occurs mainly in compromised hosts (1, 2). Its risk factors include diabetes, acidosis, corticosteroid, immunosuppressive therapy, hematopoietic disorders, organ transplant, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome, deferoxamine therapy, and malnourishment (3, 4). Kontonyiannis et al. reported the following risk factors for mucormycosis: neutropenia (<500/μL), lymphocytopenia (<1,000/μL), hyperglycemia (blood glucose level >200 mg/dL for ≥7 days before onset of infection), preexisting renal failure (serum creatinine level >2.5 mg/dL for ≥14 days before onset of infection), and significant glucocorticoid use (>600 mg cumulative dose of prednisone in the 4 weeks before the onset of infection) (5). Our case had lymphocytopenia (100-600/μL) but no leukocytopenia or hyperglycemia. He had received a cumulative dose of prednisolone exceeding 600 mg in the 4 weeks before the onset of infection.

Santo et al. reported a case of Behçet's disease complicated with pulmonary mucormycosis that was treated by high-dose corticosteroids. To our knowledge, our case is the first of renal mucormycosis with Behçet's disease (6). Anti-
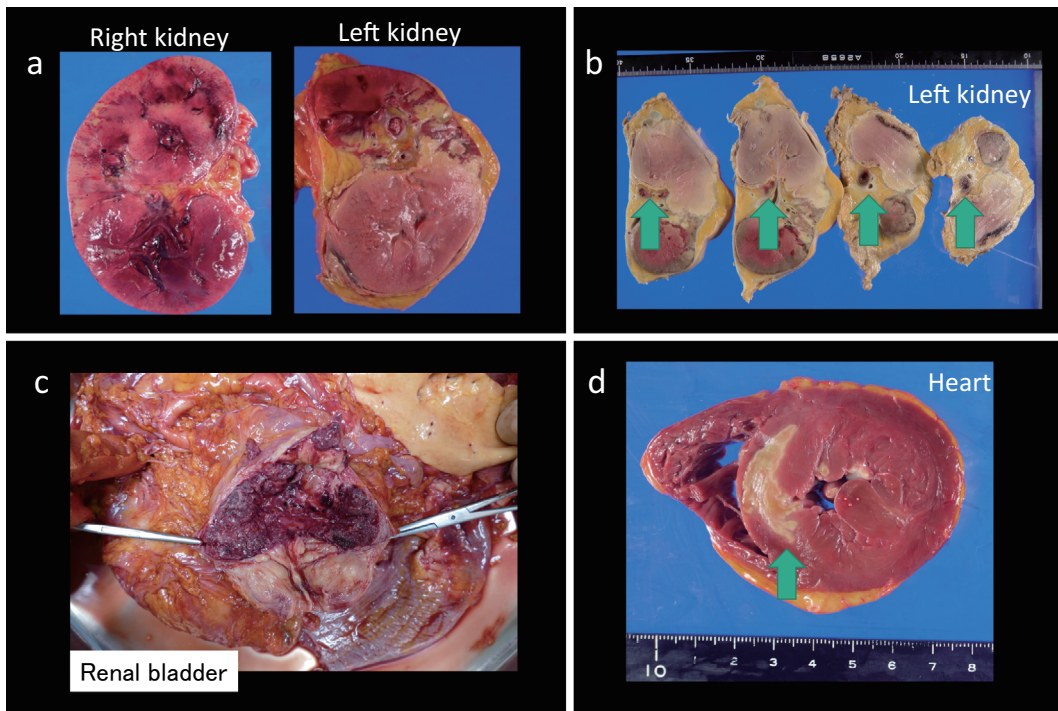
Figure 4. (a) The bilateral kidney sectioned surface. Both kidneys were enlarged (right 340 g, left 370 g) and had a variegated appearance, showing large infarcts, ischemic cortical necrosis (well-defined necrotic yellow mass), hemorrhaging, and exudate on the surface. (b) The bilateral kidney sectioned surface after fixation. The renal artery showed occlusion of the lumina by thrombi (arrow). (c) The urinary bladder. The urinary bladder showed petechial hemorrhaging over the mucosa. (d) The myocardium sectioned surface. The myocardium showed liner infarcts and ischemic cortical necrosis in the interventricular septum (arrow).
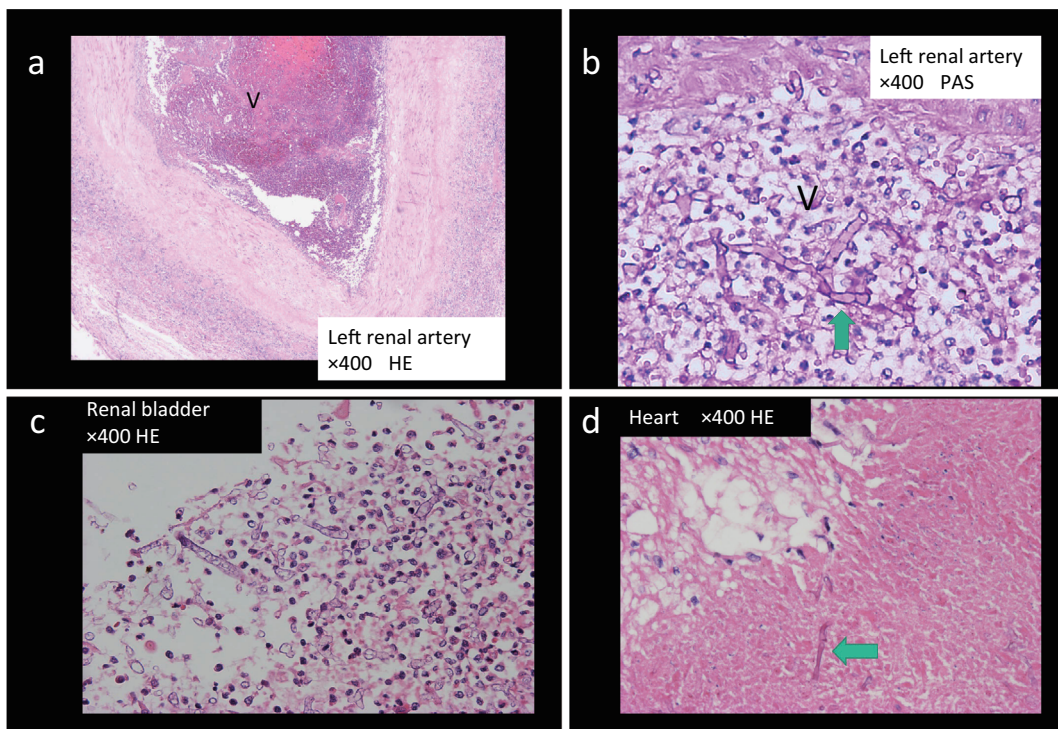

Figure 5. (a) Left renal artery [Hematoxylin and Eosin (H&E) staining ×40]. The renal artery (V) showed sub-total occlusion by a thrombus. (b) The left renal artery (PAS stain ×400). Broad, ribbon-like fungal hyphae (arrow) were present in the blood vessels. (c) Renal bladder (H&E staining ×400). Mucor hyphae were present in the urinary bladder (arrow). (d) Cardiomuscular tissue (H&E staining ×400). Mucor hyphae were present in the cardiomuscular tissue (arrow).
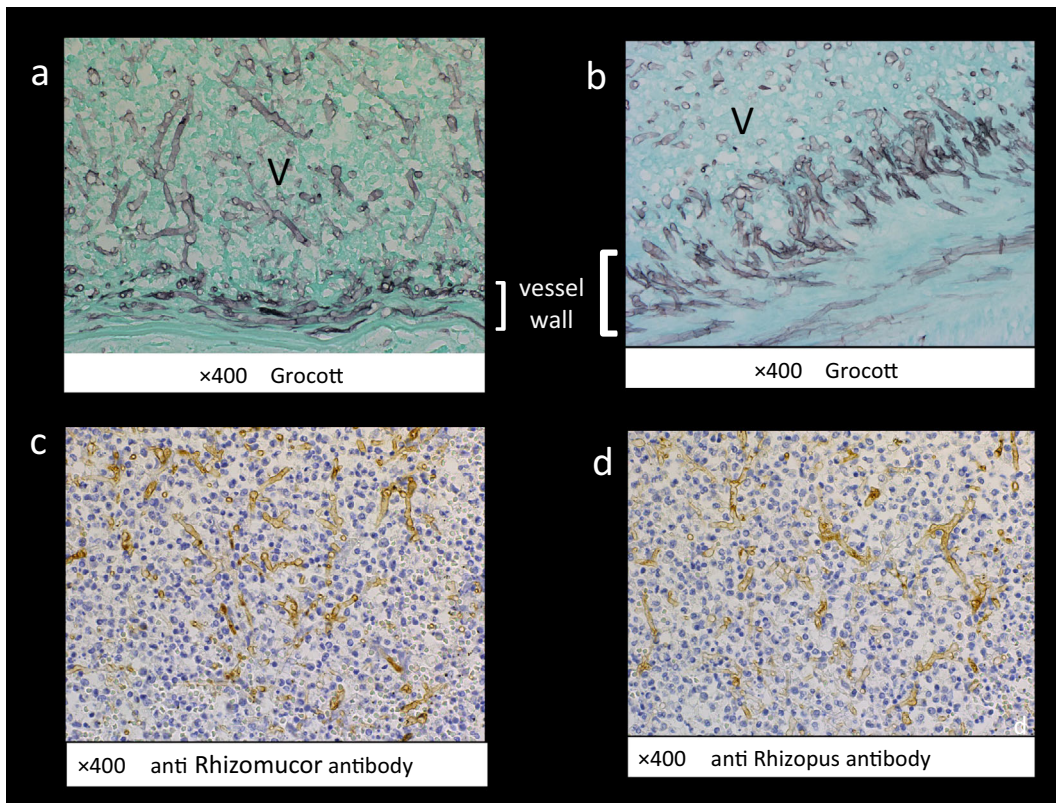
Figure 6. **(a) Right renal artery (V) (Grocott stain ×400). Broad aseptate with right-angle branching in the blood vessels adjoining the vessel wall. (b) Right renal artery (V) (Grocott ×400). Broad aseptate with right-angle branching (arrow) invading the blood vessels (arrow). (c) Right renal artery (anti-Rhizomucor antibody ×400). Immunostaining of anti-Rhizomucor antibody showed positive staining of broad aseptate with right-angle branching in the blood vessels. (d) Right renal artery (anti-Rhizopus antibody ×400). Immunostaining of anti-Rhizopus antibody showed positive staining of broad aseptate with right-angle branching in the blood vessels.**

TNF inhibitors are potent immunosuppressive medications that are licensed for the treatment of a variety of autoimmune diseases, including Behçet's disease, rheumatoid arthritis, and Crohn's disease (7). Patients treated with TNF inhibitors have an increased risk for opportunistic infections, as TNF is important in the formation and maintenance of granulomas (8, 9). Although whether or not TNF inhibitors raise the risk of infection by Mucorales is unclear, there have been sporadic reports of mucormycosis in patients with inflammatory bowel disease, rheumatoid arthritis, and psoriasis using TNF inhibitors (7-12).

The spectrum of mucormycosis includes 1) paranasal, 2) pulmonary, 3) cutaneous, 4) gastrointestinal, 5) disseminated, and 6) uncommon presentations (3). The disseminated form accounts for approximately 9% of cases of mucormycosis. Involvement of single organs, such as bone, heart, and kidney (2, 13-23), is rare. The mechanism underlying the progression of renal mucormycosis is unclear; however, hematogenous dissemination to the kidneys (14-22%) (14) and retrograde spread form lower urinary tract infection have been proposed (15, 16).

Mucormycosis is characterized by the uniform presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis. This is associated with penetration through the endothelial lining of blood vessels and hematogenous dissemination of fungus from the original site of infection to other organs (4, 6, 14, 19, 24), cardiovascular lesions, brain infarction, pulmonary infarction, and renal infarction. Renal failure is caused by occlusion of the renal arteries and/or their branches, as documented in our patient. Both small and large arteries exhibit hyphal invasion and consequent thrombosis, leading to massive cortical and medullary infarction (14-16, 18, 19, 21, 22).

While an early diagnosis is important, early recognition is difficult, as there are no specific findings and no biomarkers to identify this disease. The main clinical features of renal lesions at presentation were a fever (80%) and flank pain and oliguria (70%), which resemble symptoms of acute pyelonephritis (2, 14, 21). Laboratory features included leucocytosis (73%) and hematuria and pyuria (65%) with evidence of gross hematuria and pyuria in half of cases. Chugh et al. previously reported the characteristic CT findings of renal mucormycosis, which include enlarged non-enhancing kidneys with absent contrast excretion and low-attenuation areas suggesting intrarenal abscesses and perinephric collections (24). Tissue culture is useful (22, 23), but blood, urine

cultures (1, 14), and β-D glucan evaluations are often negative (1). Mucormycosis almost always requires histopathologic evidence of fungal invasion of the tissues (1, 22) by nephrectomy (14, 16, 22), ultrasound, and/or a CT-guided needle biopsy/aspiration (1) and perirenal fluid cytology (17, 21). Biopsies demonstrate characteristic wide (3-25 μm in diameter), ribbon-like, thin-walled, primarily aseptate (pauciseptate) hyphae that have irregular diameters, showing nondichotomous irregular branching that accompanies tissue necrosis and fungal angioinvasion. A variety of stains, including hematoxylin and eosin (H&E), Grocott-Gomori methemnamine-silver nitrate, and periodic acid-Schiff (PAS), are useful (1). However, most reported cases have been fatal, and the diagnosis was made by an autopsy (14).

Successful treatment largely depends on a timely diagnosis. It is important to perform broad surgical debridement as soon as possible, and rapid initiation of effective systemic antifungal therapy is necessary, as treatment delays are associated with increased mortality (1). However, surgery is difficult in patients with treatment-resistant underlying disease and a poor general condition (23). The agent of choice is conventional amphotericin B, triazole, posaconazole (not available in Japan). The choice of which antifungal to start should be made in parallel with attempts to establish a firm diagnosis. Because subclinical dissemination is common, the diagnostic strategy should include a thorough clinical evaluation and appropriate CT imaging of the brain, sinuses, and abdomen to "stage" the severity of infection and dissemination (1).

The mortality of renal mucormycosis is reportedly as high as 65% (15, 16). Renal failure occurs in 95.6% patients with bilateral renal involvement, and the mortality of bilateral renal infarction with acute renal failure is almost 100% (14). Our patient had several risk factors rendering him susceptible to mucormycosis. Nephrectomy was recommended, but his condition did not allow the operation.

Conclusion

In conclusion, renal mucormycosis is an important cause of renal failure in immunocompromised patients. Clinical features of mucormycosis include flank pain, a fever, sterile urine, oliguria, and imaging findings suggesting an abscess and/or infarction. Renal mucormycosis is an important cause of renal failure with renal infarction in immunocompromised patients.

The authors state that they have no Conflict of Interest (COI).

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