Mixed Fungal Infection in Early Period after Kidney Transplantation: A Case Report

Böbrek Nakli Sonrasında Erken Dönemde Mikst Fungal Enfeksiyon: Olgu Sunumu

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ABSTRACT

Invasive fungal infections have a rapid and frequently fatal course in patients with solid organ transplantations. Mostly Aspergillus spp., Mucorales spp., Candida spp. and Cryptococcus neoformans are causal pathogens for opportunistic infections. Aspergillus spp. and Mucorales spp. especially lead to invasive fungal infections at rhino-cerebral area; they show similar radiological and clinical signs and they lead to invasive fungal co-infections. In case of any doubt about invasive fungal infections, antifungal treatment should be initiated as soon as possible and immunosuppressive treatment should be considered. This case presentation is about a patient at 51 years of age who developed invasive rhino-cerebral mixed fungal infection in 4 weeks following renal transplant.

KEY WORDS: Kidney transplant, Aspergillus, Mucor, Sinusitis

ÖZ

Solid organ transplantasyonu yapılan hastalarda invaziv fungal infeksiyonlar hızlı ve çoğu zaman ölümcül seyir göstermektedir. Çoğunlukla Aspergillus, Mucor, Candida, ve Cryptococcus neoformans oppurtunistik enfeksiyon etkenleridir. Özellikle Aspergillus ve Mucor rinoserebral bölgede invaziv fungal enfeksiyona yol açarlar, klinik ve radyolojik olarak benzer bulgular gösterirler ve bazen de bir arada invaziv enfeksiyona yol açarlar. İnvaziv funfal infeksiyondan şüphelenildiğinde mümkün olan en kısa sürede antifungal tedavi başlanmalı ve immünsupresif tedavi gözden geçirilmelidir. Bu olgu sunumunda 51 yaşında, renal transplant sonrası 4. haftada invaziv rinoserebral fungal enfeksiyon gelişen bir hasta sunulmuştur.

ANAHTAR SÖZCÜKLER: Böbrek nakli, Aspergillus, Mucor, Sinüzit

INTRODUCTION

Invasive fungal infections are among the most important causes of mortality in transplant patients (1). They are mainly due to invasive *Candida* spp. (53%) and *Aspergillus* spp. (19%), *Cryptococcus* spp. (8%), non-Aspergillus molds (8%), endemic fungi (5%) and *Mucorales* spp. (2%) (2). *Aspergillus* usually affects the lungs, central nervous system, sinuses, skin, bone and urinary tract (3). Mucormycosis is manifested by rhino-orbital-cerebral and pulmonary infections in immunosuppressed transplant patients and those with diabetes mellitus (8). Invasive rhinosinusitis is an unusual form of aggressive fungal infections that appears to be increasing in frequency. The fungi most often implicated in causing invasive rhinosinusitis are species of *Aspergillus* spp., *Fusarium* spp., *Mucorales* spp. and dematiaceous (brown-black) molds. Acute fulminant infections are usually due to *Aspergillus* spp. and *Mucorales* spp (4). Mixed systemic fungal infections rarely occur in renal transplants (5). Herein we presented a case of mixed invasive fungal infection with sino-orbitocranial involvement by caused *Aspergillus* spp. and *Mucorales* spp. in the early period after kidney transplant.

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CASE REPORT

A 51-year-old woman with end-stage renal disease owing to chronic pyelonephritis, received a deceased-donor kidney transplant in 2013 after 9 years of hemodialysis. Her immunosuppressive treatment consisted of mycophenolate mofetil (MMF) and methylprednisolone after basiliximab induction. She had delayed graft function in the postoperative period. Kidney imaging studies showed normal renal perfusion and severely decreased renal concentration on scintigraphy, and elevated resistance indices on Doppler ultrasound. Renal allograft biopsy revealed normal appearance except mild interstitial edema, intratubular calcification and vacuolar degeneration in tubular epithelial cells. CD4d staining was negative. We diagnosed acute tubular necrosis and applied rabbit anti-thymocyte globulin (ATG) for rejection prophylaxis. ATG was discontinued on day 4 due to occurrence of leukopenia (1360/mm^3). During this period, blood glucose levels were in general at a range of 180 to 230 mg/dL. On the 10^{th} day, daily urine output increased to 500 cc. Then, high fever and hypotension developed. Laboratory examination of patients showed pyuria, high CRP (22 mg/dL) and procalcitonin (>32.00 ng/mL) levels. Urosepsis was diagnosed. MMF was discontinued and teicoplanin, meropenem and fluconazole were initiated. Urine and blood inoculations showed growth of Extended Spectrum Beta-Lactamase (ESBL) Escherichia coli. CMV-DNA (PCR) and serum galactomannan tests were negative. The chest high-resolution CT scan did not confirm findings of pulmonary infection in the both lungs. On 12^{th} day, she transferred to intensive care unit (ICU) due to hypoxia and hypotension, and continuous veno-venous hemodiafiltration (CVVHDF) were started. Tracheal aspirates yielded Acinetobacter baumannii Colimycin was added to treatment. On 28^{th} day, a dark blue eschar due to zygomycosis was detected on the skin of the nose (Figure 1). Ecchymotic lesions appeared in the periorbital area including the eyelids, back of nose and frontal area. Fluconazole was discontinued considering possible invasive fungal infections and liposomal amphotericin-B 3 mg/kg/day was initiated. Current lesions were worsened, exophthalmia and chemosis were developed after 24 hours, and therefore dosage of liposomal Amphotericin-B was increased to 5 mg/kg/day and trimethoprim-sulfametoxazol was added. CT examination found massive loss of sinus aeration and high-density soft tissue shadow in the paranasal sinus. Reduced discrimination between cortex-subcortex parts was seen on cranial CT, discrimination between gray matter and white matter could not be done and significant brain edema was observed. Similar findings were also reported for cerebellum and brain stem. Endoscopy examination of patient showed a necrotic feature on left and right nasal cavities. The mycological examination of sample showed hyphae and spores on direct preparation; Aspergillus fumigatus, Aspergillus niger and Mucorales spp. were isolated on fungal culture. Necrosis on back of nose was more prominent on 31^{st} day (Figure 2). The patient died 36 days later due to multiorgan failure.

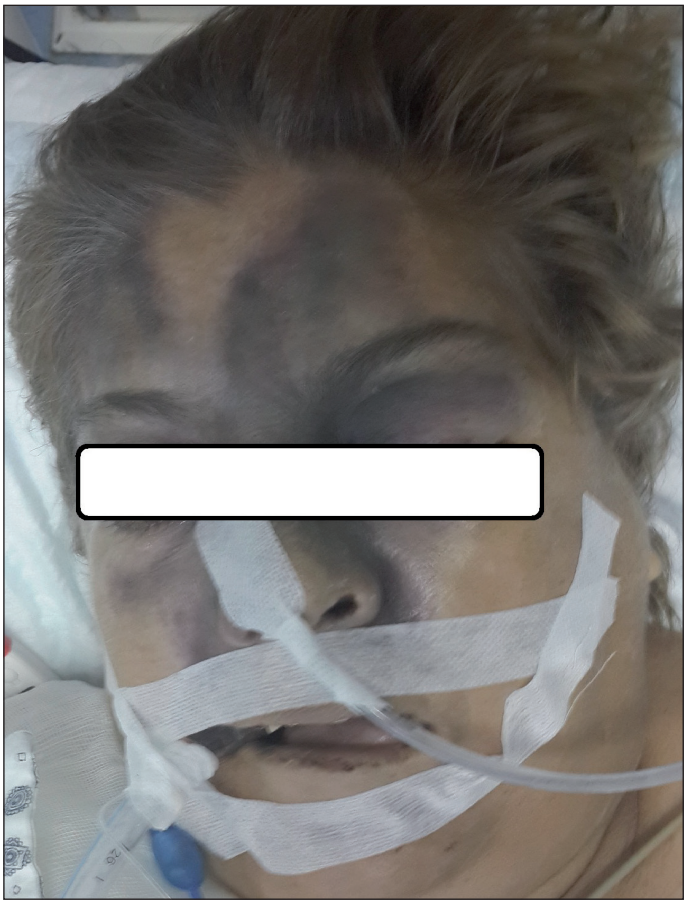

Figure 1: *A dark blue eschar was detected on the skin of the nose on day 28.*

DISCUSSION

Incidence of systemic fungal infection is 2.7% to 9.8% in renal transplant patients (5). Mortality this appears as rhino-orbito-cranial form (2). Aspergillus fumigatus (80-90%), A. flavus (5-10%) and A. niger (1-5%) are most frequently isolated agents from paranasal sinuses. Mucormycosis is also an aggressive, life-threatening and angio-invasive fungal infection leading to infarct in infected tissues. This is rare in patients with solid organ transplantation (0.2-1.2%) and 16% of them appear as rhino-cerebral infection (4).

Acute invasive fungal rhinosinusitis occur by a time course of days to a few weeks, and the histopathology demonstrates involves hyphal invasion of blood vessels with resulting tissue infarction. Aspergillus spp., or members of the class zygomycetes are the most frequent etiological agents (6). The aggressiveness of tissue invasion may vary depending upon the underlying immune status of the host. Although we stopped immunosuppressive medications except low-dose prednisolone early for the restoration of immune function, our

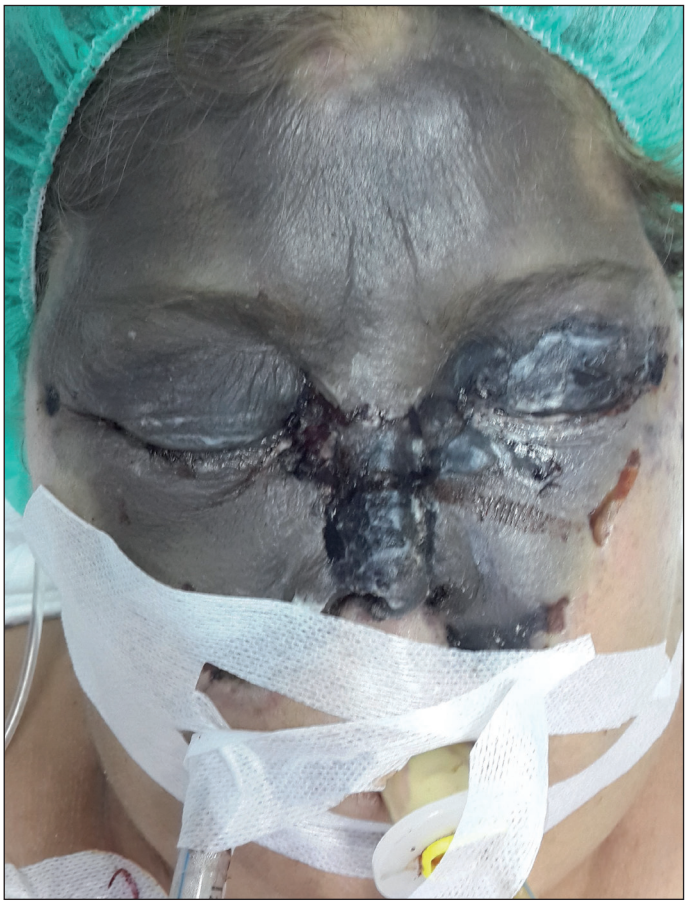

Figure 2: *Necrosis on back of nose was more prominent on day 3.*

case experienced rapidly progressive disease over the course of a few weeks. Funda et al. from Turkey reported that 8 of 207 transplant patients (4 kidney, 4 liver) developed invasive aspergillosis infection on day 24 (range; 15 to 34 days) despite the administration of fluconazole prophylaxis. 6 of patients were died (6/8) and mean time interval from diagnosis to death was 15.4 days (2-29 days) (7).

Renal transplant recipients are at a high risk of invasive fungal infections because of dose and length of immunosuppressive therapy, leukopenia, bacterial and CMV infections, use of antibiotics, allograft rejection, diabetes, renal failure, malignancy, parenteral nutrition and dialysis. The risk factors of our case were leukopenia, hyperglycemia, prolonged use of broad-spectrum antibiotics and ATG.

In our case, a bacterial infection presented with a sudden septic shock following detection of pyuria. Then, she had a secondary bacterial pulmonary infection in the ICU. In our previous study, we observed that fungal etiology was significantly higher in nosocomial pneumonia than community acquired (36.7% vs. 11.2%) (8).

Patients with acute fungal rhinosinusitis usually present acutely with fever, facial or sinus pain, nasal congestion, purulent nasal discharge, headache, and epistaxis, and can have changes in vision or mentation. A high degree of suspicion must be maintained in the immunocompromised patient with sinus complaints, especially facial pain. Our case was in the ICU, and she had no symptom except fever. In the rhinocerebral form of mucormycosis, a black eschar, which results from necrosis of tissues after vascular invasion by the fungus, is frequently seen on the palate or around the orbit. Serosanguinous material can be found in the sinuses. All of the sinuses become involved and spread to contiguous structures, such as the palate, orbit and brain, usually progresses rapidly (9). After the occurrence of the eschar, our patient's nares and oral cavity were carefully examined for necrotic areas with nasal endoscopic evaluation by an otolaryngologist. Cultures of the biopsy specimen were positive for Aspergillus fumigatus, Aspergillus niger and Mucorales spp. Surgical intervention was difficult in our case because of the extent of the severe invasion of infection, although radical surgical debridement is required in most cases to achieve cure.

A few cases of mixed fungal infection have been reported in hematological diseases and after hematopoietic stem cell transplantation (10). Patients with mixed fungemia more commonly underwent organ transplantation and prior surgery, had a lower rate of use of parenteral nutrition and intravenous lines, and had a lower incidence of shock. Zhan et al. have presented a case with Aspergillus spp. and Mucorales spp. infections of both the hepatic and renal arteries, leading the 2 arteries to rupture at the same time (5). Hofman et al. reported a case of fatal necrotic pneumonia caused by combined pulmonary invasive mucormycosis and aspergillosis in a 66-year-old renal transplant recipient. Aspergillus spp. was first identified during the course of the disease by cytological examination and culture (A. fumigatus) of bronchoalveolar fluid. Hyphae of Mucorales (Rhizopus microsporus) were subsequently identified by culture of a tissue specimen taken from the left inferior pulmonary lobe, which was surgically resected two days before the patient died (11).

The diagnosis of fungal infection is difficult because of the non-specific symptoms and signs of fungal infection, low fungus culture rate, and the difficulties and risks involved in obtaining tissue specimens from patients. When developed unexplained fever without any infectious foci in a recipient who had risk factors such as neutropenia, bacterial infection, prolonged broad-spectrum antibiotic usage and uncontrolled hyperglycemia, it can be useful performing nasal endoscopy in early period for a diagnosis of suspected fungal rhinosinusitis. In Table I it has been depicted a flow diagram showed a diagnostic approaches to acute fungal rhinosinusitis. Appropriate treatment depends on the accurate diagnosis of fungal infection with a positive culture or the identification of organisms in tissue by histopathology.

Table I: Unexplained prolonged fever and fungal rhinosinusitis in transplant recipients.

Symptoms
Fever, nasal congestion, epistaxis, facial pain, numbness, changes in mental status, diplopia, proptosis, chemosis
Risk factors
Immunosuppressive therapy, neutropenia, diabetes mellitus, advanced age, steroid therapy, HIV infection, chronic sinusitis, sinus abnormalities in the anatomy, CMV infection
Diagnostic tests
The nasopharynx and oral cavity inspection, palpation break and frontal regions, nasal culture, endoscopic examination and biopsy, visual field examination, computed tomography
Treatment
Of the lipid formulation of amphotericin B for Mucorales (5 mg / kg per day) and voriconazole for Aspergillus species (6 mg / kg iv every 12 hours for two doses, then 4 mg / kg iv every 12 hours) Surgical debridement Restoration of immunosuppressive therapy

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