American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2014; 15: 74-78
DOI: 10.12659/AJCR.890026

Received: 2013.11.12
Accepted: 2013.12.02
Published: 2014.02.15

Mucormycosis in an HIV-infected renal transplant patient: A case report and review of the literature

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 15
Final Diagnosis: Mucormycosis
Symptoms: Lower extremity swelling • respiratory failure • short of breath
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease

Background: Mucormycosis is an uncommonly encountered clinical syndrome in Human Immunodeficiency Virus (HIV)-infected patients. The syndrome is well described in solid organ transplant (SOT) patients, in whom it mainly causes pulmonary or rhinocerebral disease. Mucormycosis in HIV-infected patients who underwent SOT has rarely been described.

Case Report: In this article, we describe an HIV-infected patient with a renal transplant who developed mucormycosis, and we review the literature. A 45-year-old African-American female with a history of HIV controlled by anti-retrovirals was admitted with shortness of breath, lower extremity swelling, and respiratory failure. Bronchoscopic results confirmed Mucor on pathology. She was treated with posaconazole and caspofungin, but her condition deteriorated. Computed axial tomography (CT) scan of the head without contrast showed multiple low attenuation lesions throughout the brain parenchyma, with the largest lesion centered in the left basal ganglia with extensive mass effect with subfalcine herniation and early transtentorial herniation with acute hydrocephalus. Even though we did not have brain tissue to make a precise diagnosis, it is likely that the central nervous system involvement in this patient was due to mucormycosis.

Conclusions: In summary, we describe the case of an HIV-infected patient with renal transplant who died of disseminated mucormycosis. As the number of renal transplants in the HIV-infected population is increasing, clinicians should be aware of the possibility of disseminated mucormycosis. Early diagnosis and effective prophylaxis may alter the course of this devastating syndrome.

Keywords: Mucor • Renal Transplant • HIV

Full-text PDF: http://www.amjcaserep.com/download/index/idArt/890026

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Background

Mucormycosis is a clinical syndrome caused by invasive fungal species belonging to the subclass Zygomycetes. Patients may present with several clinical forms, the most common being rhinocerebral and pulmonary mucormycosis, which are usually acute and fulminant [1]. Mucormycosis is well described in SOT and hematopoietic stem cell transplant (HCST) recipients, but the syndrome has rarely been described in HIV-infected patients. Only 1 case has been reported in transplant recipients co-infected with HIV, despite the fact that SOT in HIV-infected patients is increasing [2,3].

Case Report

We present the case of a 45-year-old African-American woman with a history of HIV infection maintained on darunavir, ritonavir, raltegravir, and lamivudine. The patient was admitted with progressive shortness of breath on exertion for 2 days, associated with orthopnea and lower extremity swelling. The patient had no fever, chills, cough, or sputum production.

The patient had a history of HIV-associated nephropathy, for which she underwent deceased renal transplant 6 months prior to admission. The deceased donor was Cytomegalovirus-negative and Methicillin-sensitive *Staphylococcus aureus*-positive. The patient had received cefazolin pre- and post-transplantation. Post-transplantation, she was induced with basiliximab 20 mg intravenously (IV), mycophenolate 1 gm every 12 h IV, and methylprednisone 1 gm every 12 h IV for 3 days. The patient was discharged on prednisone 15 mg twice daily, tacrolimus 4.5 mg twice daily, and mycophenolate 720 mg twice daily post-transplant, which was reduced to prednisone 20 mg daily, tacrolimus 0.5 mg daily, and mycophenolate 360 mg daily during her admission at our center. She also received prophylaxis with valganciclovir, nystatin swish-and-swallow, and trimethoprim-sulfamethoxazole. Other past medical history included deep venous thrombosis, for which the patient received warfarin. There was a history of avascular necrosis of the left hip, pulmonary hypertension, and congestive heart failure.

The patient was hospitalized 1 month prior to the present admission because her creatinine increased from 2.7 mg/dL (5 months ago) to 4.96 mg/dL, despite being in therapeutic range (5–20 ng/ mL) of tacrolimus. She was suspected to have a graft rejection. She underwent a kidney biopsy, which confirmed the diagnosis and was treated with IV methylprednisolone 100 mg every 12 h for 4 days, followed by a tapering dose. Upon discharge, her creatinine was 4.38 mg/dL.

Physical examination revealed a temperature of 36°C, blood pressure of 166/96 mm Hg, pulse rate of 73 beats/ min, and respiratory rate of 20/min. Lung examination revealed rales in the left upper lobe. Lower extremities were significant for 2+ pitting edema. The other examination results were normal, including the left upper extremity where she had an arteriovenous fistula used for hemodialysis.

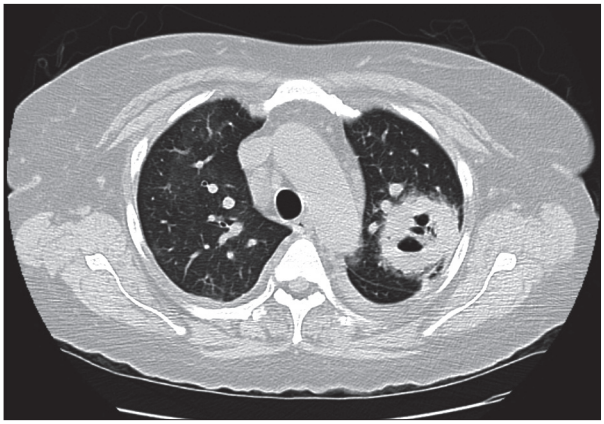

Figure 1. CT scan of the chest showing 4.7 cm thick walled cavitary mass in the left upper lobe with surrounding ground glass opacities.

Laboratory data showed a WBC of 7000/mm^3 with 83% neutrophils and 6% lymphocytes, hemoglobin of 9.3 gm/dL, platelets of 130,000/mm^3, creatinine of 3.27 mg/dL, and oxygen saturation of 97% on room air. CD4 count was 470 cu/mm (CD4% – 35.3) and HIV viral load of 26 copies/mL. Chest X-ray on admission showed pulmonary edema with trace bilateral pleural effusion. Computed axial tomography (CT) scan of the chest revealed a 4.7-cm – thick walled cavitary mass in the left upper lobe, with surrounding ground glass opacities, small nodular opacities in the right middle lobe, and patchy ground glass opacities bilaterally, enlarged mediastinal lymph nodes, and bilateral pleural effusions with left pleural thickening (Figure 1). Bronchoscopy with a biopsy of the cavitary lesion was performed, after which the patient desaturated and needed endotracheal intubation. Broncho-alveolar lavage fluid culture revealed *Klebsiella pneumoniae,* for which she received piperacillin-tazobactam. The patient's hospital course was complicated by worsening renal failure and the patient was placed on hemodialysis. Bronchoscopy specimen staining revealed fungal elements, which were broad, non-septated, and with right-angle branching, compatible with *Mucor* (Figure 2). The patient was started on oral posaconazole 400 mg twice a day and intravenous caspofungin 50 mg daily. Amphotericin B was not used, as the patient's renal functions were worsening. Fungal cultures did not yield any organism.

The clinical course was significant for the development of a new right-sided hemiparesis and obtundation. CT scan of the head without contrast showed multiple low-attenuation lesions throughout the brain parenchyma, with the largest lesion

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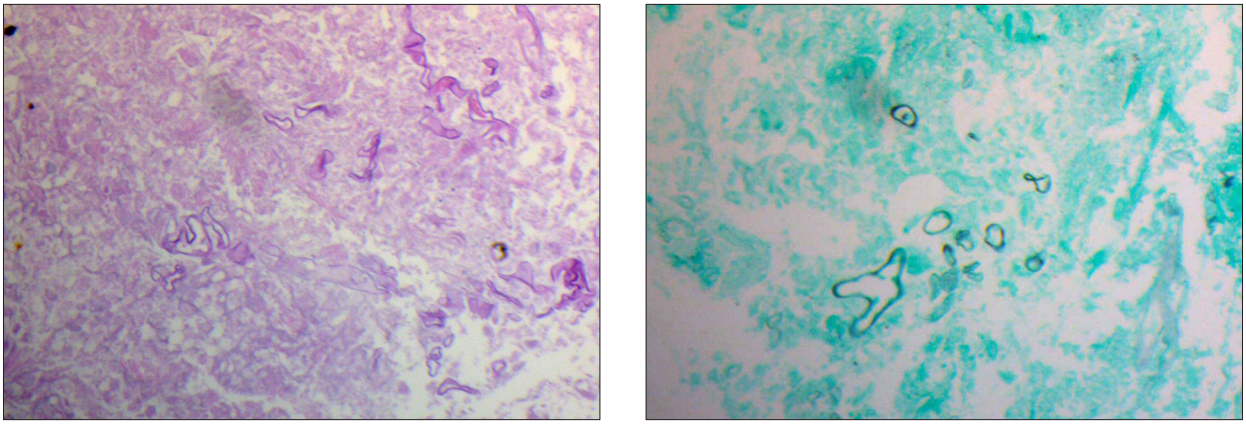

Figure 2. Hematoxylin and eosin stain (H and E) and Grocott's methenamine silver stain showing broad, non-septated and with right angle branching Mucor.

centered in the left basal ganglia with extensive mass effect with subfalcine herniation and early transtentorial herniation with acute hydrocephalus. A brain flow scan was done, which showed abnormal flow consistent with brain death. The patient died 14 days after admission. Permission for autopsy was not granted.

Discussion

Mucor was first described by Paltauf in 1885. Taxonomically, the fungus belongs to the class Zygomycetes and to the order Mucorales [4]. The organisms causing mucormycosis are *Rhizopus* species, *Mucor* species, *Lichtheimia* species (former *Absidia* species), *Cunninghamella* species, *Rhizomucor* species, *Syncephalastrum* species, *Saksenaea* species, and *Apophysomyces* species [4].

These fungi are ubiquitous saprophytes found throughout nature. They are broad (5–50 um), non-septated hyphae with right-angle branching, which characteristically involve the blood vessels, causing thrombosis and ischemia [4].

Overall, rhino-cerebral (55%) and pulmonary (30%) mucormycosis are the most common clinical forms encountered, followed by gastrointestinal tract and cutaneous forms [5]. Disseminated mucormycosis accounts for 9% of cases [1].

Pulmonary mucormycosis findings on CT scan include lung nodules, cavitation with pleural effusion, and bronchopneumonia [6]. Reversed halo sign can occasionally be seen. Since these findings are not specific to mucormycosis of the lungs, a tissue analysis is needed for accurate diagnosis [7,8]. Pre-mortem diagnosis is difficult and most cases are diagnosed at autopsy [5].

Treatment of mucormycosis includes antifungal agents and surgical resection; better outcomes have been noted when a combination of antifungal agents and surgical resection is used [9]. Amphotericin B deoxycholate (AmB) is the drug of choice [10,11]. Lipid formulations of amphotericin allow higher doses for longer periods of time and with less renal toxicity [11]. Fluconazole, voriconazole, and itraconazole do not have reliable activity against mucormycosis [11]. Recently, posaconazole has been used as a salvage therapy against Zygomycetes [2,11,12]. In a study in febrile neutropenic patients with mucositis and diarrhea, posaconazole did not achieve adequate serum levels [13]. A prospective, matched case-control study using AmB and posaconazole showed AmB to be superior to posaconazole [14]. Another retrospective study conducted in patients diagnosed with rhino-orbital cerebral mucormycosis showed that the combination of AmB and caspofungin was better than monotherapy [15]. AmB was shown to be superior to posaconazole in a study using neutropenic mice infected with *Mucor circinelloides* and treated with either AmB or posaconazole [16]. Another study in neutropenic mice infected with *Mucor* showed posaconazole to be equally effective to AmB in reducing fungal tissue burden [17].

Simultaneous use of ritonavir and tacrolimus leads to elevated blood levels of the latter drug. The area under the curve for tacrolimus may be increased up to 10-fold and half-life of the drug may be as long as 20 days [18].

Invasive fungal infections (IFI) including *Mucor,* following renal transplant recipients, occur in 1–2% of patients in developed countries [19]. The disease manifests at a median of 6 months post-transplantation and has been associated with high-dosage immunosuppressive therapy [20].

Pulmonary mucormycosis has a poor prognosis, with a mortality of 80% [5]. Patients treated with a combination of medical and surgical approaches have a significantly lower mortality of 11% compared to 68% in patients receiving only antifungal agents. Successful therapy is associated with early diagnosis [5].

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Table 1. List of patients with HIV co-infected with mucormycosis.

No.	Organ involved	Age/ sex	History of Intravenous drug abuse (IVDA)	Co-morbidities/ co-existing conditions	CD4 (cu/mm)	Method of identification	Treatment	Outcome
1.	Pulmonary (5)	43/F	No	Diabetes mellitus	370	Culture	AmB + surgery	Survived
2.	Renal (1)	27/ M	Yes	*Mycobacterium tuberculosis*	<200	Histopathology	Refused surgery Unknown medical therapy	Death
3.	Renal (1)	39/ M	Yes	*Cryptococcus meningitis*	<200	Histopathology	Surgery Cryptococcus meningitis treatment	Unknown
4.	Disseminated (9)	45/ M	In the past	*Bacillus* bacteremia *Clostridium difficile* colitis	26	Histopathology	AmB	Death
5.	Disseminated (9)	36/ F	Yes	Progressive multifocal leukoe-cephalopathy Herpes simplex esophagitis	70	Histopathology	Unknown	Death
6.	Cerebral (21)	31/ F	In the past	Squamous cell carcinoma of cervix	387	Histopathology	AmB	Death
7.	Rhinocerebral (22)	33/ M	In the past	–	20	Histopathology	AmB	Death
8.	Disseminated (2) (*Rhizomucor*)	50/ M	In the past	Liver transplantation Hepatitis C	108	Culture	Voriconazole Caspofungin	Death
9.	Pulmonary/ Presumed Disseminated (Our patient)	45/ F	Unknown	Renal transplantation Congestive heart failure Pulmonary hypertension	470	Histopathology	Posaconazole Caspofungin	Death

HIV-associated mucormycosis has been described in 7 cases (Table 1). Of these 7 patients, 5 had a CD4 count <200. Intravenous illicit drug use (past or present) was a common risk factor in the majority of patients (5 patients). Six of the described cases were diagnosed by histological appearance typical for mucormycosis; the organism grew in culture in only 1 patient. One patient had pulmonary mucormycosis. Disseminated *Mucor* was confirmed in 2 patients. AmB was used in 4 patients, 2 patients underwent surgical debridement. Of the 7 patients described, 4 died. Of the 2 patients who underwent surgical debridement in addition to antifungal treatment, 1 survived.

There is only 1 other case reported in an HIV-infected patient with SOT, in which Nichols et al. [2] described an AIDS patient with a liver transplant, diagnosed with Rhizomucor at autopsy. The patient had a history of intravenous drug use and had a CD4 count of 108 cu/mm. The patient was treated with voriconazole post-transplantation and caspofungin was added on day 6 post-transplantation when the patient's clinical status deteriorated, but the patient died despite treatment. At autopsy, mucormycosis, involving all the major organs except the CNS, was diagnosed. The organism was identified as *Rhizomucor* from autopsy specimen culture.

To our knowledge, our patient is the first reported case of pulmonary mucormycosis in an HIV-infected patient with a renal transplant. Our patient was treated with a number of immunosuppressant agents due to a suspected graft rejection, making her prone to develop mucormycosis, and, similar to other patients with a renal transplant, receiving multiple

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immunosuppressive agents [20]. The contribution of our patient's HIV infection to the development of her disseminated mucormycosis is difficult to assess, as her HIV infection was well controlled, with a viral load of 26 copies/mL and a relatively high CD4 count of 470 mm^3. The diagnosis of mucormycosis depends on identifying the organism in tissue. The BAL specimen showed non-septate right-angle branching hyphae and the CT appearance was compatible with the diagnosis of mucormycosis. These findings are similar to other cases that were also diagnosed on histology (Table 1). Although we did not have brain tissue to make a precise diagnosis, it is likely that the CNS involvement in this patient was due to mucormycosis. Our patient was treated with posaconazole and caspofungin. Posaconazole was given due to its recently shown activity in an animal model [17] and because the activity of other azoles was shown to be inferior to it and unpredictable [11]. Caspofungin was added because it has been shown to have activity against Zygomycetes [15]. Due to the patient's deteriorating renal condition, there was reluctance to use AmB.

Conclusions

In summary, we described the case of an HIV-infected patient with a renal transplant, who expired of disseminated mucormycosis. Because the number of renal transplants in the HIV-infected population is increasing, clinicians should be aware of the possibility of disseminated mucormycosis. Early diagnosis and effective prophylaxis may alter the course of this devastating syndrome.

Statement

We have no conflict of interest.

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