Invasive fungal infection by *Cunninghamella bertholletiae* in a kidney transplant patient – a dramatic report

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Received: August 4, 2016  Accepted: September 5, 2016  Online Published: September 12, 2016

DOI: 10.5430/crim.v3n4p32  URL: http://dx.doi.org/10.5430/crim.v3n4p32

**ABSTRACT**

Invasive infections caused by fungal species are uncommon. They are usually associated with poor outcomes. They usually occur in immunocompromised patients such as kidney transplant recipients. The identification of fungi in blood or in tissue culture is important to establish the correct diagnosis. Survival is conditioned by the degree of suspicion, early diagnosis and early initiation of appropriate therapy. The authors present a case of an invasive fungal infection by *Cunninghamella bertholletiae* in a renal transplant recipient.

**Key Words:** *Cunninghamella bertholletiae*, Invasive fungal infection, Kidney transplant

**1. INTRODUCTION**

The overall morbidity and mortality associated with transplantation have substantially reduced in the last years.[1] Infections are a major problem after transplantation; they are associated with reduced graft and overall survival.[2] They are the second most common cause of hospitalization in the first year after kidney transplantation and the first thereafter, with admission rates of 31.8 per 100 patients in the first year and 17.8 in the second year post-transplant, according to the U.S. Renal Data System 2014.[3] Also in the U.K., the infections are reported as the major cause of death, followed by cancer and cardiovascular disease. Bacterial infections are more frequent than fungal infections.[4] However, in the last years, a variety of opportunistic infections caused by relatively avirulent organisms such as some fungal species have emerged. This is due to the increased immunosuppression, multiple organ transplantation and environmental factors.[1, 5] Incidence rate of invasive fungal infection (IFI) in kidney transplant (KT) recipients has been reported to be 0.87%-14% and vary according to the geographical area; these infections are associated with a high mortality rate (about 50%-80%).[6] The causative agent and the risk factors vary with the timing after KT and with the duration and net dosage of immunosuppression. The symptoms are nonspecific and consequently there may be a delay in diagnosis, which may worsen the patient’s prognosis.[5]

Invasive candidiasis, cryptococcosis, and mold infections are the main IFI reported. Most cases have pulmonary involvement.[6, 8] The increased frequency of molds causing IFI in this population is the consequence of more intense immunosuppression, as well as the use of anti-*Candida* prophylaxis used in many centers.[1] The IFI caused by less frequent species increased in the last years and new pathogens have been described. This is due to developments in diagnostics,
We present a case of 63-year-old man with hypertension, peripheral arterial disease, and benign prostatic hyperplasia underwent chronic urethral catheterization. He had a chronic kidney disease of unknown etiology diagnosed more than ten years ago. He was submitted to a renal transplantation from a deceased donor (1 mismatch in A, 1 mismatch in DR, PRA 0%) one year before admission. Induction therapy was performed with prednisolone, mycophenolate mofetil (MMF), tacrolimus and basiliximab. He was under immunosuppressive therapy with MMF (250 mg bid), tacrolimus (4 mg bid) and prednisolone (5 mg id), with a serum creatinine (Scr) of 1 mg/dl. He had a past history of BK virus infection, resolved six months before. Tacrolimus levels were between 5–6 ng/ml. The patient was admitted to the emergency room with a typical angina chest pain with two hours of evolution that appeared at rest, and a history of exacerbated dyspnea, productive cough with purulent expectoration and pleuritic pain that begun one week before. He had no fever. He lost 5% of total body weight in the previous two months. There were no other family members with the same symptoms. Physical examination showed a pronounced weight loss and signs of dehydration. He had hypotension (TA 85/40 mmHg), tachycardia, no fever, and clinical signs of poor peripheral perfusion. On pulmonary auscultation, diminished breath sounds in the left hemithorax and sones were heard. Cardiac auscultation showed rhythmic sounds and systolic murmur in the mitral focus (II/VI) with no irradiation. Abdominal examination was normal. Pyuria was present. ECG showed a fascicular right hemiblock and ST elevation in the anterior and inferior leads. Troponine I was increased (2.4 ng/mL, normal level < 0.030 ng/mL). Blood gas analysis showed a metabolic acidosis with normal gap, type 1 respiratory failure and hyperlactatemia. The serum analysis showed: anemia (9.8 g/dl normocytic normochromic), leukocytosis (22,000/µl), neutrophilia (86%) with normal eosinophilic count and thrombocytopenia (120,000/µl); PCR was 270 mg/L. He presented an acute renal injury (urea of 100 mg/dl and Scr of 2.5 mg/dl, hyperkalemia (5.5 mEq/L), DHL 320 UI/L, hypoalbuminemia (3 mg/dl) with total protein and plasma glucose levels in normal range. Urinalysis showed erythrocyturia (> 50/field), leucocyturia (> 50/field) and proteinuria 20 mg/dl; there was no eosinophiluria or urinary dysmorphic erythrocytes. In chest X-ray we observed a reticular infiltrate in the left lower lobe. The kidney and abdominal ultrasound were normal. Blood and urine cultures were collected and the patient began fluids and empirical antibiotic treatment (imipenem and azithromycin), subsequently changed according to the antimicrobial susceptibility.

The transthoracic echocardiogram showed a moderate impairment of left ventricular function, left ventricular enlargement and edema of the interventricular septum. An emergency catheterization was made and it showed no ischemic heart disease. The initial response was unfavorable, with sustained hemodynamic instability, respiratory distress and oliguria. He needed hemodynamic, respiratory support and renal replacement therapy. Given the severity of his condition, the immunosuppressive therapy was reduced (MMF and tacrolimus were stopped); prednisolone (5 mg/day) was maintained. The remaining study conducted revealed blood and urine cultures with E. coli sensitive to antibiotic therapy. Thoracic-abdominal-pelvic scanner showed evidence of an abscess in the right lung with irregular contours and dimensions (0.5 cm to 3.3 cm); in the left lung it was seen a condensation image and some nodules (the largest one with 12 mm), bilateral pleural effusion and thin blade of pericardial effusion. No abscesses were found. Bronchoscopy showed an endobronchial lingual injury with partial bronchus obstruction. A biopsy was made. The fluid collected was sent for microbiological examination. Persistent severe systolic dysfunction was maintained in the transthoracic echocardiogram; the interventricular septum edema got worse. The viral, including CMV and bacterial serologic tests were negative. The patient started empiric therapy with fluconazole 24 hours after death. He died five days after admission with multiple organ dysfunction and refractory multifactorial shock. Post-mortem the microbiological of bronchoalveolar product showed the presence of Aspergillus fumigatus and Cunninghamella bertholletiae. The lung biopsy showed a mold of Cunninghamella bertholletiae fungi and some E. coli bacilli.

3. Discussion

This case describes the severity and the poor prognosis of an IFI in an immunocompromised patient.

Most of zygomycosis cases found in humans are caused by Mucoraceae species. In the Cunninghamamellaceae, only C. bertholletiae, has been proven to infect humans and it is rarely isolated as an agent of zygomycoses in immunocompromised patients.[9,11] It can be found in soil, seeds, nuts and vegetables. There are several transmission paths described in the literature – the most frequent is by inhalation.
of airborne spores in pulmonary and rhinocerebral infections. The lung is a particularly vulnerable organ to IFI due to the entry of spores in inspired air, especially in immunodeficient subjects.

The transmission by gastrointestinal tract and soft tissue infection has also been described. In a recent transplant recipient, we have always to consider the possibility of infections being transmitted by the donor; however such case it was never described with this agent. Pulmonary involvement is the most frequently, but other organs such as the sinus, the kidney and the skin can be infected. The first case was reported in 1855 by Kurtenmeister who described pulmonary mucormycosis in a patient with lung cancer.

Beyond KT recipients, this kind of infections have been described in patients with hematologic malignancies, neutropenia, AIDS, diabetes and in some, who were receiving deferoxamine treatment. The infection in immunocompetent patients are rarely described. In previously reported cases, as in our case, the clinical presentation was with fever unresponsive to antibacterial chemotherapy, dyspnea and pleuritic chest pain. Suspicious pulmonary lesions were identified at admission on chest radiographs. A prominent clinical feature of this case was the pronounced cardiac signs and symptoms. The major symptoms of our patient were chest pain and dyspnea. At admission, there were electrocardiographic changes suggestive of ischemia such as a new fascicular right hemiblock and ST elevation in the anterior and inferior leads. However, no signs of ischemia were found in cardiac catheterization. Curiously, there was an edema of the interventricular septum that increased in several hours, what can be explained by the invasion of the myocardium by fungi and explain the clinic of myocardial infarction. A cardiac involvement in a KT patient was previously described.

The extensive pulmonary involvement suggests the following sequence to explain infection: inhalation of spores, pulmonary germination, invasion of pulmonary vessels, spread to the heart and then widespread vascular dissemination. In most studies the infection started during the first 6 months after transplantation, but in others as in our case, it occurs after the first year of KT. The most important risk factors described were steroids use, acute rejection episodes associated with high steroid dosages, prolonged transplant surgery time, broad spectrum antibiotic treatment, second kidney transplants, gastrointestinal or vascular complications, and long intensive care units stay. Our patient had a lower immunological risk. His main risk factors were the immunosuppressive therapy and chronic urethral catheterization. Tacrolimus level was in therapeutic range and MMF was at lower dose. To remember, our patient had a past history of BK virus infection six months before admission and since then, the MMF was in low doses. It suggests an excessive immunosuppression and could be also a risk factor to support this evolution.

In this case, the lack of response to the antibiotic therapy should draw our attention to the possibility that the infection be caused by other agents, including fungi. For an early diagnosis it is necessary to have a high index of clinical suspicion. Prompt institution of antifungal therapy and surgical intervention when possible are important measures to improve the prognosis. For patients with pulmonary zygomycoses, antifungal treatment alone is less effective when compared to combined medical and surgical therapy. The patient started fluconazole only 24 hours before he died. Itraconazole or fluconazole don’t provide adequate coverage for zygomycetes. In some centers, routine prophylaxis with anti-fungal therapy is done after transplantation. The relative decrease in the incidence of other fungal pathogens during itraconazole or fluconazole prophylaxis can promote the increase of opportunistic infections caused by zygomycetes in these immunosuppressed patients. However, in Portugal we only made prophylaxis with nystatin during hospitalization, in the early post-transplantation period. This may explain the rare reports of IFI caused by this specie. In Portugal, in a single center study that included every KT recipients with fungal infections diagnosed between 2003 and 2013, the authors identified 45 IFI. They report only one case of pneumonia by Cunninghamella sp.

Current recommendations for treatment include amphotericin B at doses of 710 mg/kg/day. The optimal duration of therapy is unknown. The overall prognosis depends on several factors, including the infection site, the diagnosis time, type and kind of immunosuppression. Mortality rate as high as 85% has been reported. A culture confirmation is useful to establish a correct diagnosis. However, fungi are not always tissue cultured. In some cases, it is needed a longer time to their growth. So, early diagnosis remains difficult to achieve and post-mortem diagnosis is common. The earlier recognition of the high-risk patients and the known difficulty in establishing a definitive diagnosis supports the use of antifungal empirical therapy in severe cases unresponsive to antibacterial therapy. Early discontinuation of immunosuppressive drugs, under the risk of losing the graft can be vital. In this patient, corticosteroid therapy was maintained and only the tacrolimus and MMF were stopped. Perhaps the outcome would have been different if the immunosuppression was stopped and the empirical antifungal therapy had started earlier.

http://crin.sciedupress.com Case Reports in Internal Medicine 2016, Vol. 3, No. 4 34
ISSN 2332-7243  E-ISSN 2332-7251
4. CONCLUSIONS

This is the first case of pulmonary infection by Cunninghamella bertholletiae identified in our center. Aspergillus fumigatus is more frequently isolated.

This case shows that in an immunocompromised patient with a severe infection, fungi should ever be considered as an etiologic agent, especially when evolution is unfavorable although the identification of other microbiological species. The prompt reduction or even stopping the immunosuppressive therapies and the antifungal coverage of these agents, even though initially empirically, should be considered. If the treatment is not fast enough, the prognosis is usually fatal, as in this case. Unfortunately, our patient was not submitted to a clinical autopsy. It can be crucial for establishing clinical pathological correlations in cases where the clinical diagnosis is unknown or when there is an unsuspected pathology.

The emerging fungal infections pose a challenge in the treatment of KT patients. The diagnosis can be difficult, the treatment must be started early and may include the suspension of immunosuppression under penalty of losing the graft. New treatment strategies are needed to improve the patient’s outcome.

The report of new cases should be encouraged to improve and standardize our clinical practice.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES


