Disseminated invasive aspergillosis following cytomegalovirus encephalitis in a renal transplant recipient

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ABSTRACT

Cytomegalovirus (CMV) disease is common in renal transplant recipients and predisposes to secondary bacterial and fungal infections. Disseminated invasive aspergillosis is rare in those patients (0.5% of all infections), but has a mortality of almost 90%.

The authors present the case of a 65 year-old cadaveric renal transplant male recipient with a positive CMV IgG serology at the moment of renal transplantation. The initial immunosuppression was cyclosporine A, mycophenolate mofetil and prednisone and the patient was discharged on the 11th post transplant day with a serum creatinine of 3.2 mg/dl.

He was readmitted on the 43rd post transplant day with tachypnea and fever, which did not resolve even after large spectrum antibiotherapy. Serious abdominal distension with normal intestinal motility appeared, followed a few days later by an altered level of consciousness. The brain computed tomography (CT) was normal and a chest and abdominal CT revealed generalised distension of the entire digestive tract. Laboratory tests showed CMV antigenemia >1000 cells/50 thousands of leucocytes in peripheral blood and CMV genoma was later isolated from cerebrospinal fluid.

The patient initiated therapy with ganciclovir and anti-CMV gamaglobulin but, despite a marked reduction in CMV antigenemia, he developed cardiopulmonary arrest. He was then successfully reanimated and put on mechanical ventilation. A few days later a Pseudomonas aeruginosa pneumonia was diagnosed and the patient died from septic shock.

The post-mortem anatomopathologic evaluation revealed disseminated invasive aspergillosis (in brain, thyroid, lung and liver) and a bacterial pneumonia.

Key-Words: Aspergillosis; cytomegalovirus; kidney transplantation.

INTRODUCTION

Transplant recipients are at great risk of opportunistic infections as immunosuppressive drugs are administered to prevent rejection. CMV infection is an important cause of morbidity and mortality in solid organ transplant patients, with a frequency of up to 54-70%¹. The most frequent presentations of CMV disease are fever (58%), pneumonitis (26%) and enterocolitis (16%)¹. Encephalitis is a very rare presentation of CMV disease (< 1%)².
Pre transplant recipient serologic status and the degree of immunosuppression determine both the incidence and severity of the disease. Patients immunosuppressed with antithymocyte globulin or anti-CD3 monoclonal antibody are associated with a high risk of CMV disease. Viral infections, particularly CMV, induce a higher state of immunosuppression and favour secondary bacteria and fungi infections.

The incidence of systemic fungal infections in kidney transplant recipients is estimated to be around 4%. Presenting symptoms are usually non-specific, including low-grade fever, weight loss, fatigue and dry cough. The commonest causal agents include the *Candida*, *Aspergillus* and *Rhizopus* species. *Aspergillus* species are ubiquitous saprophytes commonly found in the environment that may become opportunistic fungi. Their related clinical syndromes include allergic bronchopulmonary aspergillosis, aspergiloma and invasive aspergillosis, the latter the most common type in immunosuppressed patients. In renal transplant recipients, however, invasive infection has a very low incidence (0.5% of all infections), but once it appears, its mortality is quite high, approaching 90%. It typically develops within the first 3 months of transplantation and the most common agent is *Aspergillus fumigatus*. The diagnosis requires a high degree of suspicion and the detection of *Aspergillus* in cultures and/or by histologic examination is necessary.

The authors present a case of disseminated invasive aspergillosis following CMV encephalitis, two rare clinical entities, in a renal transplant who underwent an apparently "non-aggressive" immunosuppression.

**CASE REPORT**

The authors present the case of a 65 year-old Caucasian male with end-stage renal disease of unknown aetiology, in haemodialysis treatment for five years. He had a past history of chronic bronchitis related to smoking, hypertension and abdominal aorta aneurism surgery in March 2000.

On 31/12/2004 he received a cadaveric renal allograft in another renal transplant unit. The donor was a 65 year-old Caucasian male and the cause of death was anoxic encephalopathy. He had 5 HLA incompatibilities (2 in A, 2 in B and 1 in DR) and a panel reactive antibody of 0%. The cold ischemia time was 20 hours and the initial immunosuppression was cyclosporine A (CSA), mycophenolate mofetil (MMF) and methylprednisolone. Both the donor and the recipient had positive CMV IgG serology.

The patient was discharged on the 11th post transplant day with a serum creatinine of 3.2 mg/dl and his medication was CSA (350 mg/day), MMF (2g/day), prednisone (20 mg/day) and cotrimoxazole (960 mg/day).

![Figure 1](image)

Parietal brain softening (left) and Aspergillus encephalitis (PAS x 40; window x 400) (right)
He was admitted to our renal transplantation unit on the 43rd post transplant day with tachypnoea and fever (38°C), with the physical exam showing no other alterations. The initial laboratory tests revealed a leukocyte count of 8800 x 10^6/L with 90% of neutrophils and 7% of lymphocytes, a C-reactive protein (CRP) of 6 mg/dl and a serum creatinine of 2.8 mg/dl. The chest X ray did not show pathology alterations. In spite of that, and in the face of an immunocompromised patient, empiric therapy with ceftriaxone (2g/day) and azithromycin (500 mg/day) was started.

On the 4th day of hospitalisation a serious abdominal distension with an apparent normal intestinal motility appeared and on the 8th day an altered level of consciousness, with periods of prostration and mental confusion, had installed. There were no other changes in the neurology exam.

After 5 days of antibiotic therapy, without clinical or laboratory improvement, therapy was changed to meropenem (500 mg/day), levofloxacin (500 mg/day), vancomycin (1 g each 48 hours) and voriconazole (500 mg/day) which were all maintained for 7 days, also without any clinical or laboratory improvement.

All culture and serology exams performed were negative, except for CMV antigenemia which revealed a >1000 cells/ 50 thousands of leukocytes in peripheral blood. Thus, on the 12th day of hospitalisation, when that result became available, therapy with ganciclovir (10 mg/Kg/day during 21 days) and hyperimmune anti-CMV gamaglobulin (1 mg/Kg weekly during 3 weeks) was started. CSA was then discontinued and the dose of MMF was reduced. Although these measures resulted in a subsequent and expected marked reduction in CMV antigenemia, there was no clinical improvement.

A thoracic and abdominal CT scan were performed at this time and revealed, respectively, peripheral pulmonary emphysema and a generalised distension of all digestive tract.

A bronchoscopy was also performed to investigate the pulmonary symptoms. The macroscopic aspect of the bronchial mucosa was normal and the bronchoalveolar lavage sample analysis showed no alterations in either the cytological or bacteriology exams. A colonoscopy was performed due to the abdominal distension, revealing the presence of hyperplasic micro polyps in the left colon which histological exam showed a superficial oedema and an unspecific inflammatory infiltrate of the corion. The search for CMV was negative. The patient's neurological symptoms led to a brain CT scan being performed, but it showed no significant lesions.

On the 14th day of hospitalisation, and despite all instituted measures, there was a worsening of tachypnoea.

**Figure 2**

Septic liver emboli (left) and Aspergillus in hepatic tissue (Grocott x 400) (right)
and a decrease of consciousness level and the patient entered into cardiopulmonary arrest. He was successfully reanimated and put on invasive mechanical ventilation. On the 8th day after the beginning of invasive ventilation a *Pseudomonas aeruginosa* pneumonia was diagnosed. The remaining cultural exams (blood and respiratory secretions) were all negative and serologically there was a progressive resolution of CMV infection with the therapy. Although directed antibiotherapy to pneumonia was started, there was a worsening of the clinical status and the patient died, on the 33rd day of hospitalisation (76th post transplant day), of septic shock with multiorgan failure.

During all the hospitalisation period, immunosuppression with MMF (2 g/day up to the 12th day of hospitalisation and thereafter 1g/day) and prednisone 20 mg/day was administered. CSA was maintained up to the 12th day of hospitalisation, when cyclosporinemia (C0) fluctuated between 240 and 330 ng/ml, and was then discontinued.

Although immunosuppression was not completely withheld, renal function showed a progressive worsening and haemodialysis was started on the 12th day of hospitalisation. Indeed, there was evidence of pulmonary congestion and significative uraemia (urea of 326 mg/dl and creatinine of 4.2 mg/dl). Dialysis was maintained until the patient’s death.

At autopsy, the macroscopic anatomopathological exam revealed left parietal and occipital brain softening, multinodular thyroid, septic pulmonary and hepatic focus and an intravesical polypoid lesion. The histology exam showed disseminated invasive aspergillosis affecting brain, thyroid, pulmonary and hepatic tissues, a bacterial pneumonia and a squamous cell carcinoma of the bladder.

**DISCUSSION**

Opportunistic infections are of difficult diagnosis in transplant recipients, because the existing immunosuppression makes it more likely for the atypical clinical presentations to occur. In these patients, we also have to consider the possibility of a multiple agent infection, which makes diagnosis even more difficult.

CMV infection is very common in renal transplant recipients and may favour super-infections with bacteria and/or fungi. A rapid diagnosis and an early introduction of therapy are the essentials for an effective treatment and for septic complications’ prophylaxis. The case presented reveals the existence of two serious and early infections in a renal transplant recipient who underwent an apparently “non-aggressive” immunosuppression. Although CMV disease is common in these patients, encephalitis is a very rare form of presentation (1%). It is a serious disease with a very poor prognosis that appears in highly immunosuppressed patients. Clinical signs and symptoms, such as fever, confusion, prostration and the presence of focal signs, are non-specific and common to several types of encephalitis, making diagnosis more difficult. CSF examination may be normal or may reveal hypoglycorrhachia and/or mononuclear pleocytosis. Neuromaging of CMV encephalitis is non-specific and detection of viral DNA in CSF is necessary for definitive diagnosis. Ganciclovir and/or foscarnet are the recommended therapy for CMV encephalitis, although the success rate is very limited.

In this case, fever and tachypnoea and, later, altered level of consciousness were probably of central origin. The brain CT was normal and CSF cytochemical and bacteriological examination did not reveal any alterations. Only the subsequent identification of the viral genoma in the CSF allowed a definitive diagnosis. The patient started therapy with ganciclovir and hyperimmune anti-CMV gamaglobulin with progressive reduction of CMV antigenemia. CMV antigenemia was positive and therapy was started before viral DNA detection in CSF was available.

Viral infections, particularly CMV, increase predisposition to bacterial and/or fungi infections. In this case, CMV infection was associated with subsequent emergence of *Pseudomonas aeruginosa* pneumonia and disseminated invasive aspergillosis.

The latter clinical entity is rare in a transplanted patient and risk factors for its appearance are immunosuppression with high doses of corticosteroids and/or antilymphocyte antibodies, presence of neutropenia and CMV infection. This patient was not apparently submitted to an “aggressive” immunosuppression, he had appropriate cyclosporinemia values and did not have
neutropenia, making CMV infection the apparently only predisposing factor for the appearance of this severe form of aspergillosis. On the other hand, and analysing the facts retrospectively, the patient’s relatively advanced age (for a newly renal transplanted recipient) may have contributed to a certain state of overimunosuppression. Also, the presence of a vesical tumor (unknown at the time of transplantation), may also signal the presence of a deficient immunologic environment. So, although this patient was not apparently overimmunosuppressed, he was in fact so.

Another striking fact of this patient’s illness was the progressive abdominal distension that he developed, without signs of electrolyte disturbance or altered intestinal motility. The aspect of the intestinal mucosa was normal at the colonoscopy and histology examination showed no signs of CMV at that level. One possible explanation for the amazing dilation of the digestive tract (as confirmed by the abdominal CT scan), may be the ingestion of air by the patient. This could be triggered by a central nervous system disturbance, related to his CMV encephalitis that was probably already tenuously present at the beginning of his illness.

Pulmonary infection is the most common form of invasive aspergillosis, causing hemorrhagic bronchopneumonia and the presence of solitary or multiple abscesses. In highly immunocompromised patients the infection may disseminate from pulmonary focus, affecting most commonly kidney, liver, spleen and central nervous system tissues, although infection of virtually any organ can occur. Common clinical manifestations are non-specific and include fever and signs of sepsis. This is a severe disease with an extremely high mortality (90%-99%).

Detection of galactomannan antigen, a major constituent of the Aspergillus cell wall, in serum or in respiratory secretions, by enzyme linked immunosorbent assay (ELISA), has high specificity (>85%), but a very variable sensitivity (29-100%), especially in immunocompromised patients, to the diagnosis of invasive aspergillosis. Thus, culture of the agent and/or histology of the affected tissue is required for definitive diagnosis and therefore, in 44% of the cases, the diagnosis is only achieved post mortem.

The recommended therapy for invasive aspergillosis is voriconazol although its duration is not consensual. Long term therapy is always necessary, however, for as long as 2 years. Prophylaxis is often recommended, particularly in neutropenic patients, although no beneficial effect on survival can as yet be documented.

In this case report, the patient developed progressive septic complications and diagnosis was only made after death, with histology examination showing fungal infection compatible with invasive aspergillosis in brain, thyroid, pulmonary and hepatic tissues. His final clinical picture of septic shock could also have been caused by a complicated bacterial pneumonia, which masked the real diagnosis in this case.

This case report illustrates the importance of severe opportunistic infections in immunosuppressed patients. CMV encephalitis and disseminated invasive aspergillosis are rare diseases in renal transplant recipients and their association is uncommonly described in the literature. Their diagnosis requires an elevated degree of suspicion and, even with immediate therapy institution, the prognosis is very limited.

Conflicts of interest. None declared.

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