Case Report

Desquamative interstitial pneumonia associated with concurrent cytomegalovirus and Aspergillus pneumonia in a renal transplant recipient

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Introduction

Cytomegalovirus (CMV) and Aspergillus fumigatus are opportunistic pathogens that cause fatal infections in graft recipients mainly 1–6 months after transplantation, the period of maximal immunosuppression required for the prevention of acute graft rejection. A CMV infection has been known to increase the risk of fungal infection in an immunocompromised host, and concurrent CMV and Aspergillus pneumonias have been reported in bone marrow transplant recipients [1]. Desquamative interstitial pneumonia (DIP), considered to be a non-specific pulmonary reaction to injury, is pathologically characterized by the presence of numerous macrophages within the airspace with minimal fibrosis. We report here on a patient who in his ninth post-transplant year suffered from DIP following concurrent CMV and Aspergillus pneumonias, and who was treated successfully with corticosteroids combined with antiviral and antifungal agents.

Case

A 46-year-old non-smoker renal transplant recipient in his ninth post-transplant year presented with dyspnoea and generalized weakness. He had been CMV seronegative and received a kidney from an unrelated three human leukocyte antigen-matched cadaver. He had experienced acute rejection 7 days after transplantation and had been treated by intravenous methylprednisolone, 500 mg/day for 3 days. His subsequent clinical course was unremarkable (a mildly elevated serum creatinine level of 2 mg/dl) on a standard immunosuppressive regimen of cyclosporin, prednisolone and azathioprine. Five years after transplantation, azathioprine had been changed to mycophenolate mofetil. Two months before this admission, because his serum creatinine level had increased to 4.2 mg/dl, intravenous methylprednisolone at 125 mg/day was administrated for 3 days and tapered to 20 mg/day of oral prednisolone by the time of his admission. On initial examination, his temperature was 36.5°C, pulse rate 102/min and blood pressure 140/90 mmHg. Laboratory tests showed absolute neutrophiilia (12 500/m³), serum creatinine at 3.3 mg/dl and blood urea nitrogen (BUN) at 77 mg/dl. His blood glucose was elevated (1136 mg/dl); therefore, diabetes mellitus was diagnosed and insulin therapy started. A chest radiogram was unremarkable.

Five days after hospitalization, he developed fever, 38°C, with chills and mild dyspnoea. A second chest radiogram showed newly developed bilateral multiple patchy infiltrations. Empirically, antibiotics and ganciclovir were started, but on the ninth day he complained of severe dyspnoea and his arterial blood gas analysis showed severe hypoxaemia; therefore, he was transferred to the intensive care unit for respiratory support. High resolution computed tomography (HRCT) of the chest showed bilateral ground-glass attenuation and several cavities in both lower lobes with bilateral pleural effusions (Figure 1A). CMV antigens (pp65) were detected (65/2 × 10⁶ leukocytes in peripheral blood). Since Aspergillus species were cultured from the sputum, liposomal amphotericin B was started and all immunosuppressants were discontinued, except for low doses of steroids. We also cultured Aspergillus species and CMV from the bronchoscopic specimens, in which CMV DNA was also detected by polymerase chain reaction. Intravenous ganciclovir at 1.5 mg/kg/day, liposomal amphotericin B at
1 mg/kg/day and oral itraconazol at 5 mg/kg/day were administrated for 50 days. CMV antigenaemia subsided and the fungus was no longer cultured; however, because his hypoxaemia and bilateral chest infiltrations seen on X-ray did not improve substantially, a thoracoscopic lung biopsy was performed on day 63. Histological examinations of this biopsy specimen revealed an increment of type II pneumocytes and the infiltration of inflammatory cells, mainly plasma cells, in the oedematous interstitium with diffuse temporal homogeneity (Figure 2A). Hyperplasia of myofibroblasts was observed, but fibrotic change was minimal; alveolar macrophages were aggregated in airspaces, which was consistent with desquamative interstitial pneumonia (Figure 2B). Acute-angled multiseptated hyphae were also observed in terminal bronchioles (Figure 3A), and many multinucleated giant cells containing degenerated fungal material were present in the interstitium (Figure 3B), as occurs in invasive aspergillosis. To ganciclovir and liposomal amphotericin B, intravenous methylprednisolone at 500 mg/day was added, for 3 days, tapered to oral prednisolone at 35 mg/day. His clinical symptoms and infiltrates on chest X-ray improved very rapidly. Three weeks later, an HRCT of the chest showed a significant resolution of haziness and cavities (Figure 1B). After a total dose of 11 g, the liposomal amphotericin B was stopped. His renal function remained unchanged during the course of the disease, and he was discharged without immunosuppressive agents except for oral prednisolone at 20 mg/day. However, because of the progressive deterioration of his renal function (BUN 108 mg/dl, serum creatinine 6.3 mg/dl), a kidney biopsy was done, which on histological examination revealed end-stage chronic transplant glomerulopathy. He became dependent on haemodialysis 9 months after discontinuing the immunosuppressants.

Discussion

Although its incidence in kidney transplantation is the lowest among solid organ transplantations, pneumonia in recipients is still a serious infection, leading to death in up to 50% of cases. Beyond 6 months after renal transplantation, the incidence of opportunistic infections decreases, unless the patient has been
exposed to particularly intense environmental factors, because most transplant patients who have a well functioning graft are maintained on minimal long-term immunosuppressive therapy; yet, a minority of patients experience recurrent rejections, which result in increased exposure to immunosuppressants, which in turn can lead to severe opportunistic infections by fungi, protozoa or mycobacteria. According to the data from the United States Renal Data System, which included 30,000 renal transplant recipients, the incidences of fungal infections requiring hospitalization and of CMV disease were 1.1/100 person-years and 1.26/100 person-years, respectively [2,3]. About 10% of fungal infections were *Aspergillus* pneumonias. During 3 years of follow-up, 66% of patients with fungal infections and 80% of those with CMV infections were hospitalized within the first 6 months.

Our patient was CMV seronegative before transplantation, therefore he was suspected to have a primary CMV infection. Cytotoxic drugs and other drugs that suppress T-cell function increase the risk of CMV diseases; drugs such as methotrexate, antilymphocyte globulin and OKT3 antisera are important risk factors, while steroids or neutropenia alone are not. Although mycophenolate mofetil does not seem to increase the incidence of CMV infection, it may increase the risk of clinically manifest disease in those already infected by the virus [4]. Our patient suffered from chronic graft dysfunction and this might influence the occurrence of CMV disease.

The risk factors for invasive pulmonary aspergillosis are: prolonged neutropenia, prolonged high-dose corticosteroid therapy, cytotoxic therapy, prolonged pre-transplant dialysis, acquired immune deficiency syndrome and post-transplant CMV infection [3,5]. Corticosteroids suppress macrophage function against *Aspergillus* hyphae and cyclosporin inhibits interferon-γ, which in turn is responsible for macrophage activation. In this case, histological examination revealed pulmonary parenchymal invasion by the fungus, but the infection was limited to the lung, without any evidence of dissemination to other organs, indicating chronic necrotizing *Aspergillosis* (CNA) rather than invasive pulmonary aspergillosis. CNA, sometimes called semi-invasive aspergillosis, usually occurs in middle-aged and elderly patients with underlying lung diseases such as chronic obstructive pulmonary disease and inactive tuberculosis. It has also been observed in patients with mild immunosuppression, including those with diabetes mellitus or poor nutrition, and in those undergoing low-dose corticosteroid therapy [5]. In our patient, concurrent CMV disease, uncontrolled diabetes and transient use of high-dose corticosteroids may have contributed to the development of *Aspergillus* pneumonia.

Our patient did not improve in spite of prolonged antimicrobial therapy. He was on a mechanical ventilator for >60 days because of hypoxaemia due to the severe interstitial pneumonia, despite the earlier disappearance of CMV antigenaemia and administration of >10 g of liposomal amphotericin B. Histopathological examinations showed numerous macrophages in alveolar spaces with interstitial inflammatory cell infiltration and minimal fibrosis; and these findings led us to diagnose DIP, against which a high-dose steroid treatment was successful.

DIP, first described by Liebow *et al.* in 1965, is pathologically characterized by a large number of macrophages within airspaces as well as by mild interstitial inflammatory reactions [6]. The response to steroid treatment and the 5-year survival rate of DIP are better than those of the usual interstitial pneumonia. The aetiologies of DIP are unknown, and only a few reports in the literature point to infections as causing DIP. Schroten *et al.* reported the first case of DIP associated with CMV infection in an 8-month-old boy [7], and several reports demonstrated the association of DIP with viral infections such as BK-type polyomavirus [8], hepatitis C virus [9] or influenza [10]. The aetiology of DIP in our patient is not clear, but CMV infection seems to be the best explanation for it.

This is the first case of concurrent CMV and *Aspergillus* pneumonia complicated by DIP in a renal transplant recipient, which were successfully treated by high doses of steroid combined with antiviral and antifungal agents.
When severe interstitial pneumonia occurs in a renal transplant recipient, even long after transplantation, opportunistic pathogens such as CMV or fungi should also be suspected as causative pathogens. In addition, if clinical improvement is less than expected, aggressive diagnostic and therapeutic approaches should be considered.

Conflict of interest statement. None declared.

References


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