Transpl Int (2000) 13: 79–81

BRIEF REPORT

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Influenza pneumonia in a paediatric lung transplant recipient

Received: 25 March 1999
Revised: 13 September 1999
Accepted: 12 October

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Abstract Although a common cause of morbidity and mortality in the general population, influenza infections are uncommon in lung transplant recipients and, to date, have only been associated with transient declines in pulmonary function and a relatively benign clinical course. This paper describes severe influenza pneumonia in a 13-year-old paediatric lung transplant recipient (5 months after double lung transplantation). Influenza pneumonia was diagnosed by direct fluorescent antibody testing and viral culture of bronchoalveolar lavage fluid. The patient required mechanical ventilation for 2 days due to respiratory failure and fatigue. Since his recovery from this pneumonia, he has developed obliterative bronchiolitis and currently awaits re-transplantation.

Key words Influenza · Lung transplantation · Obliterative bronchiolitis · Immunosuppression

Introduction

Influenza is a leading cause of morbidity and mortality worldwide, but relatively few cases have been described with regard to lung allograft recipients [5, 7]. In a large retrospective series of non-CMV lung infections among adult lung transplant recipients, just two were due to influenza, and both infections were associated with transient declines in pulmonary function and a benign clinical course [5]. This paper describes severe influenza pneumonia in a paediatric cystic fibrosis patient, 5 months after double lung transplantation.

Case report

A 13 year-old male with cystic fibrosis, 5 months after double lung transplantation, was admitted urgently to the emergency room with a 2-day history of cough, and severe dyspnoea. Three family members had recently suffered symptoms of viral upper respiratory tract infections (cough, coryza, and sore throat). His post-transplant course had been stable until this presentation. The patient did not receive CMV prophylaxis because both he and the donor were CMV antibody-negative. Routine bronchoscopies, with transbronchial biopsy, performed 2 and 4 months after transplantation, demonstrated normal airways and no evidence of acute rejection or viral, fungal, pneumocystis, or mycobacterial infection. He took cyclosporine (dose adjusted to maintain serum trough levels of 175–200 ng/ml), azathioprine (2 mg/kg per day), prednisone (0.2 mg/kg per day), and oral trimethoprim/sulphamethoxazole for pneumocystis carinii prophylaxis. Two months after transplantation he received 0.5 cm^3 of a trivalent influenza virus vaccine. Four months after transplantation, cyclosporine therapy was replaced with tacrolimus (0.1 mg/kg per day to target whole blood trough levels of 10–15 ng/ml) because of hirsutism. Computerized spirometry at that time revealed: FEV_1 = 1.72 l (57% predicted); FEV_1/FVC = 82%; FEF_{25-75} = 1.56 l (40% predicted).

On admission, he was transferred to the paediatric intensive care unit of Lucille Salter Packard Children's Hospital at Stanford. His temperature was 38.7 °C, heart rate 149/min, blood pressure 100/50 mmHg, and respirations 40/min (on 100% face mask). Chest auscultation revealed poor air entry and scattered rhonchi. The heart sounds and neurological exam were normal. The neck was supple and there was no peripheral oedema.

The peripheral blood white blood cell count was 12,900/mm^3 (60% mature polymorphonuclear leucocytes, 19% band forms, 9% lymphocytes, and 11% monocytes). The haemoglobin was 9.4 g/dl. Serum liver enzymes and renal and electrolyte panels

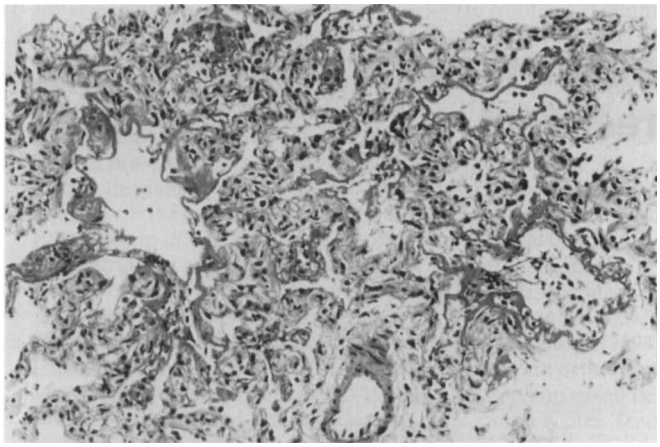

Fig. 1 High power magnification of the exudative phase of diffuse alveolar damage showing interstitial oedema and hyaline membranes lining the alveolar ducts (Haematoxylin and eosin stain × 300)

were normal. Arterial blood gas on a 100% non-rebreather facemask revealed: pH = 7.37, PCO_2 = 44 mmHg, and PaO_2 = 65 mmHg. The whole blood tacrolimus level was within the therapeutic range. A chest radiograph revealed widespread diffuse bilateral alveolar infiltrates. Intravenous tobramycin and ceftazidime, aerosolized albuterol, and high-flow oxygen were administered.

The patient was intubated and placed on mechanical ventilatory support due to profound hypoxaemia and fatigue. Fiberoptic bronchoscopy was performed. The airways and anastomoses appeared normal bilaterally. The bronchial mucosa appeared normal as well. Transbronchial biopsies (Fig. 1) showed no evidence of acute rejection or of viral inclusions. The lung parenchyma displayed a diffuse alveolar damage pattern compatible with viral infection-related lung injury. Bacterial, fungal, and mycobacterial stains and cultures of bronchoalveolar lavage (BAL) fluid were negative. The BAL direct fluorescent antibody test was positive for influenza A. BAL and nasopharyngeal cultures were both positive for influenza A. There was no evidence of infection with CMV, RSV, adenovirus, influenza type B, or parainfluenza viruses.

The diagnosis of influenza A pneumonia was made within 24 h of admission, 3 days after the onset of symptoms. The patient was administered 100 mg amantadine twice daily (via nasogastric tube) for 7 days. He required mechanical ventilation for 2 days. During his 2-week hospital course, his oxygenation gradually improved and he was discharged on prednisone and tacrolimus.

One month after discharge, his spirometry revealed: FEV_1 = 1.03 l; FEV_1/FVC = 80%; FEF_{25-75} = 0.96 l (24% predicted). The bilateral diffuse infiltrates on his chest radiograph resolved, but he began to develop progressive shortness of breath and a significant decline in pulmonary function. Six months after discharge, computerized spirometry revealed: FEV_1 = 0.43 l (14% predicted); FEV_1/FVC = 51%; FEF_{25-75} = 0.16 l (4% predicted), consistent with bronchiolitis obliterans syndrome [2]. He is currently being considered for double lung re-transplantation.

Discussion

In this paper, we report for the first time a case of severe acute respiratory failure in a lung allograft recipient due to influenza pneumonia. The diagnosis was based on the clinical features (coryza, high fever, and respiratory failure), diffuse bilateral pulmonary infiltrates on chest radiograph, direct fluorescent antibody testing of BAL fluid, and by viral culture of BAL and nasopharyngeal secretions. No other pathogen was identified on bacterial, fungal, or viral culture. His family had suffered a flu-like illness prior to the patient's illness, but serologic tests were not obtained to confirm the source of infection.

Previous reports of influenza infections complicating adult lung transplantation have described a relatively benign course, characterized by a transient deterioration in pulmonary function [5]. By contrast, influenza infection in this 13-year-old boy led to life-threatening respiratory failure that was severe enough to warrant mechanical ventilatory support for 2 days. Amantadine therapy is commonly used to treat patients suspected of having severe influenza infections, and it was administered to our patient within 72 h of the onset of his symptoms. However, in spite of prior vaccination and amantadine therapy, our case developed severe disease, which may be related to the patient's age and the duration since transplantation. Because of drug resistance mutations, the influenza virus may persist in, and be shed from, immunodeficient patients in spite of continued amantadine drug therapy [6]. Influenza infections appear particularly severe in the extremes of age. In immunocompetent children and young adults, bronchiolitis and bronchitis are more common, and more severe after viral infection. The time interval from transplantation to onset of influenza infections may be important since the immune system of the transplanted lung is poorly developed and vulnerable to infections, particularly within the first 6 months after transplantation.

Obliterative bronchiolitis (OB) is a leading cause of mortality and graft failure following lung transplantation [2]. In this case, the development of OB was simultaneous with recovery from the influenza infection and did not appear to be temporally related to the institution of tacrolimus or the discontinuation of cyclosporine therapy. No clear evidence exists that a higher incidence of OB is associated with non-CMV infections in human allograft recipients. However, the frequency of OB coincides with seasonal peaks in upper respiratory tract viral infections and, in one series, four of eight recipients with non-CMV lung infections subsequently developed OB [4]. Interestingly, influenza infection has been associated with acute renal allograft rejection [1]. These episodes are thought to be due to abnormal antiviral immune responses since the influenza virus did not infect the grafts. It is therefore possible that an abnormal im-

mune response to influenza infection might have contributed to lung allograft failure in this patient.

Vaccination against influenza is highly effective in subjects with chronic lung disease; however, its efficacy is limited in the setting of transplantation [3]. Among transplant recipients, the immune response to influenza vaccination may be impaired due to concomitant triple immunosuppressive regimens. Some nasally administered influenza vaccines may be more effective in providing protection from infection [3], although their use has not yet been evaluated with respect to lung transplant recipients. The current case underscores the need to provide more effective strategies to prevent and treat influenza infection in lung allograft recipients.

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