Influenza Pneumonia in Lung Transplant Recipients*

Clinical Features and Association With Bronchiolitis Obliterans Syndrome

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Influenza infection is increasingly recognized to cause significant morbidity and mortality in the community, especially in pediatric patients and elderly persons. Influenza infection, however, has not been well described among thoracic organ transplant recipients. We provide the first detailed clinical, radiographic, and histologic description of influenza pneumonia among three lung transplant recipients. The presentation varied considerably among the three patients and, in some cases, was atypical for influenza. Despite treatment, a persistent decline in pulmonary function occurred in all three patients after the acute illness. Interestingly, on follow-up biopsy specimens, each patient had histologic evidence of acute rejection and/or obliterative bronchiolitis. Additional research, therefore, is needed to clarify the relationship between influenza infection, acute rejection, and obliterative bronchiolitis.

Key words: allograft rejection; bronchiolitis obliterans syndrome; influenza; lung transplantation; obliterative bronchiolitis

Abbreviations: BMT = bone marrow transplant; BOS = bronchiolitis obliterans syndrome; CMV = cytomegalovirus; OB = obliterative bronchiolitis

Respiratory viruses are increasingly recognized to cause morbidity and mortality in the community. Influenza viruses, in particular, are among the most important seasonal respiratory pathogens. During the winter months, up to 10% of all patient visits to physicians are due to influenza-like illnesses. In addition, influenza may cause 10,000 to 40,000 deaths and >150,000 hospitalizations annually, especially in patients with preexisting medical conditions.

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Influenza-related illness has been described in immunocompromised persons, including solid-organ and bone marrow transplant (BMT) recipients. Between 6% and 29% of all acute respiratory infections in BMT patients are caused by influenza viruses. The incidence and significance of influenza infection after lung transplantation, however, remains unknown. In this article, we provide the first detailed description of the clinical presentation, radiographic features, histologic findings, and clinical outcomes of influenza pneumonia in three lung transplant recipients.

Case 1

A 53-year-old African-American woman had received a bilateral lung transplant in October 1997 for end-stage sarcoidosis. Although she experienced a complicated posttransplant course characterized by severe reperfusion injury, she was discharged from the hospital with acceptable pulmonary function (FEV₁ of 1.60 L or 60% predicted). The patient did well, with no episodes of allograft rejection or infection, and remained free from bronchiolitis obliterans syndrome (BOS). In April 1999, she presented with increasing shortness of breath, cough productive of yellow sputum, fatigue, and weakness. She was afebrile. Physical examination revealed diffuse rhonchi and wheezes throughout both lung fields, with decreased breath sounds at the right lung base. Chest radiography revealed homogeneous right-lower-lobe consolidation with small associated pleural effusion (Fig 1). She received 3 weeks of antibiotic treatment (cefazolin and ciprofloxacin) without improvement. Therefore, bronchoscopy was performed and the results revealed bilateral mucopurulent secretions without endobronchial lesions. Transbronchial biopsy was not performed because of hypoxemia during the procedure. Immunofluorescence staining of the lavage fluid returned positive for influenza A virus. Culture findings were negative for viruses, fungi, and bacteria. She was treated with a 2-week course of amantadine. Although the patient’s clinical condition and radiographic findings improved by discharge, her
pulmonary function remained reduced at subsequent follow-up visits. Over the next 6 months, the patient experienced a progressive decline in pulmonary function with increasing hypoxemia, and she ultimately died in October 1999. Autopsy revealed evidence of severe obliterative bronchiolitis (OB).

Case 2

A 40-year-old white man had received a heart-lung transplant in May 1998 for Eisenmenger’s syndrome secondary to a single-outlet ventricle. His early posttransplantation course was complicated by acute lung allograft rejection in May and June of 1998, and cytomegalovirus (CMV) pneumonitis in September 1998. His pulmonary function remained excellent (FEV1 of 4.05 L or 91% predicted), and results of surveillance biopsies of the heart showed no rejection. He presented to the transplant clinic in March 1999 with a 2-day history of sore throat, abdominal pain, and diarrhea. His lungs were clear to auscultation. Arterial blood gas measurements on room air revealed moderate hypoxemia and metabolic acidosis. Further laboratory studies showed acute renal insufficiency, and leukocytosis with bandemia. Chest radiography showed bibasilar heterogeneous and linear opacities. The patient was started on IV piperacillin/tazobactam and ganciclovir for possible bacterial or CMV pneumonia. Bronchoscopy showed erythematous and edematous airways without secretions. The lavage fluid was positive for influenza B on immunofluorescence. Viral, fungal, and bacterial culture findings were negative. Histologic analysis showed acute patchy pneumonitis without evidence of rejection. With continued supportive care, including gentle hydration, the patient’s symptoms, acidosis, and renal insufficiency improved significantly. Two months later, the patient’s pulmonary function was significantly worse than his baseline level (FEV1 2.39 L or 54% predicted). Transbronchial biopsy at that time revealed minimal (grade A1) lung allograft rejection. Despite augmented immunsuppression, the patient has experienced a progressive decline in pulmonary function consistent with BOS.

Discussion

Influenza is increasingly recognized to cause significant morbidity and mortality in the community, especially...
Pneumonia developed in 75% of patients with influenza infection. In our population of adult lung transplant recipients, GI symptoms predominated in two of three patients. In contrast, in our previous study of BMT patients who underwent a transbronchial biopsy, there was evidence of acute pneumonitis, but no diffuse alveolar damage. Because histologic findings are nonspecific, screening BAL fluid for respiratory viral pathogens is essential. Newer direct fluorescent antibody techniques, as were employed in our patients, permit a more rapid identification of specific respiratory viral pathogens as compared to the traditional cell culture methods. In addition, the sensitivity of rapid direct fluorescent antibody techniques proved superior in our series, as the culture finding was positive in only one patient.

Importantly, all three of our patients experienced progressive BOS that began shortly after the influenza infection. BOS is generally thought to represent a manifestation of chronic lung allograft rejection and correlates with the histologic development of OB. Autopsy confirmed the presence of OB in one of our patients. Follow-up biopsies in the other two patients demonstrated late acute allograft rejection. The association is especially striking in the two patients who developed BOS with no prior history of acute rejection or CMV infection, both of which have been identified as major risk factors for BOS.10

Because of the timing of BOS and influenza infection in these three patients, it is interesting to speculate that viral infection contributed to the development of BOS. A plausible hypothesis is that stimulation of cellular immunity in response to viral infection results in enhanced recognition of allogeneic tissue leading to acute and/or chronic allograft rejection. A direct cytopathic effect of the influenza virus was isolated only twice.7

In this article, we provide the first detailed description of influenza infection among lung transplant recipients. In normal hosts, influenza infection is characterized by the sudden onset of fever, chills, rigors, headache, malaise, myalgia, and dry cough.5 Features of infection vary among different age groups, with GI symptoms more common in children, but systemic complaints such as malaise and chills more common in adults and elderly patients. In contrast, in our population of adult lung transplant recipients, GI symptoms predominated in two of three patients.

In normal hosts, symptoms of influenza infection often improve within 3 to 5 days.8 Primary viral pneumonia can develop, however, especially in elderly and immunocompromised patients. Secondary infections with bacterial pathogens are also common, usually with Streptococcus pneumoniae or Staphylococcus aureus. All three lung transplant recipients had new findings on chest radiographs at time of presentation. The radiographic findings were nonspecific and ranged from subtle heterogeneous and linear opacities to homogeneous lobar consolidation. Although bacterial superinfection could explain the radiographic findings, the presence of influenza alone on BAL cultures in all three patients favors primary influenza pneumonia.

Little is known about the histologic changes in influenza pneumonia. The existing reports from the literature are derived from autopsies in patients who succumbed to the pneumonia, and are therefore not likely representative of patients earlier in the course of disease. Autopsy reports describe acute inflammation with a strong component of diffuse alveolar damage.9 In the two patients in our series who underwent a transbronchial biopsy, there was evidence of acute pneumonitis, but no diffuse alveolar damage. Because histologic findings are nonspecific, screening BAL fluid for respiratory viral pathogens is essential. Newer direct fluorescent antibody techniques, as were employed in our patients, permit a more rapid identification of specific respiratory viral pathogens as compared to the traditional cell culture methods. In addition, the sensitivity of rapid direct fluorescent antibody techniques proved superior in our series, as the culture finding was positive in only one patient.

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respiratory viruses on the bronchial and alveolar epithelium, however, cannot be excluded. Consistent with our observations in these patients, a seasonal onset of BOS has been described in lung transplant recipients, implicating a possible role for seasonal viral pathogens in the etiology of this condition.\(^1\) Similarly, we have previously described a high rate of BOS in patients who survived infection with respiratory syncytial virus, adenovirus, or parainfluenza virus.\(^6\) In addition, OB was recently noted to have developed in a pediatric lung transplant recipient shortly after recovery from influenza pneumonia.\(^12\)

Given the potential relationship between influenza infection and rejection, additional emphasis on prevention of infection may be warranted. Numerous studies in nonimmunosuppressed patients have demonstrated that annual vaccination with inactivated influenza vaccine leads to a reduction in influenza-related hospitalizations and deaths.\(^8,13\) The role of vaccination in solid-organ transplant recipients, however, is controversial because of conflicting data about antibody responses to influenza vaccination.\(^14,15\) Therefore, serologic testing for antibody development and booster vaccination may be indicated. In addition, aggressive vaccination of all close contacts and household members also should be considered to decrease the risks of infection in transplant recipients. Finally, several drugs, including amantadine, rimantadine, and the newer neuraminidase inhibitors, zanamivir and oseltamivir, appear effective in the prevention of infection in normal hosts.\(^8,16\) Further research is needed to determine the efficacy of these agents in transplant recipients.

In summary, we report three cases of influenza pneumonia in lung transplant recipients. The initial presentation did not always involve the respiratory tract but included predominant GI symptoms in two of three patients. New radiographic opacities consistent with viral pneumonia were seen in all cases, and histologic findings revealed acute pneumonia. Because the signs and symptoms of infection tend to be nonspecific, a high clinical suspicion for influenza infection is required and appropriate tests need to be pursued in order to make a definitive diagnosis. Significant morbidity resulted from acute infection, with all patients requiring hospitalization. More importantly, a striking association was observed between influenza infection and the subsequent development of BOS in each patient. Further research, thus, is needed to determine if influenza infection directly or indirectly contributes to the development of acute and/or chronic rejection in lung transplant recipients.

**REFERENCES**


**Continuous Calcium Chloride Infusion for Massive Nifedipine Overdose***

Yui-Ming Lam, MB; Hung-Fat Tse, MD; Chu-Pak Lau, MD, FCCP

A 37-year-old woman presented with persistent hypotension and noncardiogenic pulmonary edema after massive nifedipine overdose. Judicious use of continuous and prolonged high-dose IV calcium infusion was administered to provide sustained increases in serum ionic calcium level (approximately 2 mmol/L) and was able to improve the hemodynamic status without any major adverse reaction.

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