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Challenges in the Diagnosis of 2009 H1N1 in a Lung Transplant Patient and the Long-Term Implications for Prevention and Treatment: A Case Report

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Abstract

Although respiratory viral infections have been associated with acute rejection and bronchiolitis obliterans syndrome, the long-term impact of the novel pandemic influenza A (2009 H1N1) virus on lung transplant patients has not been defined. We describe the diagnostic challenges and long-term consequences of 2009 H1N1 infection in a lung transplant patient, discuss the potential implications for prevention and treatment, and conclude that even timely antiviral therapy may be insufficient to prevent long-term morbidity.

From June 2009 until August 2010, infection by the novel influenza A virus (2009 H1N1) was considered a pandemic by the World Health Organization. Prompted by the prevalence and severity of the illness in at-risk individuals, the International Society of Heart and Lung Transplantation (ISHLT) published guidelines for the prevention, diagnosis, and treatment of 2009 H1N1 influenza in cardiothoracic transplantation.¹ Shortly thereafter, the American Society of Transplantation (AST) and The Transplantation Society (TTS) followed with a joint guidance document for 2009 H1N1 in solid organ transplantation.²

Subsequent reports on 2009 H1N1 in transplantation have highlighted the inconsistency of signs and symptoms at presentation, the necessity for early recognition and treatment, the potential for intensive care unit (ICU) admission and mechanical ventilation, and the risk for mortality.^{3–7} Yet these reports do not address the long-term impact of respiratory viral illnesses (RVIs) in lung transplantation, which have been associated with bronchiolitis obliterans syndrome (BOS) and death.^{8–10} With this imperative, we describe the diagnostic challenges of 2009 H1N1 influenza pneumonia in a lung transplant recipient, report the effects of timely antiviral therapy, and discuss the long-term implications for prevention and treatment.

CASE REPORT

An asymptomatic, afebrile 38-year-old female with cystic fibrosis presented 5 years after bilateral lung transplantation (BOS stage 1) with acutely diminished home spirometry and worsened obstructive defect on pulmonary function testing. Within 24 hours of bronchoscopy, analysis of the bronchoalveolar lavage fluid by real-time reverse transcriptase

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polymerase chain reaction (rRT-PCR) revealed influenza A and the transbronchial biopsy (TBB) was interpreted as acute rejection (A3B1R) (Fig 1c, 1d). As the patient had yet to be vaccinated against the novel H1N1 virus (secondary to a lack of its availability), presumptive outpatient treatment for 2009 H1N1 infection was immediately initiated with oseltamivir 75 mg by mouth twice daily, and augmentation of immunosuppression was withheld. Upon hospital admission the same day, the patient had nausea, fever (38.9°C), and tachycardia (heart rate 122), at which time she also noted a family history of similar symptoms by children living at home. At this time, the remaining history, physical exam, vital signs, and chest X-ray were otherwise unremarkable, and with the exception of an elevated glucose (180 mg/dL), the blood chemistries and hematology were grossly within reference ranges. After uncomplicated therapy with intravenous fluids, correction of the hyperglycemia, and continued twice-daily oseltamivir, the patient was discharged home on hospital day 4 in good condition. Outpatient instructions included the completion of a 5-day course of antiviral therapy, after which the novel 2009 influenza A H1N1 virus was confirmed by culture and strain testing at the Illinois Department of Public Health reference laboratory. Follow-up TBB at 6 weeks no longer showed acute rejection (Fig 1e, 1f), and though her forced expiratory volume in 1 second (FEV₁) did not decline further, it never returned to preinfection levels. As such, the patient has progressed to BOS stage 2 and remains so 9 months after 2009 H1N1 influenza pneumonia (Fig 2).

DISCUSSION

The 2009 H1N1 virus presents a unique challenge in lung transplantation, and this case highlights the importance of (1) primary prevention; (2) cautious interpretation of pathology findings; (3) prompt treatment; and (4) the potential for a long-term detriment to pulmonary allograft function, even with optimal recognition and early therapy.

Epidemiology and Prevention of 2009 H1N1 in Lung Transplantation

Kumar et al have recently reported the largest series available describing 2009 H1N1 infection in solid organ transplantation.⁶ This study included 33 lung transplant recipients of the 237 patients identified. The authors' analysis, whereby lung transplant patients had a similar rate of complications to other transplant types, revealed that those receiving antiviral treatment within 48 hours of symptom onset had fewer hospital admissions ($P = .049$), fewer ICU admissions ($P = .007$), and less need for mechanical ventilation ($P = .019$). Moreover, 8/125 (6%) of those with delayed antiviral treatment died in comparison to only 1/90 (1%) with early initiation of antiviral therapy ($P = .059$), of which the single death was related to a procedural complication after recovery from influenza. Other studies directed solely at lung transplant recipients with confirmed 2009 H1N1 influenza infections have demonstrated similar outcomes. For instance, one of three cases described by Ahluwalia et al succumbed to respiratory failure, and Fox et al reported that 2/10 patients required mechanical ventilation, one of whom required ventilator support for 2 weeks, a tracheostomy, and a prolonged rehabilitation course despite antiviral treatment.^{4,5} These authors concluded that 2009 H1N1 influenza is a source of considerable morbidity for lung transplant recipients, and that along with an early diagnosis, prevention of H1N1 is critical in this patient population.

Unfortunately, the patient herein described did not have the option of vaccination against the 2009 H1N1 virus as it was not yet readily available in our area. Furthermore, postexposure prophylaxis was impossible as the window for treatment had passed. In fact, the medical team only became aware of sick family contacts upon the patient's presentation for admission to the hospital. We postulate that had the patient and/or her children been vaccinated, perhaps her illness could have been prevented.

Histological Considerations

The most detailed histological findings of H1N1 pneumonia are from postmortem studies of victims of previous pandemics. The lung pathology from these studies typically demonstrated classic exudative diffuse alveolar damage with or without hemorrhage, necrotizing bronchiolitis, wet hemorrhagic lungs, and bacterial pneumonia superinfection.^{11–13} While these reports document important pathology, the descriptions highlight fulminant and late cases of fatal pathology rather than the early onset of infection. Accordingly, little is known about the early histological changes of influenza in lung transplantation, and descriptions are mixed. Garantziotis et al described two patients at the time of influenza infection, both of whom had evidence of acute pneumonitis, though neither demonstrated findings of acute rejection.⁸ Additionally, in their report of 2009 H1N1 influenza pneumonia, Raj et al described the TBB results of a ventilated patient 5 days into her admission, which again demonstrated acute pneumonitis in the absence of rejection.³

In contrast to these reports, the TBB from the patient in our study with novel H1N1 influenza showed histological findings similar to acute rejection (Fig 1c through 1d). Such findings included perivascular and interstitial mononuclear inflammation with eosinophils (Fig 1c) and lymphocytic bronchitis with eosinophils (Fig 1d), with a paucity of neutrophils. Indeed, these findings are reflective of other studies describing lung allograft biopsies taken near the time of viral infection, which demonstrated perivascular mononuclear cell infiltration similar to that seen with acute cellular rejection.^{2,8,14,15} However, it is unclear whether the early changes of H1N1 influenza simply mimic the histological findings typical of acute rejection, or if there is indeed a concomitant acute rejection in this patient. This discrepancy is intriguing given the findings of Kumar et al, who reported that 16 of 48 (33.3%) patients with a respiratory viral infection had either a declined FEV₁ of $\geq 20\%$ or acute rejection ($\geq$ grade 2) within 3 months of their illness.¹⁰ Nonetheless, the histological findings as they relate to influenza pneumonia are nonspecific. In the context of a possible viral infection, we therefore employ a mindful interpretation of pathological findings, and suggest their use as an adjunct to other clinical and laboratory parameters in the lung transplant recipient with suspected 2009 H1N1 infection.

Diagnosis and Treatment of 2009 H1N1 Influenza in Lung Transplantation

The ISHLT cautions that traditional influenza symptoms, such as fever, malaise, cough, and rhinorrhea, may not be as commonly exhibited by the lung transplant recipient.¹ In this patient population, fever may be the most consistent indicator, though nausea and vomiting have been typical as well.⁷ Our study does support that these symptoms may indicate 2009 H1N1 influenza, though it is concerning that the symptomatology may not manifest itself early in the disease process, if at all. Therefore, additional objective measures are required in order to augment a high clinical suspicion.

In their recent study Raj et al outlined the utility of rRT-PCR as an expedient and highly sensitive means to identify H1N1 influenza.³ This has been confirmed by the Centers for Disease Control and Prevention, which indicated that the rRT-PCR assay is 99.3% sensitive for the 2009 H1N1 virus as compared to viral culture.¹⁶ Raj et al concluded that other rapid influenza diagnostic tests, such as the direct immunofluorescent antibody test, should not be used as an exclusionary test in high-risk populations, such as that of the lung transplant patient. In accordance and per the AST/TTS joint guidelines the use of rRT-PCR is the preferred methodology for the diagnosis of the novel H1N1 in lung transplantation.² Though the ISHLT originally published an approximated turnaround time of 48 hours for rRT-PCR, the assay is now commercially available for individual hospital use, and institutions such as ours have the capacity to report results within 24 hours.¹ Our case therefore demonstrates that a heightened clinical suspicion in combination with a rapid and reliable test such as

rRT-PCR can afford the lung transplant patient the benefit of early and appropriate medical intervention for infection with the 2009 H1N1 virus.

The mainstay of management of 2009 H1N1 influenza is timely initiation of antiviral therapy and should be guided by regional and national resistance patterns.^{1,2} Importantly, this includes empiric antiviral therapy in those whose history, signs, and symptoms are suggestive of viral infection. Though there have been occasional reports of oseltamivir resistance in those on prolonged therapy, current analysis of the novel H1N1 demonstrates susceptibility to both oseltamivir and zanamivir, with resistance to adamantanes. As per the AST/TTS joint report, combination therapy with an M2 inhibitor and oseltamivir or zanamivir may be indicated. They also suggest the consideration of intravenous therapy, and possibly doubling the dose of oseltamivir to 150 mg twice daily for the most severe infections.²

This case report demonstrates a successful outcome following the most current guidelines for treatment. By having empirically initiated antiviral therapy based on an acute drop in pulmonary function and rRT-PCR results, the patient was afforded both a brief hospital stay and a quick resolution of illness. However, though these initial benefits precluded admission to the ICU, mechanical ventilation, and a prolonged hospital course, the long-term effects of influenza infection are still present by way of a persistent decline in pulmonary function. Indeed, this patient's progression from BOS stage 1 to BOS stage 2 underscores the long-term consequences of RVIs in the lung transplant population.

Long-Term Impact of Respiratory Viral Infection on Lung Allograft Function

Numerous reports suggest that RVIs are an etiology for BOS, occurring within 14 months of infection in 32% to 52% of lung transplant recipients.¹⁷ The increased risk of BOS after RVI was recently evaluated by Kumar et al, who showed that biopsy-proven obliterative bronchiolitis occurred in 63% of patients within 1 year of viral infection.¹⁰ These findings not only supported their own earlier work but that of Khalifah et al, who found that lung transplant recipients had a higher risk of death from BOS ($P = .02$) following community-acquired RVI.⁹

Presently, there is no literature with which we are aware that describes the impact of infection with the 2009 H1N1 influenza on long-term pulmonary allograft function. At 9 months following pneumonia with the 2009 H1N1 virus, the lung transplant recipient in our report has had a persistent decline in FEV₁, corresponding to a progression of BOS from stage 1 to stage 2 (Fig 2). Given the evidence associating RVIs with later BOS development, we therefore presume the same for our patient, though additional reports with long-term follow-up and a greater number of cases are required to support this suspicion. Nonetheless, this patient's persistently impaired pulmonary function underscores the importance of the primary prevention of 2009 H1N1 viral infection, as even timely antiviral therapy may be not be sufficient to prevent long-term morbidity in the lung transplant population.

In conclusion, symptoms of 2009 H1N1 infection in lung transplant recipients can be unreliable, potentially delaying their treatment and resulting in a long-term detriment to pulmonary allograft function. Moreover, interpretation of transbronchial biopsies can be deceptive in the setting of influenza pneumonia, and conventional rapid influenza antigen detection can be inaccurate. We conclude that lung transplant biopsy results should be regarded with caution when influenza is suspected, that expedient diagnosis in high-risk patients should be pursued by rRT-PCR, and that infection must be treated promptly. This strategy should complement an aggressive policy of influenza prevention through exposure avoidance, immunization, and timely antiviral chemoprophylaxis when appropriate.

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Fig 1. Transbronchial biopsies comparing an example of A3B1R acute lung transplant rejection with the patient at the time of diagnosis of 2009 H1N1 influenza pneumonia, and the same patient 6 weeks following infection. (a) Example of grade A3 perivascular inflammation in acute rejection in a patient without respiratory viral infection. (b) Example of grade B1R bronchiole inflammation in acute rejection in a patient without respiratory viral infection. (c) Our patient at the time of 2009 H1N1 influenza pneumonia, grade A3 type of perivascular acute rejection. (d) Our patient at the time of 2009 H1N1 influenza pneumonia, grade B1R type of airway acute rejection. (e and f) Our patient 6 weeks post-2009 H1N1 infection with resolution of all perivascular and airway inflammation (all images hematoxylin and eosin, 400 $\times$).

Fig 2. Decline in forced expiratory volume in 1 second (FEV₁) of a lung transplant recipient following acute bronchitis of unknown etiology. More important is a sustained decline in FEV₁ after H1N1 influenza with the resulting diagnosis of bronchiolitis obliterans syndrome stage 2 (FEV₁ 57% of baseline).