A Patient who Survived Primary Seasonal Influenza Viral Pneumonia: Histologic Findings Obtained via Bronchoscopy

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Abstract

The histological findings and clinical course of primary seasonal influenza viral pneumonia have not been fully elucidated. We herein report the case of a 65-year-old man with primary seasonal influenza viral pneumonia. The patient presented with fever, myalgia, general fatigue and dyspnea of seven days duration. Chest computed tomography showed bilateral ground-glass opacity and consolidation. A rapid influenza virus antigen test was positive for influenza A virus. We diagnosed him as having community-acquired influenza pneumonia and started therapy with antibiotics plus oseltamivir; however, his symptoms, respiratory condition and radiological findings deteriorated. Polymerase chain reaction following bronchoscopy showed the bronchoalveolar lavage fluid to be positive for the influenza A virus. A right lower lobe transbronchial lung biopsy revealed type II pneumocyte metaplasia, acute and chronic interstitial infiltrates and alveolar organization without hyaline membranes or fibrin thrombi in the vascular lumen. Treatment with prednisolone at a dose of 60 mg/day (1 mg/kg) resulted in an improvement. The patient was discharged on hospital day 15. Two weeks after admission, the serum antibody titer for influenza A (H3N2) had increased significantly. No other pathogens were found either serologically or in the respiratory samples, and we diagnosed the patient to therefore have primary influenza viral pneumonia.

Key words: seasonal influenza, primary viral pneumonia, steroid, treatment, histology

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Introduction

In 2009, pandemic influenza had a strong impact on clinical practice. Pneumonia is the leading complication of influenza virus infection, and many cases of pandemic influenza H1N1 pneumonia were reported in 2009-2010. Subsequently, the serotype of H1N1 pandemic 2009 decreased, and a conventionally termed “seasonal” H3N2 virus accounted for most of the serotypes observed in Japan in 2012-2013 (1).

The comparative features of pneumonia associated with influenza virus infection can be classified into three types: primary viral pneumonia, secondary bacterial pneumonia and mixed viral and bacterial pneumonia. Primary viral pneumonia caused by seasonal influenza virus is considered

rare, and its clinical course and histological findings have not been fully elucidated. At autopsy, the spectrum of histologic changes observed in the past pandemic included tracheitis, bronchitis, diffuse hemorrhagic pneumonia, hyaline membranes lining alveolar ducts and alveoli and a paucity of inflammatory cells within the alveoli (2). However, reports describing the pulmonary histological findings of patients surviving primary influenza virus pneumonia have been limited to one report by Yeldandi and Colby (3). We recently encountered a patient who survived primary viral pneumonia caused by seasonal H3N2 influenza virus in whom a lung specimen was obtained via a transbronchial lung biopsy. We herein report this case and review the histologic findings and treatment of primary influenza viral pneumonia.

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Figure 1. Chest imaging. A chest X-ray showed bilateral ground-glass opacity (a). Chest computed tomography performed on admission showed bilateral ground-glass opacity (b); however, the pulmonary infiltrates worsened on the third hospital day (c). Ground-glass opacity and consolidation in the lung fields disappeared in June 2013 (d).

Case Report

A 65-year-old man presented to our hospital in January 2013 with a fever and dyspnea. He had developed a low-grade fever below 37.5°C, headaches, myalgia and general fatigue seven days before presentation to our hospital and had a fever of 38.5°C for three days before presentation. A chest X-ray showed bilateral ground-glass opacity (Fig. 1a), and he was admitted to our hospital. He had a past history of tuberculosis at 12 years of age and smoking from 20 to 30 years of age. He had never been vaccinated for influenza virus or pneumococcus. On admission, his respiratory rate was 20 breaths per minute without an abnormal blood pressure. Chest auscultation detected no rales or cardiac murmurs. A blood gas analysis performed on ambient air showed a pH of 7.48, a PaCO₂ of 33.7 Torr, a PaO₂ of 66.6 Torr and a HCO₃⁻ of 24.5 mmol/L. The laboratory data revealed a white blood cell count of 6,800/μL (neutrophils: 5,900/μL, lymphocytes: 600/μL and monocytes: 300/μL), a hemoglobin level of 13.9 g/dL and a platelet count of 11.5×10⁴/μL. Biochemistry demonstrated a total protein level of 7.3 g/dL, an albumin level of 4.3 g/dL, a urea nitrogen level of 15 mg/dL, a creatinine level of 0.7 mg/dL, a lactic dehydrogenase level of 210 IU/L and a C-reactive protein level of 18.6 mg/dL. Urinary antigen tests for both *Legionella pneumophila* and pneumococcus were negative; however, a

rapid influenza antigen test of a nasopharyngeal swab specimen was positive for influenza A virus. Chest computed tomography (CT) showed bilateral ground-glass opacity and consolidation (Fig. 1b). We diagnosed the patient as having community-acquired influenza pneumonia. We initiated the administration of ceftriaxone at a dose of 2 g/day along with clarithromycin at a dose of 400 mg/day and oseltamivir at a dose of 150 mg/day. On the third hospital day, the patient's dyspnea worsened, and his PaO₂ dropped to 58.5 Torr with increased areas of opacity appearing in the bilateral lung fields on CT (Fig. 1c, Fig. 2). We then administered prednisolone at a dose of 60 mg/day [1 mg/kg (4, 5)]. On the fourth hospital day, the PaO₂ increased slightly to 61.2 Torr, and the lucency of the chest X-ray partially improved. Bronchoscopy performed on the fourth hospital day showed no abnormal findings, such as inflammation of the bronchial mucosa in the bronchial lumen. Bronchoalveolar lavage (recovered 75 mL/150 mL) of the right lower lobe revealed a white blood cell count of 5.3×10³/mL (neutrophils: 40.6%, eosinophils: 0%, lymphocytes: 4.8% and macrophages: 54.6%) with negative results on a rapid antigen test for respiratory syncytial virus and adenovirus and a positive result on polymerase chain reaction (PCR) for influenza A virus. No significant pathogens, including *Mycoplasma pneumoniae* and *Legionella* spp., were isolated. A transbronchial lung biopsy of the right lower lobe disclosed erosive bronchitis, type II pneumocyte metaplasia, acute and chronic in-

Figure 2. Clinical course. The clinical course of the patient showed deterioration of the radiological findings and oxygenation following the administration of antibiotics and neuraminidase inhibitors. Corticosteroid therapy was then initiated on the third hospital day, and the PaO₂ improved. The dose of PSL was tapered and then discontinued two weeks later. The patient was discharged on the 15th hospital day. Abbreviations: CAM: clarithromycin, CTRX: ceftriaxone, HCO₃⁻: bicarbonate ion, LVFX: levofloxacin, PaO₂: partial pressure of arterial oxygen, PaCO₂: partial pressure of arterial carbon dioxide, PSL: prednisolone

Figure 3. Histological findings of the transbronchial lung biopsy. The transbronchial lung biopsy specimen exhibited type II cell metaplasia, acute and chronic interstitial infiltrates and airspace organization. [a, Hematoxylin and Eosin staining, ×100]. Immunohistochemical staining using an antibody against the type A influenza virus antigen yielded a positive result in the bronchial mucosa (arrows) (b, immunohistochemical stain ×200).

terstitial infiltrates and airspace organization (Fig. 3). There were no hyaline membranes or fibrin thrombi in the vascular lumen. Immunohistochemical staining using an antibody against the type A influenza virus antigen (OBT1551; AbD Serotec, Oxford, UK) yielded a positive result in the bronchial mucosa (Fig. 3).

Oseltamivir was administered for five days, while the dose of prednisolone was tapered then discontinued within two weeks. On the seventh hospital day, the antibiotics were changed to levofloxacin. The patient's general condition improved, and he was discharged on the 15th hospital day, at which time his PaO₂ had increased to 92.7 Torr. Two weeks

Table 1. Characteristics of the Present and a Previously Published Case from Our Hospital

	Age	Sex	Virus	Treatment						Outcome
				NI	Days ^a	Effect	Corticosteroid	Days ^b	Effect	
Present case	65	M	H3N2	+	9	-	+	10	+	Survived
Published case 1 (9)	58	M	H1N1	+	12	-	+	13	+	Survived

M: male, F: female, NI: neuraminidase inhibitor

Number of days after onset of initial symptoms that specimen for ^ainitiation of NI or ^binitiation of corticosteroid therapy.**Table 2. Histological Findings of the Present and Previously Published Cases**

	Days ^a	Pathologic findings	Immunohistochemical
Present case	11	Transbronchial biopsy: Erosive bronchitis, airspace organization, type II cell metaplasia, and acute and chronic interstitial infiltrate (alveolitis)	Bronchial wall
Published case (9)	14	Transbronchial biopsy: DAD pattern with hyaline membranes and airspace organization, bronchiolitis and alveolitis	Bronchioles
Published case (3)	unknown	Open lung biopsy: Patchy, exudate, and airspace organization. Alveolar septal edema, type II pneumocyte metaplasia, edema in alveolar spaces.	Not determined
Published case (3)	unknown	Open lung biopsy: Mild interstitial and peribronchiolar chronic inflammatory infiltrate, Type II pneumocyte metaplasia, increased alveolar macrophages, focal hyaline membranes, alveolar fibrinous exudate, and edema	Not determined
Published case (3)	unknown	Open lung biopsy: Alveolar hemorrhage, fibrinous exudate, mild acute and chronic inflammatory infiltrate of the interstitium (alveolitis), type II pneumocyte metaplasia	Not determined
Published case (3)	unknown	Transbronchial biopsy: Organizing alveolar exudates with fibroblastic polyps (OP pattern), moderate, acute, and chronic interstitial inflammatory infiltrate	Not determined
Published case (3)	unknown	Open lung biopsy: Bronchiolocentric nodules of organization with mild interstitial infiltrate (OP pattern)	Not determined
Published case (7)	9	Open lung biopsy: Necrotizing bronchitis and bronchiolitis. DAD pattern with hyaline membranes. No thrombosis or vasculitis was detected.	Not determined

M: male, F: female, OP: organizing pneumonia, DAD: diffuse alveolar damage

^aNumber of days after onset of initial symptoms that specimen for histology was obtained via bronchoscopy.

after admission, the serum antibody titer for influenza A (H3N2) had increased from <10 to 160 titers, and the antibody titers for *M. pneumoniae*, *Chlamydia pneumoniae* and *C. psittaci* were no longer elevated. In June 2013, chest CT showed the disappearance of the areas of ground-glass opacity and consolidation in the bilateral lung fields (Fig. 1d).

Discussion

No significant pathogens other than influenza virus were found in the present case, and the patient was diagnosed as having primary influenza viral pneumonia. The findings of ground glass opacity and consolidation in the bilateral lung fields were consistent with those of primary viral pneumonia reported previously (6).

Although primary viral pneumonia had been considered rare, severe cases of acute respiratory distress syndrome/acute lung injury caused by pandemic H1N1 virus were reported in the pandemic of 2009. In reports of the pulmonary autopsy findings of pandemic H1N1 2009 cases, although some patients with bacterial infection were included, a diffuse alveolar damage (DAD) pattern was noted in most cases (7, 8). There are also limited reports describing the histologic findings of seasonal influenza pneumonia autopsy cases (2, 3, 9). However, autopsy studies are naturally biased toward the most severe cases. Yeldandi and Colby reported a histopathologic analysis of six sporadic cases of patients with seasonal influenza pneumonia who underwent

lung biopsies. Five patients recovered [two were treated with corticosteroids for prior diagnoses of organizing pneumonia and one patient died, (3)]. The biopsies showed DAD with hyaline membranes in the one patient who died, while also documenting a spectrum of less severe histologic findings with a mild acute lung injury pattern and organizing pneumonia pattern in addition to confirming previously published pathologic descriptions of influenza pneumonia (10) in non-survivors. In the present patient, airspace organization, type II pneumocyte metaplasia and acute and chronic interstitial infiltrates were found. There were no hyaline membranes or fibrin thrombi in the vascular lumen that would indicate a DAD pattern. We previously reported a sporadic case of a patient who survived primary influenza viral pneumonia [Table 1, (4)]. These cases suggest variety in the severity of the histological findings of primary influenza viral pneumonia (Table 2).

Although the present patient had alveolitis with inflammatory infiltrates, no viral antigens were detected in the alveolar epithelial cells. These findings are compatible with the results of immunohistochemical analyses in humans (2) and ferrets (11), which showed a predominant expression of seasonal influenza viral antigens in the bronchi compared with other serotypes (2, 11). Due to the small sample size obtained via transbronchial lung biopsy and the limited number of cases of primary influenza virus pneumonia in survivors undergoing immunohistochemical analyses, further studies are needed to clarify the histological characteristics

of primary influenza virus pneumonia.

There are no established therapies against primary influenza viral pneumonia. The early use of neuraminidase inhibitors (NI) can reduce the development of complications, such as pneumonia (12), and current CDC guidelines (13) recommend the use of NI in hospitalized patients with influenza virus infection. However, the efficacy of NI against primary influenza viral pneumonia is unclear. In the present case, the pulmonary infiltrates and PaO₂ worsened after NI administration. In one published case, primary influenza virus pneumonia was suspected and an NI was administered; however, the patient's condition deteriorated (4), as observed in the present case. Therefore, we were unable to demonstrate the efficacy of NI, although the patients did not receive NI until the ninth and 12th days, respectively, after the onset of initial symptoms, and the delayed administration may have affected the efficacy of NI in these patients.

The present patient and our previously reported patient (4) improved with adjunctive corticosteroid therapy. Corticosteroids have known anti-inflammatory properties and can modulate inflammation, suppress the immune system and regulate the stress response. It has been suggested that at least some of the pulmonary abnormalities of fatal influenza viral pneumonia are induced by the release of host inflammatory mediators rather than by direct viral cytopathic effects (14, 15) and that corticosteroids may have a favorable effect on this phenomenon. Several large observational studies have reported the use of corticosteroids in a consistent portion of patients with influenza pneumonia, particularly severely ill patients admitted to the intensive care unit (5). In contrast, due to their association with an increased risk of adverse effects, including metabolic consequences, neuromyopathic effects and gastrointestinal bleeding or superinfection, corticosteroids are not recommended as routine adjunctive treatment in patients with community-acquired pneumonia (16). Some studies have provided evidence of the beneficial effects of corticosteroids in patients with acute respiratory distress syndrome secondary to influenza pneumonia; however, these studies suggest that the use of corticosteroids in the early-phase therapy may be harmful (17, 18). Therefore, the role of steroids in the treatment of pneumonia remains an unresolved matter that deserves further investigation. We believe that the administration of corticosteroids in the late phase may be favorable in patients with primary viral pneumonia due to the likelihood of an unfavorable inflammatory response rather than a direct viral cytopathic effect. Future studies are needed to improve patient selection and facilitate the identification of patient subgroups that can benefit from adjunctive steroid therapy.

In the present case, prednisolone was initially started at a daily dose of 1 mg/kg and subsequently tapered to 0.5 mg/kg after we confirmed a slight increase in the PaO₂ and less severe histologic findings than predicted. Secondary infections associated with prolonged steroid administration are a cause of apprehension, and because a rapid reduction in the viral load has been reported (19), we did not believe that

prolonged steroid administration was required. Therefore, the corticosteroids were tapered and ceased within two weeks. The adequate dose and duration of the administration of corticosteroids in patients with primary influenza virus pneumonia also require further investigation.

The authors state that they have no Conflict of Interest (COI).

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