INTERSTITIAL PNEUMONIA FOLLOWING TEXAS A2 INFLUENZA INFECTION

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In two patients a documented Texas A2 influenza infection was associated with the development of interstitial pulmonary disease. One patient had an acute fulminating process resulting in respiratory failure and necessitating ventilatory assistance. Open lung biopsy revealed a histologic picture consistent with usual interstitial pneumonia (UIP). The other patient had a subacute course, and the pulmonary histology showed UIP with features of desquamative interstitial pneumonia. The influenza virus may have had an etiologic role in the development of the interstitial lung disease in our two patients.

Pulmonary involvement caused by influenza virus infection may produce bronchial disease and rapidly progressive influenza pneumonia and may predispose to superinfection with bacterial pathogens. In addition, a case of Goodpasture’s syndrome associated with influenza infection has been recently reported. Pathologic examination of lung tissue from fatal cases of influenza pneumonia demonstrates diffuse alveolar edema and hemorrhage, bronchial edema and ulceration, and collections of intra-alveolar pneumocytes, round cells, and polymorphonuclear leukocytes. Diffuse interstitial fibrosis, however, is an uncommon histologic feature.

In this report we describe two patients with serologically proved Texas A2 influenza in whom severe interstitial pneumonia and fibrosis followed the viral infection. The close temporal relationship of the influenza infection to the development of interstitial lung disease in our two patients suggests that the influenza virus had an etiologic role.

CASE REPORTS

CASE 1

A 63-year-old nonsmoking man was admitted to the intensive care unit with a flu-like syndrome for one week’s duration. Chest roentgenogram obtained one week before admission was normal, and past medical history was noncontributory.

Physical examination on admission revealed cyanosis and resting dyspnea. Blood pressure was 110/60 mm Hg, pulse, 110 and regular; respiratory rate, 24; temperature, 39°C; and examination of the chest showed diffuse rales. Arterial blood gas levels (FiO₂, 0.3 by Venturi mask) were pH 7.45, Pco₂ 38 mm Hg, and Po₂ 42 mm Hg. Hemoglobin was 15 g/dl; WBCs were 7100/cu mm, with a normal differential count; and the liver function studies were moderately abnormal. Admission chest roentgenogram (Fig 1) revealed extensive bilateral infiltrates. Gram stain of the sputum showed many polymorphonuclear leukocytes and was free of bacteria. Acid-fast stain of the sputum was negative. After

FIGURE 1. Admission chest roentgenogram showing bilateral interstitial infiltrates.
viral studies and cultures were done, the patient was given erythromycin, 500 mg intravenously every six hours. On the third hospital day the patient required mechanical ventilation with a volume cycled respirator, an Fio2 of 0.6 to 1.0, and a positive end-expiratory pressure of up to 20 cm H2O in order to maintain a PO2 greater than 55 mm Hg.

As a result of continued deterioration an open lung biopsy was performed on the 16th hospital day. The open lung biopsy specimen (Fig 2) showed extensive fibrosis composed of many fibroblasts, disorganized collagen bundles, and isolated mononuclear cells. There were islands of identifiable pulmonary parenchyma scattered in the fibrotic mass. A small portion of the biopsy specimen exhibited a more subacute interstitial inflammatory process, and the alveoli in this region contained remnants of fibrin, erythrocytes, and mononuclear cells. The lung biopsy findings were interpreted as consistent with unusual interstitial pneumonia (UIP).

After the open lung biopsy, the patient received 60 mg of prednisone per day. Repeated serologic studies four weeks after admission showed a rise in hemagglutination inhibition antibody titer for A2 Texas influenza virus from 1:80 to 1:640. The patient gradually improved and was discharged 2½ months after admission. Pulmonary function studies at that time showed severe restriction, and the chest roentgenogram disclosed diffuse bilateral interstitial infiltrates. Subsequent chest roentgenograms have shown progressive clearing, with residual lower lobe streaking, and serial pulmonary function studies have shown gradual improvement with persistence of a mild restrictive defect.

Table 1—Pulmonary Function Data*

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient One</th>
<th>Patient Two</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial (3-15-78)</td>
<td>% Pred</td>
</tr>
<tr>
<td>VC</td>
<td>1.49</td>
<td>44</td>
</tr>
<tr>
<td>TLC</td>
<td>2.44</td>
<td>41</td>
</tr>
<tr>
<td>DLCO ml/min/mm Hg</td>
<td>4.3ss</td>
<td>36</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

*All volumes expressed in liters. VC = vital capacity; TLC = total lung capacity; DLCO ml/min/mm Hg = diffusing capacity for carbon monoxide expressed as ml of CO transferred per minute per mm Hg (ss = steady state; sb = single breath); and FEV1/FVC = Forced expired volume in 1 second divided by forced vital capacity, expressed as percentage.
after discharge, the patient's exertional dyspnea increased, and her chest roentgenogram failed to clear. Repeated pulmonary function studies showed an improvement in lung volumes, a decrease in the diffusing capacity for carbon monoxide, and a reduced static compliance; 0.45 L/cm H$_2$O (normal, 0.16 ± 0.5); (Table 1).

The patient was readmitted, and approximately four months after the initial presentation, an open lung biopsy was performed. The biopsy specimen (Fig 4) showed interstitial fibrosis with focal interstitial inflammatory infiltrates. These interstitial changes varied from mild to severe within the biopsy. There were focally present intra-alveolar cellular aggregates made up of both hemosiderin containing histiocytes and periodic acid-Schiff-positive pneumocytes. There was no evidence of significant vascular or pleural alterations. The lung biopsy was interpreted as consistent with UIP, with characteristics of desquamative interstitial pneumonia (DIP). She was given 50 mg of prednisone daily for six weeks, followed by gradual tapering. No significant improvement in pulmonary function studies or chest roentgenograms has been noted, and the patient has a minimally reduced exercise capacity.

**Comments**

Despite many studies documenting pulmonary damage secondary to acute influenza infection, few data are available on the long-term pulmonary parenchymal changes caused by this agent. In one of the more recent studies, Laraya-Cuassay et al\(^7\) described interstitial lung disease in biopsy specimens taken from three children, aged 5, 24, and 42 months, at 50, 166, and 51 days after the onset of the influenza pneumonia. Pathologic findings included a variable degree of bronchial and bronchiolar erosion and metaplasia, obliterator bronchiolitis, chronic interstitial inflammatory infiltrates, and the presence of intra-alveolar macrophages and pneumocytes. Mild interstitial fibrosis was present in two patients, and moderate fibrosis in the third. In one patient with minimal fibrosis, influenza virus was recovered from lung tissue culture.

In an earlier study of adults, Conte et al\(^8\) reported various pathologic sequelae of viral pneumonia. Without citing specific viral pathogens, they described several cases that resulted in interstitial fibrosis and commented on a possible etiologic relationship between the two entities.

The classic histologic pattern of acute influenza pneumonia was not seen in our two patients. Massive interstitial proliferation of fibrous tissue was present in the first patient, and marked intra-alveolar desquamation of pneumocytes and chronic interstitial inflammation were present in the second patient. The pathologic, roentgenographic, and physiologic features of our patients are most consistent with the diagnosis of UIP or fibrosing alveolitis.\(^8-11\) In addition, some features of the lung biopsy specimen in case 2, specifically the marked proliferation of intra-alveolar pneumocytes, is consistent with an element of DIP.\(^10\)

The etiology of interstitial pneumonia and fibrosis remains unclear. These pathologic entities may represent the final common pathway for the expression of many pulmonary parenchymal insults. Liebow, Livingston, and Scadding all suggest a viral etiology, but definitive evidence is lacking.\(^10-12\) One patient with interstitial pneumonia, described by Liebow, had morphologic evidence of viral infection, but this was not confirmed by serologic data or by culture.\(^10\)

One must consider, especially in case 1, that oxygen toxicity might have contributed to the increase in interstitial pulmonary tissue observed in the histologic sections of the lung. The paucity of hyaline membranes and absence of capillary proliferation, however, make it unlikely that this factor contributed significantly to the lesion.\(^18\)

The development of UIP in our two patients soon after the onset of influenza infection proved serologically and by culture suggests, but does not prove, a causal relationship. We recognize that recovery of virus from the lung itself would have been significant, but we believe that the entire picture was consistent with an influenza infection.

Patients surviving documented influenza pneumonia should be followed up to determine the incidence and severity of interstitial lung disease that might result from the antecedent infection.

**References**


![Figure 4](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21241/ on 06/11/2017)
4 Lindsay MI, Herrmann EC, Morrow GW, Brown AL. Hong Kong influenza: clinical microbiologic, and pathologic features in 127 cases. JAMA 1970; 214:1825-32

Immunodiagnosis of Allergy, Rheumatic and Infectious Diseases

The R. A. Cooke Institute of Allergy and Infectious Disease of the St. Luke's-Roosevelt Hospital Center, in cosponsorship with the American Academy of Allergy and the Columbia University College of Physicians and Surgeons, will present a postgraduate course entitled, Immunodiagnosis of Allergy, Rheumatic and Infectious Diseases. The course will be held in New York City, October 15-16. For further information, write: Dr. Elizabeth Cerst, Continuing Education Center, College of Physicians and Surgeons, 630 West 188th Street, New York City 10032.

International Conference on Lung Sounds

The Sixth International Conference on Lung Sounds will be held at the Faulkner Hospital, Boston, October 1-2. Address requests for information to: Raymond L. H. Murphy, Jr., M.D., 1153 Centre Street, Boston 02130.