Clinical Features of Three Fatal Cases of Non-specific Interstitial Pneumonia

Jiro Fujita, Ichiro Yamadori*, Shuji Bandoh, Kohichi Mizobuchi**, Ichizo Suemitsu***, Yukinobu Nakamura****, Yuji Ohtsuki***** and Jiro Takahara

Abstract

We describe the clinical courses of the 3 fatal patients (2 females and 1 male) with idiopathic non-specific interstitial pneumonia (NSIP) among 24 patients with NSIP. Lung biopsies were diagnosed to be NSIP group II in all patients. The clinical courses from onset to death of these 3 patients were 41 months, 46 months, and 91 months. A follow-up chest CT demonstrated no apparent honey-comb formation. We found that i) about 20% of patients with NSIP died of respiratory failure, ii) in the chest CT findings, apparent honey-comb formation was rare even just before death, iii) prediction of the prognosis based on the histological findings was difficult. This is the first report to describe the clinical features of deceased patients with idiopathic NSIP; the incidence of fatal cases was considered to range from 10 to 20%.


Key words: Lung biopsy, chest CT findings

Introduction

In 1994, Katzenstein and Fiorelli reported the histologic features and clinical significance of NSIP (1). The histologic features of NSIP include a varying degree of interstitial inflammation and fibrosis which appear to develop over a specific time frame (i.e., the process is temporarily uniform) (1). Katzenstein and Fiorelli reviewed 64 such cases from which three histologic patterns emerged (1). In 48% of the cases, pneumonia was characterized by a cellular interstitial infiltrate with little or no fibrosis (NSIP group I). This pattern likely corresponds to the “cellular interstitial pneumonia” described in some patients with dermatomyositis (2) and rheumatoid arthritis (3). In 38% of cases, both inflammation and fibrosis were seen (NSIP group II). In the remaining 14% of cases, dense fibrosis was the dominant histologic feature (NSIP group III)(1).

Recently, Park et al reported radiographic and CT findings (4) and clinical features (5) of 7 patients with NSIP. In addition, Bjoraker et al reported that patients with usual interstitial pneumonia (UIP) have a shorter survival than patients with other types of idiopathic chronic interstitial pneumonia including NSIP (6). More recently, Cottin et al (7), Nagai et al (8), and Fujita et al (9) described clinical features of NSIP. However, clinical courses of fatal cases of NSIP remain unclear. The purpose of this report was to describe the clinical courses of fatal patients with NSIP.

Case Report

Between March 1990 and November 1997, 24 patients (17 females and 7 males) were diagnosed with NSIP confirmed by histology. Four of 24 patients died of respiratory failure caused by NSIP. Of these, three had idiopathic NSIP and the fourth had dermatomyositis. In the present study, we excluded the patient with dermatomyositis, and therefore evaluated 3 patients with idiopathic NSIP. The diagnoses were made by open-lung biopsy in two patients, and by autopsy in one patient.

All pathologic specimens were analyzed by lung pathologists (IY and YO) according to the criteria of NSIP described by Katzenstein and Fiorelli (1). Briefly, NSIP represented a pattern of chronic interstitial pneumonia that lacked characteristic features of other specific entities such as UIP, desquamative interstitial pneumonia (DIP), hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), Langerhans’ cell granulomatosis, or chronic eosinophilic pneumonia. Lung biopsies in this group were characterized by varying proportions of chronic interstitial inflammation and fibrosis which is temporarily uniform. Pathological diagnoses of NSIP were subgrouped (groups I, II, and III) based on the criteria described by Katzenstein and Fiorelli (1).

Table 1 shows the characteristics of 3 fatal patients with...
NSIP. There were 2 females and 1 male (median age of 62). There was no underlying disease in these 3 patients. There was no digital clubbing and moist rales were auscultated in bilateral lower lung fields. Two patients were diagnosed by open lung biopsy and one patient was diagnosed by autopsy. Although apparent collagen vascular disorders were not demonstrated, the rheumatoid factor was demonstrated in 1 patient (case 2). In 1 patient (case 3), serum CA19-9 increased (up to 3,000 U/ml) according to the deterioration of both radiological and clinical findings.

The plain chest X-ray features of these patients were interstitial and patchy consolidation in both lungs, predominantly in the middle and lower lung zones (case 3, Fig. 1A). Elevations of bilateral diaphragms representing volume loss of lungs were clearly demonstrated. Importantly, although scattered ground-glass opacities was observed, honeycomb formation was also unclear even on the plain chest X-ray just before the patients’ death (example, case 3, Fig. 1B).

The CT features of these patients were interstitial and patchy parenchymal opacification in both lungs, predominantly in the middle and lower lung zones (case 3, Fig. 2A). Scattered ground-glass opacities were also the most common manifestation. On the chest CT, apparent honeycomb formation was not observed in these patients (example, case 3, Fig. 2A). Importantly, honeycomb formation was also unclear even on the chest CT just before the patients’ death (example, case 3, Fig. 2B).

Pathologically, all patients were diagnosed with NSIP group II. Obtained lung tissue from case 1 (biopsied from left S9) showed mild diffuse infiltration of lymphocytes and diffuse thickening of alveolar septa. Focal proliferation of immature

<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; Sex</th>
<th>Onset</th>
<th>Symptom</th>
<th>CRP</th>
<th>LDH</th>
<th>PaO₂</th>
<th>%VC</th>
<th>BAL (%Lym)</th>
<th>Response to steroids</th>
<th>Clinical course</th>
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<tr>
<td>1</td>
<td>62F</td>
<td>June, 1990</td>
<td>Cough, fever, dyspnea</td>
<td>12</td>
<td>328</td>
<td>65.7</td>
<td>39.7</td>
<td>8</td>
<td>Good → Poor</td>
<td>7 years 7 months</td>
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<tr>
<td>2</td>
<td>53F</td>
<td>September, 1992</td>
<td>Cough, fever, dyspnea</td>
<td>1.2</td>
<td>778</td>
<td>50</td>
<td>47.7</td>
<td>ND*</td>
<td>Good → Poor</td>
<td>3 years 5 months</td>
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<tr>
<td>3</td>
<td>66M</td>
<td>June, 1990</td>
<td>Cough, dyspnea</td>
<td>1.7</td>
<td>492</td>
<td>52.9</td>
<td>60.17</td>
<td>80</td>
<td>Good → Poor</td>
<td>3 years 9 months</td>
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*not done.

Figure 1. Plain chest X-ray findings of a fatal patient with NSIP (case 3). A: at the time of diagnosis, B: just before death. Bilateral diaphragms are elevated indicating volume loss of lungs.
Figure 2. Chest CT findings of a fatal patient with NSIP (case 3). A: at the time of diagnosis, B: just before death. No apparent honeycomb formation was observed in either chest CT.

Figure 3. Pathological findings of 3 deceased patients. (A) Infiltration of lymphocytes and proliferation of immature connective tissues are observed in the alveolar septa (case 1) (HE stain, ×33). (B) Alveolar septa are diffusely thickened by connective tissue (HE stain, ×33). Air spaces lined by metaplastic epithelium contained a mucinous substance (right, case 2). (C) Lung tissue is infiltrated by lymphocytes. Intraluminal accumulation of macrophages and focal proliferation of immature connective tissue are seen (case 3) (HE stain, ×50).
connective tissues was observed in some areas, some of which were polypoid in alveoli or alveolar ducts but many adhered widely to alveolar septa (Fig. 3A). Lymphoid follicles were scattered. Air spaces around bronchioles were slightly dilated and covered by metaplastic bronchial epithelium. Focal deposition of carbon-like substances were noted in bronchiolar walls. Obtained lung tissue from case 2 (autopsied case) showed thickening of alveolar walls by connective tissue. In addition, air spaces around bronchioles were slightly dilated and covered by metaplastic bronchial epithelium. These spaces contained mucinous substances. Infiltration of inflammatory cells was minimal (Fig. 3B). Obtained lung tissue from case 3 (biopsied from right S8) showed diffuse infiltration by lymphocytes and intraluminal accumulation of macrophages. Lymphoid follicles were observed around bronchioles. Focal proliferation of immature connective tissue was scattered (Fig. 3C).

Steroid pulse therapy was administered to all patients (methyldprednisolone 1 g/day for three days) and followed by oral corticosteroids. In all patients, although steroid therapy was effective at first, interstitial pneumonia deteriorated with the reduction of corticosteroids. Then, steroid pulse therapy and oral corticosteroids were repeated, however the pneumonia became resistant later. All patients died because of respiratory failure diagnosed by chest X-ray, chest CT, and the blood gas analyses. Clinical courses of these patients who died of respiratory failure were 41 months, 46 months, and 91 months (Table 1). Unfortunately, autopsy was not performed in 2 patients.

**Discussion**

NSIP was first described by Katzenstein and Fiorelli in 1994 (1). It has been reported that the prognosis of patients with this illness is significantly better than that for patients with UIP (1, 5, 7, 8). Katzenstein and Fiorelli reported that almost 50% of patients completely recovered after steroid therapy and the overall mortality was 11% (1). Importantly, they also described that patients who were diagnosed with NSIP group III have a worse prognosis compared with NSIP groups I and II (Table 2). Furthermore, Bjoraker et al reported that patients with UIP have a lower survival rate than patients with other types of idiopathic chronic interstitial pneumonia including NSIP (6). More recently, Cottin et al (7), Nagai et al (8), and Fujita et al (9) described clinical features of NSIP. Among these reports, Nagai et al also described 2 fatal cases in NSIP group III (Table 2) (8). From our experience, four patients (16.7%) died of respiratory failure caused by NSIP (9). Descriptions concerning the prognosis of NSIP from a literature search are listed in Table 2. According to those reports, it is suggested that 10–20% of patients with NSIP died because of respiratory failure.

Since NSIP has been described only recently, knowledge of its radiographic manifestations is limited (1, 4, 8). Both irregular linear opacities and air-space consolidations have been described as characteristic features (1, 4, 8). The CT features of NSIP have also been reported (4). In the present study, the predominant CT feature was interstitial and patchy parenchymal opacification in both lungs predominantly in the middle and lower lung zones. Scattered ground-glass opacities were also the most common manifestation. It should be noted that honeycomb formation was not found in any of our patients. More importantly, follow-up CT findings demonstrated that there was no apparent honeycomb formation even just before death, the onset of clinical symptoms. This was in contrast to UIP.

The present study revealed the following: i) about 20% of patients with NSIP died of respiratory failure, ii) on chest CT, apparent honeycomb formation was rare, even just before death, iii) prediction of the prognosis based on the histological findings was difficult. This is the first report to describe the clinical features of fatal patients with NSIP.

**References**


2) Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV. Interstitial lung disease in polymyositis and dermatomyositis: clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis 141: 727–

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**Table 2. Review of Prognosis in Patients with NSIP**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Pathology</th>
<th>Number of patients</th>
<th>Deceased cases (%)</th>
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<tbody>
<tr>
<td>Katzenstein (1994)</td>
<td>I</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>24</td>
<td>3 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>9</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Park (1996)</td>
<td>I/II/III</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Bjoraker (1998)</td>
<td>ND*</td>
<td>14</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Cottin (1998)</td>
<td>I/II/III</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Nagai (1998)</td>
<td>I</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>15</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Present report</td>
<td>II</td>
<td>24</td>
<td>4 (17%)*</td>
</tr>
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</table>

*not described. **one patient with dermatomyositis was excluded in the present study.
Fatal Cases of NSIP


