

## Case Report

# Juvenile Idiopathic Nonspecific Interstitial Pneumonia.

## Case Report and Review of Literature

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We describe a case of juvenile idiopathic nonspecific interstitial pneumonia (NSIP). This is the first report of a Japanese patient with idiopathic NSIP aged 27 years. A computed tomographic scan of the chest showed ground-glass opacities and reticular opacities in subpleural distribution. Bronchoalveolar lavage fluid revealed no specific finding except for decreased CD4/CD8 ratio of lymphocyte subset. Histopathological features on examination of thoracoscopic lung biopsy specimens were consistent with those of NSIP group III. The patient was treated with corticosteroids and immunosuppressants, but no clinical improvement was noted and the general condition has gradually worsened. Although the prognosis is generally considered to be good in patients with NSIP, some patients die as a result of progression of the disease. The prediction of prognosis based on histopathological, radiologic, and bronchoalveolar lavage cell findings in NSIP seems to be difficult at present.

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**Key Words:** juvenile onset, idiopathic nonspecific interstitial pneumonia

### Introduction

Nonspecific interstitial pneumonia/fibrosis (NSIP) was first described by Katzenstein and Fiorelli in 1994 as a diffuse interstitial pneumonia with a pathologic pattern distinct from usual, desquamative, and acute interstitial pneumonia<sup>1)</sup>. NSIP is characterized by an interstitial inflammatory cell infiltrate with or

without fibrosis; however, the most characteristic finding in NSIP is the lack of temporal heterogeneity, which is a cardinal feature of usual interstitial pneumonia (UIP)<sup>1–5)</sup>. The prognosis in NSIP is generally good compared with UIP<sup>1–11)</sup>, however it is reported that patients with NSIP group III have a worse prognosis relative to those with NSIP groups I and II<sup>1, 6, 7)</sup>. NSIP occurs mainly in middle-aged adults<sup>2, 3, 6–9)</sup>, like most other interstitial pneumonias. According to clinical reports from Japan, the average age of patients at onset in NSIP is 56.4 to 57.7 years<sup>6, 7, 10)</sup>. We report here the first Japanese patient with early onset idiopathic NSIP group III.

### Case Report

A 27-year-old Japanese man was admitted to our hospital in June 1997 for further investigation of non-productive cough and progressive exertional dyspnea. The medical history included bronchial asthma and atopic dermatitis during childhood. The father died of the progressive idiopathic pulmonary fibrosis (IPF) and diagnosed as UIP at autopsy. The uncle also died of IPF. The patient was a tobacco smoker (40 cigarettes a day) for 8 years, but reported no environmental exposure to chemicals.

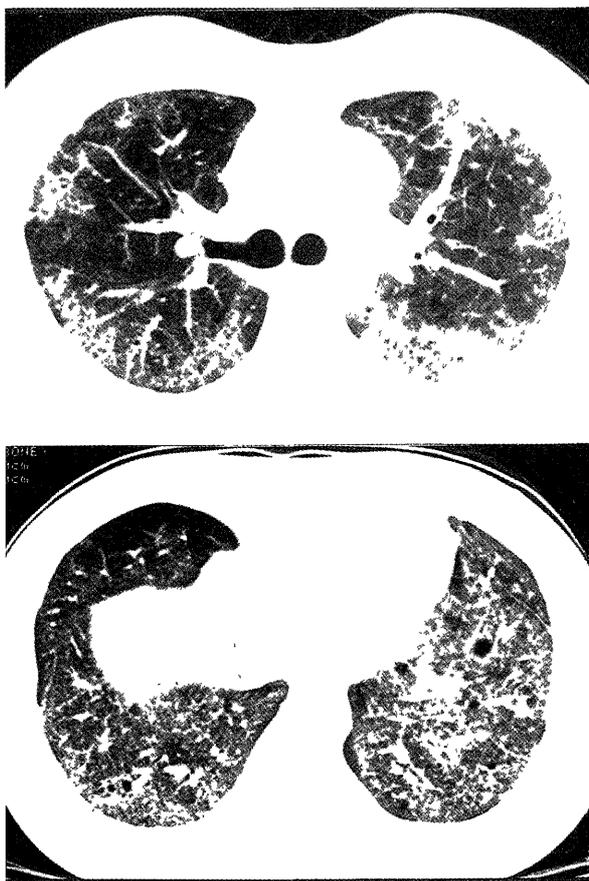
Physical examination was otherwise normal apart from bilateral basilar inspiratory fine crackles on chest examination. Although reticulonodular opacities were detected on the chest X-ray film in November 1996, the patient was not admitted to the hospital. Chest X-ray film on admission showed diffuse reticulonodular opacities in both middle and lower lung fields (Fig. 1). A computed tomographic scan of the chest showed ground-glass opacities and reticular opacities in subpleural distribution (Fig. 2). The relevant laboratory results included lactic dehydrogenase

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**Figure 1.** Chest X-ray taken at the time of diagnosis in 1997 showing diffuse reticulonodular opacities in both middle and lower lung fields.

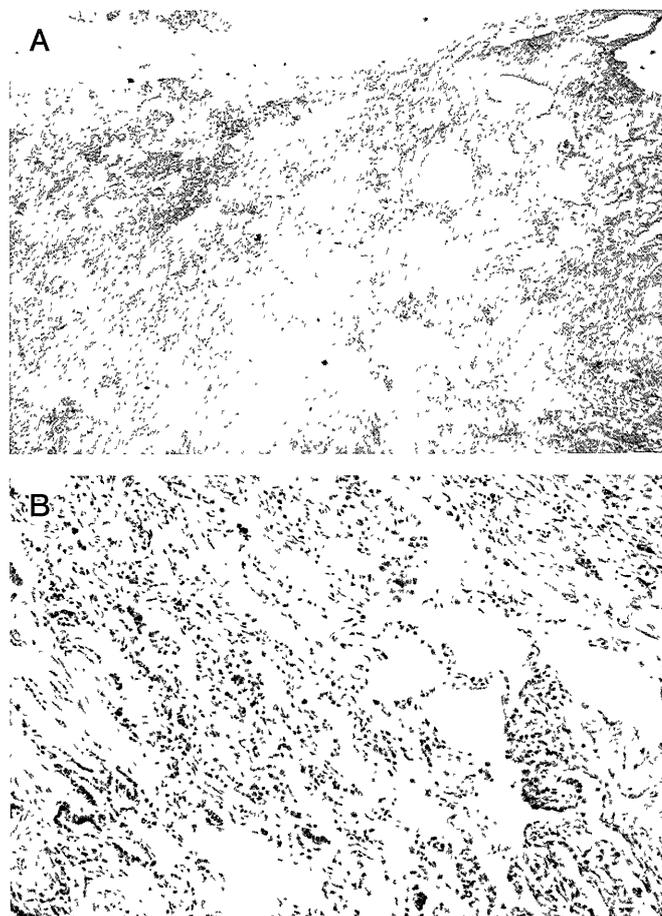


**Figure 2.** A computed tomographic scan of the chest at the time of diagnosis in 1997 showing ground-glass opacities and reticular opacities in subpleural distribution.

459 IU/L (normal range 202-435) and C-reactive protein 0.32 mg/dl (normal; negative). Antinuclear antibodies were positive ( $\times 40$ , speckled type), while rheumatoid factor and other specific antibodies for collagen vascular diseases were negative. Arterial blood gases on room air at rest were PaO<sub>2</sub> 87.5 mmHg, PaCO<sub>2</sub> 45.5 mmHg, and pH 7.376.

Pulmonary-function tests included vital capacity of 3.39 L (80.3 percent of predicted), FEV<sub>1</sub> of 2.98 L (89.5 percent of predicted), DLCO/VA of 4.092 ml/M/mmHg/L, and %DLCO 46.8 percent. Bronchoalveolar lavage (BAL) was performed using 200 ml of physiological saline. Examination of BAL fluid showed  $4.1 \times 10^5$  cells/ml including 82.6 percent macrophages, 0.3 percent neutrophils, 0.4 percent basophils, 3.8 percent eosinophils, and 12.9 percent lymphocytes. The CD4/CD8 ratio of lymphocyte subset was 0.44.

To establish a definite diagnosis, lung biopsy was performed by video-assisted thoracoscopic surgery on June 16, 1997. Pathological diagnosis was made as



**Figure 3.** Specimen obtained by thoracoscopic lung biopsy showing a mild degree of intra-airspace organization, the presence of minimal fibrosis, and subpleural honeycombing with loss of alveolar structure. Compared to UIP, temporal heterogeneity of the fibrous tissue was absent (HE stain, A  $\times 5$ , B  $\times 33$ ).

NSIP group III, based on the findings that lung tissue obtained from the left lower lobe showed a mild degree of intra-airspace organization, the presence of minimal fibrosis, and subpleural honeycombing with loss of alveolar structure. Compared to UIP, temporal heterogeneity of the fibrous tissue was absent (Fig. 3). Since dust inhalation and collagen vascular disease were ruled out, the diagnosis was idiopathic NSIP group III.

Oral prednisolone was administered at 1 mg/kg/day. Although such therapy was initially effective, deterioration of the clinical condition and worsening of

interstitial pneumonia occurred following tapering of prednisolone. Accordingly, the patient was treated with a high dose of methyl prednisolone (1g/day intravenously for three days) followed by oral corticosteroids, combined with oral immunosuppressant



Figure 4. Chest X-ray taken in 2000 showing diffuse reticular opacities and elevation of both domes of the diaphragm indicative of lung volume loss.

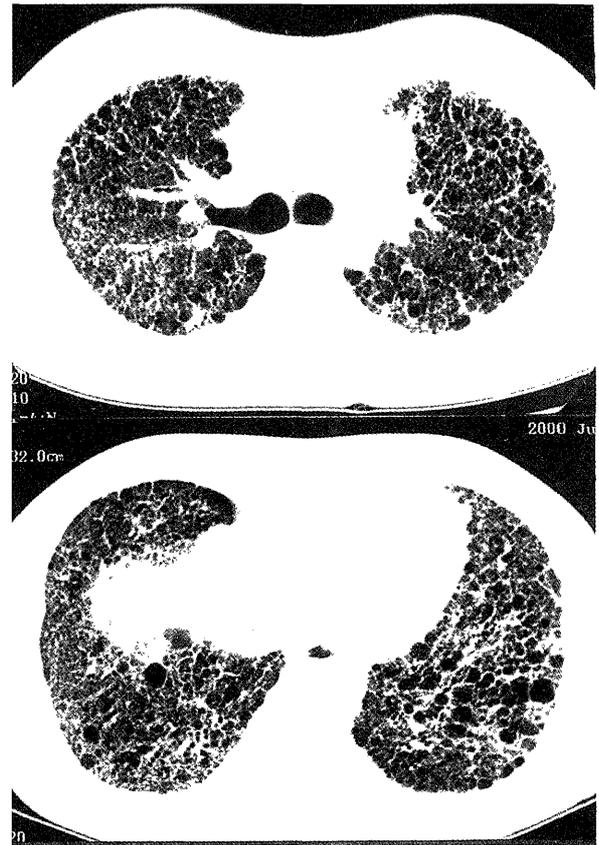


Figure 5. High resolution computed tomography of the chest taken in 2000 showing diffuse ground-glass opacities with honeycomb formation, local traction bronchiectasis, and interlobular septal thickening.

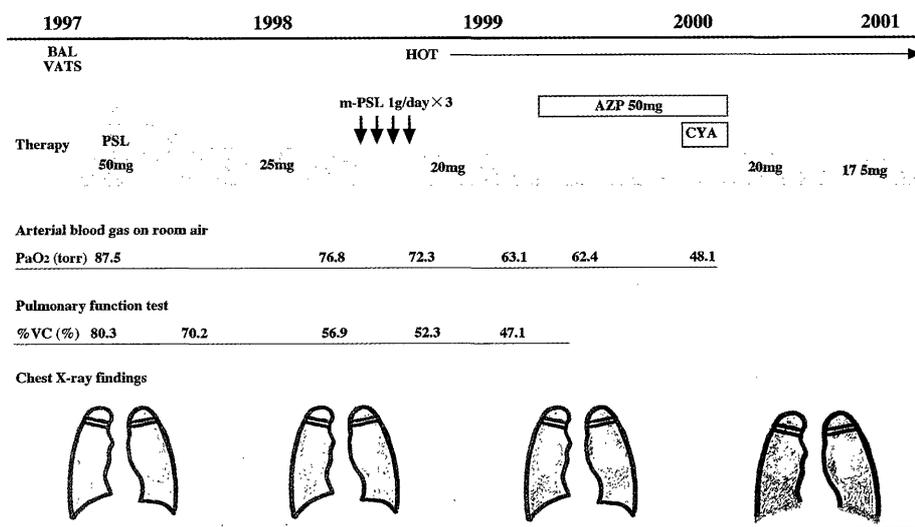


Figure 6. Summary of clinical course. Therapeutic intervention, arterial blood gases, pulmonary function tests, and schema of chest X-ray films. BAL: bronchoalveolar lavage, VATS: video-assisted thoracoscopic surgery, HOT: home oxygen therapy, PSL: prednisolone, m-PSL: methyl prednisolone, AZP: azathioprine, CYA: cyclosporin.

(either azathioprine 50 mg/day, or cyclosporin 200 mg/day). However, at that stage, NSIP showed resistance to treatment. Follow-up examination in March 2000 showed arterial blood gases on room air of PaO<sub>2</sub> of 48.1 mmHg, PaCO<sub>2</sub> of 39.8 mmHg and pH of 7.443, and serum KL-6 of 2,320 U/ml. Chest X-ray film showed diffuse reticular opacities in both lung fields and lung volume loss (Fig. 4), and high resolution computed tomography of the chest showed diffuse ground-glass opacities with honeycomb formation, local traction bronchiectasis, and interlobular septal thickening (Fig. 5). At present, the patient is on home oxygen therapy and on the waiting list for lung transplantation. Figure 6 provides a summary of the clinical course of this case.

## Discussion

Nonspecific interstitial pneumonia/fibrosis (NSIP) was first defined by Katzenstein and Fiorelli in 1994<sup>1)</sup>, and the name has gained broad acceptance<sup>4,11)</sup>. The prognosis is generally good in NSIP patients, but some patients, especially those of group II and III of NSIP die as a result of progression of the disease<sup>1, 6, 7, 10)</sup>. Recently, Travis et al.<sup>4)</sup> proposed that NSIP should be separated into cellular and fibrosing patterns because these histological patterns are associated with disease characteristics and prognosis. Based on the proposed category of NSIP, the cellular pattern generally corresponds to group I and fibrosing pattern to group II and III of NSIP, initially described by Katzenstein and Fiorelli<sup>1)</sup>. They also reported that only patients with idiopathic cellular NSIP has an excellent long-term prognosis, and that the majority of patients with idiopathic NSIP fibrosing pattern die mostly within 5 and 10 years<sup>4)</sup>. However, the prediction of prognosis based on histopathological, radiologic or bronchoalveolar lavage cell findings in NSIP seems to be difficult at present. Future studies need to evaluate this issue clinicopathologically in a large population of NSIP.

NSIP occurs most often in middle-aged adults<sup>2, 3, 6-9)</sup>. Although the disease could affect individuals at any age, cases of juvenile NSIP are comparatively rare. Several juvenile patients with NSIP were reported by Katzenstein and Fiorelli<sup>1)</sup>, while connective-tissue diseases were also included in their report. According to recent reports of idiopathic NSIP, the average age at onset was 57 years (range, 40 to 73) in the study of Bjoraker et al.<sup>8)</sup> and 43 years (range, 31 to 66) of Daniil et al.<sup>2)</sup>. Furthermore, the age of affected Japanese patients is 57.7 years (range, 40 to 69) according to Nagai et al.<sup>6)</sup> and 56.4 years (range, not

described) of Nakamura et al.<sup>7)</sup> (Table 1). In our institution, the average age at onset of patients with idiopathic NSIP is similar to those of the above two Japanese studies (52.9 years, range, 27 to 65 yr) (Table 1). However, there is no report so far that described the clinical course of juvenile idiopathic NSIP. To our knowledge, therefore, this is the first report of a Japanese patient with early onset idiopathic NSIP. Although the present case was suspected to be a hereditary interstitial lung disease, this could not be confirmed because of lack of detailed genetic examinations.

**Table 1.** Age at Onset of Patients with Idiopathic Nonspecific Interstitial Pneumonia/Fibrosis (NSIP) reported in Japan.

Reference	Overall	Group I	Group I/II	Group II/III	Group III
Nagai et al. <sup>6)</sup>	57.7±8.2*	46.50†	57.7±8.0*	58.4±8.0*	57.8±8.7*
	(n=31)	(n=2)	(n=16)	(n=29)	(n=15)
Nakamura et al. <sup>7)</sup>	56.4±9.97*	65.8±8.89*	ND	54.0±8.75	ND
	(n=30)	(n=6)		(n=24)	
Our cases	52.9±12.9*		57†	52.9±12.9*	51.7±14.6*
	(n=9)	(n=0)	(n=2)	(n=9)	(n=7)

\*: Mean ± SD, †: average, ND: not described

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