Nonspecific Interstitial Pneumonia/Fibrosis Completely Recovered by Adding Cyclophosphamide to Corticosteroids

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Abstract

Nonspecific interstitial pneumonia/fibrosis (NSIP) was first described by Katzenstein and Fiorelli in 1994 (Am J Surg Pathol 18: 136–147). Many reports have described that corticosteroids are effective for NSIP. We describe a case of group II idiopathic NSIP in whom cyclophosphamide was administered since the initial response to corticosteroids had been insufficient. Lung biopsy was performed by video-assisted thoracoscopic surgery and NSIP was diagnosed pathologically, clinically and radiologically. Although the initial response to corticosteroids was insufficient, interstitial infiltrates on chest computed tomography improved dramatically after adding intravenous cyclophosphamide followed by oral cyclophosphamide. This case demonstrates that the addition of cyclophosphamide to corticosteroids might be a useful treatment for patients with NSIP. (Internal Medicine 41: 867–870, 2002)

Key words: treatment, chest computed tomography, lung biopsy, completely remission

Introduction

Nonspecific interstitial pneumonia/fibrosis (NSIP) was first described by Katzenstein and Fiorelli in 1994 (1). NSIP has also been reported to be associated with collagen vascular disorders (1).

Many reports have described that corticosteroids are effective for NSIP (1–9). In addition, although other immunosuppressants (such as cyclophosphamide or azathioprine), have been used in patients with NSIP in whom corticosteroids were ineffective, the role of these immunosuppressants in patients with NSIP has not been clarified (1, 5–9).

In the present report, we describe a case of NSIP group II in whom interstitial infiltrates on chest computed tomography (CT) were resolved by cyclophosphamide added to corticosteroid treatment.

Case Report

A 48-year-old woman; a licensed cook, attended the outpatient clinic of the Mitoyo General Hospital with a non-productive cough and fever. Although she was treated with antibiotics, her symptoms worsened and she went to the emergency department due to dyspnea; she was then admitted to our hospital. She had not experienced any risk factors for occupational or environmental exposure to toxic materials, nor did she have hypersensitivity pneumonitis. She was a non-smoker and her previous medical history was not remarkable. There were no abnormal findings on chest computed tomography which had been taken 3-years earlier. On physical examination, she was febrile and cyanotic with a respiratory rate of 25 per minute. Her blood pressure was 114/62 mmHg. She had tachycardia without arrhythmia. Bibasilar inspiratory fine crackles were auscultated. Laboratory data showed a normal blood cell count. The electrolyte, renal and liver test was normal except for AST (51 IU/l). LDH and CRP were elevated. Autoantibodies; anti-nuclear antibody, rheumatoid factor, anti-single stranded DNA antibody, anti-double stranded DNA antibody, anti-RNP antibody, anti-Sm antibody, anti-Scl70 antibody or anti-Jo1 antibody were all negative. Arterial blood gas analysis showed PaCO₂ of 29.0, PaO₂ of 53.0 Torr, HCO₃⁻ of 23.6 mEq/l, and SaO₂ of 90.8%. Lung function studies could not be performed because of severe dyspnea. Chest X-ray and chest CT revealed areas of patchy parenchymal opacification as well as thickening of perivascular and peribronchial bundles those present bilaterally mainly in the middle and lower lung zones (Fig. 1A). Flexible bronchoscopy was performed on the day of ad-

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Figure 1. Chest CT findings of the present case. A) Mar. 4, 2001, B) April 2, 2001, C) Sept. 6, 2001.

mission, and bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed from the right middle lobe. BAL fluid showed an increased cell number (1,400 cells/ μ l), lymphocytes predominance (59%), eosinophil (7%), neutrophil (17%) and decreased CD4/CD8 ratio (0.31). Pathological evaluation of the specimen obtained by TBLB revealed compatibility with interstitial pneumonia. Based on radiological and pathological findings, acute interstitial pneumonia (AIP), bronchiolitis obliterans organizing pneumonia (BOOP), eosinophilic pneumonia, NSIP, or atypical pneumonia were considered. Therefore, intravenous methylprednisolone (1 g/day, for 3 days) followed by oral prednisolone and intravenous minocycline were administered (Fig. 2). Dyspnea and fever were improved and oral prednisolone was reduced gradually. However, at the time of prednisolone of 25 mg/day, she became febrile and her chest computed tomography findings were not so improved (Fig. 1B). In addition, arterial blood gas analysis was deteriorated (PaCO_2 30.7 Torr, PaO_2 55.0 Torr). To make

the definite pathological diagnosis, lung biopsy was performed under video-assisted thoracoscopic surgery (VATS). Histological examination revealed intraluminal growth of connective tissues which were widely adherent to alveolar walls, accumulation of xanthoma cells in alveolar cavity, and diffuse infiltration of lymphocytes (Fig. 3). Since pathological, clinical and radiological diagnosis was NSIP group II, intravenous corticosteroids were administered again. However, while receiving prednisolone (25 mg/day), she became febrile again. In addition, arterial blood gas analysis was deteriorated again (PaCO_2 33.4 Torr, PaO_2 58.2 Torr). Therefore, we added intravenous cyclophosphamide (800 mg/body $\times$ 3, weekly) followed by oral cyclophosphamide (100 mg/body). Three months after adding cyclophosphamide, her chest computed tomography revealed that interstitial infiltrates had dramatically improved (Fig. 1C). Her arterial blood gas analysis became normal which showed PaCO_2 of 39.7, PaO_2 of 97.0 Torr, HCO_3^- of 26.4 mEq/l, and SaO_2 of 97.7%, and her pulmonary function test became nor-

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Figure 2. Clinical course of the present case. Normal values: KL-6: <500 U/ml, SP-D: <110 U/ml, LDH: 70–210 IU/ml, CRP: <0.25 mg/dl.

A

B

Figure 3A. Histological findings of the present case. Pathological diagnosis was group II nonspecific interstitial pneumonia (HE stain, ×25). **B)** Histological findings of the present case. Pathological diagnosis was group II nonspecific interstitial pneumonia (HE stain, ×6.6).

mal which showed per cent vital capacity of 87.7%, and per cent forced expiratory volume in 1 second of 83.04%.

Discussion

In this report, we described a case of idiopathic group II NSIP in whom interstitial infiltrates were resolved by adding

Table 1. Review of Clinical Features of Nonspecific Interstitial Pneumonia

Author	Year	Number of patients	Male/Female	Age	Symptom*	Term (Month)	Histology**	% of Idiopathic NSIP	Immuno-suppressant***	Response/Prognosis**** of Corticosteroid plus Immuno-suppressant
Katzenstein	1994	64	26/38	46	D80, C33, F22	8.1	G1:31, G2:24, G3:9	33	Cp6, A2	6Di,
Park	1995	7	1/6	55	D100, C43	4	G1:1, G2:4, G3:2	7	0	None
Park	1996									
Kim	1998	23	1/22	55	D/S83	8	G1:5, G2:13, G3:5	21	0	None
Bjoraker	1998	14	8/6	57	D100, C85	15	G: not classifiable	14	0	None
Nagai	1998	31	15/16	57	R100, F33	2	G1:2, G2:14, G3:15	31	8 (Cp or A)	2Di, 1PD, 5PR
Cottin	1998	12	6/6	53	D100, C67, G58, B42	44	G1:3, G2:8, G3:1	6	A4, A+Cp1, A+M1, Cp1	2PD, 5PR
Fujita	1999	24	7/17	60	C83, D71, F29	31	G2:24	7	Cp3	1PD, 2PR
Daniil	1999	15	7/8	43	D100, C60	8	G: not classifiable	15	A8, Cp2, Cs1	2Di, 3PD, 6PR
Present report	2002	1	0/1	48	F, C, D	0.5	G2	1	1	CR

D: Dyspnea, C: Cough, F: Fever, S: Sputum, R: Respiratory symptom, G: General fatigue, B: Body weight loss. **G1: Groupe I, G2: Groupe II, G3: Groupe III. *** Number of cases in whom immunosuppressive agents as well as corticosteroids were used. Cp: Cyclophosphamide, A: Azathioprine, M: Methotrexate, Cs: cyclosporin. **** Di: Died, PD: Progressive disease, PR: Partial response, CR: Complete remission.

cyclophosphamide to corticosteroids. Although several immunosuppressants were used in patients with NSIP associated with collagen vascular disorders, this is the first report which describes the clinical course of an idiopathic NSIP patient in whom cyclophosphamide adding to corticosteroids was very effective.

NSIP was first described by Katzenstein and Fiorelli in 1994 (1). In the initial description of this pattern of interstitial pneumonia, NSIP was proposed as a diagnosis in specimens with findings that did not conform to the typical findings seen in usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), AIP, or BOOP (1). In addition, it has been reported that NSIP is associated with collagen vascular disorders (1).

We reviewed the clinical features of NSIP described in several reports (Table 1). There have been many reports of patients with NSIP in whom corticosteroids or other immunosuppressants were used (1–10). Although several immunosuppressants (such as, cyclophosphamide or azathioprine), were used for patients with NSIP in whom initial response to corticosteroids was not sufficient, the usefulness of these immunosuppressants for NSIP has not been established (1, 5–9). Ogasawara et al have reported successful treatment with low-dose cyclosporin A (1 mg/kg/day) in a patient with interstitial pneumonitis associated with Sjögren's syndrome who was resistant to corticosteroids (11). In addition, in NSIP associated with collagen vascular diseases, cyclophosphamide is frequently used. However, there has been no report that describes a case of idiopathic NSIP in whom interstitial infiltrates were resolved by adding cyclophosphamide to corticosteroids. The present case, however, demonstrates that cyclophosphamide added to corticosteroid therapy might be a useful treatment for

patients NSIP. Further studies are necessary to evaluate the role of cyclophosphamide in the treatment of NSIP.

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