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【 ORIGINAL ARTICLE 】

Association of Immune Thrombocytopenia and Interstitial Pneumonia

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Abstract:

Objective Chest physicians often encounter patients with interstitial pneumonia with autoimmune features. However, there have so far been few reports of patients presenting with concurrent immune thrombocytopenia (ITP) and interstitial pneumonia. The prevalence of interstitial pneumonia in patients with ITP is less well known.

Methods We surveyed patients diagnosed with ITP and interstitial pneumonia at the departments of Hematology and Respiratory Medicine to evaluate the association between these diseases.

Results Among 73 patients with ITP, 7 patients (9.6%) presented with interstitial pneumonia, including 4 patients (2%) who developed ITP in the course of 204 patients with interstitial pneumonia. All 7 patients were men. Four patients were positive for some autoantibodies. Two patients had autoimmune diseases other than ITP. There were significant differences in age and gender between the ITP patients with and without interstitial pneumonia.

Conclusion The present study suggests the possibility that the development of ITP, other autoimmune diseases, and interstitial pneumonia may be mutually associated. Advanced age and male sex in ITP may be significant predisposing factors for interstitial pneumonia. Clinicians should be aware of the potential for the coexistence of these diseases.

Key words: immune thrombocytopenia, interstitial pneumonia, autoimmune diseases

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Introduction

Immune thrombocytopenia (ITP), which is also called idiopathic thrombocytopenic purpura, is defined as an isolated low platelet count with normal bone marrow and the absence of other causes of thrombocytopenia (1). We chest physicians often encounter cases of interstitial pneumonia with autoimmune features (2), in which features of autoimmune diseases are observed, but in which none of the findings are diagnostic for a specific autoimmune disease. However, there have so far been few reports of cases involving the concurrent presence of ITP and interstitial pneumonia/pulmonary fibrosis (3-6). The prevalence of ITP in patients with interstitial pneumonia or that of interstitial pneumonia occurring in patients with ITP is less well known.

In the present study, we surveyed patients who were diagnosed with ITP and interstitial pneumonia at the departments of Hematology and Respiratory Medicine in order to evaluate the association between these diseases. In addition, we herein present four cases involving patients who developed ITP in the course of chronic interstitial pneumonia.

Materials and Methods

This was a single-center retrospective study. The study population included 73 consecutive patients with ITP who were admitted to the Department of Hematology and 204 consecutive patients with interstitial pneumonia who were admitted to our department (Respiratory Medicine) at Fukuoka University Hospital from April 2015 to January 2018. The patients' medical records were independently re-

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Table 1. The Demographic and Laboratory Findings of ITP Patients with and without Interstitial Pneumonia.

Variable	Total	ITP without IP	ITP with IP	p value
Patients	73	66	7	
Age, years	66.5 (18-88)	64 (18-88)	72.5 (69-77)	0.038
Gender, male/female	35/38	28/38	7/0	0.004
Serum PA-IgG (ng/10^7c)	153 (39-6,360)	134 (39-6,360)	581.5 (133-2,870)	0.056
Positive for other autoimmune antibodies	8 (11)	6 (9)	2 (29)	0.122

Values are reported as the group median (range) or number (%).

ITP: immune thrombocytopenia, IP: interstitial pneumonia, PA-IgG: platelet-associated IgG

Table 2. Presented Cases of Interstitial Pneumonia in Patients Who Developed ITP during the Course of Chronic Interstitial Pneumonia.

	Age/ Gender	Platelet count (/μL)	Complication	Autoantibodies	Previous therapy	Therapy for ITP	Outcome of interstitial pneumonia	Outcome of ITP
Case 1	77/M	18,000	MPA, alveolar hemorrhage	MPO-ANCA, RF, ANA	none	PSL	slowly progressive	improvement
Case 2	77/M	6,000	alveolar hemorrhage	PR3-ANCA, RF, ANA	none	PSL, γ globulin	slowly progressive	improvement
Case 3	69/M	15,000	none	none	none	none	stable	natural improvement
Case 4	75/M	2,000	none	none	temporary steroid therapy for GBS	PSL	progressive	improvement
Case 5	71/M	3,000	none	none	none	PSL	slowly progressive	improvement
Case 6	81/M	1,000	alveolar hemorrhage	none	none	PSL	stable	improvement
Case 7	77/M	50,000	none	none	none	PSL	stable	stable

M: male, ITP: immune thrombocytopenia, PSL: prednisolone, MPA: microscopic polyangiitis, RF: rheumatoid factor, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, ANA: antinuclear antibody, GBS: Guillain-Barré syndrome

viewed by 2 clinicians (H.K. and H.I.) with 16 and 24 years of experience as chest physicians, respectively. The presence of interstitial pneumonia was confirmed based on the chest computed tomography (CT) findings, fine crackles on auscultation, and an elevated serum level of Krebs von den Lungen-6 (KL-6). A diagnosis of ITP was confirmed by hematologists based on the diagnostic criteria for ITP (1).

The chi-squared test was used to compare categorical variables and the Mann-Whitney U test was used to compare continuous variables between ITP patients with and without interstitial pneumonia. p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SPSS Statistics 22 for Windows software program (IBM, Chicago, USA).

Results

Among the 73 patients who were diagnosed with ITP at the Department of Hematology, 7 (9.6%) who simultaneously presented with interstitial pneumonia, including 4 patients (2%) who developed ITP in the course of chronic interstitial pneumonia (n=204) at the Department of Respiratory Medicine. All 7 patients were Japanese men and 6 patients were positive for serum platelet-associated IgG (PA-IgG), including one patient with microscopic polyangiitis (MPA) and one patient with a history of Guillain-Barré syndrome. Some patients were positive for serum PR3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) or centromere antibody, but they did not meet the specific diagnostic criteria for connective tissue diseases. As shown in Table 1, there were significant age and sex differences between the ITP patients with and without interstitial pneumonia. Although the ITP patients with interstitial pneumonia tended to show higher serum PA-IgG values in comparison to those without interstitial pneumonia, the difference was not statistically significant.

Table 2 summarizes the data of the 7 patients who were diagnosed as ITP with interstitial pneumonia, including their age, sex, complications, and other autoantibodies, previous therapies for comorbidities, and the outcomes of interstitial pneumonia and ITP. We herein present 4 patients who developed ITP in the course of chronic interstitial pneumonia at the Department of Respiratory Medicine.

Case 1

The patient, a 77-year-old male non-smoker was admitted to our hospital because of a mild dry cough, elevated serum levels of KL-6 (749 U/mL; normal range <500 U/mL) and

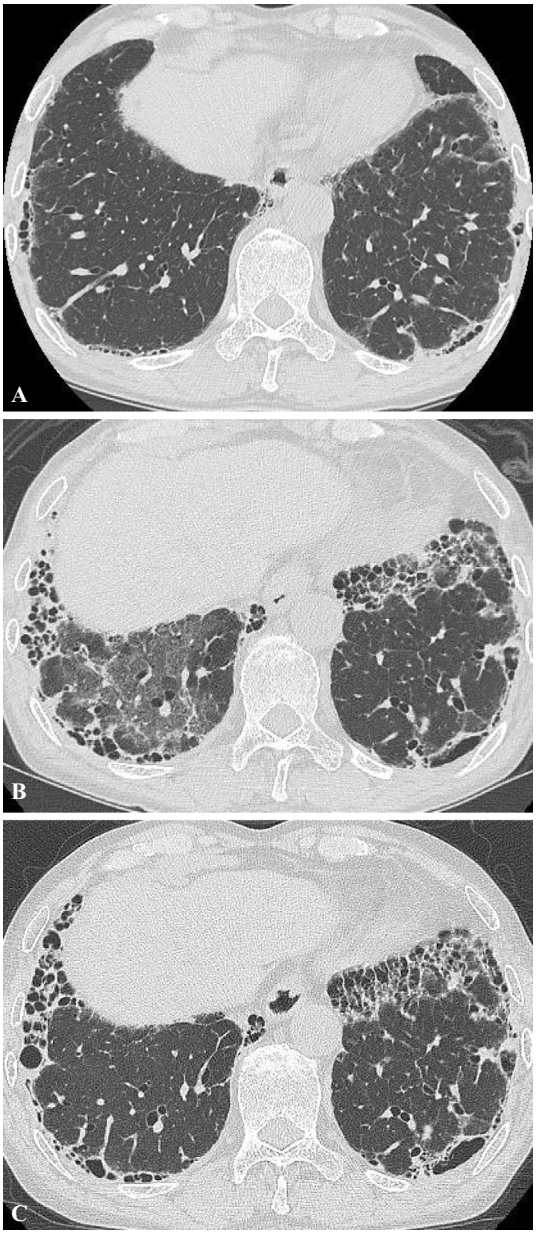

Figure. Representative chest computed tomographic scans (case 2), showing subpleural fibrotic change of the lower lobes bilaterally in June 201X (A), additional ground-glass attenuation at the diagnosis of ITP with alveolar hemorrhage in September 201X+2 (B), and a progression of the fibrotic changes in January 201X+3 (C).

reticular changes in both lower lung lobes on chest CT. The patient showed positive findings for serum myeloperoxidase-ANCA (25.7 U/mL), rheumatoid factor (159 IU/mL) and antinuclear antibody (ANA; ×80), although he did not meet the diagnostic criteria for either MPA or rheumatoid arthritis at that time. After 5 months of observation without treatment, the patient developed an alveolar hemorrhage with thrombocytopenia. The peripheral platelet count was 18,000/μL. He was diagnosed with both ITP and MPA. The alveolar hemorrhage and thrombocytopenia were successfully treated with oral corticosteroids, but his pulmonary fibrosis was found to be slowly progressive.

Case 2

The patient, a 77-year-old male current smoker (smoking history: 30 pack-years), had been observed for chronic interstitial pneumonia (Figure A) without treatment for 2 years. He was admitted because of hemosputum and purpura and very low level of platelet (6,000/μL). A serum analysis revealed the following findings: PR3-ANCA, 26 U/mL; rheumatoid factor, 225 IU/mL; and antinuclear antibody, ×80. However, the patient did not meet the diagnostic criteria for granulomatosis with polyangiitis or rheumatoid arthritis and was instead diagnosed with ITP with alveolar hemorrhage (Figure B). He was subsequently treated with platelet transfusion, steroid pulse therapy and intravenous gamma globulin. However, the patient's reticular changes in both lungs slowly deteriorated (Figure C).

Case 3

The patient, a 69-year-old male ex-smoker (smoking history: 40 pack-years), had been observed for pulmonary fibrosis without treatment for 2 years. He was admitted for a general check-up and thrombocytopenia was incidentally detected. The platelet count was 15,000/μL. There was no deterioration on chest images. The patient's thrombocytopenia naturally improved thereafter.

Case 4

The patient, a 75-year-old male ex-smoker (smoking history: 50 pack-years), had been observed for histopathologically-diagnosed idiopathic pulmonary fibrosis without treatment since 2010. The patient developed Guillain-Barré syndrome with facial nerve palsy and was successfully treated with corticosteroids in 2016. After 5 months of observation without treatment, he showed purpura with thrombocytopenia. His platelet count was 2,000/μL. Although the patient had been diagnosed with ITP and steroid therapy was thus initiated, his pulmonary fibrosis temporarily became exacerbated during the tapering of the steroid dosage.

Discussion

Interstitial pneumonia associated with ITP is very rare. In the present study, the incidence of ITP in patients with chronic interstitial pneumonia was 2%. This percentage is a higher value in comparison to the estimated number of ITP patients in Japan (approximately 20,000) (7). On the other hand, the incidence of interstitial pneumonia in patients with ITP was 9.6%, which is higher than the prevalence rate of idiopathic interstitial pneumonias in Japan (10 patients per 100,000 population) (8). However, this was a single-center retrospective study, the study population was small, and there are only a small number of reports of cases involving concurrent ITP and interstitial pneumonia (3-6). Thus, further prospective comparative studies targeting a larger cohort are required to accurately estimate the prevalence.

ITP can be classified as primary (occurring on its own) or secondary (occurring alongside another condition). Autoimmune diseases, chronic infections, medications, pregnancy, and certain cancers are common secondary triggers (1). Fontana et al. (3) reported the cases of 3 patients who developed interstitial pneumonia during the course of ITP and suggested that platelet destruction may have triggered inflammation in the lung, leading to interstitial pneumonia. Platelets are known to release cytokines, recruit white blood cells, activate complement and promote inflammation and immune-mediated disorders (9). However, thus far no studies have proven a direct association between platelets and the development of interstitial pneumonia/pulmonary fibrosis.

In the present study, we investigated ITP patients with chronic interstitial pneumonia. Some cases were positive for autoantibodies other than PA-IgG, and 2 cases had autoimmune disease (MPA and Guillain-Barré syndrome). This suggests that-assuming ITP is associated with interstitial pneumonia/pulmonary fibrosis-autoimmune mechanisms rather than platelets themselves may be closely related to the lung lesions.

The present study suggests the possibility that the development of ITP, autoimmune disease, and interstitial pneumonia is mutually associated. However, this remains a matter of speculation.

The main chest CT finding in the presented cases of ITP with interstitial pneumonia was a chronic fibrosing pattern (subpleural reticular changes in both lower lobes); however, this was not exactly a characteristic finding in ITP patients with interstitial pneumonia because the study population was very small.

In the present study, there were significant age and sex differences between the ITP patients with and without interstitial pneumonia. This indicates that advanced age and a male sex may be risk factors that predispose ITP patients to interstitial pneumonia. Unlike a previous report (3), all of our 7 patients were diagnosed with interstitial pneumonia prior to the onset of ITP. Two of the 7 patients were associated with alveolar hemorrhaging, but thrombocytopenia itself rarely causes alveolar hemorrhaging. Therefore, elderly male patients with ITP, who develop alveolar hemorrhaging, might simultaneously have interstitial pneumonia. Clinicians should be aware of the potential coexistence of these diseases However, further studies are needed, and more cases should be collected to elucidate the relationship between ITP and interstitial pneumonia and the pathogenesis.

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

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