Adult-onset Still's disease-associated interstitial lung disease represents severe phenotype of the disease with higher rate of haemophagocytic syndrome and relapse

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ABSTRACT

Objective. *Adult-onset Still's disease (AOSD) is an inflammatory disorder characterised by sustained fevers, arthritis, and skin involvement. Interstitial lung disease (ILD) is a rare manifestation, and its clinical characteristics have yet to be determined.*

Methods. *We sought to examine the clinical characteristics of AOSD-associated ILD. We retrospectively investigated 78 patients diagnosed as AOSD. ILD was diagnosed based on chest high-resolution computed tomography (HRCT). Clinical characteristics were compared between patients with and without ILD. Relapse was defined as sustained fevers, re-emergence of arthritis, and skin involvement after remission. We further investigated the pathological features of ILD on available samples.*

Results. *Patients with ILD, found in 9 of 78 (11.5 %), had older age of onset (mean age 62.6) than those without ILD (mean age 38.8) ($p<0.01$). The 3-year survival rates were comparable between patients with ILD (92.5%) and those without ILD (88.9%) ($p=0.23$). Patients with ILD had a higher cumulative rate of haemophagocytic syndrome (HPS) and relapse than those without ($p<0.0001$ and $p=0.009$, respectively). Chest HRCT showed marked thickening of the interlobular septa, the bronchovascular bundles, or the visceral pleura in all cases. There was no honeycomb or volume loss. Pulmonary pathological findings revealed marked thickening of the visceral pleura and the interlobular septa.*

Conclusion. *Patients with ILD might have higher risks for HPS and relapse. Careful observation and appropriate therapeutic intervention might be needed.*

Introduction

Adult-onset Still's disease (AOSD) is an inflammatory disorder initially characterised by sustained fevers, arthritis, and skin involvement (1), of which diagnosis (2) and treatment (3-6) are still challenging. Among other clinical manifestations, interstitial lung disease (ILD) has been rarely reported, seen in 2–6% of cases in retrospective series (7, 8). While Bujak *et al*. first reported two cases of AOSD involved pulmonary infiltrative shadow in 1973 (9), few other reports describe AOSD-associated ILD and its histological analysis in detail (10, 11).

AOSD patients with haemophagocytic syndrome (HPS) tend to have a poorer prognosis (12), and 39.1% of patients experience relapse (7). Since intensive immunosuppressive therapy may be required in most cases with HPS and relapse, careful management is needed in clinical settings. Although these factors are known to result in a poor outcome, prognostic factors predicting HPS and relapse have not been found.

We here investigated characteristics in patients with ILD compared with those without. Further, we studied the association of already known risk factors such as HPS and relapse with patients with ILD.

Patients and methods

Patients

This was a retrospective analysis performed on 78 patients of AOSD that underwent chest high-resolution computed tomography (HRCT) at our hospitals, diagnosed between August 2008 and March 2013. The diagnosis of AOSD was confirmed on the basis of Yamaguchi or Fautrel classification criteria for AOSD (13, 14). Exclusion criteria were infection, tumours, and other

connective tissue diseases. All the patients were examined by chest HRCT and abdominal CT for screening. The diagnosis of ILD was based on HRCT findings. This study was approved by the ethics committee of our hospitals (approval number 2145, 11-14).

Data collection

Patient clinical data before initial treatment, including age, gender, smoking history, clinical manifestations, findings on chest HRCT, and results of pulmonary function tests were collected. The collected data in patients with ILD and those without ILD were compared. Remission was defined as the absence of articular, systemic, and laboratory evidence of disease activity for at least 2 consecutive months (15). Relapse was defined by recurrent systemic or articular flares after achieving remission and requiring therapy (15). The diagnostic criteria of a 2004 haemophagocytic lymphohistiocytosis trial (16) were employed, its diagnosis being made when 5 of 8 of the following findings were satisfied: fever >38.5°C, splenomegaly, peripheral blood cytopenia, hypertriglyceridaemia or hypofibrinogenaemia, haemophagocytosis, low or absent NK cell activity, ferritin >500 ng/mL and elevated soluble IL-2 receptor. Liver dysfunction was defined as >2 × the upper normal limit of AST/ALT. We further investigated the pathological features of ILD on available tissue samples.

Statistical analysis

Quantitative variables are presented as the mean ± standard deviation (SD). Quantitative data were analysed using the Mann-Whitney U-test. The chi-squared test was used to compare category data. The cumulative HPS rate and relapse rate were calculated using the Kaplan-Meier method, and differences between the two groups were tested using a log-rank test. $p<0.05$ was considered statistically significant.

Results

Clinical characteristics in AOSD patients with and without ILD

ILD was found in 9 of 78 patients (11.5%). The clinical characteristics of 9 patients with ILD were compared with those in 69 patients without ILD (Table I). Older age ($p=0.00007$), higher CRP ($p=0.0002$) and/or serum ferritin ($p=0.03$), initial prednisolone (PSL) dose ($p=0.03$), rate of calcineurin inhibitor ($p=0.003$) and/or tocilizumab use ($p=0.005$), higher incidence of HPS ($p=0.0004$), and higher relapse rate ($p=0.009$) were seen in patients with ILD than those without ILD. Relapses of HPS were not seen in our AOSD patients during the follow up. The ground-glass opacities were found in 50% of the ILD patients at the initial presentation and disappeared after the treatment. One patient died because of ILD exacerbation in ILD groups, and two died of pneumocystis pneumonia and myocarditis in non-ILD ($p=0.31$).

Table I. Comparison between patients with ILD and those without ILD.

Characteristics	ASD with ILD (n=9)	ASD without ILD (n=69)	*p*
Female, n (%)	7 (77.8)	52 (75.4)	0.62
Age (years old)	62.6 ± 11.9	38.8 ± 18.1	<0.01
Initial clinical manifestation			
Fever, n (%)	9 (100.0)	69 (100.0)	1.0
Rash, n (%)	9 (100.0)	66 (95.7)	0.73
Arthritis, n (%)	8 (88.9)	66 (95.7)	0.38
Splenomegaly, n (%)	4 (44.4)	42 (60.9)	0.32
Liver dysfunction, n (%)	7 (77.8)	49 (71.0)	0.51
Serositis, n (%)	2 (22.2)	5 (7.2)	0.18
Dyspnea, n (%)	5 (55.6)	5 (7.2)	<0.01
Initial laboratory findings			
ESR (mm/h)	81.8 ± 38.7	72.3 ± 41.4	0.27
Leukocytes ($\times10^4/\mu L$)	1.7 ± 0.8	1.4 ± 0.8	0.16
LDH (IU/L)	901.7 ± 811.5	820.7 ± 1383.7	0.41
CRP (mg/dL)	16.5 ± 3.0	10.5 ± 7.1	<0.01
KL-6 (U/mL)	2549.4 ± 2263.2	-	-
Ferritin ($\times10^4$ ng/mL)	5.2 ± 5.6	1.1 ± 1.1	0.03
sIL-2R (U/mL)	1787.6 ± 1077.9	1612.7 ± 1021.2	0.35
Treatment			
PSL (mg/day)	50.6 ± 9.5	41.6 ± 25.3	0.03
MTX, n (%)	4 (44.4)	32 (46.4)	0.91
CNI, n (%)	7 (77.8)	19 (27.5)	<0.01
Infliximab, n (%)	2 (22.2)	3 (4.3)	0.10
Etanercept, n (%)	1 (11.1)	3 (4.3)	0.40
Tocilizumab, n (%)	3 (33.3)	5 (7.2)	0.05
Periods to ILD onset (months)*	7.4 ± 6.7	-	-
Periods to HPS onset (months)#	8.2 ± 13.7	1.8 ± 0.5	0.30
HPS, n (%)	6 (66.7)	6 (8.7)	<0.01
Cumulative relapse rate, n (%)	5 (62.5)	13 (20.3)	<0.01
Survival rate, n (%)	8 (88.9)	67 (97.1)	0.31

Data are expressed as either n (%) or value ± SD.
ESR: erythrocyte sedimentation rate; sIL-2R: soluble interleukin-2 receptor; PSL: prednisolone; MTX: methotrexate; CNI: calcineurin inhibitor (cyclosporine or tacrolimus); HPS: haemophagocytic syndrome.
*Periods from diagnosis of AOSD to ILD onset.
#Periods from diagnosis of AOSD to HPS onset.

Radiological, pathological, and pulmonary functional findings of ILD

The chest HRCT showed marked thickening of the interlobular septa, the bronchovascular bundles, and the pleura in all patients with ILD. Representative chest HRCT findings are shown in Figure 1 A-D. These findings involved both lungs homogeneously in all patients, except for one limited to lower lobe predominance. There was no honeycomb. Pulmonary function tests revealed no reduction of forced vital capacity in five measurable patients. Pathological findings in ILD showed marked thickening of the visceral pleura and of the interlobular septa in a deceased patient because of acute interstitial pneumonia (Fig. 1 E-F).

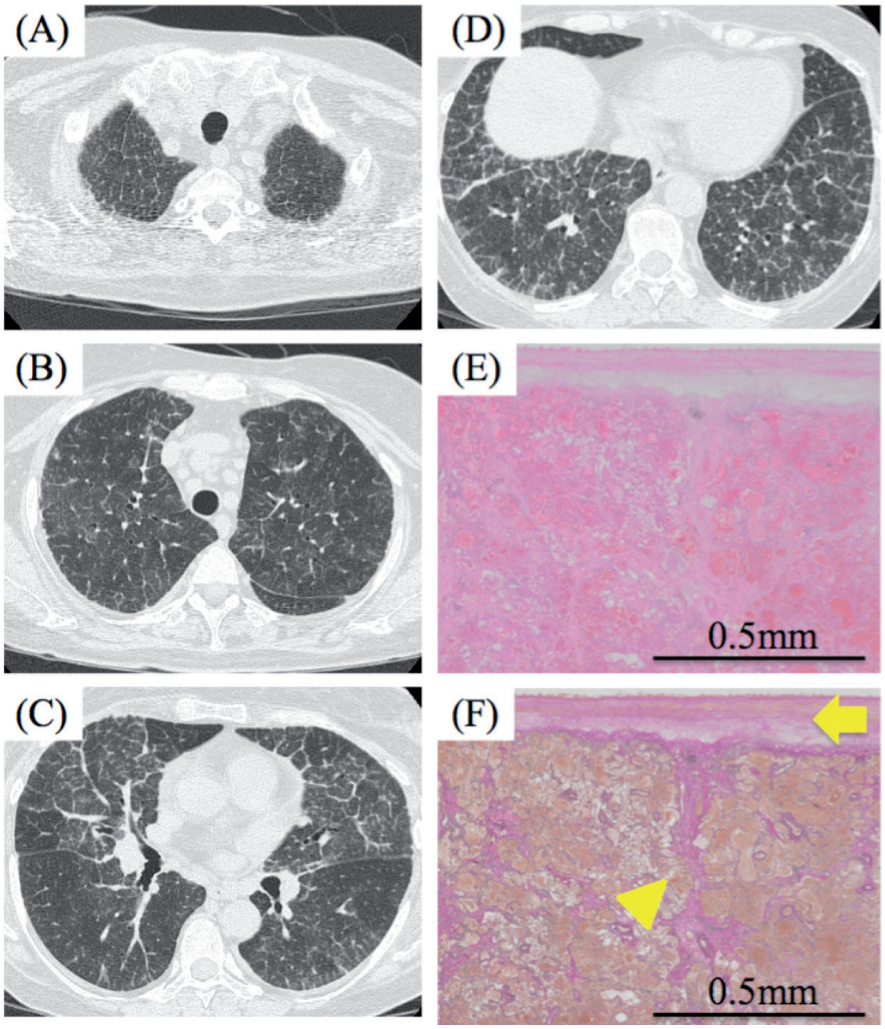

Fig. 1. Representative images of chest high-resolution computed tomography and pathological features of the lung in adult-onset Still disease with associated interstitial lung disease.
(**A** to **D**). A typical chest high-resolution computed tomography shows that the interlobular septa, the bronchovascular bundles, and the pleura are markedly thickened in all cases similarly. There is no honeycomb.
(**E**-**F**). A lung biopsy specimen reveals marked thickening of the interlobular septa (arrowhead) and the visceral pleura (arrow) by (**E**) haematoxylin and eosin stain and (**F**) Elastica van Gieson stain.

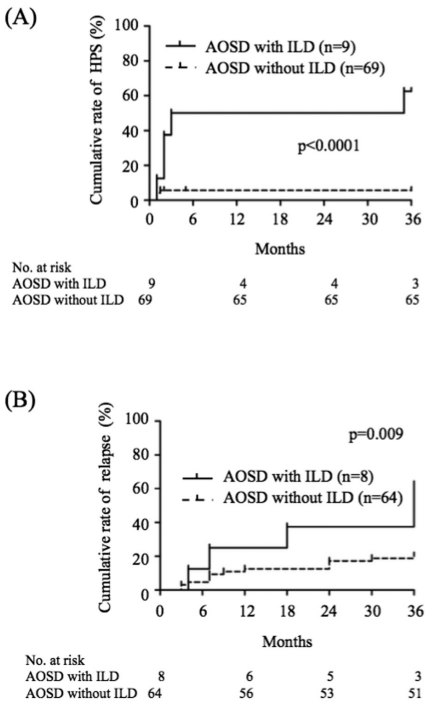

Fig. 2. Cumulative rate of hemophagocytic syndrome (HPS) and relapse.
We evaluated the cumulative rate of HPS (**A**), and relapse rate (**B**) for 3 years after induction therapy between patients with interstitial lung disease and those without.
AOSD: adult-onset Still's disease.

Cumulative rate of HPS and relapse

We next examined the incidence of HPS and relapse for 3 years since diagnosis of AOSD (Fig. 2). A significantly higher cumulative rate of HPS and relapse were observed in patients with ILD compared with those without ILD (p<0.0001 and p=0.009, respectively) (Fig. 2 A-B).

Multivariate analysis for risk factors of HPS and relapse in patients with AOSD

We conducted multivariate analysis for the risk factors associated with HPS and relapse in patients with AOSD (Tables II, III). We selected initial characteristics that were significantly different at baseline as covariates and found that ILD was independently associated with HPS and relapse (HPS: odds ratio [OR] 32.50, 95% confidence interval [CI] 6.40–212.00, p<0.0001, relapse: OR 5.22, 95% CI 1.10–37.65, p=0.04).

Discussion

Our results suggest that AOSD patients with ILD represent severe phenotype of the disease with higher CRP and higher serum levels of ferritin as well as higher rate of HPS and relapse.

Previous reports showed that patients with AOSD and ILD may be rare but life-threatening complication. Asanuma and Ohta *et al*. reported the prevalence of ILD in AOSD was 2-6% (7, 8). Gerfaud-Valentin *et al*. reported that among 30 patients (their own institution 3, literature 27) with AOSD-ILD, 12 developed ARDS, and 2 of 12 (16.7%) died because of exacerbation of ARDS (10). Although they investigated the clinical features of patients with ILD, the association between clinical, pathological, and radiological features of the lung, and the progression of AOSD, were not elucidated. To the best of our knowledge, this is an analysis of the largest number of patients with AOSD having ILD showing the association with clinical outcome.

The pathogenesis of ILD has not been clearly identified in AOSD. It is well known that hypercytokinaemia with activation of inflammatory cytokines such as IL-6 plays a crucial role in the pathogenesis of AOSD. As previously described, hypercytokinaemia is also associated with multicentric Castleman disease (MCD) and 50–64% patients with MCD are complicated by ILD (17-19). Hence, its pathophysiology of ILD might be comparable to that in AOSD patients. In MCD-ILD, thickening of

Table II. Multivariate analysis for risk factors of HPS in patients with ASD.

Parameters	Odds ratio	95% confidence interval	*p*
Age (years old)	1.01	0.98-1.05	0.51
ILD	32.50	6.40-212.00	<0.01
CRP (mg/dL)	1.09	0.99-1.22	0.09
Ferritin (ng/mL)	1.00	0.99-1.00	0.28
PSL (mg/day)	1.00	0.98-1.02	0.64

HPS: haemophagocytic syndrome; ILD: interstitial lung disease; PSL: prednisolone.

Table III. Multivariate analysis for risk factors of relapse in patients with ASD.

Parameters	Odds ratio	95% confidence interval	*p*
Age (years old)	1.01	0.98-1.03	0.79
ILD	5.22	1.10-37.65	0.04
CRP (mg/dL)	1.01	0.98-1.17	0.12
Ferritin (ng/mL)	1.00	0.99-1.01	0.13
PSL (mg/day)	0.99	0.98-1.01	0.38

ILD: interstitial lung disease; PSL: prednisolone.

the bronchovascular bundle and the interlobular septa was observed in 83% of chest HRCT scans (20). Pathologically, inflammatory cell infiltration consisted mainly of plasma cells surrounding the bronchovascular bundles and the interlobular septa (21). Since these findings were similar to those seen in our patients, hypercytokinaemia may also play a role in initiating ILD in AOSD. The association between ILD and HPS manifestation in AOSD supports this point of view. ILD involvement might be a useful risk factor for HPS or relapse induced by hypercytokinaemia.

Macrophage activation syndrome (MAS)/HPS is common manifestation in systemic juvenile idiopathic arthritis (JIA). Since MAS in patients with systemic JIA can develop multiorgan failure and a fatal outcome, early diagnosis and appropriate treatment such as canakinumab and tocilizumab have been required and classification criteria for MAS was newly developed (22). Same as JIA population, patients with AOSD who developed to MAS also tend to have worse prognosis but its predictor has been poorly developed. In our study, AOSD patients with ILD developed MAS/HPS more frequently than those without. Our findings may help identifying patients who could be potentially at risk for MAS/HPS.

In this study, the survival rate over 3 years was not significantly different between the two groups (AOSD with ILD: 89.9%, AOSD without ILD: 95.7%, p=0.23). A similar survival rate has been reported (93.4%) in patients with AOSD having ILD (10). Comparing with AOSD-associated ILD, 3 years survival in connective tissue disease-associated ILD has been reported as 67% (23). A better outcome in AOSD with ILD may be explained by the lack of honeycomb and the preservation of lung capacity. Longitudinal study with extended patients population may be required to determine the survival in patients with ILD.

This study was a small single-centre, retrospective design, and only a Japanese population was assessed. It might be difficult to conclude that ILD is independently associated with HPS and relapse because it could be a result of a severe disease course with hypercitokinaemia and the sampling bias which were older patients, more serious disease and more aggressive therapy. These factors could influence the results in the rate of relapses and the development of HPS. Furthermore, as patients were selected retrospectively, selection bias was present as follows: induction and maintenance therapy were decided by the attending physicians and only the patients who could be observed for 3 years were selected. A multi-centre, prospective study is required to confirm our findings.

AOSD patients with ILD may represent severe phenotype of the disease. Careful assessment and appropriate therapeutic intervention is needed in this population, who have potential risk for HPS or relapse.

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