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Case report

# Clinical features of three cases with pulmonary alveolar proteinosis secondary to myelodysplastic syndrome developed during the course of Behçet's disease

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ABSTRACT

We have previously reported that myelodysplastic syndrome (MDS) is the most common underlying disease in cases of secondary pulmonary alveolar proteinosis (PAP). Here, we present 3 MDS cases in which PAP developed during the course of Behçet's disease (BD). All patients carried trisomy 8 in the bone marrow. Chest HRCT scans showed variable distribution of ground glass opacities, but none of the scans showed so called "crazy paving appearance". Two patients with intestinal BD who underwent potent immunosuppressive therapy died of sepsis. These findings demonstrate that PAP secondary to MDS may be occasionally associated with BD.



Abbreviations: BAL, bronchoalveolar lavage; BD, Behçet's disease; GGO, ground glass opacity; HRCT, high-resolution computed tomography; MAC, *Mycobacterium avium complex*; MDS, myelodysplastic syndrome; PAP, pulmonary alveolar proteinosis; RA, refractory anemia; RAEB, RA with excess blasts; SLB, surgical lung biopsy; SPAP, secondary PAP; WLL, whole lung lavage

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## 1. Introduction

Pulmonary alveolar proteinosis (PAP) is a respiratory disease characterized by accumulation of phospholipids and surfactant proteins within the alveolar lumen and terminal bronchioli. PAP is classified into 3 groups on the basis of etiology: autoimmune PAP (APAP), secondary PAP (SPAP), and unclassified PAP. We previously reported that hematological disorders such as myelodysplastic syndrome (MDS) are the main underlying conditions in SPAP, and are observed in more than 70% of the cases of PAP [1]. However, the precise mechanism underlying the pathogenesis of this condition remains unclear.

Behçet's disease (BD) is a chronic, relapsing, inflammatory disease of unknown etiology that presents with oral aphthae, genital ulcers, uveitis, and skin lesions. Intestinal involvement is seen in 3–26% of cases, with a higher frequency in Asian than European countries. The disease is frequently intractable and may present with severe complications such as hemorrhage, perforation, and infection [2].

In a large cohort study of BD, which included 661 cases, PAP was not reported as a complication [3]. However, 2 BD cases with concomitant PAP have been reported in other studies [4,5]. When we studied the incidence of BD in the 40 Japanese cases of SPAP recorded in our database, we found 5 cases, including the 2 mentioned above. In this report, we present the clinical, radiological, and pathological features of the remaining 3 patients with SPAP and BD, and discuss the characteristic disease features common to all 5 cases, including those previously reported.

SPAP was diagnosed as described previously, with confirmation of the absence of serum GM-CSF autoantibodies [1,6]. BD was diagnosed according to the Behçet Disease Research Committee of Japan criteria [7]. Onset of BD was defined by the emergence of at least 2 symptoms attributable to BD [8]. High-resolution computed tomography (HRCT) images of the chest at the time of diagnosis were evaluated by 2 radiologists (M.A and H.I) as previously reported [6]. Consent was obtained from all identified patients by the treating physicians, and the study was approved by The

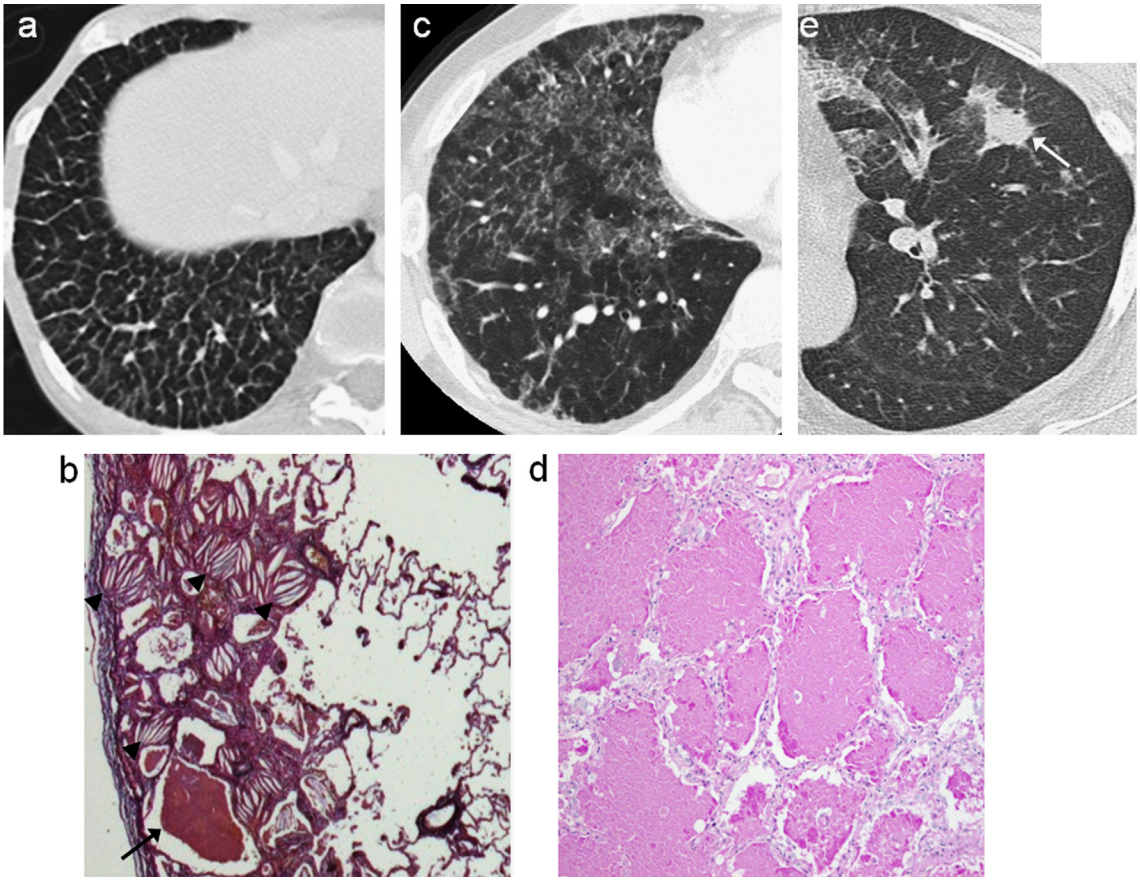


**Fig. 1 – (a) Chest HRCT in Case 1 showed diffuse apparent interlobular septal thickening. (b) Lung histology on surgical lung biopsy (SLB) (left S8) in Case 1. Elastica van Giesson stain (EVG), ×40, of the lung biopsy specimen showed interstitial infiltration of inflammatory cells with many cholesterol clefts in the perilobular areas (arrow heads). Amorphous material was found in the alveolar lumen (arrow), although it was not a predominant finding. (c) Chest HRCT in Case 2 showed predominant bilateral diffuse GGO in the upper and middle lobes. (d) Autopsy findings of the lung (PAS stain, ×100) in Case 2 showed diffuse alveolar septal thickening with mild cellular infiltration and with PAS-positive granular material within the alveolar spaces. (e). Chest HRCT in Case 3. Initial HRCT showed bilateral diffuse GGO, and multiple dense opacities developed later (arrow). The dense opacity had resolved with MAC treatment.**

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## 2. Case presentation

Case 1 involved a female patient who developed oral and genital ulcers and papulopustular skin lesions at 32 years of age. The patient was diagnosed with intestinal BD 5 years later, and with MDS with refractory anemia (RA) and myelofibrosis at 46 years of age. Intestinal BD was diagnosed and prednisolone treatment was started at a dose of 40 mg/day and tapered to 5 mg/day. At 49 years of age, the patient was diagnosed with PAP on the basis of chest HRCT (Fig. 1a) and typical histologic findings in surgical lung biopsy (SLB) (Fig. 1b). Two years later, she was admitted to the hospital due to an exacerbation of intestinal BD and leukemic transformation of MDS. Despite receiving intensive treatment with steroid pulse, cyclosporine A, and infliximab, the intestinal involvement remained refractory without improvement of persistent peritonitis. During treatment, the patient developed pneumonia caused by methicillin-resistant *Staphylococcus aureus* combined with *Mycobacterium avium complex* (MAC). This led to sepsis, with a fatal outcome 6 months after admission. The severity of PAP remained unchanged during the entire disease course.

Case 2 involved a male patient who developed oral ulcers and papulopustular skin lesions at 26 years of age. The patient was diagnosed with intestinal BD the following year, and MDS (RA) 5 years later. BD was refractory to long-term treatment with prednisolone combined with sulfasalazine. Thereafter, azathioprine combined with etanercept was administered for several weeks, but did not yield any improvement. At 33 years of age, the patient was admitted for treatment of intractable intestinal BD, when he was diagnosed with PAP on the basis of the findings of chest HRCT (Fig. 1c) and BAL. Whole lung lavage (WLL) could not be performed due to persistent fever, although no pathogen was detected. The patient died of PAP deterioration and septic shock 2 months after admission. Autopsy findings revealed

**Table 1 – Clinical features of secondary pulmonary alveolar proteinosis complicated with Behçet's disease.**

| | Case 1 | Case 2 | Case 3 | Literature case 1 [4] | Literature case 2 [5] | Control ($n=35$) |
|---|---|---|---|---|---|---|
| *At diagnosis of PAP* | | | | | | |
| Age | 49 | 33 | 50 | 51 | 39 | 53 (24–77) |
| Gender | F | M | F | F | F | M/F 21/14 |
| Smoking history[a] | NS | S | S | S | S | S/NS/NA 19/11/5 |
| Respiratory symptoms | none | cough | DOE | DOE | cough | 16/35 (46%) |
| Diagnostic procedure | SLB | BS | SLB | BS | BS | BS/SLB 27/8 |
| Serum KL-6 (U/mL) | 936 | 1220 | 1050 | 1960 | 4160 | 2040 (358–20210) |
| Serum CEA (ng/mL) | 2.0 | 12.6 | NA | 3.3 | 39.5 | 3.9 (0.5–36.0) |
| *HRCT findings* | | | | | | |
| GGO pattern[b] | Diffuse | Diffuse | Diffuse | Patchy | Mixed | Diffuse 12/17 (71%) |
| 'Crazy-paving' appearance | – | – | – | + | + | 1/17 (6%) |
| Subpleural sparing | – | – | – | + | – | 6/17 (35%) |
| Thickening of interlobular septa | + | – | – | – | + | 4/17 (24%) |
| Pathological findings | SLB | Autopsy | SLB | N/A | N/A | |
| Distribution | Perilobular | Diffuse | Patchy | | | |
| Cholesterol clefts | Remarkable | Rare | Moderate | | | |
| *Behçet's disease* | | | | | | |
| HLA-B51 | – | – | N/A | N/A | N/A | |
| Oral ulcer | + | + | + | + | + | |
| Eye lesion | – | – | + | – | – | |
| Skin lesion | + | + | + | + | + | |
| Genital ulcer | + | – | + | + | + | |
| Intestinal lesion | + | + | – | – | + | |
| MDS | + | + | + | + | – | 22 (63%) |
| WHO classification | RA | RA | RAEB-2 | RAEB-1 | | |
| Trisomy 8 | + | + | + | + | | 5/22 (23%) |
| WPSS | 2 | 1 | 3 | 3 | | |
| Duration of BD prior to the onset of MDS | 14 Years | 5 Years | 6 Months | 14 Years | | |
| Treatment before MDS onset[c] | P, S, C, T | P, S, A, T | Celecoxib | Colchicine | | |

Data are expressed as median (range). The control cohorts are patients with secondary pulmonary alveolar proteinosis but without Behçet's disease. NS, never smoked; DOE, dyspnea on effort; BS, bronchoscopy; SLB, surgical lung biopsy; RA, refractory anemia; RAEB, RA with excess of blasts; WPSS, WHO classification-based Prognostic Scoring System (1, low; 2, intermediate; 3, high-risk group); HRCT, high-resolution computed tomography; GGO, ground glass opacity and N/A, not available.

[a] S, current or former smoker.

[b] Mixed, mixed patchy geographic and diffuse pattern; patchy, patchy geographic pattern.

[c] P, prednisolone; S. sulfasalazine;C, cyclosporine A; T, TNF α inhibitors and A, azathioprine.

invasive aspergillosis in the lung, but there was no evidence of leukemic transformation in the bone marrow.

Case 3 involved a female patient who developed uveitis at 38 years of age, which subsequently resolved without treatment. At the age of 48 years, she developed genital ulcers, skin lesions, and oral ulcers, and was diagnosed with complete BD. Six months later, abnormal shadowing was seen on a chest HRCT scan (Fig. 1e), and pancytopenia developed. The patient was diagnosed with PAP and MAC infection by surgical lung biopsy, and MDS (RA with excess blasts [RAEB] type 2) by bone marrow aspiration. Although lung opacity improved with treatment for MAC, the patient showed deterioration of PAP in the subsequent 2 years and required long-term oxygen therapy. The patient underwent WLL and showed improvement of lung opacity and oxygenation.

## 3. Discussion

In this report, we present 3 patients who developed SPAP during the course of BD and MDS. Their clinical, radiological, and pathological data, as well as those of the 2 cases of SPAP and BD already published in the literature [4,5] and the 35 cases of SPAP without BD in the Japanese SPAP registry [1] are summarized in Table 1. The clinical courses of the 3 patients are shown in Fig. 2. Notably, all 3 patients as well as another patient described in the literature [4] carried trisomy 8 in the bone marrow, and the onset of BD consistently preceded the onset of MDS and SPAP in these patients. HRCT features showed diffuse homogenous patterns in the distribution of ground glass opacity with or without thickening of the interlobular septa, which is characteristic for SPAP [6]. Generally, the clinical, serological, and radiological features of SPAP with BD were similar to those seen in the controls (Table 1). Lung pathology findings were variable with respect to the extent of surfactant accumulation, the amount of cholesterol clefts, and the distribution of lesions. Intestinal BD may be associated with fatal infections due to the use of potent immunosuppressive therapy.

The co-occurrence of BD and MDS has been reported mainly in Japan and Korea [8–16]. These case reports were collected, and the demographic features are summarized in supplementary Table S1. A total of 64 cases of MDS complicated with BD or suspected BD have been reported during the period from 1988 to 2012. The meta-analysis revealed a high frequency of intestinal lesions (66%), trisomy 8 (80%) and a low frequency of ocular lesions (13%). In contrast, a nationwide survey of 3187 BD patients in Japan demonstrated a distinct distribution of intestinal and ocular involvements in 15.5% and 69.1%, respectively [8]. Thus, the disease phenotype of the 5 patients with SPAP and BD (Table 1) is similar to the phenotype of MDS-associated BD described in the literature. This is exemplified by the occurrence of trisomy 8 in the present cases. Since the general frequency of trisomy 8 is only 10–15% in MDS [17], MDS with trisomy 8 is likely to be a risk factor for both BD [9–11] and PAP [4], and they occasionally develop together, as in the 3 cases presented in this report. Immunosuppressive therapy for BD can cause MDS, which may subsequently cause SPAP. However, immunosuppressive drugs had not been administered in both case 3 and the case in the literature [4] until the onset of MDS (Table 1).

Previous large cohort studies have demonstrated a mortality rate of 5–9.8% during a follow up period of 7.7–19 years [18,19]. However, the effect of immunosuppressive treatment or the presence of intestinal lesions on mortality has not been evaluated. Patients with BD complicated with MDS were frequently treated with immunosuppressive drugs (Table S1). Of those, 89% and 94% with and without the intestinal involvements respectively, underwent immunosuppressive

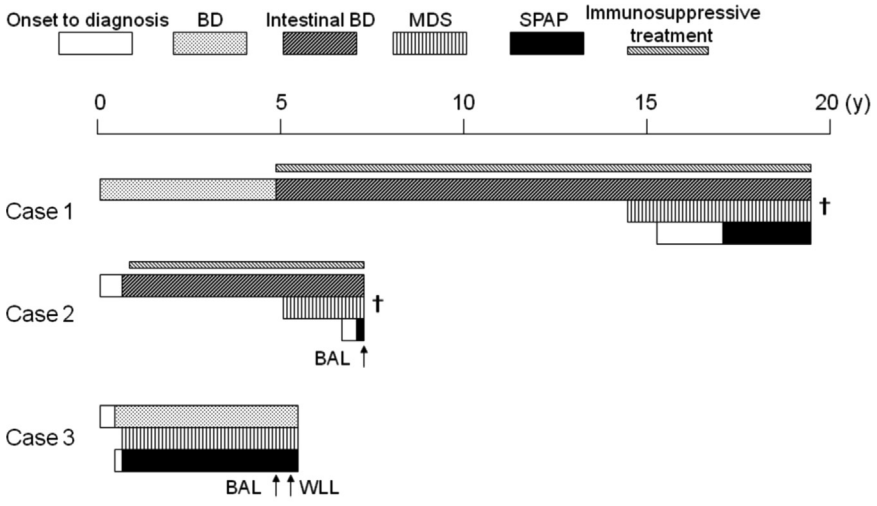


**Fig. 2 – Clinical course and prognosis of the patients. Time course of the 3 diseases (BD, Behcet disease; MDS, myelodysplastic syndrome and SPAP, secondary alveolar proteinosis) are shown. Treatments for BD were as follows: prednisolone (5–50 mg/day), sulfasalazine and TNF-$\alpha$ inhibitors in cases 1 and 2, cyclosporine A in case 1, azathioprine in case 2, celecoxib in case 3. Causes of death were as follows: Case 1: leukemic transformation and sepsis due to MRSA and MAC infection; Case 2: sepsis with unknown pathogen and PAP progression.**

therapy. It is noteworthy that the mortality rate after such therapy was higher in those with intestinal involvement (41%) than those without involvement (21%). In 5 of 12 deceased cases with intestinal lesions, the cause of death was severe infection. Consistently, 2 fatal cases presented here and another previously published case [5] showed intestinal involvement, and therefore required potent immunosuppressive therapy.

In conclusion, SPAP secondary to MDS is a rare complication during the course of BD. The clinical features other than BD-related findings were not distinguished from those seen in SPAP without BD.

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## Conflict of interest

The authors have no conflicts of interest.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2013.05.005.

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