



## Case report

# Recurrent idiopathic pulmonary hemosiderosis after long-term remission presented with Sjogren's syndrome: Idiopathic no more?

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## ABSTRACT

We report a case of recurrent idiopathic pulmonary hemosiderosis after a long-term remission presented with Sjögren's syndrome. The patient was diagnosed with IPH due to repeated pneumonia and blood sputum in his childhood. He was admitted to our hospital due to exertional dyspnea and dry cough with bilateral ground-glass opacity in chest computed tomography at the age of 32. Video-assisted thoracoscopic surgery was performed and the specimens showed nonspecific interstitial pneumonia pattern with diffuse, chronic alveolar hemorrhage, suggesting recurrence of IPH. He was also diagnosed with Sjögren's syndrome. Further immunological studies will reveal the pathogenesis of IPH.

## 1. Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a rare unknown origin disease characterized by diffuse alveolar hemorrhage primarily in children. Recurrent alveolar bleeding may eventually induce pulmonary hemosiderosis and fibrosis. Systemic glucocorticoids are the main therapy, although some patients require additional immunosuppressive agents. The prognosis of IPH is generally poor (more than 60% of IPH patients succumb to the disease with a median survival period of 2.5–5 years [1]), however one paper showed some cases have a longer survival [2]. Herein we report a case of recurrent idiopathic pulmonary hemosiderosis after a long-term remission presented with Sjögren's syndrome.

## 2. Case report

A 32-year-old Japanese male chef was admitted to our hospital due to exertional dyspnea and dry cough that lasted for half a year

accompanied by bilateral ground glass opacity in chest computed tomography (CT). He also had repeated pneumonia since childhood. He was admitted in a pediatric hospital due to blood sputum and anemia at the age of 7, where he was diagnosed with IPH on the basis of hemosiderin-laden phagocytosis in the bronchoalveolar lavage fluid (BALF) without apparent cause of alveolar bleeding. He had been treated with systemic corticosteroid until 18 years of age. He had ceased to go to the hospital afterward because of remission. There was no history of IPH in his family. He was never a smoker, and had no occupational or environmental cause for pulmonary fibrosis and diffuse alveolar hemorrhage.

Physical examination showed following: SpO<sub>2</sub>, 94% (room air, rest); body temperature, 36.0 °C; heart rate, 70/min; blood pressure, 120/60 mmHg; and bilateral crackles. Arterial blood gas levels were as follows: pH 7.39, PO<sub>2</sub> 63.1 Torr, PCO<sub>2</sub> 39.5 Torr, HCO<sub>3</sub> 23.6 mmol/l. Laboratory examinations demonstrated moderate leukocytosis (10,040 cells/mm<sup>3</sup>), elevated C-reactive protein (3.06 mg/dL), markedly elevated Serum Krebs von den Lungen-6 (KL-6) levels

**Abbreviations:** IPH, Idiopathic pulmonary hemosiderosis; CT, computed tomography; BALF, bronchoalveolar lavage fluid; KL-6, Krebs von den Lungen-6; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; <sup>18</sup>F-FDG PET, Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose; VATS, video-assisted thoracic surgery; NSIP, non-specific interstitial pneumonitis

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**Table 1**  
Laboratory findings on the admission.

Hematology		Blood chemistry		Serological test		Cardiolipin Ab	
WBC	10400/ $\mu$ l	TP	8.1 g/dl	CRP	3.06 mg/dl	$\beta$ -D-glucan	(-)
Neu	66.2%	Alb	4.0 g/dl	IgG	2287 mg/dl	sIL-2R	603 U/ml
Lym	22.6%	BUN	9 mg/dl	IgG4	25.2 mg/dl	Trichospron Ab	1.03 (+)
Bas	0.3%	Cre	0.55 mg/dl	HIV Ab	(-)		
Eo	5.9%	T-bil	1.3 mg/dl	HTLV-1 Ab	(-)	<b>ABG</b>	
Mono	3.4%	AST	22 U/L	KL-6	4903 U/ml	(Room air, rest.)	
RBC	$5.57 \times 10^6$ / $\mu$ l	ALT	26 U/L	SP-A	94.4 ng/ml	pH	7.393
Hb	16.2 g/dl	$\Gamma$ -GT	17 U/L	SP-D	17.2 ng/ml	PO <sub>2</sub>	63.1 Torr
Plt	$14.6 \times 10^3$ / $\mu$ l	LDH	257 U/L	ANA	$\times 320$	PCO <sub>2</sub>	39.5 Torr
		Glu	93 mg/dl	RF	26 IU/ml	HCO <sub>3</sub>	23.6 mmol/L
		Na	138 mmol/L	CCP Ab	(-)		
<b>Coagulation</b>		K	4.2 mmol/L	ds-DNA Ab	(-)	<b>Spirometry</b>	
PT	80%	Cl	104 mmol/L	Sm Ab	(-)	VC	2.18 L
PT-INR	1.13	Ca	9.4 mg/dl	SS-A Ab	240 U/ml	%VC	46.6%
APTT	36.4 sec	ACE	4.9 U/L	SS-B Ab	(-)	FVC	2.09 L
Fib	393 mg/dl	Ferritin	237 ng/ml	RNP Ab	(-)	%FVC	45.3%
D-dimer	1.3 $\mu$ g/ml			Scl-70 Ab	(-)	FEV1	1.93 L
PS	85%			Jo-1 Ab	(-)	%FEV1	47.4%
PC	83%			GBM Ab	(-)	%DLco	31.3%
ATIII	78%			PR3-ANCA	(-)	DLco/VA	3.84 ml/min/mmHg
				MPO-ANCA	(-)		



**Fig. 1.** Chest radiograph on the admission shows diffused bilateral ground-glass opacity, particularly in the lower lung field.

(4903 U/mL), positive anti-nuclear antibody with a titer of 1:320 and positive anti-SS-A antibody (240 U/mL, normal < 7.0 U/mL) (Table 1). An enzyme-linked immunosorbent assay for myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3-ANCA were negative. Chest radiograph showed reticulonodular opacities in the bilateral lower field (Fig. 1).

The patient was diagnosed with Sjögren's syndrome, based on the presence of anti SS-A antibody and positive for lacrimal gland biopsy. His disease fulfilled two criteria out of four listed in the Revised Japanese Criteria for Sjögren's Syndrome (1999) [3].

Chest computed tomography (CT) showed diffuse ground-glass attenuation, preferentially located in the lower lobes (Fig. 2) with lymphadenopathy in the mediastinum. The pulmonary function test revealed restrictive impairment of spirometry (vital capacity (VC)

2.18 L, 46.6% of predicted) with decreased diffusing capacity for carbon monoxide (DLco/VA 3.84 mL/min/mmHg, 31.3% of predicted). Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro - D-glucose (<sup>18</sup>F-FDG PET) showed the inflammatory FDG activity in the lungs (SUVmax = 3.4), hilar and mediastinum lymph nodes (Fig. 3).

Examination of BALF showed an increased total cell count of  $7.8 \times 10^5$ /mL, almost normal cell fraction (84.5% macrophages, 11.5% neutrophils, 3.1% lymphocytes, and 0.9% eosinophils), with 2% hemosiderin-laden macrophages (Fig. 4), and positive for iron staining, suggesting alveolar hemorrhage. Examination of endobronchial ultrasound-guided transbronchial needle aspiration of the enlarged lymph node in the mediastinum revealed no specific finding.

The lung biopsy specimens of the right segments S2 and S8 obtained by video-assisted thoracic surgery (VATS) showed uniform interstitial fibrosis and mild chronic inflammation with lymphoid follicles, suggesting nonspecific interstitial pneumonia (NSIP) pattern (Fig. 5A–D). There are some areas of pigmented macrophages and multinucleated giant cells filling into alveolar spaces (Fig. 5E). The Prussian blue stain identified the mineral deposits throughout vascular elastic fibers, so-called endogenous pneumoconiosis (Fig. 5F). Neither vasculitis nor capillaritis was observed. Those findings of alveolar hemorrhage were consistent with the diagnosis of pulmonary hemosiderosis.

Hence the diagnosis of recurrent pulmonary hemosiderosis presented with Sjögren's syndrome was confirmed, the patient was started on prednisone 0.5 mg/kg/day, and the symptoms were almost completely resolved. The dose of prednisone was successfully tapered to 0.1 mg/kg/day; however we can not cease the dose of prednisone mainly concerning recurrence.

### 3. Discussion

IPH is a rare disease that repeats alveolar hemorrhage of unknown origin and is a disease with bloody sputum or hemoptysis, anemia, and pulmonary infiltrates. There are about 500 cases in the world, and most

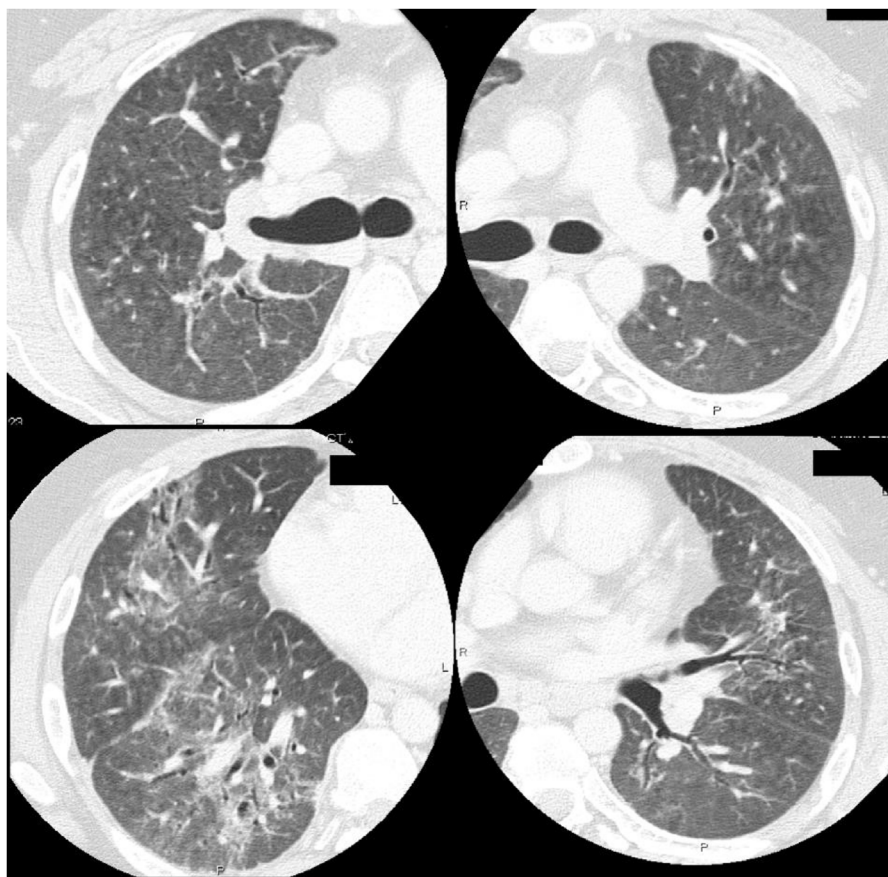


Fig. 2. Chest computed tomography on the admission shows diffused ground-glass opacity, patchy areas of consolidation with slightly light granular shadow in the upper lobes but absence of honeycombing.

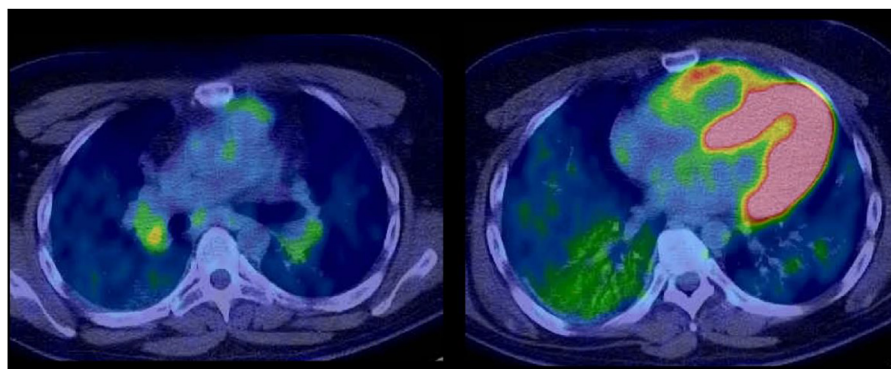


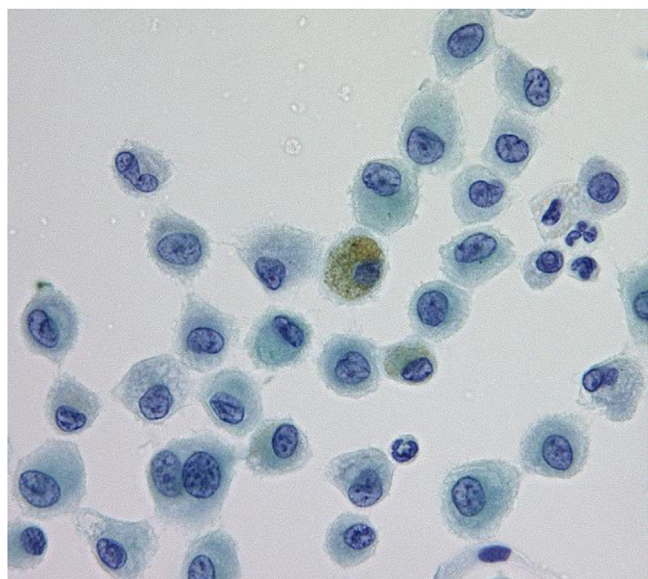
Fig. 3.  $^{18}\text{F}$ -FDG PET shows the inflammatory FDG activity in the lungs, hilar and mediastinum lymph nodes.

cases develop by the age of 30 [4].

The etiology is unknown, but some hypotheses had been proposed such as the immunological theory: circulating antibodies against cow's milk have been detected in a number of children with this disease [5–7]. Coexistence of celiac disease and IPH has been reported, and introduction of a gluten-free diet has been associated with the remission of pulmonary symptoms [8–11]. Furthermore, approximately 25

percent of patients with IPH alive for more than 10 years subsequently develop autoimmune disorders, such as rheumatoid arthritis [12]. In fact, one case report showed IPH recurrence after remission of 15 years associated with Sjögren's syndrome [13]. As the case report showed, IPH recurrence following a long-term remission can occur [13]. On the other hand, Sjögren's syndrome could seldom cause alveolar hemorrhage [14–17]. Pulmonary manifestations of Sjögren's syndrome are



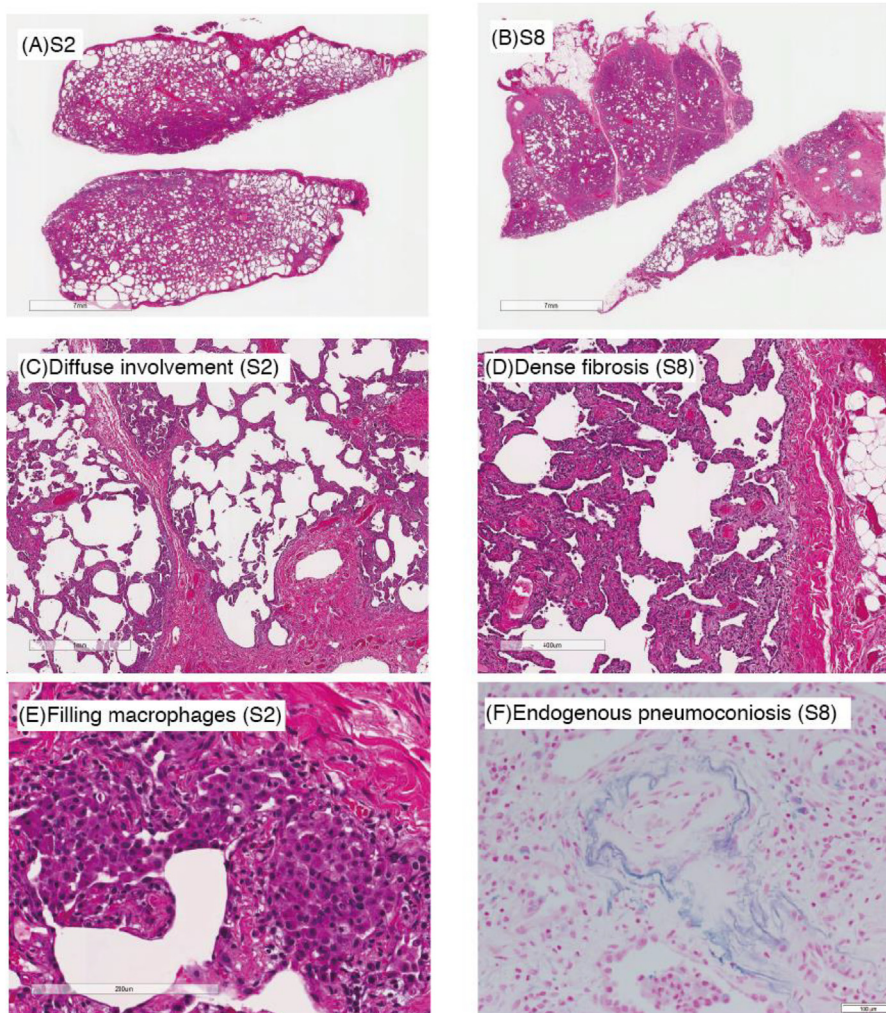


**Fig. 4.** Papanicolaou staining shows 2% of hemosiderin-laden macrophages in the bronchoalveolar lavage fluid.

relatively common and more frequent in patients with SS-A antibody [18]. Cryoglobulinaemia can occur as a complication of Sjögren's syndrome and can lead to diffuse alveolar hemorrhage [16]. Unfortunately we did not measure the levels of cryoglobulin before starting prednisone so that we could not deny the existence of cryoglobulinemia in this case. From a point of view in the epidemiology of both idiopathic pulmonary hemosiderosis and Sjögren's syndrome, it is unlikely to be a simple comorbidity. According to these facts, we concluded that IPH has certainly relapsed, but may have some relationship with Sjögren's syndrome in this case.

Recurrent hemorrhage can result in the presence of free iron in lung tissue [19] and chronic inflammation [20] which can eventually lead to pulmonary fibrosis [21–23]. In fact, most patients develop pulmonary fibrosis within 5 years of presentation [8]. However, Sjögren's syndrome can also lead to pulmonary fibrosis. In this case, there is a possibility that both recurrent hemorrhage and Sjögren's syndrome may lead to pulmonary fibrosis of NSIP pattern.

In conclusion, we experienced a case of recurrent IPH after long-term remission accompanied by Sjögren's syndrome. Further immunological studies may unveil the precise mechanism of IPH.



**Fig. 5.** Histopathological findings of the lung from video-assisted thoracoscopic surgery shows a temporally uniform interstitial fibrosing process (nonspecific interstitial pneumonia pattern) and the mineral deposits throughout vascular elastic fibers, so-called endogenous pneumoconiosis visualized by the Prussian blue stain (F).

## Conflict of interest

The authors have no conflicts of interest.

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