

# Early diagnosis of idiopathic pulmonary haemosiderosis: increased haemosiderin-laden macrophages in repeat bronchoscopy

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## Keywords

Diffuse alveolar haemorrhage, haemosiderin-laden macrophages, idiopathic pulmonary haemosiderosis.

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## Abstract

Idiopathic pulmonary haemosiderosis (IPH) is a diagnosis of exclusion, which is characterized by persistent or recurrent episodes of alveolar haemorrhage. Early diagnosis of IPH, especially in the case of first-time manifestation, is challenging because previous episodes of alveolar haemorrhage are often difficult to prove. Repeated episodes of alveolar haemorrhage can result in chronic iron-deficient anaemia and irreversible interstitial fibrosis; thus, early recognition and intervention are desirable in terms of clinical outcome. We report a case of IPH that was diagnosed early by confirming the presence of an increased number of haemosiderin-laden macrophages with alveolar haemorrhage in repeat bronchoscopy. We wanted to highlight that decreased but sustained attenuation of ground-glass opacities on high-resolution computed tomography does not always correlate with successful remission in patients with IPH. Repeat bronchoscopy can be useful in the early recognition of IPH, especially in the case of sustained opacities a few months after alveolar haemorrhage.

## Introduction

Idiopathic pulmonary haemosiderosis (IPH) is a diagnosis of exclusion, which is characterized by persistent or recurrent episodes of alveolar haemorrhage (AH) [1]. Diffuse alveolar haemorrhage (DAH) is suspected when a patient presents with bloody sputum, anaemia, diffuse pulmonary infiltrates, and hypoxemic respiratory failure. It can be caused by several underlying conditions, including vasculitis, pulmonary renal syndrome, collagen vascular diseases, drug-induced infection, celiac disease, and bone marrow transplantation [2]. Although chest radiography and high-resolution computed tomography (HRCT) are effective for DAH detection, bronchoscopy should be performed to confirm diagnosis. Bloody bronchoalveolar lavage (BAL) fluid containing haemosiderin-laden macrophages (HLMs) can confirm the diagnosis of AH.

Early diagnosis of IPH, especially in the case of first-time manifestation, is challenging because previous episodes of AH are often difficult to prove. Repeated episodes

of DAH can result in chronic iron-deficient anaemia and irreversible interstitial fibrosis [2]. Although there is no established treatment for DAH, corticosteroids and immunosuppressants are empirically used [1]. IPH mostly occurs at younger ages; thus, early recognition and intervention are desirable in terms of clinical outcome.

We report a case of IPH diagnosed early by confirming increased HLMs in repeat bronchoscopy.

## Case Report

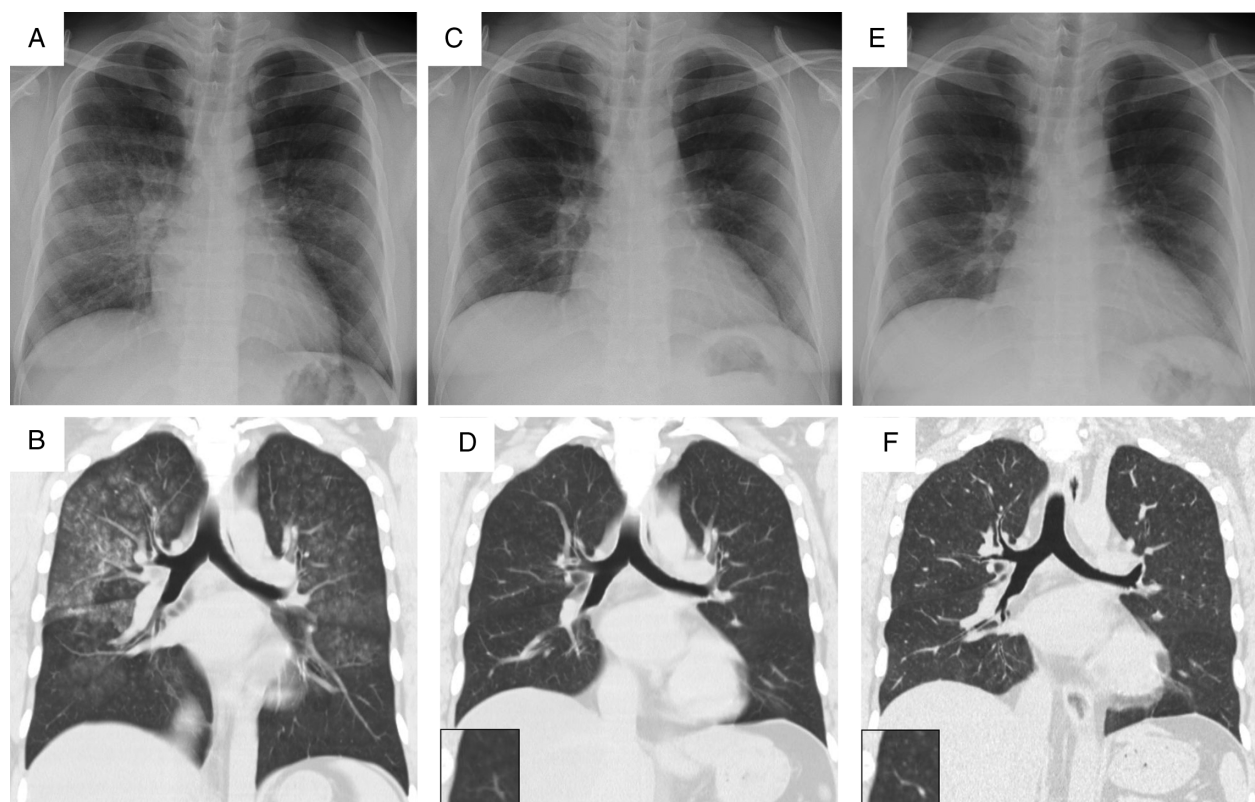
A 25-year-old man visited our hospital due to 3-day, first onset of bloody sputum. He had no medication history, family history of haematological and gastrointestinal disorders, or allergies to foods, including wheat. He was a current smoker of 10.5 pack-years but had no experience with illicit drugs and chemicals. His vital signs were normal. Respiratory sounds were slightly rough on deep inhalation but without rales in both lung zones. Other examinations were unremarkable.

Routine laboratory tests revealed mild anaemia and moderate thrombocytopenia. Haemoglobin level was 11.8 g/dL. Serum iron and ferritin levels were normal at 97 µg/dL and 195.5 ng/mL, respectively. Platelet count was  $7.2 \times 10^4/\mu\text{L}$ . Liver and renal functions were normal. Occult blood was not identified in urine. Chest radiography showed confluent opacities and widespread consolidation in both lung fields (Fig. 1A). HRCT showed diffuse ill-defined ground-glass opacities (GGOs) throughout the lungs (Fig. 1B). Spirometric evaluation was almost normal.

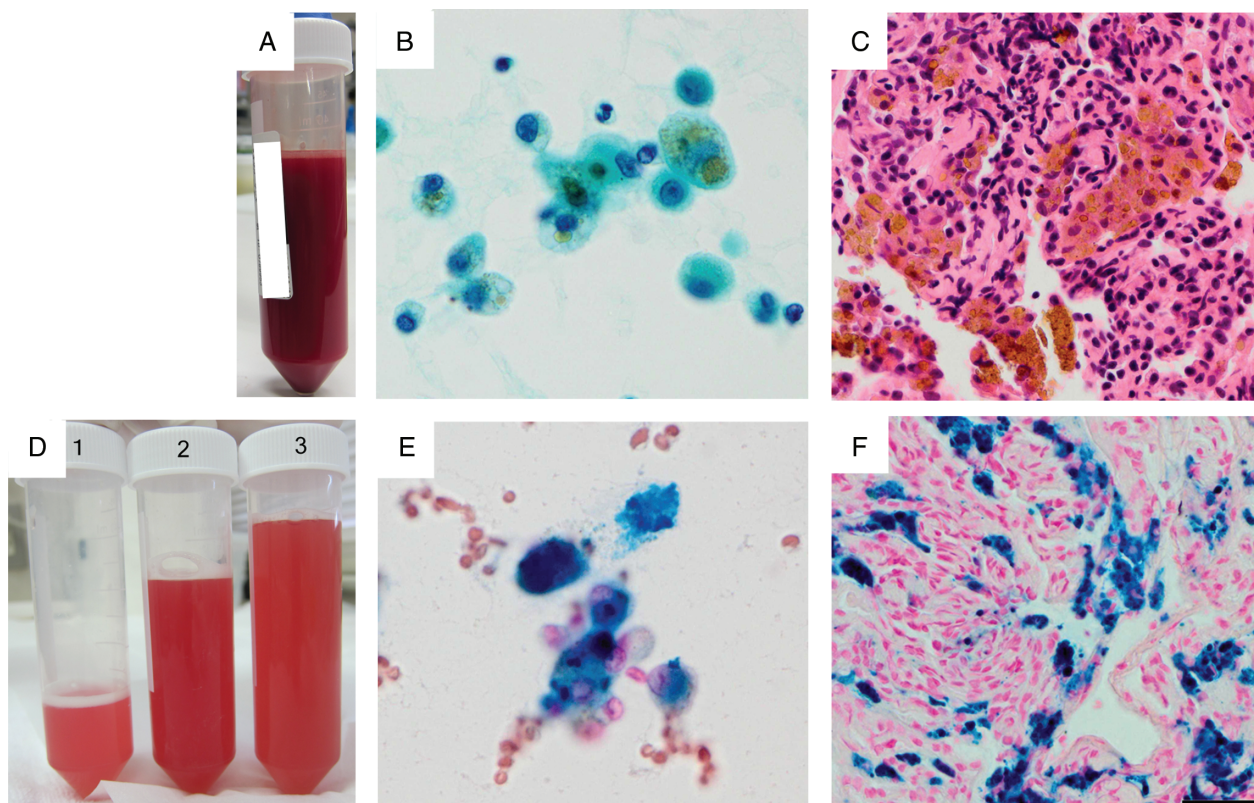
The major manifestation was bloody sputum. He was first admitted for observation. On day 3 (D3) of hospitalization, bronchoscopy was performed, and highly bloody BAL fluid was collected (Fig. 2A). The percentage of HLMs in the total 200 identified macrophages was 67.5% (Fig. 2B). Intravenous methylprednisolone, 1 g daily, was

empirically started because urgent massive DAH due to underlying vasculitis and collagen tissue diseases could not be ruled out.

Further laboratory tests, including detection of antinuclear, anti-neutrophil cytoplasmic, and anti-glomerular basement membrane antibodies, were negative. Interferon-gamma-release assays for tuberculosis were negative. Screening tests for viral infection, including influenza, hepatitis B, and hepatitis C virus; HIV; and cytomegalovirus were also negative. No cardiac diseases were found on cardiac ultrasonography. Transbronchial lung biopsy specimen revealed AH, accumulation of HLMs, and interstitium without vasculitis (Fig. 2C). On D6, oral prednisolone, 60 mg (approximately 1 mg/kg) daily, was administered. Bloody sputum gradually resolved, but mild anaemia and moderate thrombocytopenia persisted. Bone marrow



**Figure 1.** Chest radiograph and high-resolution computed tomography (HRCT) findings. (A, B) Day of admission. Chest radiograph showing widespread ground-glass opacities (GGOs) in both lung fields and partial confluent infiltration in the right lung field. An HRCT image showing diffuse, ill-defined GGOs with centrilobular distribution throughout the lungs. The results of the pulmonary function test were as follows: Vital capacity (VC), 3.59 L; VC % of predicted (%VC), 84.3%; forced vital capacity (FVC), 3.99 L; forced expiratory volume in first 1 s (FEV<sub>1</sub>), 3.18 L; ratio of FEV<sub>1</sub> to FVC (FEV<sub>1</sub>/FVC), 79.7%; diffusing capacity for carbon monoxide (DL<sub>CO</sub>) % of predicted, 77.9%. (C, D) Day 45 of hospitalization. Chest radiograph showing evident remission of opacities in both lung fields after administration of steroid therapy. Lung volumes seem to be decreased compared to those observed on the day of admission. An HRCT image showing GGOs, whose attenuations were decreased but evidently remained throughout the lungs. Insets: Magnification of GGOs of the right upper lobe. (E, F) Three months post-discharge. Chest radiograph showing no obvious opacities and infiltrates on the course of gradual reduction of prednisolone. An HRCT image showing sustained GGOs throughout lungs. Insets: Magnification of GGOs of the right upper lobe. The results of the pulmonary function tests were as follows: VC, 3.45 L; %VC, 70.5%; FVC, 3.41 L; FEV<sub>1</sub>, 2.55 L; FEV<sub>1</sub>/FVC, 74.7%; DL<sub>CO</sub>, evaluation not performed.



**Figure 2.** Bronchoscopic examination findings. (A–C) First-time bronchoscopy performed on day 3 of hospitalization. (A) Highly bloody bronchoalveolar lavage (BAL) fluid. Three serial BAL fluids were mixed. The BAL fluid was highly bloody starting from the first collection. (B) Haemosiderin-laden macrophages (HLMs) identified in BAL fluid. The percentage of HLMs in the total 200 identified macrophages is approximately 67.5%. Papanicolaou stain. Magnification 400x. (C) Transbronchial lung biopsy specimen revealed alveolar haemorrhage, accumulation of HLMs, and interstitium without vasculitis. Magnification 200x. Haematoxylin–Eosin stain. (D–E) Repeat bronchoscopy performed on day 50 of hospitalization. (D) Slightly diluted bloody BAL fluid. The BAL fluid became progressively bloodier. (E) An increasing number of HLMs in BAL fluid. The percentage of HLMs in the total 200 identified macrophages is approximately 87.5%. Haemosiderin particles are highlighted with iron stain. Magnification 400x. (F) Transbronchial lung biopsy specimens revealed the same findings seen in Figure 2C in addition to significantly increased HLMs. Haemosiderin particles are highlighted with iron stain. Magnification 200x.

biopsy did not reveal any haematological disorders. Considering the side effects of long-term steroid therapy, prednisolone was gradually decreased by 5–10 mg weekly.

On D45, opacities and infiltrates were hardly identified on a chest radiograph (Fig. 1C). However, HRCT showed GGO, where attenuations were decreased but sustained throughout the lungs (Fig. 1D). On D50, bronchoscopy was repeated to reassess for the presence of AH. Progressively bloodier BAL fluid (Fig. 2D) and an increasing number of HLMs (87.5%, Fig. 2E) were identified. Transbronchial lung biopsy specimens revealed the same findings along with significantly increased HLMs, consistent with persistent DAH (Fig. 2F). A diagnosis of IPH was established. On D55, he was discharged with a prescription for prednisolone of 20 mg/day.

Three months post-discharge, chest radiographic finding was almost normal (Fig. 1E), but GGOs remained

throughout the lungs on HRCT (Fig. 1F). Vital capacity was slightly decreased on spirometry. Because he did not have any complaints, prednisolone was slowly tapered to 10 mg/day. Periodical follow up is ongoing.

## Discussion

Interestingly, decreased but sustained attenuations of GGOs on HRCT do not always correlate with successful remission in IPH. Acute pulmonary haemorrhages usually resolve rapidly during remission. Although HLMs usually appear within 50 h after pulmonary haemorrhages [3], a small amount of HLMs may appear in normal individuals, smokers, or patients with pneumonia [4]. A percentage of HLMs higher than 36% strongly suggests pulmonary haemosiderosis [5]. Estimated clearance time of HLMs from the lung is within 2–4 weeks after haemorrhage [3]. For

these reasons, increased numbers of HLMs in BAL fluid a few months after haemorrhage suggest persistent AH. In this case, HLMs on D50 post-DAH onset were increased despite decreased but sustained attenuations of GGOs on HRCT. Repeat bronchoscopy can be useful in the early recognition of IPH, especially in the case of retained opacities after AH on HRCT.

IPH can induce insidious pulmonary fibrosis. The exact aetiology, incidence, and prevalence are unknown, but 80% of IPH is diagnosed in the first decade of life. The remaining is adult-onset IPH diagnosed before 30 years of age. The history varies from acute onset with haemoptysis and dyspnoea to insidious processes like fatigue and progressive exertional dyspnoea. Radiologically, diffuse GGO was mostly found in the acute phase and variable degrees of fibrosis in the chronic phase. The exact prognosis is undetermined, but most deaths are related to acute and chronic respiratory failure or cor pulmonale due to severe pulmonary fibrosis [1,2]. In this case, it was difficult to identify subtle change with chest radiography alone. We prefer performing HRCT in conjunction with pulmonary function testing at follow up.

We could not reveal any specific underlying causes or identify the association with mild anaemia and moderate thrombocytopenia. Although bone marrow transplantation can be a cause of DAH, we could not locate any reports describing DAH with a background of haematological disorders, such as myelodysplastic syndrome or idiopathic thrombocytopenic purpura.

In conclusion, HRCT with repeat bronchoscopy can be useful in the early diagnosis of IPH.

## Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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