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# Long-term clinical course of idiopathic pulmonary haemosiderosis with rheumatoid arthritis

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Anti-cyclic citrullinated peptide antibodies, idiopathic pulmonary haemosiderosis, pneumothorax, rheumatoid arthritis.

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## Abstract

Idiopathic pulmonary haemosiderosis (IPH) is a rare cause of diffuse alveolar haemorrhage during childhood, and its precise pathophysiology and long-term clinical course remain unclear. A 31-year-old man was diagnosed with IPH at four years of age and had recurrent episodes of haemoptysis. The patient's symptoms responded well to steroids. However, pulmonary fibrosis and the cystic region in the lung progressively worsened. At age 27, the patient developed polyarthritis with positive anti-cyclic citrullinated peptide antibodies. The patient also developed hand synovitis, which was diagnosed with ultrasonography. These results indicate complications from rheumatoid arthritis. The patient's dyspnoea gradually worsened, and at the age of 31, he developed pneumothorax and an acute exacerbation of IPH. The clinical course from ages 4 to 31 included progressive chronic respiratory failure because of pulmonary fibrosis, acute exacerbations, complications with rheumatoid arthritis, and deliberation regarding lung transplantation. The development of rheumatoid arthritis after the onset of IPH supports the theory of an autoimmune mechanism of IPH.

## Introduction

Idiopathic pulmonary haemosiderosis (IPH) is a rare disease (estimated annual incidence of 0.24 cases per 1,000,000 children [1]) characterized by recurrent episodes of diffuse alveolar haemorrhage. The majority of cases occur in children under 10 years of age. These patients present with haemoptysis, dyspnoea, and anaemia. There are two published paediatric case series of IPH from France and India that have examined the clinical features and treatment regimens (follow-up durations: median of 5.5 years in France [2] and mean of 2.3 years in India [3]). However, the precise pathophysiology and long-term clinical outcomes remain unknown. In this case study, we describe an IPH patient who developed rheumatoid arthritis, pneumothorax, and respiratory failure more than 20 years after the initial diagnosis.

## Case Report

A 31-year-old man was first hospitalized at four years of age with haemoptysis, iron deficiency anaemia, and diffuse parenchymal infiltrates observed by chest imaging. An open-lung biopsy disclosed extensive alveolar haemorrhage with haemosiderin-laden macrophages. There was no evidence of vasculitis or other diseases observed, and the patient was diagnosed with IPH. The patient experienced recurrent episodes of haemoptysis during childhood, and by age 15, his symptoms gradually responded to treatment with prednisolone (10 mg every other day).

At age 27, the patient developed polyarthritis involving the shoulders, wrists, and hands, with morning stiffness. The laboratory results indicated the presence of anti-cyclic citrullinated peptide antibodies (anti-CCP) at a concentration of >300 IU/mL, a rheumatoid factor level of 117 IU/mL, and a C-reactive protein concentration of 1.0 mg/mL. The laboratory tests for other collagen diseases and vasculitis, including antinuclear (ANA), anti-extractable nuclear antigen, anti-neutrophil cytoplasm (ANCA), and anti-glomerular basement membrane antibodies, were negative. A joint ultrasonography showed synovitis of the metacarpophalangeal joints with power Doppler activity. As a result, rheumatoid arthritis was additionally diagnosed. The patient was administered

salazosulfapyridine (1000 mg/day) and achieved an acceptable response with reduced arthralgia.

The patient's dyspnoea gradually worsened for several months before he developed polyarthritis. Chest CT scans showed pulmonary fibrosis and cystic lesions in both upper lobes. There were also diffuse centrilobular ground-glass opacities that had been previously observed (Fig. 1). A bronchoscopy was performed to evaluate the activity of pulmonary haemosiderosis. The bronchoalveolar lavage (BAL) fluid was bloody and contained many haemosiderin-laden macrophages (>80% of the total number of macrophages, Golde index of 270). A pulmonary function test showed a restrictive pattern (% vital capacity [VC] 53.8, forced expiratory volume in one sec [$FEV_1$]/forced vital capacity [FVC] 83.5%) and a decreased carbon monoxide diffusing capacity (diffusing capacity for carbon monoxide [DLCO] 31.4% of predicted) (the changes with time are shown in Table 1). The patient was provided home oxygen therapy at 28 years of age.

**Table 1. Chronological changes of the pulmonary function tests.**

| Age (years) | 18 | 22 | 27 | 32 |
|---|---|---|---|---|
| VC (L) | 2.10 | 2.27 | 2.14 | 1.56 |
| %VC (%) | 53.9 | 58.9 | 53.8 | 40.2 |
| FVC (L) | 2.07 | 2.27 | 2.18 | 1.62 |
| $FEV_1$ (L) | 1.84 | 1.90 | 1.82 | 1.54 |
| %$FEV_1$ (%) | 50.6 | 53.6 | 51.3 | 44.9 |
| $FEV_1$/FVC (%) | 88.8 | 83.7 | 83.5 | 95.1 |
| DLCO (mL/min/mmHg) | 10.26 | 9.90 | 6.64 | 6.66 |
| %DLCO (%) | 44.0 | 43.7 | 31.4 | 32.8 |

DLCO, diffusing capacity for carbon monoxide; $FEV_1$, forced expiratory volume in one sec; FVC, forced vital capacity; VC, vital capacity.

At the age of 31, the patient was admitted to our hospital with fever, cough, and dyspnoea without haemoptysis. The chest X-rays showed the presence of a pneumothorax on the right side (Fig. 2A). The chest CT scans showed relatively large subpleural cysts of the apex in the right upper lobe (Fig. 2B) and worsened diffuse ground-glass opacities of the left lower lobe (Fig. 2C). The laboratory data showed an elevated white blood cell count (17,200/μL) and an elevated C-reactive protein concentration (2.2 mg/dL). There was no evidence of anaemia (Hb 17.1 g/dL). The patient received chest drainage upon hospital admission. However, on the second day after admission, he developed severe respiratory failure. The patient was intubated, and mechanical ventilation was initiated. A bronchoscopy revealed bloody secretions in all areas of the bronchus but no bacterial pathogens. Therefore, steroid pulse therapy was performed, followed by prednisone (60 mg/day) for an acute exacerbation. The patient's condition gradually improved, and on the ninth day of hospitalization, a bullectomy was performed for persistent air leaks. After the patient's condition improved and stabilized, he was

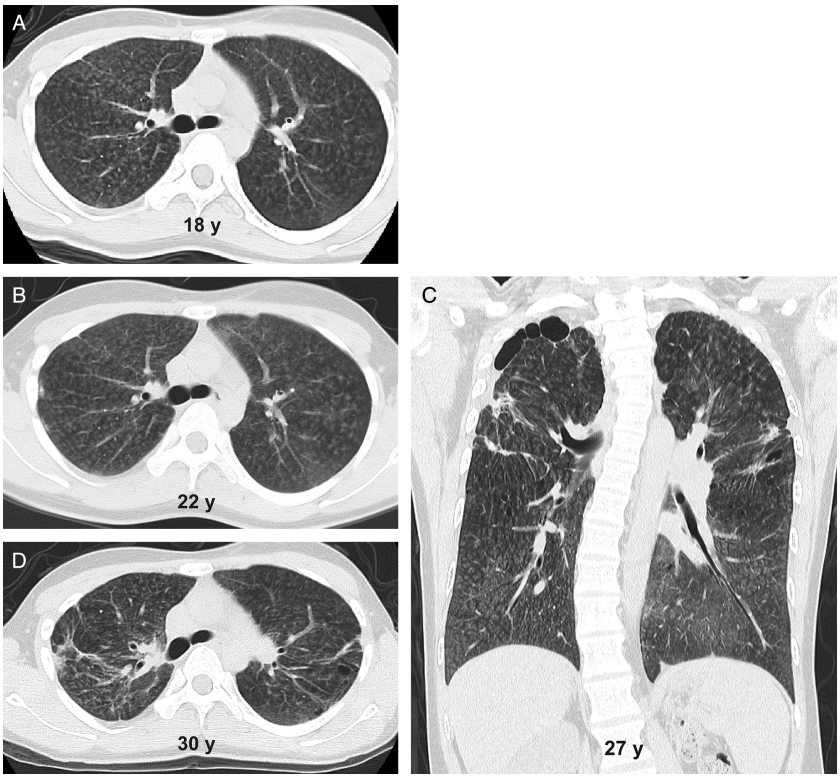


**Figure 1.** Longitudinal course of computed tomography (CT) images of the chest. (A) CT showed diffuse centrilobular ground-glass opacities at 18 years; (B) at 22 years; (C) at 27 years, fibrotic changes in both upper lobes were recognized; and (D) at 30 years, the fibrosis changes deteriorated.

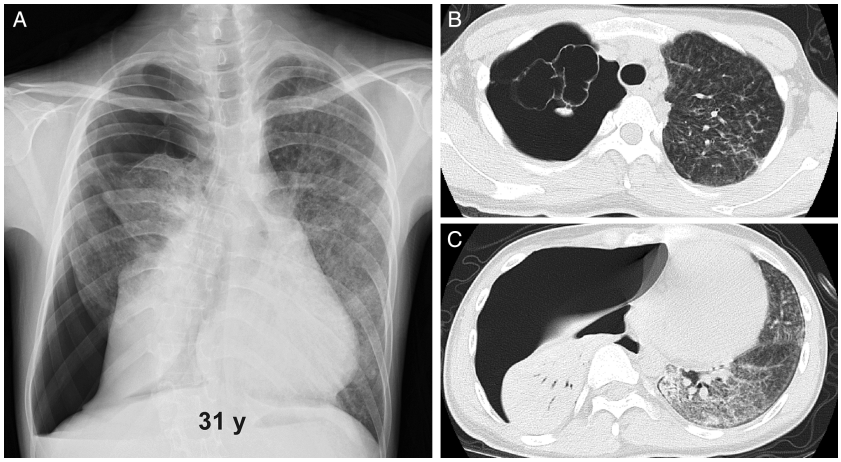


**Figure 2.** Chest images on admission at 31 years. (A) A chest radiograph showing pneumothorax on the right side. (B, C) Chest computed tomography images showing subpleural cysts at the apex of the right lung and worse diffuse ground-glass opacities of the left lower lobe.

extubated on the second postoperative day. The prednisolone dose was tapered to 20 mg/day, and he was discharged from the hospital. The patient is now considering lung transplantation in Japan.

## Discussion

We describe a case of IPH whose long-term clinical outcome from 4 to 31 years of age was observed. The patient's clinical course was diagnosed by an open-lung biopsy at 4 years of age. However, complications of rheumatoid arthritis began at 27 years of age, and chronic respiratory failure due to pulmonary fibrosis occurred at 28 years of age. The patient then had a pneumothorax and acute exacerbation of IPH at 31 years of age. The patient is currently applying for lung transplantation.

The complication of rheumatoid arthritis after the onset of IPH in the present case suggests an autoimmune pathogenesis. Although the aetiology of IPH remains unknown, various hypotheses have been suggested. For example, there may be allergic, environmental, genetic, and autoimmune origins [2]. The association of IPH and autoimmune diseases such as celiac disease, rheumatoid arthritis, or other immune diseases was previously reported. These findings support the theory of an autoimmune mechanism [2,4,5]. Additionally, there are reports of IPH patients who developed rheumatoid arthritis-like disease six months to seven years after the diagnosis [5]. Our patient had no evidence of any autoimmune disease until he developed rheumatoid arthritis 24 years after the onset of IPH. It is possible that the long period between the onset of IPH and the presentation of rheumatoid arthritis occurred because the glucocorticoids used to treat IPH masked the manifestations of polyarthritis.

A recent review of IPH thoracic imaging showed pulmonary fibrosis and honeycombing in the basilar and subpleural lower lobe regions in an end-stage patient [6]. Conversely, the progression of fibrosis and cystic lesions in the present case was mainly observed in the upper lobe of the lung even though haemoptysis and anaemia had been suppressed by steroid therapy. This cystic lesion caused the pneumothorax (see Fig. 2). Corticosteroids have been used alone or in combination with immunosuppressant drugs to treat IPH in previous cohort studies, and favourable responses have been observed in many cases [2,3]. When pulmonary fibrosis progresses despite the use of corticosteroids, lung transplantation can be a treatment option. However, in a previous case report of lung transplantation for IPH, a young patient who underwent bilateral single-lung transplantion experienced a recurrence of IPH in the transplanted lungs three years later [7]. There are currently no reported successful cases of lung transplantation for IPH. Therefore, our patient must carefully consider the value of lung transplantation.

We described the case of a 31-year-old patient diagnosed with IPH at four years of age. This report indicates that rheumatoid arthritis developed after the onset of IPH. These findings support the theory of an autoimmune mechanism of IPH. Therefore, managing pneumothorax, respiratory failure, and complications of immune diseases may be necessary in IPH patients.

### Disclosure Statements

No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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