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## Case report

## Rare causes of anemia in children: Two cases of idiopathic pulmonary hemosiderosis

Jing Yang<sup>1</sup>, Ruo Yan Gou<sup>1</sup>, Xia Ding, Li Li Shao, Gui Xia Ma, Qian Ni<sup>\*</sup>

Department of Pediatrics, Lanzhou University Second Hospital, Lanzhou, China

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## ABSTRACT

Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of diffuse alveolar hemorrhage (DAH) with unknown etiology. Hemoptysis, dyspnea, anemia, diffuse infiltration in chest radiography and presence of hemosiderin-loaded macrophages (HLMs) in the sputum, gastric content or bronchoalveolar lavage fluid (BALF) are the major characteristics for diagnosis of IPH. Here we present two pediatric patients with IPH. Patient 1 was repeatedly misdiagnosed with bronchopneumonia because of diffuse infiltration in her chest X ray, but her anemia was repeatedly ignored. Patient 2 was misdiagnosed with nutritional anaemia because she did not have dyspnea or hemoptysis, and her chest computed tomography (CT) only revealed mild alveolar infiltrates. IPH must be included in the differential diagnosis in patients with long-term anemia who respond poorly to the hematopoietic supplements. CT is superior to X-ray in detecting alveolar hemorrhage.

IPH is a rare cause of diffuse alveolar hemorrhage (DAH) with unknown etiology. It frequently occurs in children under ten years of age. Although IPH has a low incidence rate of 0.24–1.23 cases per million people, it has a high mortality rate of more than 50% [1,2]. Clues to the diagnosis of IPH include hemoptysis, cough, dyspnea, iron-deficiency anemia, signs of alveolar hemorrhage on chest X-ray or chest CT, and presence of HLMs in BALF, sputum or gastric fluid. Among these clues, presence of HLMs is highly suggestive of IPH. Meanwhile, other diseases that can lead to diffuse alveolar hemorrhage, such as vasculitis, autoimmune diseases, tuberculosis, and bronchiectasis, must be excluded before a diagnosis of IPH can be made. Misdiagnosis of IPH frequently occurs because of its low incidence, lack of respiratory symptoms or typical X-ray characteristics, often leading to mistreatments, as reflected in our two cases as described below.

## 1. Case 1

A 7-year-old girl was admitted to the hospital in April 2018 with worsening dyspnea, cough for the previous one month, and bloody-tinged sputum for four days. Chest X-ray performed in a local hospital showed large patches on bilateral lungs. She was treated for bronchopneumonia for one month, and her symptoms and radiological findings did not improve. Upon question, the patient had severe anemia four years ago and received blood transfusion for treatment. Bone marrow examination at that time showed hyperplastic anemia. She lost follow-up in the past four years.

On admission, the patient had a stable overall condition except she had mild shortness of breath. Blood chemistry was normal. Her

<sup>\*</sup> Corresponding author. Department of Pediatrics, Lanzhou University Second Hospital, 730030, Lanzhou, China.

E-mail address: [nateliqian@yeah.net](mailto:nateliqian@yeah.net) (Q. Ni).

<sup>1</sup> Jing Yang and Ruoyan Gou contributed equally to this work.

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respiratory rate was 30 breaths/min. Breathing sounds were decreased mildly on both sides, with rales in bilateral lower zones. She had no signs of cyanosis, pallor, jaundice, lymphadenopathy or hepatosplenomegaly.

Laboratory examinations revealed mild anemia (hemoglobin 93 g/L). Her serum bilirubin levels were normal. The direct Coombs test was negative, and coagulation test results were within normal ranges. Tests of anti-glomerular basement membrane antibodies, antinuclear antibodies, anticardiolipin antibodies, rheumatoid factor, perinuclear antineutrophil cytoplasmic antibodies, and cytoplasmic antineutrophil cytoplasmic antibodies were all negative. A chest CT examination showed bilateral alveolar infiltrates (Fig. 1A). HLMs were discovered in sputum.

Based on the clinical and laboratory findings, and exclusion of other causes of intra-alveolar hemorrhage, she was diagnosed with IPH. She was treated with methylprednisolone (1.6 mg/kg daily) for one month, followed by dose tapering. A month later, her symptoms disappeared, hemoglobin increased to 120 g/L, and chest CT significantly improved (Fig. 1B). Her hemoglobin level continued to improve over the five months follow up. The dynamic changes in the blood biochemistry are presented in Table 1.

## 2. Case 2

A 9-year-old girl with a history of anemia for five years, and cough and fever for 14 days presented to our hospital on June 2019. She did not have dyspnea or hemoptysis. The patient received blood transfusion for severe anemia one year ago. A bone marrow examination three months ago showed hyperplastic anemia. She had been treated with ferrous sulfate, folic acid, and vitamin B<sub>12</sub> for three months, with no improvement in her hemoglobin levels. On physical examination, she had moderate pallor and mild splenomegaly, with no cyanosis, jaundice, lymphadenopathy or hepatomegaly. Mild rales were auscultated on the base of the left lung.

Blood biochemistry showed a hemoglobin level of 71 g/L. Serum bilirubin levels were normal. The direct Coombs test was negative, and coagulation test results were within normal ranges. Antinuclear antibodies, anti-glomerular basement membrane antibodies, rheumatoid factor, anticardiolipin antibodies, perinuclear antineutrophil cytoplasmic antibodies, and cytoplasmic antineutrophil cytoplasmic antibodies were all negative. Chest CT showed mild alveolar infiltrates (Fig. 1C). HLMs were discovered in BALF.

The patient was diagnosed with IPH. Oral prednisone was started at 2 mg/kg/day for one month, followed by dose tapering. During the 4-month follow-up period, her hemoglobin increased to 102g/L-115 g/L, chest CT significantly improved (Fig. 1D). The dynamic changes in the blood biochemistry are presented in Table 1 and 2.

## 3. Discussion

IPH is a rare lung hemorrhagic disease that is characterized by recurrent or chronic hemoptysis, iron deficiency anemia, and diffuse parenchymal infiltration on the chest radiography. In severe cases, chest tightness, shortness of breath, dyspnea, and even respiratory failure may occur. Alveolar hemorrhage results in abnormal hemosiderin deposition in pulmonary macrophages. Therefore, the discovery of HLMs in BALF, sputum, or gastric fluid is essential for IPH diagnosis. Although the etiology of IPH remains unclear, a variety

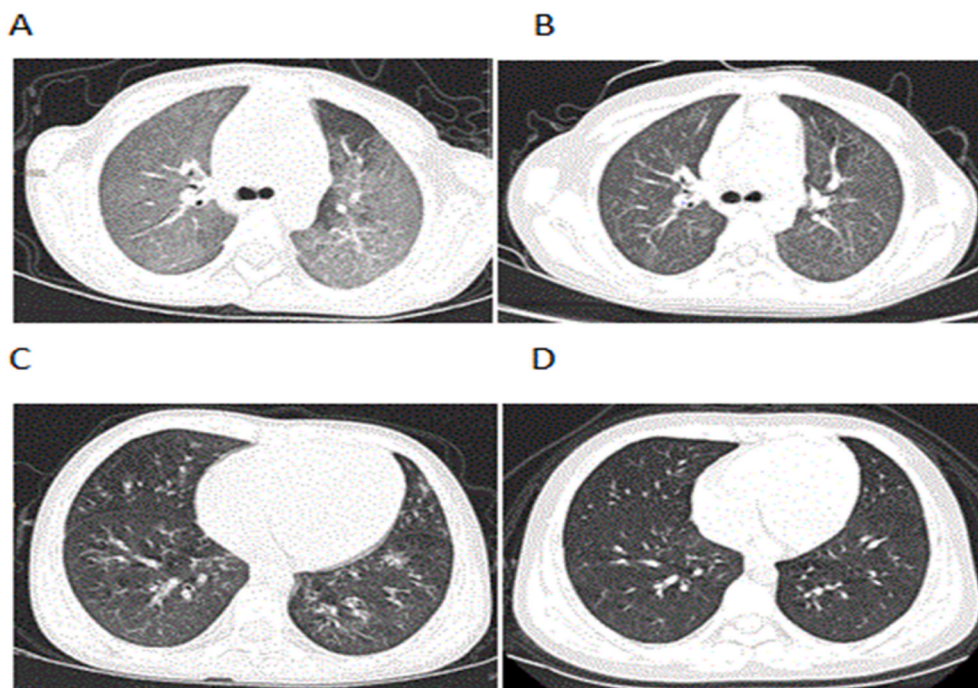


Fig. 1. Chest CT findings before and after treatments. Diffuse intra-alveolar hemorrhage in Case 1 (A) and mild bilateral alveolar infiltrate in Case 2 (C) significantly improved following one month of treatment (B) and four months of treatment (D) respectively.

**Table 1**

The dynamic changes in HGB (g/L) in the two patients before and after treatments of the first four months.

	Admission	1st month	2nd month	3rd month	4th month
Case1	93	120	110	117	127
Case2	71	115	109	111	118

**Table 2**

The result of laboratory examinations in case 2.

Parameter (Unit)	June 2019	July 2019	August 2019	September 2019	October 2019	Reference Range
WBC ( $\times 10^9/L$ )	4.1	8.0	5.2	6.3	5.7	5.0–12.0
NE (%)	40	57	60	50	53	50–70
LY (%)	52	37	34	43	41	20–40
RBC ( $\times 10^{12}/L$ )	1.90	3.96	3.63	3.70	3.43	4.00–5.00
HGB (g/L)	71	115	109	111	102	110–160
HCT (L/L)	0.169	0.370	0.334	0.331	0.313	0.330–0.420
MCV (fl)	88.9	93.4	92.0	89.5	91.3	80.0–100.0
MCH (pg)	37.4	29.0	30.0	30.0	29.7	26.0–34.0
MCHC (g/L)	420	311	326	335	326	320–360

WBC, white blood cell count; NE, neutrophil ratio; LY, Lymphocyte ratio; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin, MCHC, mean corpuscular hemoglobin concentration.

of factors have been suggested including genetics, environment, allergies, autoimmunity, and infection. Because of the rarity of the disease and lack of specific clinical manifestations in pediatric patients, IPH is often misdiagnosed as anemia or respiratory infection. This can lead to delayed treatment and poor outcomes. Therefore, early diagnosis and treatment are important for improving the prognosis of IPH patients.

In our report, the patients in the two cases all had chronic anemia. In the Patient 1, her hemoglobin level was mildly low in the previous four years prior to admission, and she needed no blood transfusion. She was repeatedly treated for lower respiratory tract infections until she developed hemoptysis and worsening dyspnea. We reasoned that her mild anemia and atypical chest X-ray findings did not raise the paediatricians awareness of IPH. Hence, we think chest CT scan should be a better alternative for patients with IPH because it provides more radiological details than a chest X-ray.

Patient 2 had severe chronic anemia that had not responded to the Iron and vitamin supplements. Chronic anemia was mostly her only symptom. She never had hemoptysis or shortness of breath, and her chest CT only showed mild alveolar infiltrates. HLMs in BALF turned out to be an important basis for the diagnosis of this patient.

In clinical practice, anemia is present in all IPH patients [3,4], whereas typical respiratory symptoms or prominent radiological findings may be missing in some patients. Presence of HLMs in sputum, gastric content, or BALF provides a critical clue to the IPH diagnosis, but it should be noted that the sensitivity of HLMs may vary with where they are found, e.g., the sensitivity of HLMs in diagnosing IPH can be 92% if they are present in BALF whereas the sensitivity drops to 30% if HLMs are only found in gastric juice [5].

In summary, IPH should be considered in patients with chronic anemia if they do not respond to the hematopoietic material supplements. IPH patients may not have hemoptysis or dyspnea. Examination for HLMs in body fluids should constitute an integral part of the diagnostic workups, but the sensitivity may vary in that the presence of HLMs in BALF is associated with much higher sensitivity than the HLMs being presenting in sputum or gastric fluid. CT scan is a superior imaging study to routine X-ray in detecting alveolar hemorrhage.

### Declaration of competing interest

There is no conflict of interest in this paper.

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