

Idiopathic Pulmonary Hemosiderosis With Allergic Asthma Diagnosis in a Pediatric Patient

İrem Eldem, MD,* Talia İleri, MD,† Elif İnce, MD,† Fikret Asarcıklı, MD,‡
Esra Pekpak, MD,† Hasan F. Çakmaklı, MD,† Koray Ceyhan, MD,‡ and
Zümriit Uysal, MD†

Summary: Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder with unknown pathogenesis that usually presents in the first decade of life. As a result of diffuse alveolar hemorrhage, respiratory symptoms such as cough attacks, hemoptysis, dyspnea, and recurrent and refractory iron-deficiency anemia (IDA) are observed. We present an 8-year-old girl who was followed up with recurrent IDA and allergic asthma and later diagnosed with IPH. IPH was confirmed by the presence of hemosiderin-laden macrophages in bronchoalveolar lavage obtained by bronchoscopy and exclusion of the secondary causes of pulmonary hemosiderosis. Glucocorticoids and iron supplementation were started. Clinical and laboratory improvement was observed with therapy. Our case illustrates that refractory/recurrent IDA with any pulmonary symptoms may be the only presenting feature of IPH.

Key Words: anemia, children, diffuse alveolar hemorrhage, pulmonary hemosiderosis

(*J Pediatr Hematol Oncol* 2015;37:e435–e437)

Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder with an incidence of 0.24 to 1.23 cases per million in selected populations and 30% of cases occur in children.^{1,2} Its pathogenesis is unclear, possibly of an immunologic mechanism, causing a defect in the basement membrane of the pulmonary capillary, or of toxic origin.^{3,4} Pulmonary hemosiderosis results from recurrent bleeding into the alveolar spaces and in the interstitial lung tissue, which may lead to fibrosis, restrictive lung disease, and even death, if left untreated.

Diffuse alveolar hemorrhage may occur as a primary disease of the lungs or a secondary condition associated with cardiac disease, bleeding disorders, systemic vasculitides, and celiac disease.⁵ Trigger factors such as gliadin, moulds, and cow's milk proteins should be considered.

Diagnosis is suggested by the triad of hematemesis, anemia, and pulmonary infiltrates and is secured by the finding of hemosiderin-laden macrophages (siderophages) in bronchoalveolar lavage (BAL) fluid. Recurrent iron-deficiency anemia (IDA) without any pulmonary signs may be the only presenting feature of IPH. Iron-replacement therapy would treat for the iron deficiency caused by recurrent bleeding episodes, but treatment with glucocorticoids and/or

other immunosuppressant drugs is necessary to prevent recurrent bleeding episodes and iron deficiency.⁶

The aim of this paper is to present our observations relating to an 8-year-old girl who presented with recurrent IDA and allergic asthma, later diagnosed with IPH.

CASE REPORT

A 7-year-old girl presented to our pediatric hematology outpatient clinic with 2 years of recurrent pallor and weakness. Although she denied of any previous hemoptysis, hematemesis, or concomitant respiratory symptoms, she was hospitalized due to bronchiolitis at 6 months of age. She also had been treated with inhaler bronchodilators for allergic asthma until 5 years of age. Her weakness episodes began at 5 years of age and generally followed a tonsillopharyngitis infection. Her mother reported that she occasionally experienced burning sensation of the throat without any sign of tonsillopharyngitis. She had hemoptysis only once after vomiting about a week ago. She was diagnosed with IDA at an outlying hospital and was treated with oral iron supplementation. The symptoms recurred couple of times after iron supplementation was discontinued. She was hospitalized at the outlying hospital for diagnosis of anemia etiology and treatment about 1 year ago. Laboratory investigations had shown the following: Hb: 4.2 g/dL, RBC: $2.42 \times 10^{12}/L$, HCT: 13.5%, MCV: 55.8 fL, MCH: 17 pg, MCHC: 31 g/dL, and RDW: 21.8%. The reticulocyte count was 4%. Iron studies showed a ferritin level of 3 ng/mL, serum iron level of 36 µg/dL, total iron binding capacity of 341 µg/dL, and transferrin saturation of 10%. She was transfused with red blood cells at that time due to hemodynamic instability. Physical examination revealed tachycardia, stunted growth, profound skin and mucous membrane pallor, 2/6 systolic murmur, and hepatomegaly (2.5 cm below the costal margin). Laboratory investigations showed anemia with Hb: 6.3 g/dL, RBC: $3.42 \times 10^{12}/L$, HCT: 21.8% MCV: 63 fL, MCH: 18 pg, MCHC: 28.9 g/dL, RDW: 22%, CRP: 11 mg/dL, and ESR: 34 mm/h. The peripheral smear showed microcytosis, hypochromia, and poikilocytosis with anisocytosis. The reticulocyte count was 3%. Iron studies showed a ferritin level of 55 ng/mL, serum iron level of 16 µg/dL, total iron binding capacity of 396 µg/dL, and transferrin saturation of 4%. Although the ferritin level was within normal limits, when the high ESR was taken into consideration the patient was diagnosed with IDA. Patient was hospitalized for observation and further studies to outline the reason for recurrent and refractory IDA. Upper gastrointestinal endoscopy was normal. Gastrointestinal and renal blood losses were excluded.

During admission, Hb decreased to 5.6 g/dL; tachypnea and hypoxia developed. Patient was transfused with red blood cells with this clinical worsening. The working diagnosis was cardiac failure due to severe anemia or respiratory problems. A chest X-ray identified bilateral parenchymal infiltrate (Fig. 1). A chest computed tomography was subsequently performed, which revealed patchy areas of ground-glass opacification and reticular appearance (Fig. 2). Recurrent IDA, respiratory signs, and laboratory findings pointed to "Pulmonary hemosiderosis." Bronchoscopy was performed for definitive diagnosis. BAL fluid was bloody

Received for publication February 7, 2015; accepted June 30, 2015.
From the Departments of *Pediatrics; †Pediatric Hematology; and
‡Pathology, Ankara University School of Medicine, Dikimevi,
Ankara, Turkey.
Reprints: İrem Eldem, MD, Department of Pediatrics, Ankara University School of Medicine, Dikimevi 06100, Ankara, Turkey (e-mail: irem.eldem@gmail.com).
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showing active bleeding. Microscopic examination of the lavage fluid revealed hemosiderin-laden macrophages (Fig. 3).

Secondary causes of pulmonary hemosiderosis were investigated. Coagulation tests, serum immunoglobulin levels, and echocardiography were normal. ANA, anti-dsDNA, ANCA, antglomerular basement membrane proteins were negative. Celiac antibodies and cow milk-specific IgE were also negative.

On the basis of the above results, a diagnosis of IPH was made and prednisolone was started at 2 mg/kg/d. Hypoxia and anemia resolved on steroid treatment. She was hospitalized again 2 times at an outlying hospital with anemia after upper respiratory infections due to pulmonary hemorrhage attack related to steroid taper. She is being followed up by the pediatric pulmonology department and is currently clinically well at 17 months after diagnosis and has not been on steroid treatment for a month.

DISCUSSION

IPH is a rare but potentially fatal disease in children.⁷ Hemoptysis, typical infiltrate on chest X-ray, and IDA is the classic triad of IPH. However, recurrent and refractory anemia may be the leading symptom to diagnosis.^{8,9}

IDA is the most common nutritional deficiency in the world. Nutritional IDA is commonly seen at 6 to 24 months of age and adolescence. IDA requires additional workup particularly after these age groups. Blood loss must be considered as a possible cause in every case of IDA.

In diffuse alveolar hemorrhage, alveolar macrophages accumulate large amounts of iron in short periods of time and ferritin levels can be misleading. In our patient, peripheral smear findings were typical for IDA, but low transferrin saturation with normal iron-binding capacity, normal ferritin level, and high ESR are clues for chronic inflammation. Ioachimescu and colleagues explained that plasma ferritin levels may be normal or elevated because of the alveolar synthesis and release into circulation. However, this does not reflect the iron deposits of the body.⁷ However, alveolar macrophages that ingested large amounts of hemosiderin produce proinflammatory molecules leading to chronic inflammation and fibrosis if bleeding occurs repeatedly.⁶ So we believe that normal ferritin levels can be

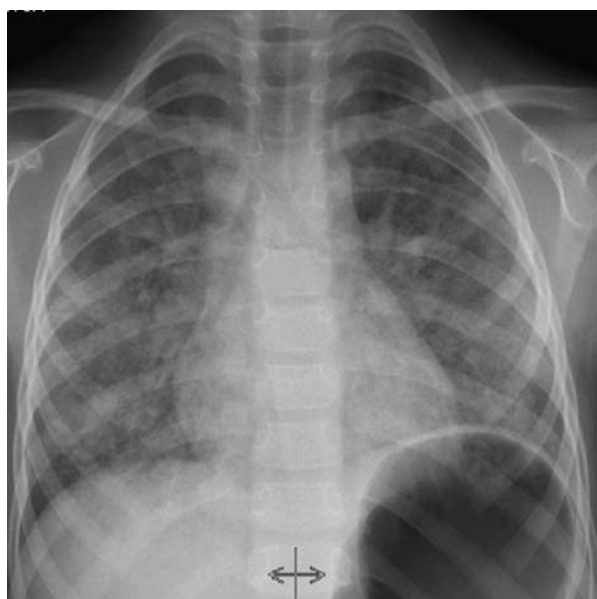


FIGURE 1. Chest X-ray of the patient with idiopathic pulmonary hemosiderosis showing bilateral diffuse infiltration.



FIGURE 2. Chest computed tomography of the patient with idiopathic pulmonary hemosiderosis showing bilateral ground-glass opacity.

explained by chronic inflammation. Increased acute phase reactants in our patient also support this hypothesis.

Our patient was routinely evaluated for the possible causes of IDA. She was screened for hemoglobinopathy, anemia of chronic disease, and hypothyroidism. Although occult blood in stool was negative, upper gastrointestinal tract endoscopy was performed to exclude chronic blood loss and intestine absorption disorders. In our patient a simple chest X-ray led the diagnosis. IPH definitive diagnosis was made by exclusion of other aforementioned systemic diseases that can cause pulmonary hemorrhage and the presence of hemosiderin-laden macrophages in the BAL fluid. Bronchoscopy is an important and easily performed diagnostic tool to evaluate such complex patients.

The patient experienced recurrent bronchiolitis attacks, diagnosed with asthma and treated with inhaler bronchodilators, until she was 5. However, she did not have any allergic history or improvement with bronchodilators. We speculate that her past history of asthma attacks and respiratory symptoms were related to pulmonary hemorrhage episodes.

Treatment of the acute episode of IPH with steroids (starting with 2 mg/kg/d of prednisolone and tapering slowly) for 6 months, followed by low doses has been shown

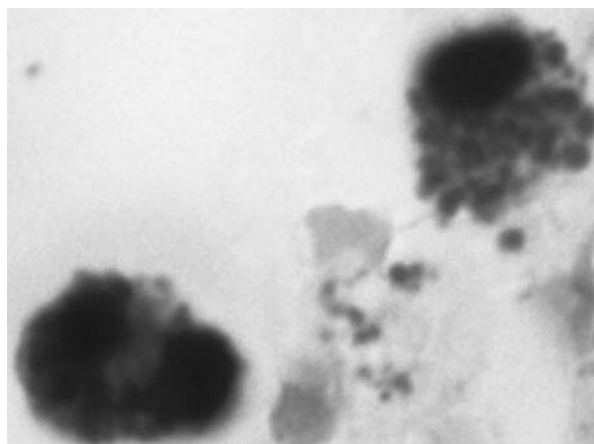


FIGURE 3. Perl prussian blue staining of the bronchoalveolar lavage fluid.

to be beneficial.¹⁰ Other immunosuppressant agents such as azothiopurine, hydroxychloroquine, cyclophosphamide, and methotrexate have been used with variable benefit in steroid refractory patients.² The course of the disease was considered to be poor, but Saeed et al have reported 86% 5-year survival in their 17 study patients.¹¹

Red blood cell transfusion was given only once in our clinic, when she developed heart failure symptoms due to severe anemia. Parenteral iron therapy can be an option due to chronic hemorrhage instead of transfusions. However, after diagnosis of IPH and initiation of steroid therapy, pulmonary hemorrhage episodes were quite diminished.

CONCLUSIONS

In conclusion, refractory/recurrent IDA with any pulmonary symptom may be the only presenting feature of IPH. The symptoms can mimic asthma attacks. To avoid a possible delay in diagnosis, in a patient with recurrent and unexplainable anemia and with any pulmonary symptom, chest X-ray with bilateral perihilar infiltration should lead to suspect pulmonary hemorrhage.

REFERENCES

1. Kjellman B, Elinder G, Garwicz S, et al. Idiopathic pulmonary hemosiderosis in Swedish Children. *Acta Paediatr Scand*. 1984;73:584–588.
2. Ohga S, Takahashi K, Miyazaki S, et al. Idiopathic pulmonary hemosiderosis in Japan: 39 possible cases from a survey questionnaire. *Eur J Pediatr*. 1995;154:994–995.
3. Salih ZN, Akhter A, Akhter J. Specificity and sensitivity of hemosiderin-laden macrophages in routine bronchoalveolar lavage in children. *Arch Pathol Lab Med*. 2006;130:1684–1686.
4. Pedersen FM, Milman N. Idiopathic pulmonary hemosiderosis. *Ugeskr Læger*. 1996;158:902–904.
5. Kabra SK, Bhargava S, Lodha R, et al. Idiopathic pulmonary hemosiderosis: clinical profile and follow up of 26 children. *Indian Pediatr*. 2007;44:333–338.
6. Nuesslein TG, Teig N, Rieger CH. Pulmonary haemosiderosis in infants and children. *Pediatr Respir Rev*. 2006;7:45–48.
7. Ioachimescu OC, Sieber S, Kotch A. Idiopathic pulmonary hemosiderosis revisited. *Eur Respir J*. 2004;24:162–170.
8. Chen KC, Hsiao CC, Huang SC, et al. Anemia as the sole presenting symptom of idiopathic pulmonary hemosiderosis: report of two cases. *Chang Gung Med J*. 2004;27:824–829.
9. Derbent M, Ozacay F, Saatci U, et al. Severe iron deficiency anemia in a child with idiopathic pulmonary haemosiderosis: a case report. *Turk J Pediatr*. 2002;44:258–260.
10. Kiper N, Gocmen A, Ozcelik U, et al. Long-term clinical course of patients with idiopathic pulmonary hemosiderosis (1979–1994): prolonged survival with low-dose corticosteroid therapy. *Pediatr Pulmonol*. 1999;27:180–184.
11. Saeed MM, Woo MS, MacLaughlin EF, et al. Prognosis in pediatric idiopathic pulmonary hemosiderosis. *Chest*. 1999;116:721–725.