

Idiopathic Pulmonary Hemosiderosis Presenting as a Rare Cause of Iron Deficiency Anemia in a Toddler - A Diagnostic Challenge

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Iron deficiency anemia is the most common cause of anemia in all age groups. Idiopathic pulmonary hemosiderosis is an extremely rare etiology of iron deficiency anemia seen predominantly in the pediatric population. Idiopathic pulmonary hemosiderosis is characterized by the triad of symptoms consisting of iron deficiency anemia, diffuse pulmonary infiltrates, and hemoptysis. The clinical presentation is extremely variable, and all three symptoms may not always be seen. Due to the rarity of the disease and the variability in clinical presentation, diagnosis is usually delayed. Early diagnosis and treatment with corticosteroids prevents further episodes of recurrent alveolar hemorrhage and improves the clinical outcome. Hence, a high index of suspicion is required for the diagnosis of this condition in young patients presenting with severe iron deficiency anemia and diffuse pulmonary infiltrates. We report a toddler with idiopathic pulmonary hemosiderosis whose initial clinical presentation was severe iron deficiency anemia.

CASE PRESENTATION

A 3-year-old female was transferred from an outside hospital for the management of severe anemia with a hemoglobin (Hb) of 2.6 g/dL (normal age specific range is 10.5 to 14 g/dL) and hematocrit (Hct) of 8% (normal age specific range is 33 to 42%). Her mother reported that she had a progressively decreasing appetite, worsening fatigue, and lethargy for a period of two weeks. She did not have fever. Other pertinent symptoms, including worm infestation and bleeding tendencies such as hematuria, hemoptysis, hematemesis, hematochezia or melena were absent. The patient had no significant travel history. There was no exposure to pets or farm animals. The family history was not contributory. She was hospitalized in another hospital eight months ago for the same complaints. Her hemoglobin and Hct at that time were 3 g/dL and 9%, respectively. Chest radiograph showed diffuse pulmonary infiltrates. She was diagnosed with pneumonia and was treated with intravenous ceftriaxone. Her anemia was managed with two units of packed red blood cell transfusion. Post transfusion Hb and Hct were 7g/dL and 21%, respectively. She was discharged home on oral iron supplementation but was lost to follow-up.

Physical examination at transfer demonstrated a pale looking girl whose weight was 12 kg and height was 90 cm (both values were in the 10th percentile for the age). Vital signs revealed an axillary temperature of 99°F (normal range is 96-99°F), heart rate of 130/min (normal age specific range is 90 - 150 beats per minute), respiratory rate of 30/min (normal age specific range is 22 - 30 breaths per minute), blood pressure of 90/55 mm of Hg (normal blood pressure values for 3-year-old female are 87/48 mm of Hg [50th percentile] and 104/66 mm of Hg [95th percentile]), and oxygen saturations (SpO₂) of 100% in room air. Her mucous membranes were pale in appearance. Cardiovascular examination demonstrated a 2/6 ejection systolic murmur (flow murmur) at the base of heart in addition to normal heart sounds. Normal breath sounds without any adventitious sounds were heard on both sides of the chest. No mass or organomegaly was felt in the abdomen.

Her complete blood count revealed a Hb of 2.5 g/dL and Hct 7.5%. Other hematological indices included a mean corpuscular volume (MCV) of 62.9 fL (normal age specific value is 81 fL), mean corpuscular hemoglobin (MCH) of 18 pg (normal age specific value is 24 - 30 pg), reticulocyte count of 7.2% (normal age specific range is 0.5 - 1 %) and red cell distribution width (RDW) of 20.9% (normal range

is 11 - 15%). Erythrocyte morphology showed microcytosis, hypochromia, and anisocytosis. Her white cell count was $9.9 \times 10^9/L$ (normal range is $5-15.5 \times 10^9/L$) with a differential count of neutrophils 66%, lymphocytes 30%, and monocytes 4% (normal age specific range is neutrophils 33-42%, lymphocytes 50-59%, monocytes 5%, and eosinophils 3%). Her platelet count was $318 \times 10^9/L$ (normal range is $150-350 \times 10^9/L$). Iron studies demonstrated serum iron of 16 microgram/dL (normal range 50-170 microgram/dL), ferritin of 4 ng/mL (normal range 10 - 60 ng/mL), total iron binding capacity of 388 microgram/dl (normal range 126-382 g/dL). Iron deficiency anemia (IDA) was diagnosed from the above parameters. Further investigations, including urinalysis, C-reactive protein, coagulation panel, serum electrolytes, renal function panel, liver enzymes, and hemoglobin electrophoresis, were all within normal limits.

A history of recurrent anemia and the presence of chest infiltrates in the past prompted us to suspect diffuse alveolar hemorrhage (DAH). Chest radiograph done in our hospital showed diffuse bilateral alveolar infiltrates in the upper lobes, perihilar region, and in the lower lobes (Figure 1). Computed tomogram (CT) scan of chest confirmed the patchy alveolar infiltrates in both lungs (Figure 2). Broncho-alveolar lavage (BAL) revealed the presence of abundant Prussian blue-stained hemosiderin-laden macrophages (Figure 3). An open lung biopsy confirmed diffuse alveolar hemorrhage (DAH) and the presence of numerous hemosiderin-laden macrophages (Figure 4). There was no evidence of pulmonary vasculitis or fibrosis. The biopsy picture favored the diagnosis of pulmonary hemosiderosis.

Further investigations for the workup for DAH revealed negative serology for antinuclear antibodies (ANA), c and p antineutrophil cytoplasmic antibodies (c and p-ANCA), anti-double stranded DNA antibodies (dsDNA), antiglomerular basement membrane antibodies (GBM), antiphospholipid antibodies, anticardiolipin antibodies, and lupus anticoagulant. The rheumatoid factor was negative. The RAST immunoCAP for IgE antibodies against cow's milk protein was negative. After carefully ruling out all the known causes of DAH, the diagnosis of idiopathic pulmonary hemosiderosis (IPH) was made. The patient received a total of four units of packed red blood cell transfusions over a period of one week. After the fourth transfusion, Hb and Hct increased to 11 g/dL and 33%, respectively. Oral prednisolone (2 mg/kg/day) was started and improvement in appetite and activity was noticed within one week. She was discharged home on oral iron supplementation and a weaning regimen of oral prednisolone. Complete resolution of symptoms was noticed at the one-month follow-up visit. Chest radiograph demonstrated complete disappearance of the lung opacities, and Hb and Hct remained stable at 10.5 g/dL and 31%, respectively.

DISCUSSION

Iron deficiency anemia (IDA) is the most common cause of anemia in children worldwide. The common etiological

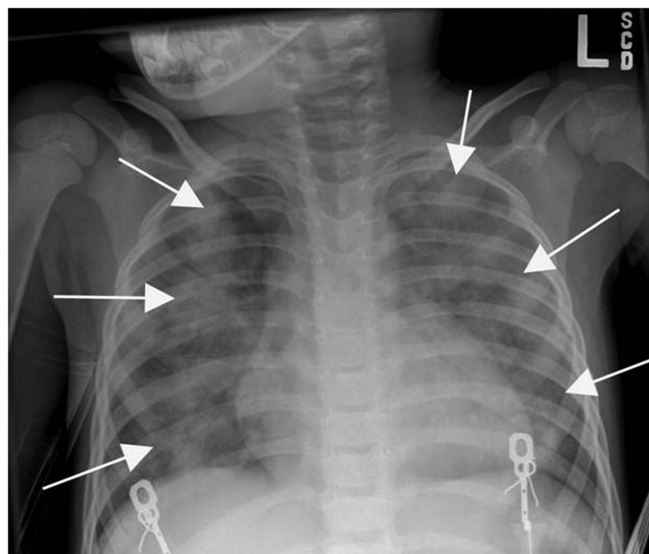


Figure 1: Chest radiograph on admission showing bilateral diffuse pulmonary infiltrates (white arrows).

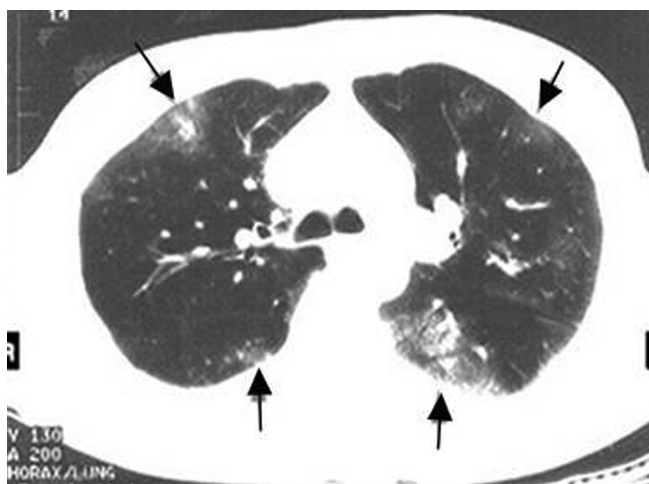


Figure 2: Computed tomogram of the chest on admission showing pulmonary infiltrates (black arrows).

factors implicated for iron deficiency are decreased iron intake (prolonged breast feeding, cow's milk feeding without iron fortification), decreased iron absorption (malabsorption and short gut syndromes), increased iron requirement (during active growth in early childhood), and chronic blood loss (excessive menstrual loss, inflammatory bowel disease). Idiopathic pulmonary hemosiderosis (IPH) is an extremely rare cause of IDA and a potentially lethal disease of unknown etiology. IPH belongs to a heterogeneous group of disorders that cause recurrent episodes of diffuse alveolar hemorrhage (DAH), resulting in pulmonary hemosiderosis.

In general, pulmonary hemosiderosis can be either primary or secondary to underlying diseases. The primary causes of pulmonary hemosiderosis include IPH, Goodpasture syndrome, and Heiner's syndrome (cow's milk

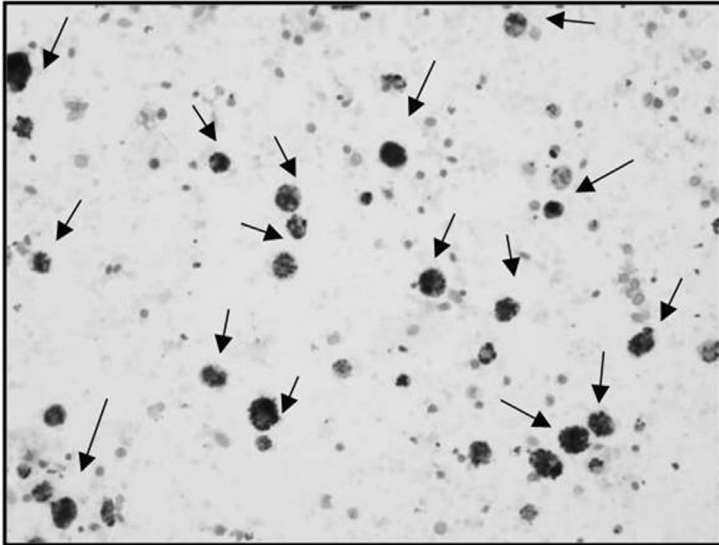


Figure 3: Broncho-alveolar lavage showing numerous Prussian blue-stained hemosiderin laden macrophages (black arrows).

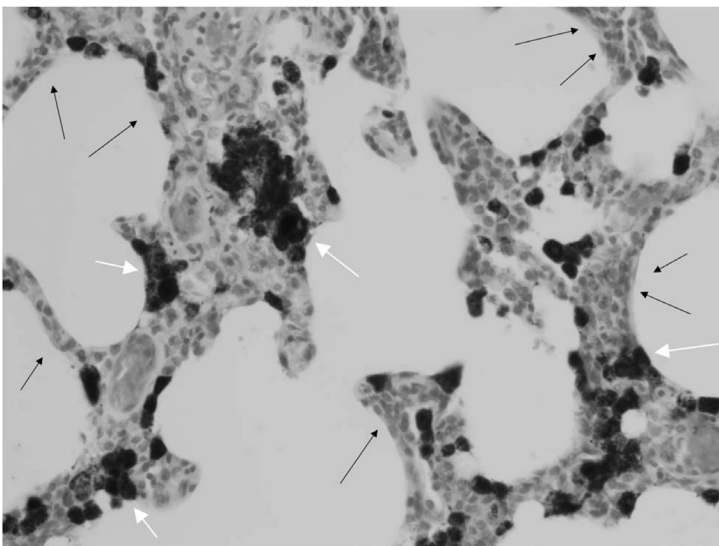


Figure 4: Open lung biopsy showing alveolar hemorrhage (black arrows) and numerous Prussian blue-stained hemosiderin-laden macrophages (white arrows).

hypersensitivity). Some of the common secondary causes include cardiovascular diseases such as congestive heart failure, pulmonary hypertension and mitral valve stenosis or collagen vascular diseases such as Wegener's granulomatosis, rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, and Henoch-Schonlein purpura. IPH is diagnosed when no underlying etiology for DAH is found after a thorough workup. Therefore, IPH is a diagnosis of exclusion, and it is characterized by the triad of iron deficiency anemia, hemoptysis, and diffuse pulmonary infiltrates in the chest radiograph.¹

Historically, IPH was first noted by Virchow in 1864 as

brown lung induration.² Later, Ceelen described IPH in detail in two children in 1931.³ The exact prevalence of IPH is unknown, but estimates obtained from Swedish and Japanese retrospective studies vary from 0.24 to 1.23 cases per million population.^{4,5} In general, the presentation of IPH is usually before the age of 10 years, which accounts for almost 80% of the cases.⁶ The remaining 20% of cases are diagnosed between 10-30 years of age.⁶ The exact cause of IPH is currently unknown, and an autoimmune mechanism is the most accepted etiology.⁷

The classical triad of symptoms (iron deficiency anemia, hemoptysis, and diffuse pulmonary infiltrates) may not always be present. As young children tend to swallow the blood, the episodes of hemoptysis usually go unnoticed. Respiratory signs and symptoms, such as coughing, wheezing, tachypnea, dyspnea, and crackles, are commonly seen. Similar to the patient reported here, pallor can rarely be the only presenting symptom.⁸ This high variability in clinical presentation makes the diagnosis very difficult and challenging. A high index of clinical suspicion is therefore required for the diagnosis of IPH. A delay in diagnosis or a misdiagnosis is not uncommon and is well documented in the literature. Pulmonary infiltrates are usually mistaken either for pneumonia or tuberculosis. In one study of 26 children with IPH, the mean delay in diagnosis was 30 months from the onset of symptoms.⁹

Bronchoalveolar lavage (BAL) or gastric aspirates usually demonstrate the presence of hemosiderin laden macrophages. The gold standard test for diagnosis of IPH is the lung biopsy. Histopathology demonstrates the presence of an alveolar hemorrhage and Prussian blue stain positive hemosiderin laden macrophages (HLM). In chronic cases, hypertrophy of the alveolar septa and pulmonary fibrosis may be seen. Lung biopsy also helps to rule out the other causes of DAH, such as Goodpasture syndrome, Wegener's granulomatosis, systemic lupus erythematosus, and Henoch-Schonlein purpura. The differential diagnosis for IPH also includes cow's milk protein hypersensitivity (CMPH), known additionally as Heiner's syndrome. In CMPH, the common symptoms reported are nasal congestion, repeated ear infections, wheezing, vomiting, diarrhea, and failure to thrive. The symptoms usually improve with the elimination of cow's milk protein from the diet and recur on reintroduction. High titers of antibodies such as IgG precipitating antibodies and milk-specific IgE antibodies are often demonstrated.

Corticosteroids are the mainstay of treatment for IPH. In an acute episode of bleeding, corticosteroids are potentially life saving. Also, long-term steroid therapy usually reduces both mortality and morbidity by decreasing the number of episodes of bleeding into the pulmonary parenchyma. If left untreated, recurrent episodes of bleeding will ultimately lead to fibrosis, restrictive lung disease, and eventually death. In view of the side effects from long-term oral steroids, inhaled corticosteroids have also been

tried in some centers with variable success. The other immunomodulant medications commonly used for IPH are hydroxychloroquine, azathioprine, and cyclophosphamide. The clinical course of IPH is extremely valuable. Due to rarity of this condition and inadequate follow-up, the prognosis of IPH is difficult to interpret. Saeed et al¹⁰ reported an 86% five-year survival rate for IPH patients with long-term immunosuppressive therapy; whereas in another study, out of 68 patients with IPH, 20 died at an average period of 3.3 years.⁷ The most common causes of death include massive pulmonary hemorrhage resulting in shock/respiratory failure or recurrent bleeding in the lung resulting in pulmonary hemosiderosis and fibrosis. Few cases of lung transplantation have been reported with limited success.

CONCLUSION

Idiopathic pulmonary hemosiderosis is a rare cause of iron deficiency anemia in childhood. Due to the variability in presenting symptoms, diagnosis of IPH can be potentially delayed. Clinicians should have a high index of suspicion for diagnosing this condition in children presenting with severe iron deficiency anemia. Early diagnosis and aggressive management with corticosteroids and immunosuppressive drugs may improve the outcome.

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