A child with recurrent pallor and hemoptysis: Diagnostic challenges

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A 7-year-old girl presented with severe pallor, cough, and massive hemoptysis. She had been previously hospitalized twice within the time span of 2 years for severe pallor and hemoptysis, each time requiring 2 U of blood transfusion. In the recent episode, blood examination was suggestive of iron deficiency anemia, chest radiograph yielded bilateral pulmonary infiltrate, computed tomography scan of lungs showed ground glass pattern, and bronchoalveolar lavage revealed hemosiderin-laden macrophages. Investigations to exclude any secondary causes of pulmonary hemosiderosis were negative. The child was diagnosed as a case of idiopathic pulmonary hemosiderosis and treated with prednisolone.

Introduction

Pulmonary hemosiderosis is a rare condition with abnormal accumulation of hemosiderin in the lungs. It is characterized by the triad of iron deficiency anemia, hemoptysis, and multiple alveolar infiltrates on chest radiograph. It may occur as a primary phenomenon, most commonly seen in children or secondary to cardiac, systemic vascular, or hemorrhagic diseases, which is more common in adults \cite{1}. The uncommon characteristic of the disease may be related to the fact that it is usually underdiagnosed \cite{2}. It is often diagnosed as a case of hypochromic or microcytic anemia, which is difficult to treat. Late diagnosis may yield poorer prognosis. Therefore, early definitive diagnosis and aggressive immunosuppressive therapy of idiopathic pulmonary hemosiderosis (IPH) are required to prevent pulmonary fibrosis and mortality in these patients \cite{3}.

Case report

A 7-year-old female child, born of a nonconsanguineous marriage, presented with two episodes of massive hemoptysis with exertional dyspnea for the last 2 days. There was past history of hospital admission twice, first time with only pallor at 5 years of age and second time with pallor and hemoptysis 3 months back. Each time she was transfused with 2 U of packed cells and discharged with iron supplementation, as the blood reports were suggestive of iron deficiency anemia. There was no history of recurrent fever, skin lesions, bleeding from any other site, arthritis, bone pain, any drug intake, or any contact with Tuberculosis (TB). Her appetite, bladder, and bowel habits were normal.

At the time of admission, the child had severe pallor, respiratory distress, tachypnea, and tachycardia. Her weight was 18 kg (between third and fifth percentile for age) and height was 119 cm (between 25th and 50th percentile for age). Local examination of mouth and nose did not reveal any source of bleeding. There were bilateral coarse crepitations on chest auscultation. The liver was enlarged 3.5 cm below the costal margin with associated tenderness. Other systems were normal.

On investigation, hemoglobin was 3.5 g\% with hypochromia, microcytosis, and anisocytosis on peripheral smear. Total leukocyte count was 9800/mm\textsuperscript{3} (neutrophil: 57\%, lymphocyte: 38\%, eosinophil: 4\%, monocyte: 1\%, and basophil: 0\%), and platelets were adequate with high erythrocyte sedimentation rate (118 mm in first hour). Serum ferritin level was low (4.6 mg/l) and total iron binding capacity was high (560 mg/dl), suggestive of iron deficiency anemia. Coagulation profile (including bleeding time, prothrombin time, and activated partial thromboplastin time), liver function test, renal function test, and echocardiography were normal. Stool for occult blood was positive. Routine urine examination was normal. Antinuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti Glomerular Basement Membrane (anti GBM) antibody, and Mantoux test were negative. Serum IgE level was normal.

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Chest radiograph revealed diffuse bilateral patchy pulmonary infiltrates (Fig. 1). High-resolution computed tomography of the thorax showed patchy ground glass attenuation in both lungs (likely to be diffuse alveolar hemorrhage), not associated with any bronchial thickening (Fig. 2). Pulmonary function test yielded restrictive pattern of lung disease (forced vital capacity 70% of predicted, forced expiratory volume in 1 s 76% of predicted, and forced expiratory volume in 1 s/forced vital capacity 108% of that predicted for age and sex). Pearl staining of bronchoalveolar lavage (BAL) demonstrated a significant number of hemosiderin-laden macrophages (HLM) (Fig. 3). Therefore, the child was diagnosed to be a case of IPH. Screening for celiac disease was carried out and antitransglutaminase 2 antibody was negative.

Initially after admission she was rescued with 2 U of whole blood and supplemental oxygen. She was put on oral prednisolone at a dose of 2 mg/kg/day, which was later tapered to 1 mg/kg/day after 2 weeks. Her condition improved after about 7–10 days of therapy. After 1 month of treatment, chest radiograph was clear (Fig. 4) and there was no further hemoptysis during the next 6 months.

Discussion

IPH is a rare disease of unknown etiology. The clinical picture of IPH was first documented by Ceelen in 1931 [4]. Our patient also presented with similar findings. The disease occurs most frequently during the first decade of life. Cases are distributed equally among male and female populations [5]. The incidence is reported from 0.24 to 1.23 cases per million populations.

The diagnosis is based on the presence of iron deficiency anemia, characteristic chest radiograph, and demonstration of HLM in the BAL [6] as was carried out in our patient. Findings of siderophages in gastric lavage fluid are also suggestive of IPH, but that was not required in our case, as the BAL fluid was positive for HLM. Tender hepatomegaly was there probably because of an evolving congestive heart failure due to sudden-onset severe pallor. In cases of...
massive hemoptysis, children tend to swallow some amount of blood, which can make the stool 'occult blood positive', as found in our patient.

The diagnosis of IPH can be confirmed only after excluding other causes of pulmonary hemorrhage, such as mitral stenosis with congestive cardiac failure, periarteritis nodosa, Wegener’s granulomatosis, Goodpasture’s syndrome, systemic lupus erythematosus, coagulopathies, etc. In our patient, investigations such as echocardiography, antineutrophil cytoplasmic antibody, antinuclear antibody, anti-GBM antibody, and coagulation profile were all found to be negative, thus excluding these common causes of pulmonary bleeding.

On the other hand, if we consider differential diagnoses of alveolar siderophages only, the above-mentioned causes are again the prominent ones along with a few others, such as acute respiratory distress syndrome, macrophage activation syndrome, etc. Both conditions are associated with sudden-onset deterioration in the setting of a pre-existing disease and are rarely recurrent. Pulmonary hemorrhage is not a very common presentation in them. Laboratory criteria for diagnosis of macrophage activation syndrome require presence of cytopenias of multiple cell lines or elevated liver enzymes. Thus, none of these are consistent with the presentation and investigation pattern of our case.

There have been a number of reports indicating association of celiac disease with IPH, also known by the eponym Lane–Hamilton syndrome [7]. However, screening of celiac disease was found to be negative in this case.

The pathogenesis of IPH is still not well-defined, and there are numerous theories about it. Most theories are related to autoimmune factors. Approximately one-half of the patients die within 1–5 years usually from acute pulmonary hemorrhage and progressive respiratory failure. The average duration of life in those dying from the disease is about 2.5 years after the onset of symptoms, if not treated properly [8].

The treatment of pulmonary hemosiderosis is largely supportive. Patients with acute crisis may require oxygen, mechanical ventilation, and blood transfusions. The majority of cases will respond to corticosteroids. There is no clear-cut recommendation about the duration of corticosteroid therapy. Usually, prednisolone has to be continued in the lowest possible dose to prevent recurrence of bleeding episodes. Steroid-sparing drugs are needed in cases of steroid toxicity. Other immunosuppressive drugs such as cyclophosphamide, cyclosporine, and chloroquine may also be effective during acute bleeding episodes and in cases resistant to steroid [9–12]. Recently, plasmapheresis and plasma exchange have also been used [13]. As reported in a scientific letter in 2007 [14], researchers found a beneficial role of the antioxidant N-acetylcysteine in preventing pulmonary bleeding and reducing the maintenance dose of corticosteroids, but there are insufficient pieces of evidence to recommend their routine use. Our patient responded to prednisolone and there has been no recurrence in the next 6 months. We can conclude that a high degree of suspicion is required to diagnose this rare disease in a child, especially if presented with recurrent hemoptysis and unexplained pallor requiring multiple blood transfusions. Findings of the triad (chest infiltrates in radioimaging, anemia, and HLM in BAL) can help our way forward toward reaching the ultimate diagnosis and thereby instituting early and definitive treatment to reduce mortality and complications.

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Conflicts of interest
There are no conflicts of interest.

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