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CASE REPORT

Idiopathic Pulmonary Hemosiderosis

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Abstract:
Recurrent or chronic pulmonary hemorrhage is rare in children. Idiopathic pulmonary hemosiderosis (IPH) manifests as hemoptysis, diffuse parenchymal infiltrates on chest radiographs and microcytic hypochromic anemia. The hemoptysis, anemia and pulmonary infiltrates present may be mistaken for more common diseases, delaying the diagnosis and further management. Idiopathic pulmonary hemosiderosis is a disorder of unknown etiology. Treatment of IPH includes immunosuppressive drugs along with supportive measures.

Key words: Idiopathic pulmonary hemosiderosis, Anemia, Hemoptysis, Tuberculosis, Pneumonia
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Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a relatively uncommon but potentially fatal occurance in pediatrics. The etiology of IPH is broad and includes auto immune diseases like systemic vasculitis and Goodpasture`s syndrome; antiphospholipid antibody syndrome; pulmonary infections; drug reactions; bone marrow and solid organ transplantions; mitral stenosis; coagulation disorders caused by diseases or anticoagulant drugs; isolated pauci-immune pulmonary capillaritis and idiopathic [1,2].

Recurrent diffuse alveolar bleeding in the lower airways may become severe and present with anemia or respiratory compromise, leading on to pulmonary hemosiderosis and fibrosis [1,3,4]. Ultimately restrictive lung disease will develop and may lead to death [5]. Many children and young adults swallow rather than expectorate the mucus, which may prevent recognition of hemoptysis, the primary presenting symptom of this disorder. The hemoptysis present may be mistaken for more common diseases like tuberculosis, pneumonia, foreign bodies, cardiac disease or bleeding disorders [6, 7].

Case Report

We report a 8 year old boy admitted with cough, fever, hemoptysis and anemia on and off for two years duration, which had increased since 15 days, earlier he was managed elsewhere with antibiotics, hematinics, a 'course of anti tubercular treatment' and packed cell transfusions four times in two years. There was no family history of similar complaints or contact with tuberculosis or history of atopy in the family. He was immunized for the age, he was averagely built and nourished. He had fever, tachycardia, tachypnea, pallor, chest in-drawing and hepatomegaly. The patient was diagnosed as severe pneumonia with anemia.

His investigations revealed Hb of 7 gm/dl, TC of 7200, DC- N-50%, L-43%, E-6%. M-1% and B-

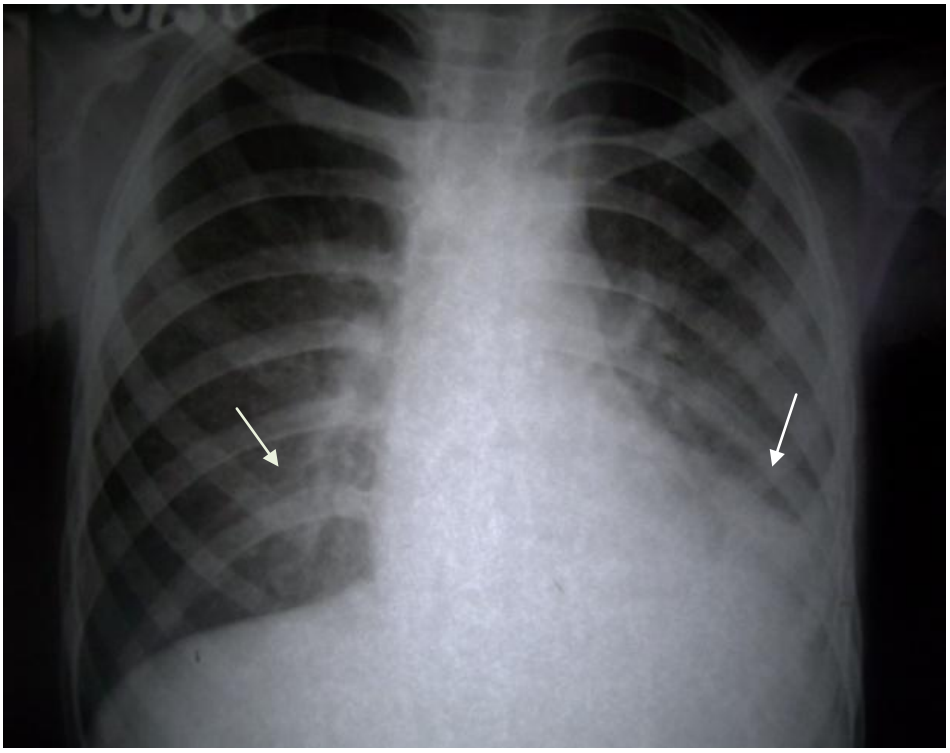

Figure 1. Chest x ray showing bilateral non-homogenous opacities and consolidation over both lower lobes.

0%, ESR- 40 mm at the end of 1st hr, PCV- 22%, platelet count of 4.1 lakhs, MCV-76fl, MCH-22 pg, MCHC-28 g\dl, PS had microcytic hypochromic RBCs with few tear drop cells, target cells and polychromatophilic cells. Reticulocyte count was 2%. ABG showed hypoxemia. Chest x ray showed bilateral non-homogenous opacities and consolidation over both lower lobes (Figure 1). He was started on antibiotics and supportive measures including packed cell transfusion. In view of similar past history and blood transfusions he was investigated further.

His investigations showed normal urine, renal functions, liver functions, serum electrolytes, RBS, HIV was negative by ELISA, Montoux negative, serum iron was 142 microgms\dl, TIBC was 300, bone marrow showed erythroid hyperplasia with megaloblastic change, C3 was 118mg\dl, ANA negative, PR3-ANCA (C-ANCA) negative.

CT chest showed diffuse ground glass opacities in both the lung fields, few centrilobular nodules, multiple small emphysematous bullae in the subpleural region and para septal emphysema (Fig 2). Broncho alveolar lavage done showed – numerous hemosiderin laden macrophages (sideroblasts). Thoracoscopic lung biopsy showed lung parenchyma with extensive intra alveolar accumulation of hemosiderin laden macrophages along with large areas of intra alveolar hemorrhage. Also seen were areas of interstitial fibrosis and mononuclear inflammatory cell aggregates, features consistent with pulmonary hemosiderosis.

A diagnosis of Idiopathic pulmonary hemosiderosis was made and started on oral prednisolone. His symptoms started improving and prednisolone was tapered after 3 months, he had no recurrence of symptoms, his hemoglobin was 13 mg\dl, chest radiography was showing clearing of opacities after a follow up of 6 months.

Discussion

Pulmonary hemorrhage is uncommon but potentially life threatening occurrence in children. Many children and young adults swallow rather than expectorate the mucus, which may prevent the recognition of hemoptysis. Hemoptysis must always be separated from episodes of hemetemesis or epistaxis, as they can present similarly in children [17].

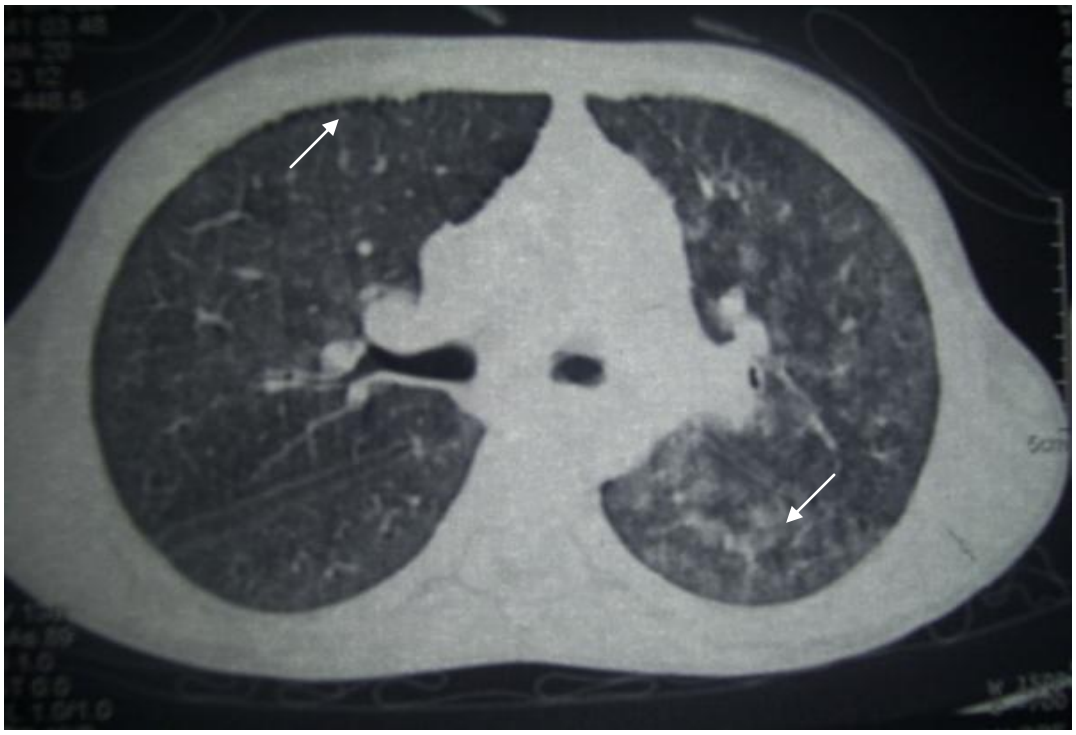

Figure 2. CT Chest showing diffuse ground glass opacities in both the lung fields, few centrilobular nodules, multiple small emphysematous bullae in the subpleural region and para septal emphysema

Idiopathic pulmonary Hemosiderosis (IPH) is characterized by hemoptysis, dyspnoea, diffuse parenchymal infiltrates on chest radiographs and microcytic hypochromic anemia [1,2]. Following alveolar bleeding the alveolar macrophages convert the hemoglobin's iron into hemosiderine within 36-72 hours. As the hemosiderine-laden macrophages reside for up to 4-8 weeks in lungs, the term pulmonary hemosiderosis can be reserved for recurrent or persistent intra alveolar bleeding [8-10].

Idiopathic pulmonary Hemosiderosis (IPH) was first described by VIRCHOW in 1864 as "brown lung induration"[11]. Ceelen in 1931 described in detail about IPH in the autopsy findings of children with the disease [12]. Waldenstorm established the first ante mortem diagnosis of IPH in 1944. [7,13]

IPH is a rare condition with an unknown incidence and prevalence in children. A Sweedish study published in 1984, by retrospective record review from 1950 to 1979, estimated an incidence of 0.24 per million children per year [16]. And another study from Japan estimated ~1.23 cases per million in a retrospective case analysis [17]. In children generally, the manifestations of IPH are seen before the age of 10 years. Nearly 80% of cases occur in this age group. The rest 20% of cases occur in adults and are typically diagnosed before the age of 30 years. The ratio of male to female is equal in childhood, and males are only slightly more affected in the adults [2, 14, 15].

The conditions that present with chronic pulmonary hemorrhage are diverse and in some patients extensive investigative work up for a specific etiology may be negative. The diagnosis of IPH is made when there is evidence of chronic or recurrent diffuse alveolar hemorrhage and exhaustive evaluation for primary and secondary etiologies are negative. A biopsy specimen should not reveal any evidence of granulomatous disease, vasculitis, infection, infarction, immune complex deposition, malignancy or any other features of associated primary or secondary conditions [1, 17].

Pulmonary hemosiderosis can be classified as primary or secondary [17]. Primary Pulmonary

hemosiderosis is described as encompassing the diagnosis of IPH, Goodpaster syndrome (anti basement membrane antibody disease), and Heiners syndrome (Cow's milk protein hyper reactivity). Among these, Goodpaster syndrome is the most common cause of pulmonary hemorrhage [5]. Secondary Pulmonary hemosiderosis includes diverse group of etiologies. Among these are cardiac causes of pulmonary hemosiderosis such as congestive heart failure, pulmonary hypertension, and mitral valve stenosis. Vasculitic and collagen vascular diseases such as systemic lupus erythematosis, rhematoid arthritis, Wegener's granulomatosis and Henoch-Schonlein purpura are important group to be considered in the differential diagnosis. Inherited or acquired coagulopathies are also encountered. Prematurity is also a recognized risk factor for hemorrhage. Pulmonary hemosiderosis has been described in association with celiac disease. Post infectious processes such as hemolytic uremic syndrome and immunodeficiency syndromes including chronic granulomatous disease have also been implicated.

There are few etiological hypothesis put forward for IPH including genetic theory, autoimmune theory, allergic theory, environmental theory, and metabolic theory. The common delineator being postulated structural lesions of the alveoalar-endothelial membrane.

The clinical presentation of pulmonary hemorrhage varies from acute, fulminant hemoptysis, to chronic cough and dyspnoea, repetitive hemoptysis, fatigue, or only asymptomatic anemia. In children failure to thrive and anemia (and less often hemoptysis) can be the presenting findings [1, 14]. Symptoms may be of the underlying and associated disease process rather than pulmonary hemorrhage. Atypical presentation of IPH may include complete heart block, infants presenting with severe anemia requiring repeated blood transfusions and absence of hemoptysis [2-4].

The clinical course includes two phases First, an acute phase of "IPH exacerbation", corresponding to intra alveolar bleeding. These episodes manifested as cough, dyspnoea, hemoptysis and sometimes respiratory failure. Secondly, the chronic phase characterized by a slow resolution of previous symptoms with or without treatment.
The physical examination also differs in the two clinical phases. The acute phase has symptoms and signs of respiratory failure, cough and hemoptysis or worsening anemia and, at the other end of spectrum, an absolutely normal examination. The chronic phase includes pallor, emaciation, failure to thrive, hepato-splenomegaly and some times normal examination. In patients with fibrosis, bilateral crackles and clubbing may be present [17].

The lung tissues appear brown secondary to the presence of hemosiderine from repeated episodes of pulmonary bleeding. On macroscopy the lungs demonstrate so called "brown induration", due to infiltration with iron and with various degree of fibrosis [11]. The presence of blood in air ways or alveoli indicates recent hemorrhage [2]. Hemosiderine-laden macrophages are seen with recovering, recurrent or chronic pulmonary hemorrhage. It takes 48-72 hours for the alveolar macrophages to convert iron from RBCs into hemosiderine. Other non specific pathological findings can include thickening of alveolar septae and hypertrophy of type II pneumocytes. Fibrosis may be seen with chronic disease [2, 5, 17]

Pulmonary hemosiderosis is associated with decreased hemoglobin and hematocrit. The classical finding is a microcytic, hypochromic anemia. The reticulocyte count is elevated. The anemia of IPH can mimic a hemolytic anemia [5]. Serum iron is reduced, iron binding capacity is generally elevated. WBC and differential count may indicate infection or eosinophilia. A stool examination may be heme-positive secondary to swallowed blood. Renal and liver functions should be reviewed. A urine analysis should be obtained to assess for evidence of nephritis. A coagulation profile, quantitative immunoglobin assay (including IgE), and complement studies are recommended. Sputum examination, although not very sensitive, can demonstrate intra alveolar bleeding, by hemotoxylin-eosin and Prussian blue (Perl's) stains [18].

Broncho-Alveolar Lavage (BAL) from involved areas has higher diagnostic yield than the sputum examination [19-21].

The predominant cellular types are the alveolar macrophages, filled with hemosiderine, intact erythrocytes and occasionally neutrophils. Testing for ANCA, ANA, anti-dsDNA, RF, anti-phospholipid antibody, Anti-GBM antibodies evaluates for a number of primary and secondary etiologies. Raised ESR is a nonspecific finding.

Pulmonary function tests (PFTs) show in general a restrictive pattern of variable severity [17, 22]. The diffusing capacity of carbon monoxide (DLCO) may be low or normal in the chronic phase but is likely to be elevated in the acute hemorrhagic phase. Respiratory insufficiency can occur and can be either manifested at rest, or latent, only on exertion.

There is no pathognomic finding of IPH. The chest radiograph may show evidence of acute or chronic disease. During acute phase the chest radiograph may show diffuse alveolar type infiltrates, predominantly in the lower lung fields, with corresponding ground glass attenuation on the high resolution CT scan. With the chronic disease fibrosis, lymphadenopathy and nodularity may be seen [23].

There are no controlled studies or, large longitudinal survey of patients with IPH. So the current management of disease is result of observational studies of patients over the years. Supportive therapy includes volume resuscitation, supplemental oxygen, ventilator support and transfusion of blood products. If an associated treatable condition exists, surgical or medical therapy should be directed at the underlying condition.

In IPH, early treatment with systemic corticosteroids is the treatment of choice. Therapy is generally initiated at 2-5 mg/kg/day and decreased to 1mg/kg/day every other day after resolution of the acute symptoms. Early corticosteroid therapy appears to decrease episodes of recurrent hemorrhage. This therapy may also help in decreasing progression to fibrotic disease [18]. A subgroup of patients may not respond optimally to corticosteroid therapy alone. In these cases immunosuppressive agents such as methotrexate, cyclophosphamide, azathioprine and chloroquine have been used with variable results [1, 5, 18]. Kabra SK et al. [1] have shown that inhaled corticosteroid used during the steroid tapering stage after the acute phase, had a positive effect on improvement in the outcome of IPH cases.

In chronic disease, lung transplant has been performed in cases which are refractory to immunosuppressive therapy. In two reported case studies, IPH has recurred in the transplanted lungs [24, 25].

The most frequent cause of death is acute respiratory failure secondary to massive diffuse alveolar hemorrhage and chronic respiratory failure and cor pulmonale due to severe pulmonary fibrosis. Kabra SK et al studied 26 children with IPH and found out that older age, longer duration of illness, history of hemoptysis and jaundice were associated with poor response to therapy [1]. In another case series, 68 patients with a mean follow up of 4 years, 20 patients had died, 17 had recurrent exacerbations, 12 had chronic active disease and 19 remained asymptomatic [2]. A more recent review by Muhammad M saeed et al [5] reported a 5 year survival rate of 86%. Spontaneous remissions have been documented.

Summary:

Idiopathic pulmonary hemosiderosis (IPH) is diffuse alveolar hemorrhage syndrome with no detectable underlying disease. IPH is characterized by recurrent or chronic pulmonary hemorrhage and accumulation of iron within the alveolar macrophages. Clinically, it manifests as a triad of hemoptysis, diffuse parenchymal infiltrates on chest radiographs and microcytic hypochromic anemia. Its etiology remains unknown, there is no definitive treatment. Treatment includes oral corticosteroids and other immunosuppressive drugs like azathioprine, cyclophosphamide, hydroxychloroquine and inhaled corticosteroids [5,6].

Our case had repeated bleeding in to the lungs with severe anemia which was refractory to treatment. He also required repeated blood transfusions for the same. Elsewhere initially he was managed as a case of pulmonary tuberculosis

with a course of anti tubercular treatment. Nutritional iron deficiency anemia is common disease in our children, as is pulmonary tuberculosis which may mislead us to treat with hematinics, antibiotics or anti tubercular drugs without benefit. A high index of suspicion in the relevant clinical setting will overcome the delay between the onset of illness and diagnosis and helps in appropriate management of this uncommon disease.

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