

Microcytic Hypochromic Anemia in Idiopathic Pulmonary Hemosiderosis: A Diagnostic Pitfall

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Idiopathic pulmonary hemosiderosis (IPH) is a rare, life-threatening disease of uncertain etiology, characterized by recurrent intra-alveolar hemorrhages and usually afflicting young adults or children(1). Symptoms of lung hemorrhage are often few and atypical(2). Consequently, the condition may go unrecognized for a few years or months, presenting as recurrent iron deficiency anemia with no actual hemoptysis(3). Failure to diagnose and treat the syndrome in early stages could result in progression and eventual respiratory failure because of pulmonary fibrosis(4). This communication shares the experience of three cases of IPH, diagnosed over a two year

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Received for publication: December 31, 1993;

Accepted: March 31, 1994

period wherein the dominant clinical manifestations of recurrent microcytic hypochromic anemia had caused considerable diagnostic difficulties.

Case Reports

Case 1: A 6-year-old boy, from a good socioeconomic background, presented with a history of recurrent episodes of pallor over the preceding 18 months. The first bout of illness was associated with fever, cough and maculopapular rash (interpreted as measles). The anemia had responded well to parenteral injections of Imferon. Subsequent development of episodic pallor every 4 to 6 months had necessitated hospitalization in teaching hospitals on at least two occasions. A predominantly microcytic hypochromic blood picture led to a thorough, unsuccessful, investigational search for the etiological basis of iron deficiency. He received several courses of both oral and parenteral iron therapy. Blood transfusions (at least twice) and anti-helminthics resulted in temporary relief. A fresh episode of acutely oncoming pallor in January, 1990 prompted a referral to PGIMER.

Examination revealed an alert child of average build and nourishment with moderate pallor. The systemic examination was unremarkable. The results of investigations were as follows: Hb: 6.0 g/dl; TLC : $8.0 \times 10^9/L$; HbF <1% with normal hemoglobin electrophoresis; plasma Hb 5 mg/dl; urinary Hb: not detected; G6PD screening: normal; serum iron : 15 mg/dl; TIBC : 320 mg/dl; serum and red cell folate and serum vitamin B₁₂ : normal, Ham's sucrose lysis test negative; stool for occult blood negative x 3 times; barium meal follow-through examination, renal and liver function tests within normal limits.

The investigations confirmed an iron

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deficiency anemia but failed to determine its etiological basis. Oral iron therapy was restarted and hemoglobin was maintained at levels of around 100 g/dl for the subsequent 10 months (Fig. 1), at which time hospitalization became necessary for fever, cough and worsening pallor. His Hb had fallen to 4.5 g/dl and the chest X-ray revealed bilateral, fluffy, alveolar opacities (Fig. 2). A trial of antitubercular drugs (isonex, rifampicin and pyrazinamide) produced no benefit and his hemoglobin fell repeatedly inspite of several packed red cell transfusions. The appearance of small amounts of hemoptysis, three weeks later, coupled with deterioration of respiratory distress prompted a search for blood loss occurring into the lungs. The possibility was confirmed when

repeated gastric aspirates and sputum specimens were shown to have hemosiderin laden macrophages. Investigations aimed at ascertaining a cause for the alveolar hemorrhage were all negative, thus establishing a final diagnosis of idiopathic pulmonary hemosiderosis (IPH). Antitubercular treatment was stopped. Parenteral hydrocortisone, packed red cell transfusions and oxygen helped in tiding over the acute phase. Azathioprine in an initial dose of 2.5 mg/kg/day resulted in steady improvement over the next four weeks. The child has remained asymptomatic during a follow up period of over 34 months since his last hospitalization in January, 1991. He has been off hematinics. Azathioprine was gradually tapered off and stopped in January, 1993. There has

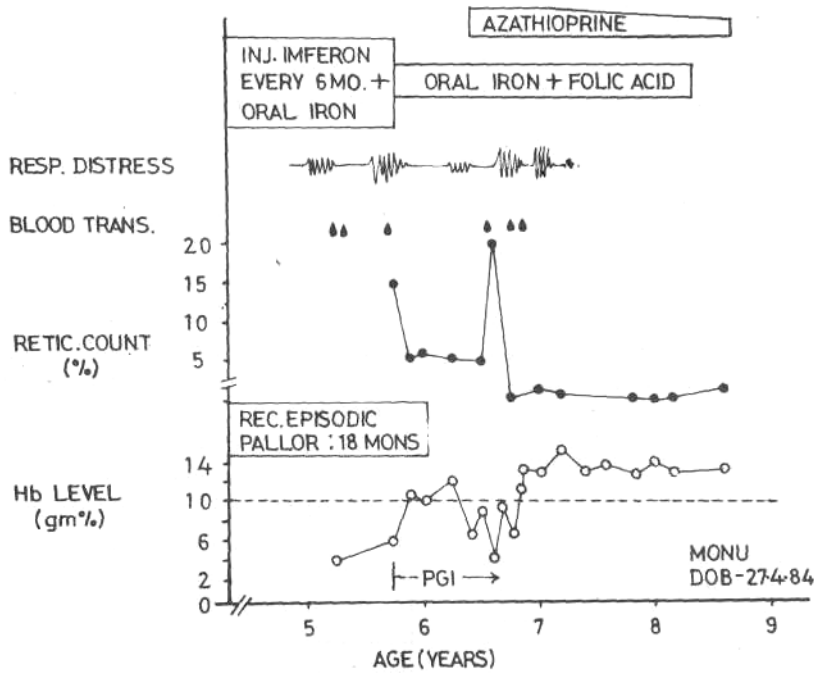


Fig. 1. Clinical course of Case 1.

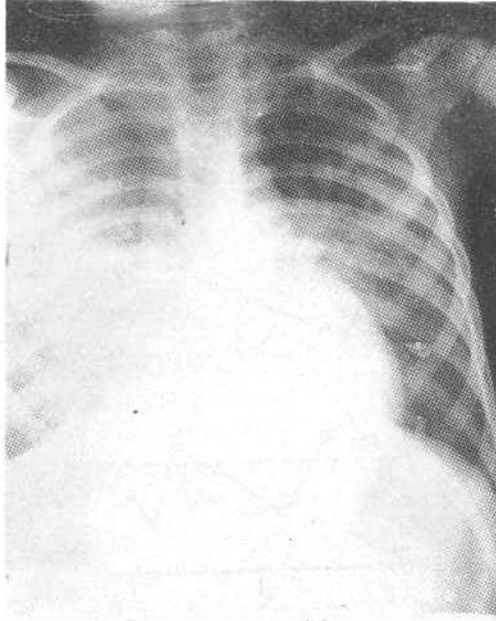


Fig. 2. X-ray chest showing bilateral, fluffy alveolar opacities (Case 1).

been significant clearing in the alveolar opacities in a recent chest X-ray (*Fig. 3*). He has been transfusion independent and his hemoglobin has remained in excess of 12.0 /dl.

Case 2: A 5^{1/2}-year-old son of a Captain in the Army, presented with two distinct episodes of moderate to severe pallor in the ear preceding referral to PGIMER (*Fig. 4*). The progression of anemia was over days and was associated with moderate grade fever, cough and mild hemoptysis. The recurrent nature of this microcytic, hypochromic

anemia had proved enigmatic. A trial of antitubercular drugs prescribed on the basis of diffuse pulmonary infiltrates on a chest X-ray had failed to induce an adequate response. Except for moderate pallor, there were no remarkable features on general physical and systemic examinations.

After documenting the presence of microcytic, hypochromic anemia, a clinical diagnosis of IPH was promptly confirmed by demonstrating hemosiderin laden macrophages in gastric aspirate and sputum specimens and by excluding known causes

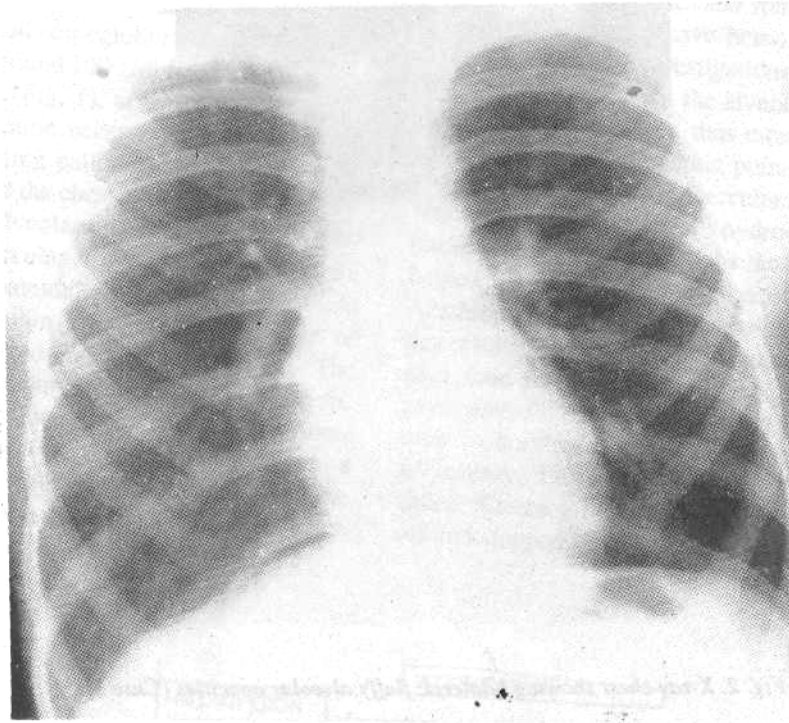


Fig. 3. X-ray chest showing significant clearing of alveolar opacities (Case 1).

of alveolar hemorrhage. Azathioprine was started in a dose of 2.5 mg/kg/day and increased to 3.75 mg/kg/day after his hemoglobin showed a decline in the initial few weeks. It picked up thereafter and has been maintained at values ranging from 11.0 to 12.6 g/dl since August, 1992. Azathioprine has been gradually reduced to a dose of less than 1.0 mg/kg/day and a recent chest X-ray has demonstrated almost complete clearance of the pulmonary infiltrates. He was asymptomatic and well when last assessed in the Pediatric Hematology Clinic in October, 1993.

Case 3: A 6V2-year-old boy, was admitted, in September 1992, with severe anemia and respiratory distress. The child had been

receiving Ayurvedic therapy for a couple of months for pallor, which had been observed after an episode of malenic stools. The recent deterioration had occurred about 3 days prior to hospitalization and was characterized by fever, hemoptysis, hematemesis and hematochezia. He had a hemoglobin of 3.0 g/dl and a TLC of $12.8 \times 10^9/L$ with 82% polymorphs. The PBF revealed a predominantly microcytic, hypochromic picture. Extensive bilateral, diffuse, reticulonodular opacities were seen in a skiagram of the chest. He had type-I respiratory failure with mild acidosis.

There was progressive worsening of his respiratory failure that led to a cardiorespiratory arrest after another bout of bleeding.

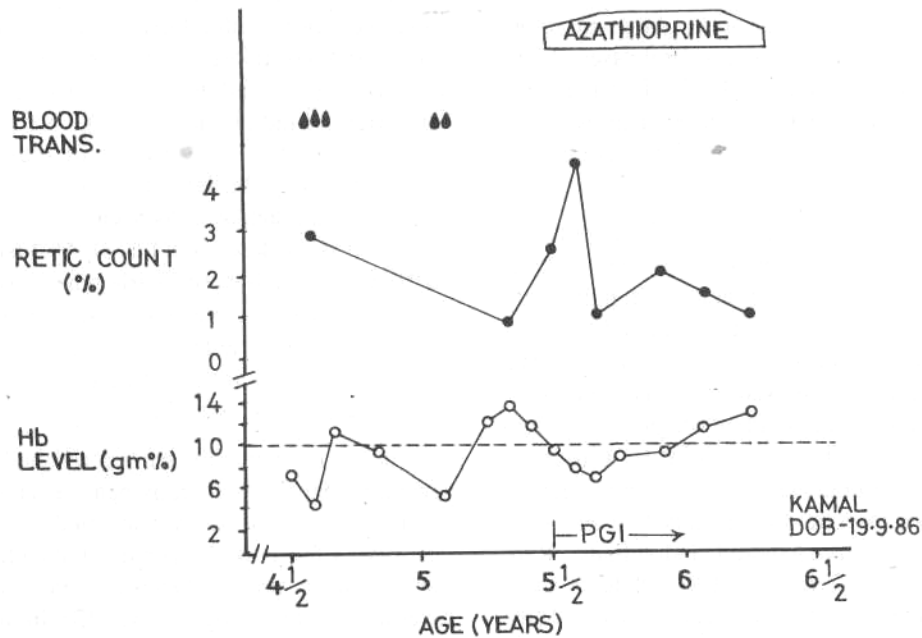


Fig. 4. Clinical course of Case 2.

Intubation showed fresh blood pouring out from the larynx. He died about 10 hours after hospitalization. Histopathological examination of the lungs demonstrated evidence of recent and past pulmonary hemorrhage with interstitial fibrosis, features consistent with a histopathological diagnosis of IPH.

Discussion

Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder and refers to recurrent alveolar hemorrhages that occur in the absence of hemodynamic abnormalities, infection, coagulopathy or systemic disorders such as anti-basement-membrane antibody (ABMA) disease, systemic lupus erythematosus (SLE) or vasculitis(4). Most cases of IPH have been reported in children aged be-

tween 1 to 7 years. Kjellman *et al.*(5) have defined the following criteria for diagnosis: (i) iron deficiency anemia, in which other causes of anemia have been excluded; (ii) chronic or recurrent pulmonary symptoms such as cough, hemoptysis and dyspnea; (iii) microscopic findings of siderophages in sputum or gastric juice and/or typical microscopic findings in lung biopsy material or in autopsy specimens. The manifestations of the three cases described in this communication satisfy all these features and reflect the total spectrum of presentation. Lack of awareness of the entity resulted in considerable delay in diagnosis in Case 1 and proved fatal in Case 3, a fact acknowledged in earlier reports of IPH wherein diagnosis was seldom made whilst the patient was

living(6). Since the first report by Gelen in 1931 of pulmonary fibrosis and massive hemosiderin deposition in the lungs in autopsies of two children(7), several cases of IPH have been documented. The fact that over 75% of the patients are now diagnosed during life indicates that clinicians have greater awareness of the disease(8).

The pathogenesis of IPH remains obscure. A defect in vasomotor control, leading to an intermittent increase in pulmonary vascular resistance, was suggested by Soergel and Sommers(8) but catheterization data have failed to substantiate this hypothesis. In an interesting epidemiological investigation of 30 children with IPH, Cassimos, *et al.*(9) implicated environmental factors, perhaps insecticides, as causative agents in genetically predisposed individuals. Rare occurrences of familial IPH(10) have similarly lent credence to a genetic basis. Most authors now believe in an autoimmune disturbance(11-13) and cite the following reasons in support of an immune etiology for IPH(4,11): (i) alveolar hemorrhage in IPH is similar to that observed in ABMA disease, SLE and other immune diseases; (ii) IP and celiac sprue have coexisted in several individuals; (iii) IgA is elevated in over 50% of cases; and (iv) immunosuppressive agents have often proved beneficial.

In its typical form, IPH in children presents with a triad of anemia, dyspnea and hemoptysis(5,10,11). Symptoms may, however, be few and atypical. Presentation with recurrent, episodic iron deficiency anemia of obscure etiology, as in Case 1, poses diagnostic difficulties for the uninitiated physician. Similarly, fever and cough at the onset may result in such patients being treated for pneumonia for long periods before the diagnosis is actually suspected(2,9). X-rays of the chest may be entirely normal

in the early stages but often show reticulonodular opacities affecting the perihilar and lower zones with relative sparing of the apices and costophrenic angles. Shadows tend to migrate and may even disappear. The extent of radiological findings often do not correlate with the severity of clinical symptomatology. Miliary stippling or massive confluent shadows, as seen in Case 3, have also been described(12,13). Diffusion coefficient for radioactive carbon monoxide show >30% rise if there is an acute bleed as the carbon monoxide attaches to the hemoglobin in the alveoli. This figure decreases as the disease progresses(3).

The rarity of the disease has resulted in several modalities of therapy being attempted in IPH. Splenectomy was tried in the late 1940's but is no longer recommended. Steroids have proved beneficial in acute cases and in preventing relapses(13). Immunosuppressive treatment, using azathioprine, has been successful in inducing symptomatic improvement and stabilizing radiographic appearances and pulmonary function(2,12,13). The drug, administered over several months, has produced similar benefits in two of our cases. Other modalities such as plasmapheresis, nasal budenoside, sodium chromoglycate, pulse methyl prednisolone and intravenous IgG have been tried in the past decade with good short term results(15,16). The latter two drugs may be particularly useful in cases with massive pulmonary hemorrhage. In a recent communication, Bush *et al.*(17) have reported beneficial effects of chloroquin in two cases with IPH.

Iron deficiency anemia of dietary origin is rampant in developing countries. A microcytic hypochromic blood picture is, therefore, a very common occurrence. Failure to respond to or recurrence after

adequate iron replacement therapy focusses attention on the gastrointestinal tract. As is illustrated by our cases, occult pulmonary hemorrhage is often not considered, because of the rarity of the condition. It is recommended that appropriate investigations be carried out to exclude IPH in cases with microcytic, hypochromic anemia who fail to demonstrate the expected response to treatment. Early recognition of IPH and prompt institution of immunosuppressive therapy would help in minimizing pulmonary damage.

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