

## CASE REPORT

# Pitfalls in the diagnosis of idiopathic pulmonary haemosiderosis

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Idiopathic pulmonary haemosiderosis is a very rare but devastating disorder. Diagnosis is sometimes difficult and the clinical course exceedingly variable, as illustrated by this report of a girl, aged 2 years 4 months, with severe iron deficiency anaemia. There was no response to iron therapy and transfusions. Sustained and striking reticulocytosis associated with low haptoglobin mimicked haemolytic anaemia. Positive faecal blood test was documented after repeated testing. There were no pulmonary symptoms. A chest radiograph showed bilateral diffuse alveolar infiltrates. Bronchoalveolar lavage fluid showed numerous siderophages. High resolution computed tomography of the thorax revealed early pulmonary fibrotic changes. Recurrent reticulocytosis appeared to be a very useful sign of recurrent bleeding episodes.

Iron deficiency anemia (IDA) is a common disorder in paediatric practice. The haematological response to iron is usually remarkable within the first month of therapy. Idiopathic pulmonary haemosiderosis (IPH) is a rare cause of IDA and is often not considered unless the typical triad is present or until other possibilities have been excluded. The disease is usually lethal and leads to progressive pulmonary fibrosis if left untreated.<sup>1</sup> We describe a child with IPH whose initial presentation was IDA. At the time of diagnosis, she had no respiratory symptoms. Early fibrotic changes of the lungs were confirmed 50 days after the onset of first symptoms of IPH. The clinical presentation, haematological manifestations, diagnosis, and pathogenesis of IPH are discussed.

### CASE REPORT

On 10 February 2001, a girl aged 2 years 4 months was referred with suspected haemolytic anaemia. She had a one month history of poor appetite, tiredness, constipation, and pallor. However, no fever, cough, vomiting, dyspnoea, or cyanosis was noted. Eleven days prior to admission, microcytic hypochromic anaemia was found at a local hospital, with haemoglobin (Hb) 4.3 g/dl, mean corpuscular volume (MCV) 61  $\mu\text{m}^3$ , serum iron 13  $\mu\text{g}/\text{dl}$ , total iron binding capacity 305  $\mu\text{g}/\text{dl}$ . Iron therapy was started and red blood cell (RBC) transfusions given. With no apparent source of bleeding, recurrent anaemia was noted four days later. On admission, physical examination revealed a pale and pasty looking child with the following positive findings: body temperature 37.4°C; heart rate 142/min; respiratory rate 32/min; blood pressure 110/60 mm Hg; body weight 11 kg; body height 91 cm. A mild hepatosplenomegaly was noted. Results of laboratory testing showed RBC  $3090 \times 10^9/\text{l}$ , Hb 6.8 g/dl, MCV 79.9  $\mu\text{m}^3$ , reticulocytes 10.1%, nucleated red blood cells (NRBC) 1/100 WBC, white blood cells (WBC)  $15.8 \times 10^9/\text{l}$  (no eosinophils), platelets  $485 \times 10^9/\text{l}$ , aspartate aminotransferase (AST) 42 U/l, blood urea nitrogen (BUN) 14 mg/dl, creatinine 0.4 mg/dl, sodium

146 mEq/l, potassium 4.4 mEq/l, serum iron 13  $\mu\text{g}/\text{dl}$ , total iron binding capacity 310  $\mu\text{g}/\text{dl}$ . Serum ferritin was 149.8 ng/ml, and copper 141.7  $\mu\text{g}/\text{dl}$ . The red cells were hypochromic and microcytic with a two cell population. Routine urinalysis, faecal occult blood, direct Coombs' test, and Hb electrophoresis were all negative. Serum vitamin B<sub>12</sub>, folate concentrations, and blood glucose-6-phosphate dehydrogenase quantitation were all normal. Examination of the bone marrow showed erythroid hyperplasia with absent iron stores, consistent with IDA. Oral iron therapy was begun and the patient was discharged. Two weeks later, follow up complete blood count data showed RBC  $2320 \times 10^9/\text{l}$ , Hb 6.1 g/dl, MCV 105.6  $\mu\text{m}^3$ , and reticulocytes 42%.

On 1 March 2001, the patient was hospitalised as an emergency admission because of general weakness and refusal to eat. Her parents had noticed passage of intermittent black coloured stools despite the fact that she was taking iron therapy regularly. She did not have cough, dyspnoea, or haemoptysis. There were no remarkable changes from previous physical examination. The breath sounds were clear. The anaemia persisted with RBC  $2180 \times 10^9/\text{l}$ , Hb 5.8 g/dl, MCV 105.5  $\mu\text{m}^3$ , and reticulocytes 16.1%. Haptoglobin was <24.3 mg/dl. Stool analysis revealed 4+ occult blood. She received a blood transfusion the next day. Meckel's diverticulum scan, panendoscopy, and sugar water test were all negative. The whole picture was suggestive of gastrointestinal blood loss, but the lesion could not be found.

A chest radiograph showed bilateral diffuse alveolar infiltrates with consolidations over the right upper lobe. Bronchoalveolar lavage (BAL) fluid showed numerous haemosiderin laden macrophages. Pulmonary haemosiderosis was diagnosed. High resolution computed tomography of the thorax revealed bilateral diffuse ground glass appearance associated with early fibrotic changes. On 15 March, treatment with prednisolone (2 mg/kg/day) was begun. Antinuclear antibody was negative, C<sub>3</sub> and C<sub>4</sub> were normal, antineutrophil cytoplasmic antibodies (perinuclear staining) (p-ANCA) were found positive and the radioallergosorbent (RAST) test for milk was weakly positive. She was discharged on iron therapy and prednisolone. The haemoglobin rose to 15.4 g/dl within one month and serum haptoglobin returned to normal (40.7 mg/dl). The reticulocyte count gradually reduced to normal (it was 19.3% on 15 March). Iron therapy was continued for three months. However, when trying to taper prednisolone, recurrent bleeding episodes were noted, associated with reduced Hb and reticulocytosis. The anaemia improved after the dosage was increased.

**Abbreviations:** ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; BAL, bronchoalveolar lavage; BUN, blood urea nitrogen; IDA, iron deficiency anaemia; IPH, idiopathic pulmonary haemosiderosis; NRBC, nucleated red blood cell; MCV, mean corpuscular volume; RAST, radioallergosorbent test; RBC, red blood cell; WBC, white blood cell

## DISCUSSION

Pulmonary haemosiderosis is defined as an abnormal accumulation of haemosiderin in the lungs, which results from a diffuse alveolar haemorrhage.<sup>2</sup> It may occur as a primary process in the lung or secondary to cardiac diseases, bleeding disorders, collagen vascular diseases, or systemic vasculitis. IPH is a diagnosis of exclusion. An estimated incidence of 0.24 and 1.23 cases per million children per year has been reported in selected populations.<sup>3,4</sup> Virchow first described IPH in 1865 as "brown lung induration".<sup>5</sup> The onset of IPH in children often begins before 10 years of age; it is characterised by the triad of IDA, haemoptysis, and diffuse parenchymal infiltrates on chest x ray.<sup>1,2,6</sup> However, any one of these features may be the first presenting manifestation, and the clinical course is exceedingly variable. In general the intensity and duration of the haemorrhages determine the clinical course. Few patients have overt haemoptysis; the amount of blood expectorated is considerably less than the amount actually lost, particularly in infants and young children who swallow their sputum.<sup>7</sup> Swallowed blood may lead to positive faecal occult blood, mimicking gastrointestinal bleeding. Pulmonary fibrosis may be apparent two months after the clinical onset.<sup>7</sup> In this patient interstitial fibrosis had been detected by high resolution computed tomography scan but with no pulmonary symptoms, 50 days after the onset of the first symptoms of IPH.

Initially IDA was considered as either dietary in origin or caused by occult bleeding. However, the patient was referred with the suspected diagnosis of haemolytic anemia because of unusual haematological responses. Sustained reticulocytosis, normoblastaemia, macrocytosis, and low haptoglobin raised the possibility of ongoing haemolysis. IPH can mimic haemolytic anaemia: mean red cell survival time is reduced because of deposition of RBC in the lungs,<sup>8</sup> and absorption of haemoglobin from the lungs induces a rise in plasma bilirubin and urine urobilinogen. However, previous studies have shown no evidence of abnormally increased intravascular haemolysis in this disorder.<sup>1</sup> The initial serum haptoglobin was not detectable in our patient, possibly because of increased consumption after massive pulmonary haemorrhage. Reduction of haptoglobin was documented in an 11 year old girl when IPH was diagnosed after a prolonged course of IDA.<sup>8</sup>

In this patient, repeated stool examinations were necessary to finally document 4+ faecal blood test, but an intensive search for a gastrointestinal lesion was unrevealing. Positive findings on chest x ray examination prompted the BAL procedure, which led to the diagnosis of IPH. The haematological data in this patient could be a reflection of intermittent and massive occult blood loss (to the lungs) under iron therapy. The high absolute reticulocyte counts had sustained for over 33 days, ranged from five to 13 times the normal values (339 900–974 400/mm<sup>3</sup>). In a previous study using <sup>51</sup>Cr tagged red cells, it was estimated that during periods of active lung bleeding in a patient, 3–11% of circulating red cells were lost daily; when in clinical remission, this value was from 0–3%. During recovery from the bleeding episode, RBC production rate was five times the normal values.<sup>1</sup> The anaemia in IPH is typically microcytic and hypochromic, and iron deficiency anaemia may be the only clinical finding.<sup>9</sup> The serum iron and transferrin saturation are low despite an excessive accumulation of iron in the lungs. Our patient had microcytic RBC and high serum ferritin at initial presentation, which was a paradox of iron deficiency anaemia, reflecting the non-mobilisable haemosiderin iron located in the lungs.<sup>6</sup>

In addition to corticosteroid therapy and immune modulation, patients associated with IDA are treated with iron. Iron therapy can normalise the anaemia, but most patients continue to have episodes of pulmonary haemorrhage despite therapy.<sup>10</sup> Patients treated with an extended course of therapy were reported to achieve a better outcome.<sup>11</sup>

The cause of IPH remains unclear. Many authors suggest that it has an immunological pathogenesis.<sup>6,10–13</sup> This patient had a weakly positive RAST test for milk, but no other clinical manifestations of cows' milk sensitivity. A positive test for p-ANCA at the initial assessment may indicate the presence of alveolar capillary or glomerular vasculitis.<sup>14</sup> Measurement of ANCA has been recommended for all patients with pulmonary alveolar haemorrhagic syndromes<sup>15</sup>; it serves as a sign of poor prognosis<sup>12</sup> and the key predictor for development of an immunological disorder.<sup>11</sup> Environmental or toxic factors may precipitate the disease in genetically predisposed individuals.<sup>16</sup> Haemolysin stachylysin, a  $\beta$  haemolysin and pore forming toxin produced by *Stachybotrys chartarum*,<sup>17</sup> has been associated with pulmonary haemorrhage/haemosiderosis in an infant.<sup>18,19</sup> The role and significance of stachylysin in IPH are now under investigation.

In summary, this patient had protracted bleeding to lungs but pulmonary symptoms were absent. A chest radiograph should be included in a serial work up for unexplained anaemia or IDA where the bleeding source is obscure. In the context of iron deficiency anaemia in IPH, sustained moderate or extremely high reticulocytosis and low haptoglobin can occur. It may be a useful parameter of continuous occult bleeding, and is an interesting association with IDA under treatment. High resolution computed tomography scan of the thorax is a useful tool in diagnostic evaluation.

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## POSTCARD FROM DOWN UNDER.....

### Burn baby burn

Most of us have probably had a bit of sunburn. In my youth the occasional burn was a badge of honour, especially when achieved in pursuit of a suntan in the closing days of an overseas vacation. A fair skinned and freckled friend of mine recalls the teenage use of olive oil resulting in excruciating sunburn.

We know better than that now, though, don't we? Of course we do, but these days we and our patients choose—and can afford—to take holidays where there is a lot of sunshine.

Sun exposure is an important health issue in Queensland, where one in three adults will have some sort of skin malignancy in a lifetime. There are three main factors contributing towards this. Firstly there is the latitude, with the tropic of Capricorn running through Rockhampton, and the southernmost part of the state at a mere 28 degrees south. Secondly there is the equitable climate, with places like the Sunshine Coast truthfully boasting 300 days of sunshine a year. And thirdly, there is the hole in the ozone layer, somewhere in the Southern Hemisphere which, if you think about it, isn't like a punch biopsy, but must represent the end point in a thinning process extending for unknown thousands of kilometres around the actual hole.

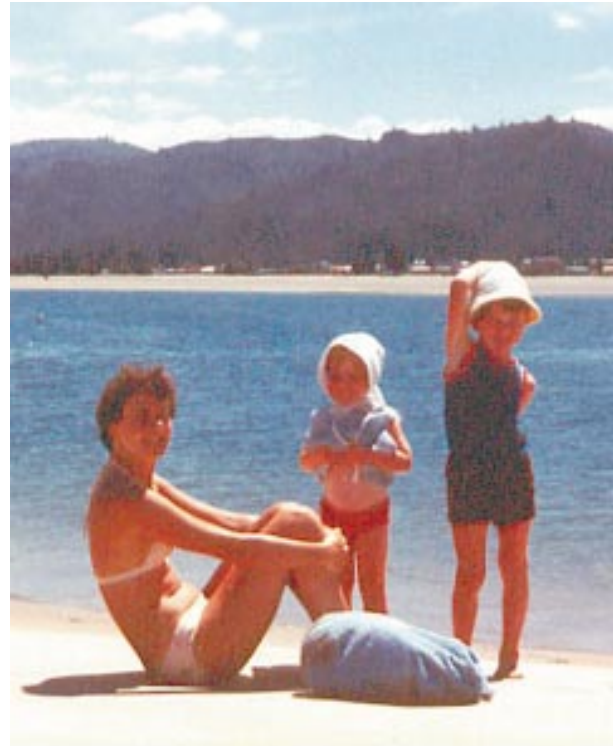
The consequences of this have been well demonstrated in research from the Centre for Astronomy and Atmospheric Research at the University of Southern Queensland, based in Toowoomba, 100 km inland from Brisbane. Scientists there have shown that if you spend the whole of a Queensland summer in good shade, you'll get as much UV exposure as if you spend the whole of an (uncharacteristically) sunny British summer in direct sunlight. This confused me until I was reminded why the sky was blue, which is because shorter wavelengths of light are more scattered by the atmosphere than longer ones. UV light, with an even shorter wavelength than blue, is, in effect, getting to you wherever you have direct sight of the sky. Years ago on elective in Jamaica I received an object lesson in this; I omitted the sunscreen when taking a long walk on a cloudy day, with very painful consequences.

The Australian slip-slap-slop campaign aims to address the fact that people—and especially children—will continue to go into the sun. The message is as follows:

Slip on a T-shirt; preferably a long sleeved one. You can buy UV opaque shirts, which, unlike cotton, retain their opacity when wet from perspiration or swimming. Unofficially rated at sun protection factor (SPF) 300 or more—officially in Australia you are only allowed to go up to 30—they can be bought in trendy surf brands like Billabong and Quicksilver. For good protection they have to be worn quite tight, which means that mine demonstrates starkly to me that I'm destined never to have "six pack" abdominal definition; sadly more of a keg or beer barrel.

Slap on a hat, preferably a wide brimmed one. Mine has never quite recovered from being worn in a sub-tropical downpour, and now is not so much Clint Eastwood as Quentin Crisp. While you're at it you should slip on a good pair of sunglasses, with good UV filters. With luck they'll make you look trendy, will prevent you from squinting and hopefully, in the long term, reduce cataract formation.

Slop on the sunscreen. Really do slop it on, which is to emphasize the fact that a thumbnail blob is enough for an area the size of your



**Figure 1** T-shirts and sun hats on a beach Down Under.

hand. Reapply after swimming or perspiring, remembering that reapplication doesn't prolong the effect, but instead reinforces whatever factor you were starting at. The "sloping it on" attitude is helped by the fact that sunscreen is very affordable in Australian shops, contrasting with British prices which seem to imply that it is a luxury item. Total block—zinc creams for high exposure points like lips and nose—come in fun luminous colours, and their popularity is boosted by their use by some high profile cricketers and tennis players.

Much of your lifetime risk of melanoma is acquired in childhood, during "binge" exposure to the sun, as during a fortnight in the Spanish sunshine. Skin protection is therefore a paediatric health issue. The challenge, for me at least, is how best to get the message across while looking like Quentin Crisp with a keg. Well, at least my sunglasses are cool...

**I D Wacogne**

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