CASE REPORTS

Idiopathic pulmonary haemosiderosis: report of two cases and review of the literature

P. BAILEY
M.B., Ch.B.

B. M. GRODEN
M.D., F.R.C.P.(Glas.), F.R.C.P.(Edin.)

Ballochmyle Hospital, Mauchline, Ayrshire

Summary

Idiopathic pulmonary haemosiderosis (IPH) is a rare disorder affecting mainly children and adolescents, and is usually fatal. However, there is increasing evidence that the aetiology of this condition is immunological, and that immunosuppressives may prolong remission.

Two cases are reported, one of which has the atypical feature of a malabsorption syndrome. This has not been previously reported. The literature is reviewed and current ideas on the postulated immunological basis to IPH are discussed.

Introduction

Idiopathic pulmonary haemosiderosis (IPH) is an uncommon disorder, the features of which have been fully described previously (Soergel and Sommers, 1962a, b; Ognibene and Johnson, 1963). Intermittent haemorrhages into the alveoli result in a variable degree of haemoptysis and iron deficiency anaemia which is the commonest mode of presentation. Respiratory symptoms may be initially slight or absent; as the disease progresses with further haemorrhages, increasing dyspnoea is likely to occur owing to secondary pulmonary fibrosis. Pulmonary hypertension and cor pulmonale have been reported (Roberts, Montessori and Patterson, 1972). A mild defect in carbon monoxide transfer is often the only abnormality of respiratory function tests. Lymphadenopathy, splenomegaly and finger clubbing may occur.

Most cases present in childhood or adolescence when the sex incidence is equal, although increasing numbers of cases are being recognized in adults, when twice as many males as females are affected (Ognibene and Johnson, 1963; Jiji and Hofkin, 1974). There is no familial incidence and there is no difference between children and adults or between the sexes in the course of the disease (Soergel and Sommers, 1962a). The course of the disease is variable, and spontaneous remissions may occur. The haemorrhages may be small and occur over many years without haemoptysis and with little clinical effect, or there may be a rapid downhill course and early death owing to a massive pulmonary haemorrhage.

At the times of the pulmonary haemorrhages, infiltrations may be seen on the chest X-ray, usually sparing the apices. These X-ray changes may resolve or they may persist. As the disease progresses, nodular-reticulation due to fibrosis may be evident in the chest X-ray. Haemosiderosis is confirmed by the presence of haemosiderin-filled macrophages in the sputum or gastric washings. Other causes of pulmonary haemosiderosis should be excluded and final confirmation of IPH is obtained by lung biopsy. Despite the iron deficiency anaemia, the iron within the macrophages is not available for haemoglobin synthesis, but is chelatable by desferrioxamine (Hyatt et al., 1972).

Case reports

Case 1

An 11-year-old girl presented in October 1973 with an iron deficiency anaemia. There was a history of lassitude, dyspnoea and pallor since an apparent respiratory infection a few weeks previously. She was pale, but clinical examination was otherwise negative. The following investigations were carried out: haemoglobin 5.2 g/dl; MCHC 28%; film of peripheral blood showed hypochromic erythrocytes; reticulocytes 8%. Serum iron 5.2 μmol/l (normal 14–39 μmol/l); TIBC 77 μmol/l (normal 62–100 μmol/l); saturation 6.9% (normal 15–50%). Red cell fragility, blood urea and electrolytes, serum haptoglobins, and serum IgM were all normal but both serum IgA and IgG were low. Chest X-ray was normal. Faecal occult blood and all virology studies were negative. Faecal stercobilinogen was raised at 570 mg/100 g (normal 30–220 mg/100 g). Barium meal showed an irritable...
pylorus and an irritable duodenal cap but no evidence of ulceration.

After transfusion the haemoglobin rose to 10.5 g/dl and the patient was discharged on oral iron. Two weeks later, the haemoglobin was 9.8 g/dl; MCHC 33%; WBC 8.8 x 10^9/l with a mild eosinophilia of 7%; reticulocyte count 8%. The faecal stercobilinogen and immunoglobulins were then normal. Sternal arrow examination showed marked erythroid hyperplasia. The whole picture was suggestive of chronic blood loss, but a source was not found. Follow-up continued and her anaemia persisted, requiring frequent courses of oral iron. In December 1974 she was seen after a ‘chest infection’; chest X-ray at this time showed diffuse mottling through both lung fields with widening of the mediastinum suggesting enlarged paratracheal glands (Fig. 1a). The significance of this X-ray was not realized at this time, perhaps because of the absence of haemoptysis.

She continued on oral iron, and although the anaemia persisted with a haemoglobin of near 10 g/dl, there were no ill effects until March 1976 when, after a further apparent respiratory infection, she again became listless and anorexic. She was pale with a loose cough, but the chest was clinically clear. The chest X-ray showed general infiltration of the lung fields and enlargement of the mediastinal glands. Her haemoglobin was 8.9 g/dl; the erythrocytes were hypochromic; serum iron 6.9 μmol/l; TIBC 54.6 μmol/l; saturation 12%. Faecal occult bloods were initially positive but later became negative. Serum haptoglobins were low; blood urea and electrolytes were normal; there was a low titre (1/16) of cow’s milk protein antibodies; FEV₁ 1550 ml; FVC 2100 ml; FEV₁/FVC 73%. The diagnosis of IPH was now considered, and examination of gastric washings revealed haemosiderin-filled macrophages.

She was re-admitted in April 1976 with a haemoglobin of 5.3 g/dl. She was tired, dyspnoeic and pale. She was transfused to a haemoglobin of 10 g/dl.

Fig. 1. (a) Case 1. Chest X-ray, December 1974. (b) Case 1, Chest X-ray, May 1976.
with clinical improvement. Prednisolone 5 mg 4 times daily was commenced in an attempt to reduce the severity of the pulmonary haemorrhages. She was again admitted in May 1976 in a collapsed state; she was pale, dyspnoeic and markedly distressed. Haemoglobin was 6.5 g/dl. Chest X-ray showed increased infiltration of the lung fields (Fig. 1b). Blood transfusion was commenced, but during the transfusion she suffered a massive pulmonary haemorrhage and died.

At post-mortem, both lungs were completely consolidated and a reddish-brown colour on section. The hilar and mediastinal glands were markedly enlarged and brown in colour. The heart showed some left ventricular hypertrophy (weight 280 g). All other organs, including the kidneys, were normal. The lung histology confirmed the diagnosis of pulmonary haemosiderosis (Fig. 2).

Case 2

A 7-year-old boy presented in November 1965 as a case of iron deficiency anaemia. The results of investigations were as follows:

- Haemoglobin 5.1 g/dl; MCHC 26.5%; film showed hypochromia with a mild eosinophilia of 8%; serum iron 5.2 μmol/l; faecal occult blood showed a trace only. Chest X-ray showed a slight loss of translucency at the right base with increased lung markings at this area consistent with infection. The patient was given a course of parenteral iron and continued on oral iron, his haemoglobin rising to 11 g/dl.

  A rash was present on his buttocks, and skin biopsy confirmed it to be dermatitis herpetiformis. In view of the association of this skin condition with malabsorption syndromes, intestinal biopsy was performed and the specimen showed partial villous atrophy. There was also biochemical evidence of malabsorption with alactasia, and there were sucrase and maltase deficiencies. He remained reasonably well until February 1971 when he presented again with severe anaemia, the haemoglobin being only 2.2 g/dl. Serum B₁₂ and folate were normal; faecal occult blood was negative. He was transfused and a repeat jejunal biopsy showed partial villous atrophy.

---

**Fig. 2. Case 1. Lung histology, stained with Prussian Blue. Numerous macrophages full of iron pigment are seen within an alveolus.**
He was continued on oral iron. Sternal marrow biopsy showed marked erythroid hyperplasia of normoblastic type. Barium studies revealed no abnormality. Serum calcium, phosphorus and plasma-proteins were all normal. His anaemia was still considered to be due to malabsorption. He required three further courses of parenteral iron to maintain his haemoglobin at about 12 g/dl.

In March 1976 he was re-admitted with chest pain and dyspnoea. Haemoglobin was 8·4 g/dl and faecal occult bloods were positive. Examination revealed signs of mitral valve regurgitation, and aortic stenosis and regurgitation, and he gave a history of rheumatic fever at 6 years old. Chest X-ray showed a fine granularity in both lung fields and it was suggested that this was due to iron deposits. It was only considered that the degree of anaemia, together with the lack of iron stores and the amount of iron given over the years, was more suggestive of chronic blood loss than of malabsorption. Radiochromium studies were performed to estimate the blood loss in his stools, but only a minimal loss of 6 ml/day was found. A 5-day faecal fat collection showed excessive fat loss consistent with a history of malabsorption. Further intestinal biopsy was attempted on 2 occasions but was unsuccessful.

The possibility of pulmonary haemosiderosis was now considered and haemosiderin-filled macrophages were found in his sputum. It was felt that the pulmonary haemosiderosis was unlikely to be due to his rheumatic valvular disease unless pulmonary hypertension was present. There was no clinical evidence of this, but to exclude it positively, cardiac catheterization was carried out. All intracardiac pressures were normal, and no shunts were demonstrated. A lung biopsy confirmed idiopathic pulmonary haemosiderosis (Fig. 3).

In September 1976 he was commenced on azathio-prine 150 mg daily, since there are reports that this drug is useful in maintaining remission (Steiner and Nabrady, 1965; Byrd and Gracey, 1973; O'Donohue, 1974). He was again admitted in November 1976 with cough producing rust-coloured sputum. Haemosiderin-filled macrophages were found in the sputum. The chest X-ray showed no change from the previous one. His haemoglobin was 11·9 g/dl. Respiratory function tests were normal, and tests for L.E. cells, rheumatoid factor and anti-nuclear factor were all negative. Immunoglobulins were normal. A reducing course of oral steroids was given and the cough and sputum ceased.

Follow-up of this patient continues (March 1978).

![Fig. 3. Case 2. Lung histology, stained with H & E. Numerous macrophages can be seen in the lower half of the field.](http://pmj.bmj.com/first-published-as/10.1136/pgmj.55.642.266.on.1April.1979)
Discussion

The aetiology of IPH is unknown. In the cases described by Ceelen in 1931 (Henke and Lubarsch, 1931) abnormalities of the elastic fibres of the pulmonary capillaries were found and he suggested that the disease is due to a primary developmental abnormality of these fibres. Other cases, however, usually at a less advanced stage, have not shown these changes and they are now considered to be secondary to the haemorrhage (Soergel and Sommers, 1962b).

The aetiology has been suspected to be of an immunological nature since 1954 (Steiner, 1954) and there is some evidence for this: blood eosinophilia has been found in several cases including the 2 cases reported here; lymphadenopathy and splenomegaly may be present; cold agglutinins have been found in other cases; one series of 31 cases in children revealed a significant increase in serum IgA in the patients, without any rise in IgG or IgM, and with no change in salivary IgA (Valassi-Adam et al., 1975). Furthermore, the disease has shown a variable response to therapeutic methods aimed at immune disorders such as splenectomy, steroids and immunosuppressives (Barlow, 1946; Soergel and Sommers, 1962a; Steiner and Nabrandy, 1965; Byrd and Gracey, 1973; O'Donohue, 1974). Antibodies against cow's milk protein have been found in some children with pulmonary infiltrates and anaemia, and these children have shown a response to withdrawal of cow's milk protein from their diet (Heiner's syndrome) (Heiner, Sears and Kniker, 1962; Ziai, 1976). The relationship of this phenomenon to IPH is not clear, and cow's milk protein antibodies have also been found in other respiratory diseases of children.

Two studies of IPH, where the lung tissue was examined by electron microscopy, have demonstrated focal ruptures in the capillary basement membrane with 'leakage' of red blood cells from the capillaries into the alveoli (Hyatt et al., 1972; Donald, Edwards and McEvoy, 1975). These basement membrane lesions were associated with cytoplasmic vacuolation and hyperplasia of the alveolar cells. It has been suggested that this is the basic pathological lesion in IPH and is mediated by an auto-immune reaction. However, no studies so far have demonstrated fixation of immunoglobulins in the capillaries or alveoli, nor serum antibodies against basement membrane, in cases of IPH.

Pulmonary haemosiderosis may be secondary to several other conditions such as mitral stenosis, chronic left heart failure, haemolytic anaemia, chronic leukaemia, bronchiectasis and pulmonary carcinoma with haemorrhage, but the lung histology is different from that of IPH (Soergel and Sommers, 1962b). Pulmonary haemosiderosis may also occur as part of the picture of a collagen disease; it has been reported in association with systemic lupus erythematosus (SLE) (Kuhn, 1972; Byrd and Trunk, 1973) and also in a patient who developed manifestations of multiple collagen disorders including rheumatoid arthritis, SLE, and Wegener's granulomatosis (O'Donohue, 1974). Whether these are true associations of distinct clinical entities, perhaps due to some basic alteration of immune status, or whether they are merely varying manifestations of a common pathogenic process, remains to be determined. The significance of malabsorption and partial villous atrophy in Case 2 is uncertain, although it may reflect a more general disturbance of basement membrane function.

Also, IPH bears certain similarities to another disease which has variously been reported as a distinct entity and also as a different manifestation of the same disease—Goodpasture's syndrome. In this syndrome there are pulmonary haemorrhages associated with an acute or chronic glomerulonephritis. As in IPH there is an iron deficiency anaemia, patchy infiltration on the chest X-ray, and haemosiderin-filled macrophages in the sputum. The renal lesion may not be clinically apparent initially although microscopic haematuria and proteinuria are present at some stage of the disease. Compared with IPH, Goodpasture's syndrome occurs in an older age group and there is a much higher male incidence; in one series the ratio of male to female with the disease was 9 : 1 (Benoit et al., 1964). The course of Goodpasture's syndrome is generally much shorter with death usually occurring within 3 years. Massive pulmonary haemorrhage or uraemia are the usual causes of death.

More is known about the immunological basis to Goodpasture's syndrome. In several cases, antibodies against alveolar and glomerular basement membrane have been found in the serum, and electron microscopy studies have shown linear deposits along the basement membrane suggestive of a type II (cytotoxic) immunological reaction. Recently, a case of Goodpasture's syndrome was reported in which focal deposits were present on the basement membrane, suggestive of a type III (immune complex) reaction (Agodoa et al., 1976). A case of IPH with focal deposits on the basement membrane of the pulmonary capillaries of what might be immune complexes has been reported but this patient subsequently developed manifestations of SLE, and therefore the significance of this finding is not clear (Elliot and Kuhn, 1970; Kuhn, 1972).

It has been suggested that ultrastructural differences, visible by electron microscopy, between IPH and Goodpasture's syndrome will distinguish the 2 conditions in the absence of a clinically
detectable renal lesion (Donald et al., 1975). The differences may be explained by considering the alveolar cell as the immune reaction’s ‘shock’ organ in IPH; since the alveolar cell is partly responsible for maintaining the integrity of the basement membrane, damage to the cell leads to the focal ruptures in the membrane previously described. In Goodpasture’s syndrome, the ‘shock’ organ is considered to be the basement membrane itself.

Heiner’s syndrome may be a variant of IPH where cow’s milk protein acts, by itself or as a hapten, antigenically. The foreign antigen may either (i) be similar to basement membrane antigens as to promote a type II reaction, or (ii) cause production of soluble antibodies, form immune complexes which are then trapped in the basement membrane in a type III reaction.

The relationship between all these phenomena requires further elucidation.

There is as yet no proved therapy for patients with IPH. There have been reports that splenectomy induced a remission in IPH (Barlow, 1946; Steiner, 1954), but Soergel and Sommers (1962a) concluded that splenectomy provided no significant benefit.

After the immunological nature of IPH was proposed by Steiner (1954) corticosteroids were tried in several instances. Initially they seemed of great value, but subsequent review shows that, while they may reduce the haemorrhage of the acute episode, they do not alter the long-term prognosis.

Since then, several authors have reported success with other immunosuppressives, particularly azathioprine (Steiner and Nabradi, 1965; Byrd and Gracey, 1973). They appear to have achieved a remission after 18 to 24 months’ treatment. A further possible line of treatment is plasmaphoresis, which removes the immune complexes from the blood in an attempt to reduce the suspected continuing immune damage to the ‘shock’ organs. This is being tried in Goodpasture’s syndrome (Lockwood et al., 1976; Rossen et al., 1976) and may offer an effective and non-toxic treatment for these diseases.

Conclusion

IPH is a serious disorder which is usually fatal. The aetiology remains obscure although there is increasing evidence that there is an immunological basis. Its relationship to Goodpasture’s syndrome and the collagen diseases is still not clear. Steroids and immunosuppressives have been used in treatment and, perhaps with plasmaphoresis, seem to offer the best hope for these patients. Since the disease is rare, it is difficult to ascertain from individual cases the overall effects of treatment. Improved collection of data and collation of all facts relating to cases of IPH and an attempt to co-ordinate and assess therapeutic regimens is required.

Acknowledgments

We wish to thank Dr Charlotte Nisbet, consultant haematologist, for providing the stimulus to this study; Dr John Morrow for allowing us to report Case 1; and the pathologists and photographer at Ballochmyle Hospital for preparing the photographs.

References

Agodoa, L.C.Y., Striker, G.E., George, C.R.P., Glassock, R. & Quadracci, L.J. (1976) The appearance of nonlinear deposits of immunoglobulins in Goodpasture’s syndrome. American Journal of Medicine, 61, 407.

Barlow, A.D. (1946) Pulmonary haemosiderosis. Proceedings of the Royal Society of Medicine, 39, 131.

Benoit, F.L., Rulon, D.B., Theil, G.B., Doolan, P.D. & Watten, R.H. (1964) Goodpasture’s syndrome: a clinicopathological entity. American Journal of Medicine, 37, 424.

Byrd, R.B. & Gracey, D.R. (1973) Immunosuppressive treatment of idiopathic pulmonary haemosiderosis. Journal of the American Medical Association, 226, 458.

Byrd, R.B. & Trunk, G. (1973) Systemic lupus erythematosus presenting as pulmonary haemorrhage. Chest, 64, 128.

Donald, K.J., Edwards, R.L. & McEvoy, J.D.S. (1975) Alveolar capillary basement membrane lesions in Goodpasture’s syndrome and idiopathic pulmonary haemosiderosis. American Journal of Medicine, 59, 642.

Elliot, M.L. & Kuhn, C. (1970) Idiopathic pulmonary haemosiderosis: ultrastructural abnormalities in the capillary walls. American Review of Respiratory Disease, 102, 895.

Heiner, D.C., Sears, J.W. & Kniker, W.T. (1962) Multiple precipitins to cow’s milk in chronic respiratory disease. American Review of Diseases of Childhood, 103, 634.

Henke, F. & Lubarsch, O. (1931) Handbuch der spezielle pathologische Anatomie und Histologie. Vol. 3. J. Springer, Berlin.

Hyatt, R.W., Adelson, E.R., Halazun, J.F. & Lukens, J.N. (1972) Ultrastructure of the lung in idiopathic pulmonary haemosiderosis. American Journal of Medicine, 52, 822.

Jui, V. & Hofkin, G.A. (1974) Idiopathic pulmonary haemosiderosis. Southern Medical Journal, Nashville, Tenn., etc., 67, 488.

Kuhn, C. (1972) Systemic lupus erythematosus in a patient with ultrastructural lesions of the pulmonary capillaries previously reported in the Review as due to idiopathic pulmonary haemosiderosis. American Review of Respiratory Disease, 106, 931.

Lockwood, C.M., Rees, A.J., Pearson, T.A., Evans, D.J., Peters, D.K. & Wilson, C.B. (1976) Immunosuppression and plasma exchange in the treatment of Goodpasture’s syndrome. Lancet, i, 711.

O’Donohue, W.J. (1974) Idiopathic pulmonary haemosiderosis with manifestations of multiple connective tissue and immune disorders. American Review of Respiratory Disease, 109, 473.

O’Donohue, A.J. & Johnson, D.E. (1963) Idiopathic pulmonary haemosiderosis in adults. Archives of Internal Medicine, 3, 161.

Roberts, L.N., Montessori, G. & Patterson, J.G. (1972) Idiopathic pulmonary haemosiderosis: case report with pulmonary function tests and cardiac catheterization data. American Review of Respiratory Disease, 106, 904.

Rossen, R.D., Duffy, J., McCready, K.B., Reisberg, M.A., Sharp, J.T., Hersh, E.M., Eknoyan, G. & Suki, W.N.
(1976) Treatment of Goodpasture's syndrome with cyclophosphamide, prednisone, and plasma exchange transfusions. *Clinical and Experimental Immunology*, 24, 218.

Soergel, K.H. & Sommers, S.C. (1962a) Idiopathic pulmonary hemosiderosis and related syndromes. *American Journal of Medicine*, 32, 499.

Soergel, K.H. & Sommers, S.C. (1962b) The alveolar epithelial lesion of idiopathic pulmonary hemosiderosis. *American Review of Respiratory Disease*, 85, 540.

Steiner, B. (1954) Essential pulmonary hemosiderosis as an immunohematological problem. *Archives of Disease in Childhood*, 29, 391.

Steiner, B. & Nabrady, J. (1965) Immunoallergic lung purpura treated with azathioprine. *Lancet*, i, 140.

Valassi-Adam, H., Rouska, A., Karpouzas, J. & Matsaniotis, N. (1975) Raised IgA in idiopathic pulmonary hemosiderosis. *Archives of Disease in Childhood*, 50, 320.

Ziai, M. (1976) Anemia, shortness of breath and asthma in an infant. *Clinical Pediatrics*, 41, 976.