Singapore Med J 1998; Vol 39(5):211-216

Idiopathic Pulmonary Haemosiderosis – A Case Report

S C Y Ng, B W Lee, F Chia

ABSTRACT

Idiopathic pulmonary haemosiderosis (IPH) is a disorder characterised by the triad of haemoptysis, diffuse parenchymal infiltrates on chest roentgenogram and iron-deficiency anaemia. It is a diagnosis of exclusion and the prognosis is bleak despite the varied management options. We report a case of IPH occurring in a child who presented at four months of age with cough, wheeze, haemoptysis and pallor and whose symptoms are currently controlled with high-dose inhaled budesonide and low-dose oral prednisolone.

Keywords: idiopathic pulmonary haemosiderosis, haemoptysis, iron-deficiency anaemia, inhaled budesonide, oral prednisolone

INTRODUCTION

Idiopathic pulmonary haemosiderosis (IPH) or Ceelen-Gellerstedt disease is a rare condition consisting of the characteristic triad of haemoptysis, diffuse parenchymal infiltrates on chest roentgenogram and iron-deficiency anaemia[1]. The three most recent large series of childhood IPH were from Greece[2,3] and Sweden[4], which gave an annual incidence rate of 0.24 cases per million children.

Pulmonary haemosiderosis was first described by Virchow in 1865 as 'brown lung induration'[5]. It describes the major pathologic finding of this disease, which is the characteristic accumulation of iron within the pulmonary macrophages as haemosiderin[6]. It may occur either as a primary disease of the lungs or as a secondary complication of a cardiac condition or systemic vascular disease. The primary form of pulmonary haemosiderosis of which IPH is one variant, occurs more frequently in childhood than do the secondary forms. Other variants of primary pulmonary haemosiderosis are associated with gluten enteropathy (coeliac disease)[7-10], cow's milk protein allergy (Heiner syndrome)[11] and immune complex glomerulonephritis (Goodpasture's syndrome)[12].

Idiopathic pulmonary haemosiderosis usually presents in infancy or within the first decade of life. The sex incidence is equal. The true incidence of both the primary and secondary forms of pulmonary haemosiderosis is unknown. Several familial cases of IPH have been reported[13,14] but the exact mode of inheritance has not been clearly defined.

This case of idiopathic pulmonary haemosiderosis is what we believe to be the first ever reported in an Asian (Malay) child.

CASE REPORT

MS was the first and only child of a non-consanguineous marriage. He was born full-term by normal vaginal delivery at 38 weeks gestation. His birthweight was 2330g. Apgar scores were 9 at 1 minute and 10 at 5 minutes. Both parents had a history of heroin addiction and were undergoing drug rehabilitation. MF first presented at the age of four months with cough, wheeze, low-grade fever and anaemia. Clinical examination confirmed pallor but there was no evidence of haemolysis. He had marked intercostal and subcostal retractions plus fine inspiratory crepitations and end-expiratory rhonchi. *Klebsiella pneumoniae* was isolated from his sputum and he was treated as for acute bronchiolitis with supervening bacterial infection. Iron supplements were also commenced. He was discharged home after one week.

He persisted in having recurrent attacks of chest infection usually precipitated by upper respiratory tract infections requiring hospitalisation once every few months. Fever, cough and wheezing with radiological evidence of consolidation typify these multiple admissions. However, apart from one admission whereby nasal aspirates were positive for respiratory syncytial virus, his symptoms usually resolve with short courses of antibiotics even though bacterial cultures from his respiratory tract were repeatedly negative. During one of these hospitalisations at age 11 months, he was severely anaemic with a haemoglobin level of 5.4 g/dL. Further review of his dietary history revealed that only milk and cereals were taken with a particular dislike for meat, eggs or vegetables. Investigations supported a diagnosis of severe iron-deficiency anaemia with a normal haemoglobin electrophoretic pattern and negative screens for haemolysis and occult bleeds. There was no family history of atopy.

MF had dysmorphic features, notably low-set ears, hypertelorism and an anti-mongoloid slant of his palpebral fissures but these did not constitute any particular syndrome. Chromosomal culture analysis done was consistent with that of a normal male karyotype. Developmentally, he was appropriate for age except for mildly delayed speech and language.

Department of Paediatrics
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074

S C Y Ng, MB ChB, M Med (Paed)
Registrar

B W Lee, M Med (Paed), MD, FAMS
Associate Professor

F Chia, M Med (Paed), FRACP, FAMS
Consultant

Correspondence to:
Dr S C Y Ng

MF was readmitted to hospital at 18 months when he presented with acute respiratory distress and haemoptysis. He was intubated because of progressive hypoxaemia. Radiography of the chest revealed a 'white-out' appearance of both lung fields with air bronchograms seen, which was consistent with an ARDS (adult respiratory distress syndrome) picture. Repeated bacterial cultures of the tracheal aspirates were negative and so were smears to exclude pneumocystis carinii and tuberculosis. Cotrimoxazole was commenced empirically and he was subsequently extubated after three days. IgM against cytomegalovirus was positive but his chest condition improved without the need for anti-viral therapy. His CD4/CD8 ratio was normal, human immunodeficiency virus detection by PCR was negative and general immunoglobulin studies (IgG,A,M and E) were normal apart from a slightly elevated serum IgA level. The chloride sweat test was within normal limits and ANCA markers were negative. Repeated urine microscopy and examination did not reveal any haematuria or proteinuria.

Bronchoscopic lavage was positive for haemosiderin-laden macrophages which was supportive of pulmonary haemosiderosis. A high-resolution computerised axial tomographic scan of the lungs showed non-specific patchy consolidation of both lower lobes and collapse/consolidation of the right upper lobe. However, no lung biopsy had been performed. MF was subsequently commenced on high-dose oral prednisolone (2 mg/kg/day) resulting in significant improvement in his respiratory status. This was shortlived as he developed acute bleeding from a duodenal ulcer on two occasions, most likely aggravated by the use of high-dose steroids.

He had since remained oxygen and steroid-dependent as attempts to wean him off high-dose oral steroids and maintain him on inhaled beclomethasone for persistent wheezing were unsuccessful.

MF developed signs and symptoms of congestive cardiac failure and cor pulmonale at 19 months of age which initially responded to frusemide. However, his condition deteriorated again three months later, which was confirmed by changes seen on chest radiography, electrocardiography and two-dimensional echocardiography. He improved with assisted ventilation (nasal Continuous Positive Airway Pressure) and the addition of spironolactone and captopril.

Attempts were again made to wean him off high-dose oral steroids and maintain him on inhaled steroids so as to minimise the long-term complications of high-dose steroids. He was started on nebulised budesonide 500 micrograms every 12 hourly on 16 July 1996, increasing to 500 micrograms every 8 hourly ten days later. Budesonide metered-dose inhaler puffs 200 micrograms 4 times a day were administered via an aerochamber on 7 August 1996 and increased to 400 micrograms 4 times a day after two weeks. Budesonide nebuliser therapy was subsequently stopped two days later. The oral prednisolone dose was gradually tailed down starting 16 August 1996 over three weeks from 2 mg/kg/day to 0.5 mg/kg every alternate day. Inevitably, he still required increased oxygen, more regular salbutamol/ipratropium bromide nebuliser therapy and short courses of high-dose oral steroids whenever he contracted nosocomially-acquired infections.

MF had severe failure to thrive with weight and height centiles both below the third and the occipitofrontal circumference between the third and the tenth. This is a consequence of his chronic lung disease and the effects of prolonged high-dose oral steroids.

DISCUSSION

Ceelen-Gellerstedt disease or idiopathic pulmonary haemosiderosis (IPH) is characterised by the triad of haemoptysis, diffuse parenchymal infiltrates on chest roentgenogram and iron-deficiency anaemia. Since it was first described by Virchow in 1865, diagnosing the condition had been difficult, its course had been exceedingly variable and the progress had remained poor despite the differing treatment options. The average survival is about 2.5 years after the onset of symptoms[3].

Idiopathic pulmonary haemosiderosis differs clinically in children and adults. In adults, the disease is typically chronic with no sudden changes in clinical status, chest radiograph or respiratory function. Children, on the other hand, typically have acute episodes of haemoptysis and breathlessnes superimposed on their chronic disease. Lung function deteriorates rapidly with appearance of radiographic opacities but the carbon dioxide diffusion capacity appears to rise rather than fall because of haemoglobin in the alveoli. Nevertheless, ultrastructural damage is more severe in children in accordance with the classical clinical picture[15].

CLINICAL FINDINGS

Idiopathic pulmonary haemosiderosis usually presents with either a fulminant onset with recurrent episodes of acute haemoptysis or an insidious onset with anaemia, dyspnoea and poor weight gain[6]. MF initially posed a major diagnostic problem as he presented with recurrent episodes of chest infections easily treatable with antibiotics but continued to have residual bronchospasm which only responded to prolonged high-dose steroids. Immunodeficiency was ruled out and the diagnosis clinched when his haemoglobin dropped to 5.4 g/dL during one admission. On physical examination, there is striking variation in signs according to the severity of the disease[16]. Pallor, dyspnoea, cough, rales and rhonchi are common abnormalities. There is hepatosplenomegaly in 20% of patients. Fever is common in patients with iron-deficiency anaemia[1]. Recurrent episodes of pulmonary haemorrhage over several years may cause signs of chronic lung disease such as cyanosis, finger clubbing, dyspnoea and pulmonary hypertension. Pulmonary hypertension and cor pulmonale may

eventually lead to death from right heart failure[15] although death from uncontrolled haemorrhage is more common[17].

Coincident with the recurrent pulmonary haemorrhage would be the presence of a microcytic, hypochromic anaemia with low serum iron and ferritin stores. This is thought to be due to iron sequestration by the pulmonary macrophages and therefore, not available for haemoglobin synthesis in the bone marrow. A mild haemolytic anaemia can also be present with a positive direct Coombs' test, which suggests an immunologic basis. Eosinophilia occurs in about 20% of patients[16].

The stools may be positive for occult blood which is derived from swallowed blood-tinged saliva. As such, gastric aspirates stained with Prussian blue may be positve for haemosiderin-laden macrophages, as in the case of MF. Similar cells can be identified in the sputum or bronchial lavage fluid.

PATHOGENESIS

In some primay forms of pulmonary haemosiderosis, immunologic studies may reveal specific anti-cow's milk antibodies of the IgG, IgE or IgD isotypes[8,11,18] or an asociated IgA deficiency[16]. Others may be a form of microscopic polyarteritis with associated segmental, necrotising crescentic glomerulonephritis[19,20] and are positive antineutrophil cytoplasmic antibodies directed against myeloperoxidase (perinuclear IgG type)[12,20]. The presence of p-ANCA antibodies in pulmonary renal vasculitic syndromes[21-23] is well-described but they have not been reported in the context of idiopathic pulmonary haemosiderosis. Antibodies may also be formed against the glomerular basement membrane in Goodpasture's syndrome[12,24]. Gluten enteropathy with subtotal villous atrophy on jejunal biopsy has also been reported to be associated with idiopathic pulmonary haemosiderosis. Circulating avian, gliadin and reticulin antibodies were found with improvement of symptoms on a gluten-free diet[7-10].

In a patient with idiopathic pulmonary haemosiderosis, erythrocyte superoxide dismutase activity was found to be reduced and the erythrocytes showed easy peroxidisability. These findings were correlated with haemolyis, iron-deficiency anaemia and a shortened survival of the erythrocytes. Thus, antioxidant enzymes and peroxidase reactivity of erythrocytes should be carefully evaluated though the aetiological significance remains unknown[25].

Genetic factors too, have a role to play in the pathogenesis, but the precise mode of inheritance is unclear. Two sibling pairs were reported to have pulmonary haemosiderosis with the grandmother of one of these pairs also having haemoptysis and iron-deficiency anaemia[13,14]. Thirteen of twenty-six children with pulmonary haemosiderosis from central Greece, where intermarriage is commonplace, showed a familial tendency without a clear Mendelian pattern of inheritance[2].

DIAGNOSIS

The diagnosis of idiopathic pulmonary haemosiderosis has always been difficult. Satisfying the triad of haemoptysis, iron-deficiency anaemia and radiological findings may not be easy, as radiographic findings on chest films although suggestive are non-specific, as was found to be so in our patient.

Demonstration of haemosiderin-laden macrophages either in the sputum, bronchoalveolar lavage or gastric fluid may be supportive[4,6,26]. Pulmonary function tests may show impaired diffusion, decreased compliance and severe airway obstruction. Total lung capacity can be normal or increased. During acute pulmonary haemorrhage, the arterial oxygen tension and oxygen saturation may decrease substantially without any change in the arterial carbon dioxide tension. However, there is increased carbon monoxide uptake (DLCO) because of its affinity for sequestered haemoglobin in the alveoli[27-29].

Quantitative serial scintigraphic scanning with autologous red blood cells labelled with ^{51}Cr, ^{59}Fe or ^{99m}Tc[30,31] can be used to demonstrate the haemorrhagic process in pulmonary haemosiderosis. C-labelled carbon monoxide clearance has been used but this requires a cyclotron for production of the isotope[28]. Other forms of imaging have been used to aid diagnosis such as Computerised Axial Tomogram scanning[32,33] and Magnetic Resonance Imaging (high signal intensity on T1 and low intensity on T2-weighted images)[34].

Of course, transbronchial or open lung biopsy provides the definitive diagnosis of idiopathic pulmonary haemosiderosis[6,35,36]. Lung biopsy, being an invasive procedure, is usually not performed unless it will influence the course of management. In IPH, the major ultrastructural changes usually involve the capillary endothelium and its basement membrane. Focal interruptions of the pulmonary capillary basement membrane may predispose to bleeding into the alveoli. The characteristic manifestation is haemosiderin-laden macrophages in both the interstitium and the alveolar spaces of the lungs, as was found in our patient which helped confirm our diagnosis of IPH. In addition, acute inflammatory changes, alveolar epithelial hyperplasia and degenerative sloughing of the epithelial cells occur. Recognised sequelae of episodic endothelial injury plus capillary wall damage and repair include thickening of the capillary basement membrane, perilymphangitis, hypertrophy of the bronchial arterial muscle, degeneration of the elastic fibres and interstitial fibrosis[37-39].

The general morphology of the lungs is usually intact apart from the intra-alveolar haemorrhage seen. Imrnunofluorescence studies of the lungs may reveal deposits of fibrinogen and fibrin. In Goodpasture's syndrome, linear deposits of immunoglobulin and complement occur on the basement membrane.

Lung biopsy of a patient with pulmonary haemosiderosis and anti-basement membrane antibodies in the serum revealed fine deposits of iron and calcium in the alveolar basement membrane and

the elastic laminae of the pulmonary vessels[40]. Haemosiderin-laden macrophages may undergo necrosis with release of iron-containing substances which accumulate and damage the basement membrane, causing further haemorrhage. This theory may explain why patients continue to be symptomatic even when antibodies have not been demonstrated or have disappeared from the serum[41].

MANAGEMENT

The management of pulmonary haemosiderosis is first directed at identifying underlying causes and treating them, such as gluten enteropathy, cow's milk protein allergy and collagen vascular diseases. If respiratory distress is present, oxygen therapy with assisted ventilation may be required. Transfusion may be necessary if the anaemia is acute and severe.

Use of corticosteroids or other immunosuppressants are generally advocated for control of symptoms but are not effective for acute haemorrhage[42-44]. Adrenocorticotrophic hormone (ACTH) (10 to 25 units daily), methylprednisolone (2 mg/kg/day) or hydrocortisone (8 mg/kg/day) intravenously is initially started, followed by maintenance prednisolone at 1 to 2 mg/kg/day. However, maintenance treatment with corticosteroids is often prolonged because of recurrent disease. Side-effects of long-term high-dose oral steroids may be preventable by the use of inhaled steroids[45-47], as in our patient. Therapeutic doses of beclomethasone dipropionate[45], budesonide[46] and flunisolide[47] have been used without any effect on endogenous glucocorticoid production, bone mineralisation and growth rate. Inhaled steroids have been proven to be useful in altering the long-term course of idiopathic pulmonary haemosiderosis by reducing the associated complications.

Other immunosuppressants have been used to treat life-threatening pulmonary haemorrhage such as azathioprine[44,48,49], chlorambucil[6] and cyclophosphamide[50]. Azathioprine and cyclophosphamide have also been shown to be effective in inducing remission after failure of corticosteroids[51,52] but they are not without any adverse effects. For example, cyclophosphamide, besides having the commonly reported side-effects of bone marrow suppression, haemorrhagic cystitis, interstitial pulmonary fibrosis, sterility and secondary malignancy, is also implicated in causing veno-occlusive disease of the liver[53].

Intavenous liposteroid[54] or lipid emulsion containing dexamethasone was used successfully in two patients with pulmonary haemorrhage refractory to pulsed methylprednisolone therapy. This has the advantage of targeted, controlled release of drugs at the principal sites of action and therefore, minimises systemic side-effects. Chloroquine[55,56] can also induce remission and was chosen because of its relative lack of toxicity compared with other immunosuppressants (regular opthalmic checks are essential because of retinal toxicity). One patient with pulmonary haemosiderosis and abundant mast cells in the lung biopsy responded to treatment with disodium cromoglycate(38).

Haemosiderosis associated with IgA deficiency has improved with repeated transfusions with plasma or blood[16]. Iron chelating agents such as desferrioxamine have been given either intramuscularly or by subcutaneous infusion to help control iron deposition in the lungs[57]. There have been reports that splenectomy induced remission in some patients[58-60] but not in others[1]. Plamapheresis and plasma exchange either alone or in combination with steroids or immunosuppressants have been usually used in the acute phase of idiopathic pulmonary haemosiderosis and Goodpasture's syndrome[61,62].

PROGNOSIS

The prognosis in idiopathic pulmonary haemosiderosis is difficult to establish because of its rarity and variability. Most case reports did not follow up the patients' progress except for the three large series done in Greece[2,3] and Sweden[4].

There are as yet no data to prove that any therapeutic modality improves the final outcome of idiopathic pulmonary haemosiderosis. Reports of temporary improvement achieved with a certain treatment were counteracted by others which did not. The weak points of these studies were the short observation periods, the small number of patients and the lack of suitable controls (due to disease rarity).

Chryssanthopoulos et al[3] attempted to determine prognostic criteria in their epidemiologic survey of thirty Greek children. Their findings were as follows:

(1) The severity of the disease did not determine the survival
(2) Females survived longer
(3) The young age of the patients at the onset seemed to carry a less favourable prognosis
(4) The common therapeutic modalities in use such as corticosteroids, splenectomy, antibiotics and blood tranfusions had not proved to be beneficial

Unless we can establish the exact pathogenesis and pathophysiology of idiopathic pulmonary haemosiderosis, patients with this life-threatening condition would ultimately succumb to respiratory failure as a consequence of pulmonary fibrosis, pulmonary hypertension and cor pulmonale.

ACKNOWLEDGEMENTS

The authors would like to thank the following doctors who have contributed to the diagnosis and management of our patient: Drs OM Chay, DYT Goh, RC Selvadurai, YJ Lim and PS Ho.

REFERENCES

1. Soergel KH, Sommers SC. Idiopathic pulmonary hemosiderosis and related syndromes. Am J Med 1962; 32:499-511.
2. Matsaniotis N, Karpouzas J, Apostolopoulou E, Messaritakis J. Idiopathic pulmonary haemosiderosss in children. Arch Dis Childh 1968; 43:307-9.
3. Chryssanthopoulos Ch, Cassimos Ch, Panagiotidou Ch. Prognostic criteria in idiopathic pulmonary hemosiderosis in children. Pediatr 1983; 123-5.
4. Kjellman B, Elinder G, Garwicz S, Svan H. Idiopathic pulmonary haemoderosis in Swedish children. Acta Paediatr Scand 1984; 73:584-8.
5. Virchow R. Die Krankhaften Geschwulste, Part 2. 1864, A Hirschwald, Berlin.
6. Levy J, Wilmott RW. Pulmonary hemosiderosis. Pediatr Pulm 1986; 2(6):384-91.
7. Reading R, Watson JG, Platt JW, Bird AG. Pulmonary haemosiderosis and gluten. Arch Dis Childh 1987; 62:513-5.
8. Fossati G, Perri M, Careddu G, Mirra N, Carnelli V. Pulmonary hemosiderosis induced by cow's milk proteins: a discussion of a clinical case. Pediatr Med Chir 1992; 14(2):203-7.
9. Perelman S, Dupuy C, Bourrillon A. The association of pulmonary hemosiderosis and celiac disease. Apropos of a new case in a child. Ann Pediatr Paris 1992; 39(3):185-8.
10. Yacoub M, Mahjoub H, Abroug S, Bousnina M, Harbi A, Essoussi AS. Idiopathic pulmonary hemosiderosis, celiac disease and cardiomyopathy. Arch Pediatr 1994; 1(6):587-90.
11. Heiner DC, Sears JW, Kniker WT. Multiple precipitins to cow's milk in chronic respiratory disease. Am J Child 1962; 103:634-54.
12. Van der Ent CK, Walenkamp MJ, Donckerwolcke RAMG, van der Laag J, van Diemen-Steenvoorde R. Pulmonary hemosiderosis and immune complex glomerulonephritis. Clin Nephrol 1995; 43(5):339-41.
13. Breckenridge RL Jr., Ross JS. Idiopathic pulmonary hemosiderosis: a report of familial occurrence. Chest 1979; 75:636-9.
14. Beckerman RC, Taussig LM, Pinnas JL. Familial idiopathic pulmonary hemosiderosis. Am J Dis Child 1979; 133:609-11.
15. Morgan PGM, Turner-Warwick M. Pulmonary haemosiderosis and pulmonary haemorrhage. Br J Dis Chest 1981; 75:225-42.
16. Pulmonary hemosiderosis. In: Kendig EL, Chernick V, eds. Disorders of the respiratory tract in children. Philadelphia: WB Saunders, 1983:430-42.
17. Grill C, Szogi S, Bogren H. Fulminant idiopathic pulmonary hemosiderosis. Acta Med Scand 1962; 171:329-34.
18. Boat TF, Polmar SH, Whitman V et al. Hyperreactivity to cow's milk in young children with pulmonary hemosiderosis and cor pulmonale secondary to nasopharyngeal obstruction. J Pediatr 1975; 87:23-9.
19. Leaker B, Cambridge G, du Bois RM, Neild GH. Idiopathic pulmonary haemosiderosis: a form of microscopic polyarteritis? Thorax 1992; 47:988-90.
20. Blanco A, Solis P, Gomez S, Valbuena C, Telleria JJ. Antineutrophil cytoplasmic antibodies (ANCA) in idiopathic pulmonary hemosiderosis. Pediatr Allergy Immunol 1994; 5(4):235-9.
21. Falk RJ, Jennette CJ. ANCA with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med 1988; 318:1651-7.
22. Tervaert JWC, Goldschmeding R, Elema JD, Limburg PC, van der Giessen M, Hitema MG et al. Association of autoantibodies to myeloperoxidase with different forms of vasculitis. Arth Rheum 1990; 33:1264-72.
23. Jennette JC, Falk RJ. Antineutrophil cytoplasmic autoantibodies and associated diseases: a review. Am J Kidney Dis 1990; 15:517-29.
24. Wilson CB, Dixon FJ. Antiglomerular basement membrane antibody induced glomerulonephritis. Kidney Int 1973; 3:74-89.
25. Kobayashi Y, Arai M, Yoshimitsu K, Yoshimitsu T, Mori M, Kittata E et al. Significance of erythrocyte lipid peroxidation and superoxide dismutase activity in a patient with idiopathic pulmonary haemosiderosis. Eur J Pediatr 1984; 143 (1):64-6.
26. Ziesche R, Costabel U, Guzman J, Matthys H. Cytologic and immunocytologic findings in bronchoalveolar lavage as a contribution to the differential diagnosis of chronic lung hemorrhage. Pneumologie 1990; 44(1):299-300.
27. Turner-Warwick M, Dewar A. Pulmonary hemorrhage and pulmonary hemosiderosis. Clin Radiol 1982; 33:361-70.
28. Ewan PW, Jones HA, Rhodes CG et al. Detection of intrapulmonary hemorrhage with carbon monoxide uptake-application in Goodpasture's syndrome. N Engl J Med 1976; 295:1391-6.
29. Bowley NB, Hughes JBM, Steiner RE. The chest x-ray in pulmonary capillary hemorrhage: correlation with carbon monoxide uptake. Clin Radiol 1979, 130:413-7.
30. Miller T, Tanaka T. Nuclear scan of pulmonary hemorrhage in idiopathic pulmonary hemosiderosis. AJR 1979; 132:120-1.
31. Kurzweil PR, Miller DR, Freeman JE, Reiman RE, Mayer K. Use of sodium chromate Cr 51 in diagnosing childhood idiopathic pulmonary hemosiderosis. Am J Dis Child 1984; 138:746-8.
32. Niimi A, Amitani R, Kurasawa T, Hashimoto H, Kato M, Bandoh K et al. Two cases of idiopathic pulmonary hemosiderosis: analysis of chest CT findings. Nippon Kyobu Shikkan Gakkai Zasshi 1992; 30(9):1749-55.
33. Akyar S, Ozbek SS. Computed tomography findings in idiopathic pulmonary hemosiderosis. Respiration 1993; 60(1): 63-4.
34. Geoffrey DR, Edwards DK III, Reicher MA, Doemeny JM, Carson SH. Diagnosis of pulmonary hemosiderosis by MR Imaging. AJR 1989; 152:573-4.
35. Wyllie WG, Sheldon W, Bodian M, Barlow A. Idiopathic pulmonary haemosiderosis (Essential Brown Induration of the Lungs). Quart J Med 1947; 65:25-51.
36. Corrin B, Jagusch M, Dewar A, Tungekar MF, Davies DR, Warner JO, Turner-Warwick M, Empey D. Fine structural changes in idiopathic pulmonary haemosiderosis. J Pathol 1987; 153:249-56.
37. Soergel KH, Sommers SC. The alveolar epithelial lesions of idiopathic pulmonary hemosiderosis. Am Rev Respir Dis 1962; 85:540-52.
38. Dolan J, McGuire S, Sweeney E, et al. Mast cells in pulmonary hemosiderosis. Arch Dis Child 1984; 59:276-9.
39. Mohri N, Noda M. Idiopathic pulmonary hemosiderosis: an autopsy case. Acta Pathol Jpn 1965; 15:75.
40. Brambilla CG, Brambilla EM, Stoebner P, et al. Idiopathic pulmonary hemorrhage. Ultrastructural and mineralogic study. Chest 1982; 81:120-3.
41. Teplitz C, Farrugia R, Irwin RS. Idiopathic pulmonary hemosiderosis (IPH): ultrastructural observations on the role of interstitial ferritin diffusion and hemosiderin localization in the pathogenetic progression of IPH. Am Rev Respir Dis 1979; 119 (suppl 2):176.
42. Browning JR, Houghton JD. Idiopathic pulmonary hemosiderosis. Am J Med 1956; 20:374-82.
43. Saha V, Ravikumar E, Khanduri U, Date A, Ponnaiya J, Raghupathy P. Long-term prednisolone therapy in children with idiopathic pulmonary hemosiderosis (letter). Pediatr Hematol Oncol 1993; 10(1):89-91.
44. Rossi GA, Balzano E, Battistini E, Oddera S, Marchese P, Acquila M, Fregonese B, Mori PG. Long-term prednisone and azathioprine treatment of a patient with idiopathic pulmonary hemosiderosis. Pediatr Pulmonol 1992; 13(3):176-80.
45. Johansson SA, Andersson KE, Brattsand R, Gruvstad E, Hedner P. Topical and systemic glucocorticoid potencies of budesonide, beclomathasone dipropionate and prednisolone in man. Eur J Resp Dis 1982; 63 (suppl 122): 74-82.
46. Elinder G. Budesonide inhalation to treat idiopathic pulmonary haemosiderosis (letter). Lancet 1985; 1(8435):981-2.
47. Tutor JD, Eid NS. Treatment of idiopathic pulmonary hemosiderosis with inhaled flunisolide. South Med J 1995; 88(9):984-6.
48. Miolin A, Radojicic B. Idiopathic pulmonary hemosiderosis successfully treated with Imuran. Acta Med Jugos 1970; 24:61-6.

49. Yeager H Jr, Powell D, Weinberg RM. Idiopathic pulmonary hemosiderosis: Ultrastructural studies and response to azathioprine. Arch Intern Med 1976; 136:1145-9.
50. Colombo JL, Stolz SM. Treatment of life-threatening primary pulmonary hemosiderosis with cyclophosphamide. Chest 1992; 102(3):959-60.
51. Lapena S, Blanco A, Solis P, Linares P, Gomez S, Hernanz-Sanz JL. Risk factors in the outcome of idiopathic pulmonary hemosiderosis. An Esp Pediatr 1985; 23:5-11.
52. Bagnato L, Grilli C, Portioli P, Biella C, Carnelli V. Long-term evaluation of immunosuppressive therapy in pediatric pulmonary hemosiderosis. Pediatr Med Chir 1986; 8:671-4.
53. Modzelewski JR Jr, Daeschner C, Joshi W, Mullick FG, Ishak KG. Veno-occlusive disease of the liver induced by low-dose cyclophosphamide. Mod Pjthol 1994; 7(9):967-72.
54. Ohga S, Nomura A, Suga N, Hikino S, Kira R, Matsuzaki A, Masuda K, Ueda K. Liposteroid against refractory pulmonary haemorrhage in idiopathic pulmonary haemosiderosis. Eur J Pediatr 1994; 153(9):687-90.
55. Bush A, Sheppard MN, Warner JO. Chloroquine in idiopathic pulmonary haemosiderosis. Arch Dis Child 1992; 67(5):625-7.
56. Zaki M, al-Saleh Q, al-Mutari G. Effectiveness of chloroquine therapy in idiopathic pulmonary hemosiderosis. Pediatr Pulmonol 1995; 20(2):125-6.
57. Cavaliery S. Desferrioxamine with corticosteroids in case of idiopathic pulmonary hemosiderosis. Francastoro 1963; 56:389.
58. Barlow AD. Pulmonary hemosiderosis: Proc R Soc Med 1946; 39:131-2.
59. Steiner B, Nabrady J. Immunoallergic lung purpura treated with azathioprine. Lancet 1965; 1:140-1.
60. Steiner B. Immmunoallergic lung purpura treated with azathioprine and with splenectomy. Helv Paediatr Acta 1969; 24:413.
61. Kincaid-Smith P, D'arice AJF. Plamapheresis in rapidly progressive glomerulonephritis. Am J Med 1978; 65:564-6.
62. Lockwood CM, Russell B, Wilson CB, et al. Plasma exchange in nephritis. Adv Nephrol 1979; 8:383-418.