

Pulmonary Haemosiderosis with Juvenile Idiopathic Arthritis in a Malaysian Child

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SUMMARY

A rare case of childhood pulmonary haemosiderosis with juvenile idiopathic arthritis is discussed, with particular reference to treatment with hydroxychloroquine and sildenafil for pulmonary hypertension which occurs secondary to this disease.

KEY WORDS:

Pulmonary haemosiderosis, Juvenile idiopathic arthritis, Hydroxychloroquine, Sildenafil, Pulmonary hypertension

INTRODUCTION

The syndrome of pulmonary haemosiderosis (PH) is characterised clinically by a triad of pulmonary infiltrates, iron deficiency anaemia, and haemoptysis. Pulmonary haemosiderosis may be idiopathic (iPH), associated with cow's milk allergy, or with antibodies to basement membrane of the lung. Disorders known to cause secondary PH include: pulmonary venoocclusive disease associated with ventricular failure, mitral stenosis with pulmonary hypertension; generalised vasculitides such as those associated with systemic lupus erythematosus and immune-complex-mediated glomerulonephritis; and generalised haemorrhagic disorders, including purpuric syndromes and coagulopathies associated with sepsis. However, its occurrence in association with arthritis is rare both in adults and children^{1,2}.

CASE REPORT

A 14-year-old Malay girl first presented at the age of four years with fever, cough and haemoptysis. She was noted to have a patent ductus arteriosus (PDA) of moderate size, confirmed by echocardiography (ECHO). A Chest radiograph (CXR) revealed an enlarged heart with right upper lobe consolidation. The full blood count at the time revealed a haemoglobin (Hb) of 102g/L, MCV 68.3 fL, MCH 20.4 pg, MCHC 29.9 g/dL. Her sputum culture grew *Haemophilus influenzae* and she was treated for pneumonia with intravenous ampicillin and she received diuretics.

The PDA was ligated one year later. Six months after, she was admitted for haemoptysis associated with fever, cough, wheeze and pallor. Her Hb decreased to 54g/L and the peripheral blood film showed hypochromic, microcytic red cells (MCV 53.9 fL, MCH 14.5 pg, MCHC 26.9 g/dL). She had iron deficiency anaemia on the basis of a normal

haemoglobin electrophoresis and a low serum ferritin and low iron on bone marrow aspirate and trephine biopsy. Sputum examination was positive for haemosiderin-laden macrophages, but her urine and stool examinations were negative for haemosiderin and occult blood respectively. She also did not respond to oral iron therapy. A repeat ECHO showed no residual PDA and no evidence for pulmonary hypertension and serial CXRs revealed diffuse radiological changes. At the age of six years, the diagnosis of pulmonary haemosiderosis was made.

She continued to have recurrent cough, haemoptysis and wheeze, and improved with nebulized salbutamol and prednisolone at doses of 2 mg/kg/day.

At the age of 11 years, she developed polyarthritis involving both wrists, left shoulder, both knees and ankles, and increasing dyspnoea, cough and reduced effort tolerance. Physical examination revealed a cushingoid appearance with moon facies, abdominal striae, clubbing of the fingers with wasting of the small muscles of her hands (Figure 1), reduced range of movement in affected joints, and ankle oedema. Auscultation of her chest revealed bilateral rhonchi, basal crepitations and a loud second heart sound. An ocular examination was normal. Blood investigations showed the following results: rheumatoid factor positive, erythrocyte sedimentation rate 90mm/hour, C-reactive protein (CRP)>96mg/L, complements C₃ 1.35 g/L (normal = 0.6-1.3g/L) and C₄ 0.275 g/L (normal=0.2-0.6g/L), Hb 148 g/L, total white cell count 9.3 x 10⁹/L, platelet count 430 x 10⁹/L, anti-nuclear antibody (ANA) positive (titre 1:≥320), anti-double strand DNA (anti-dsDNA) negative, anti-SS-A (anti-Ro) negative, and the anti-streptolysin O titre (ASOT) 200 iU/ml. An ECHO demonstrated evidence of pulmonary hypertension, with a dilated right atrium, right ventricle and pulmonary artery, and mild tricuspid regurgitation (TR) with a measured gradient of 94mmHg on continuous wave (CW) Doppler. Again her symptoms improved with nebulised salbutamol and systemic corticosteroids.

One year later, she was worse with tachypnoea at rest (NYHA Stage IV), polycythaemia, with an SaO₂ of 87% on 2L/min nasal oxygen. A high resolution CT scan of the thorax (Figure 2) showed evidence of interstitial lung changes with a ground glass appearance consistent with PH. Prednisolone and salazopyrine were tried, but did not provide relief. A lung function test showed an FEV₁ of 1.0L (56.2% predicted)

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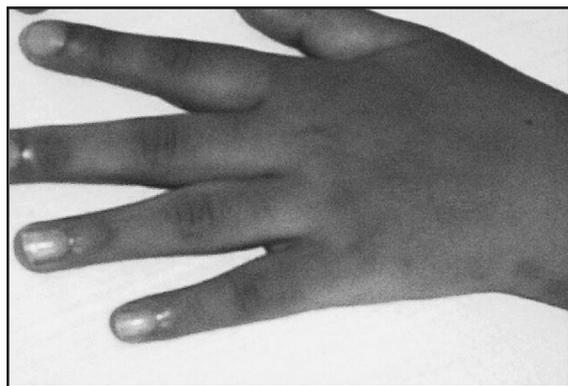


Fig. 1 Photomicrograph of left hand showing clubbing, spindle-shape fingers and wasting of muscles of the hand (permission from her parent and her consent was obtained).

with FVC of 1.1L (42.3% predicted) and FEV1/FVC ratio of 0.9. A trial of oral hydroxychloroquine (CHQ) 125 mg daily was commenced. Oral sildenafil 25mg tds, frusemide and spironolactone were also added for the control of her pulmonary hypertension. Prednisolone was then tapered and discontinued, and CHQ was slowly increased to 250mg daily over a period of three months. With this treatment her symptoms have been under control for the last two years. Her SaO₂ under room air ranged from 96-98%, her ESR dropped to 41 mm/hour and her joint stiffness and finger clubbing resolved. A repeat ECHO revealed that her TR had reduced significantly to 44 mmHg.

DISCUSSION

Even though the diagnosis of PH in this patient was not histologically proven as no lung biopsy was performed, the presentation of recurrent haemoptysis, persistent iron deficiency anaemia, presence of haemosiderin-laden macrophages in the sputum, diffuse radiological changes and a restrictive pattern of lung function are characteristic features of PH. The presence of polyarthritis of the small joints associated with rheumatoid factor and ANA is highly suggestive of rheumatoid factor positive juvenile idiopathic arthritis.

Pleuropulmonary disease such as transient pneumonitis, interstitial reticular and nodular infiltrates, pleural and pericardial effusions, and patchy pleural infiltrates is seen in only about 4% of children with juvenile idiopathic arthritis (JIA)³. Pulmonary haemosiderosis has been reported to occur after the presentation of arthritis and arthralgia^{1,2}. Chu *et al* (2002)¹ described a 3-year-old girl who had PH six-months after the diagnosis of JIA and Topaloglu *et al* (2000)² described a 3-year-old boy who developed PH and JIA two years after the initial presentation of iron deficiency anaemia and arthralgia. In our patient, the presentation of arthritis occurred six-years after the onset of PH.

The pathogenesis of iPH remains a mystery although cow's milk allergy, tobacco smoke, pesticide exposure and possibly other unidentified environmental factors are thought to

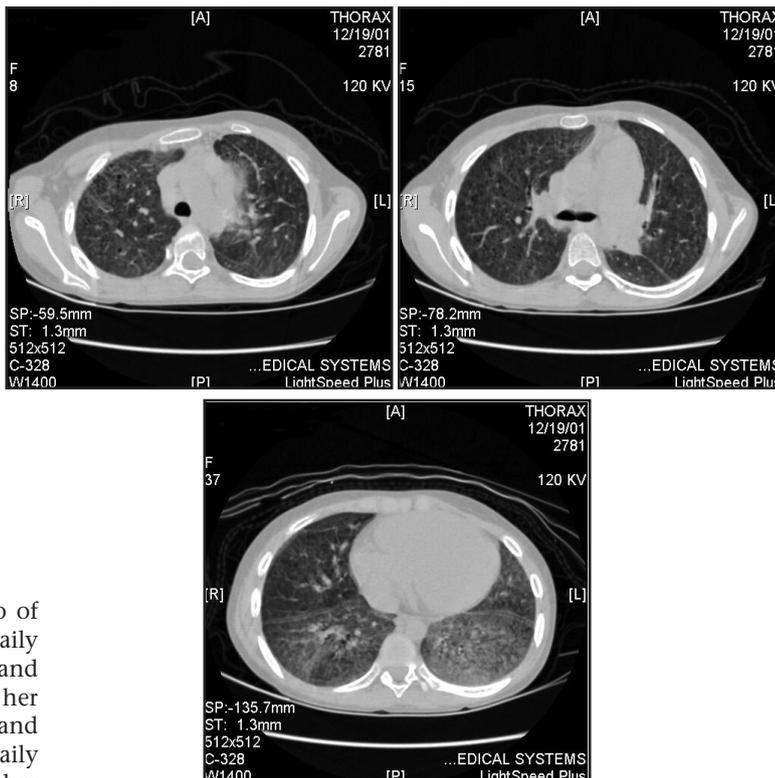


Fig. 2: CT scans demonstrating pulmonary fibrosis especially in lower lobes consistent with pulmonary haemosiderosis. Top left showing fibrosis at both upper lobes. Top right showing lung tissue at the level of bifurcation of the bronchi and again fibrosis of lung tissue. Bottom left demonstrating pneumonic consolidation of both lower lobes with thickening of pleural fissures.

trigger an immune response leading to iPH in a susceptible child³. This seems plausible as many cases of iPH do respond to immunomodulation therapy. Immune-complex deposition is also thought to occur in other secondary forms of PH such as rheumatoid arthritis, systemic lupus erythematosus, and mixed connective disease. Immunological tests should also be included in the serial work up for patients presenting with PH, as it can also be used for prognosis as children having a positive ANA or ANCA are more likely to develop an immunological disorder, as in our patient.

The variable course and rarity of the disease makes assessment of treatment difficult. Various drugs including corticosteroids and other immunosuppressives such as CHQ and azathioprine have been used in the treatment of PH³.

This patient showed a moderate response to prednisolone initially, but developed significant side effects from excessive steroid use. Hydroxychloroquine has been reported to be effective for pulmonary haemosiderosis,⁴ but the response is slow, and with patience we were able to wean this child completely off steroids. Sildenafil had been found in limited trials⁵ to be effective in controlling pulmonary hypertension secondary to lung pathology. It is a phosphodiesterase⁵ inhibitor that prevents the breakdown of cyclic guanosine monophosphate involved in vasodilation. This was used to

Case Report

control her pulmonary hypertension and was associated with a marked reduction in her TR jet to 44mmHg, and a marked improvement in her effort tolerance. While the course of PH is variable, progressive pulmonary fibrosis and subsequent pulmonary hypertension can complete the disease and should be looked for.

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