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Case Report

A Child with Unusually Severe Anaemia Paediatric Idiopathic Pulmonary Haemosiderosis: From Diagnosis to Treatment

JWCH ***Cheng***, L ***Lee***, YY ***Lam***, WK ***Chiu***

Abstract A 3-year-old boy YC presented with pallor after an episode of upper respiratory tract infection. Blood tests revealed iron deficiency anaemia and extensive workup for its causes were unremarkable. On identifying persistent pulmonary infiltrates on a contrast computerised tomography scan, workup went along the direction of diffuse alveolar haemorrhage and the ultimate diagnosis of idiopathic pulmonary haemosiderosis (IPH) was confirmed by bronchoalveolar lavage and thorascopic lung biopsy. Although rare, IPH has a variety of presenting symptoms and should be considered as a differential diagnosis for unexplained anaemia. Physicians must be vigilant for complications from the disease itself and its treatment. Management options are variable but mainstay treatment consists of corticosteroid therapy with or without adjuvant immunosuppressants.

Key words *Anaemia; Diffuse alveolar haemorrhage; Haemosiderin; Haemosiderosis; Hydroxychloroquine; IPH*

Case Report

YC was born full term from non-consanguineous healthy parents. His developmental milestones, immunisation history and growth history were unremarkable.

YC presented with pallor after an episode of viral illness in May 2015 at the age of 21 months. He had no symptoms of anaemia or bleeding tendencies. Physical examination showed a child with body weight at 3rd to 10th percentile. He had pallor, but no petechiae. Abdominal examination was unremarkable. Chest examination revealed no deformity, symmetrical air entry with normal breath sounds. Per rectal examination yielded tarry stool. Other systems were unremarkable. Chest X-ray (CXR) showed right lung haziness.

His haemoglobin level (Hb) was 4.6 g/dL. It was microcytic hypochromic anaemia with MCV, MCH and RBC at 64.9fL, 18.7 pg and $2.3x10^{12}$/L respectively. Blood film showed aniso-poikilocytosis, microcytosis, hypochromasia, polychromasia, and target cells. Reticulocyte count was elevated at $235x10^{9}$/L (4.93%). White blood cell count, platelet count, liver function test, renal function test, C-reactive protein and erythrocyte sedimentation rate were normal. Haemoglobin pattern was normal. He was iron deficient with iron level and total iron binding capacity of 2.8 umol/L and 84.7 umol/L respectively.

YC's severe iron deficiency anaemia was treated with blood transfusion. He was asked to increase dietary meat portions and supplemented with Ferrum Hausmann.

One month later YC's Hb dropped from 8.3 to 4.5 g/dL despite good drug compliance and being asymptomatic. Five blood transfusions were given between June to September 2015 due to repeated significant Hb drop. Extensive workup along the differential diagnoses of production problems, haemolysis, infective causes, autoimmune causes, and gastrointestinal blood loss however did not give any positive clue except for faecal

Department of Paediatrics and Adolescent Medicine, United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Kowloon, Hong Kong SAR, China

JWCH **Cheng**（鄭正禧） *MBBS, FHKAM(Paed), PGDipClinDerm(QMUL)*
L **Lee**（李寶儀） *MBBS, FHKCPaed, FHKAM*
YY **Lam**（林英彥） *MBBS, FHKAM(Paed), PGDipClinDerm(QMUL)*
WK **Chiu**（趙華強） *MBBS, FHKCPaed, FHKAM*

Correspondence to: Dr JWCH **Cheng**
Email: cch278@ha.org.hk

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occult blood being positive. Otherwise Meckel's scan, oesophagealgastroduodenoscopy, laparoscopy, ultrasound abdomen and red cell scans were all unremarkable.

YC was admitted in September 2015 for wheezing. He was afebrile but tachypnoeic and tachycardic. Chest examination revealed bilateral expiratory wheezes. CXR demonstrated bilateral diffuse lung haziness which was not previously present. Hb was 7.4 g/dL with marked reticulocytosis. Because of the discrepancy between wheezing and CXR findings, an urgent contrast computerised tomography (CT) thorax and high resolution CT thorax was requested, showing bilateral diffuse pulmonary infiltrates which suggested pulmonary haemosidersosis (Figure 1).

To confirm the radiological suspicion, bronchoalveolar lavage was proceeded yielding pinkish bronchial aspirates, with histopathological analysis showing numerous haemosiderin laden macrophages (Figure 2). It was otherwise negative for bacterial, fungal and tuberculosis studies. Then YC underwent thorascopic lung biopsy which showed no capillaritis indicative of other causes of diffuse alveolar haemorrhage. Further workup for related autoimmune diseases included radioallergosorbent test (RAST) for cow's milk protein allergy, anti-glomerular basement membrane (anti-GBM) antibody and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA). The diagnosis of idiopathic pulmonary haemosiderosis (IPH) was made after ruling out other secondary causes of diffuse alveolar haemorrhage (DAH).

YC was offered a 3-day course of intravenous methylprednisolone 30 mg/kg/dose for acute flares which was gradually weaned down to maintenance oral prednisolone at 1 mg/kg on alternate days. Top up of maintenance oral prednisolone to 1 mg/kg/day daily with concurrent addition of oral hydroxychloroquine 4.5 mg/kg/day as a steroid-sparing agent and adjuvant therapy was needed (2 months after pulse methylprednisolone) before YC became free from bleeding episodes. He was also put on inhaled fluticasone at 200 mcg/kg/day. Henceforth YC remained asymptomatic with a stable Hb level since May

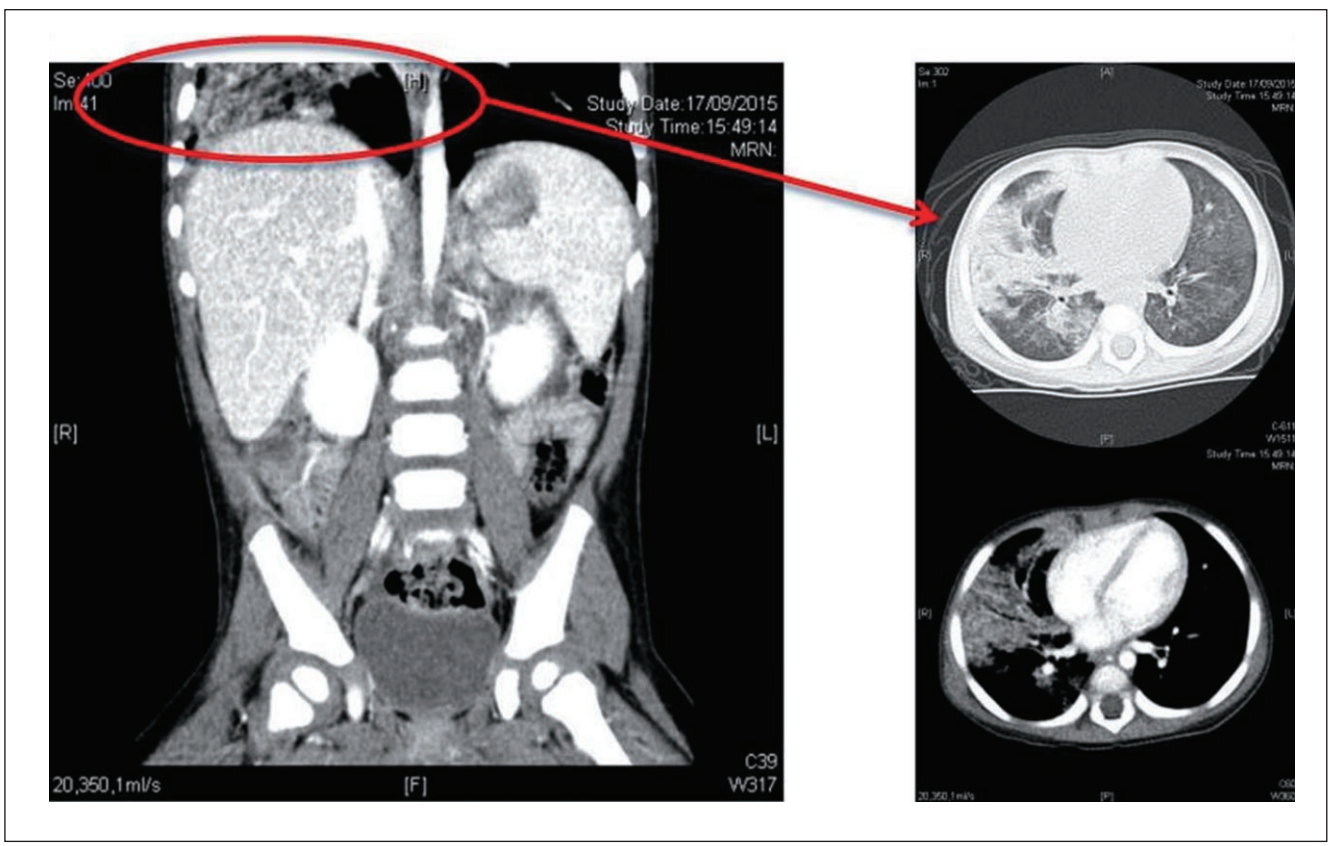

Figure 1 Contrast CT thorax and high resolution CT thorax showing bilateral diffuse pulmonary infiltrates suggestive of pulmonary haemosiderosis.

2016. The daily dose of oral Prednisolone was tailed down to alternate days after 17 months. The inhaled Fluticasone was weaned in 8 months' period. Hydroxychloroquine has been continued up till present. He is regularly followed up for monitoring of growth, side effects of long term steroid use, lung function and any signs of autoimmune diseases.

Discussion

IPH is a rare disease entity that mainly affects patients under 10 years of age.[1-3] Classically it is characterised by haemoptysis, anaemia and pulmonary infiltrates, and confirmed by alveolar haemosiderin laden macrophages in bronchoalveolar lavage.[1,4,5] Incidence of paediatric IPH

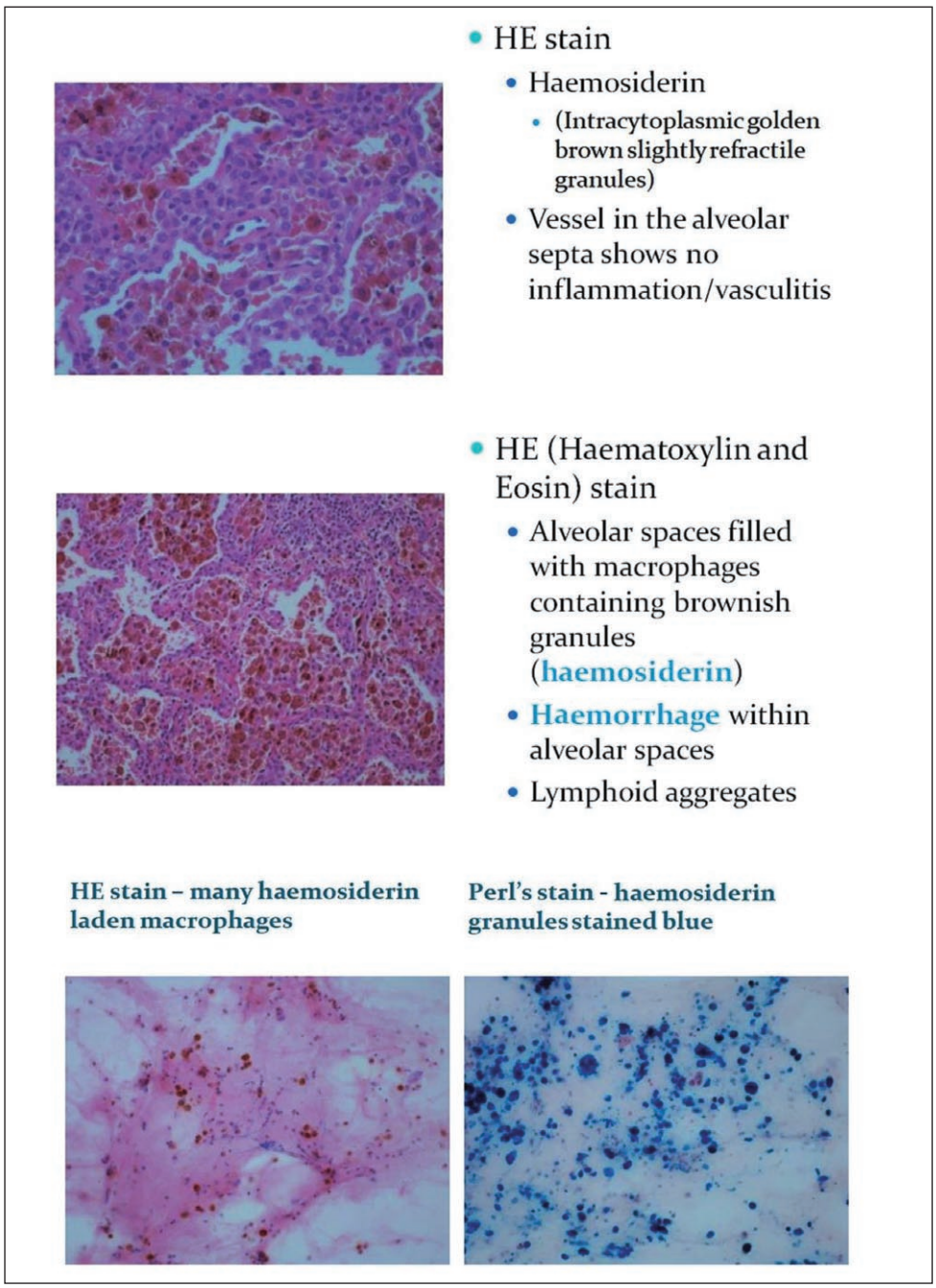

Figure 2 Histopathological analysis of bronchoalveolar lavage using HE and Perl's stains showing numerous haemosiderin laden macrophages.

varies in different localities, with reports ranging from 0.24 patients/million people/year in Sweden[4] to 1.23/patients/million people/year in Japan.[6]

Clinically patients can present with anything between an insidious onset of mild respiratory symptoms, as with our patient, to acute life-threatening respiratory failure. The high variability of presentation makes diagnosis difficult, with delay in diagnosis ranging from 1 to 6.3 years.[3]A lack of respiratory symptoms does not preclude the diagnosis.[5] In our patient, the only clue was iron deficiency anaemia with exacerbation by viral illness. Diagnosis relies on high suspicions for unexplained iron deficiency anaemia, with radiological and histological confirmation.

Radiologically CXR or CT thorax typically shows bilateral diffuse pulmonary infiltrates. Bronchoalveolar lavage shows the pathognomonic haemosiderin-laden macrophages in bronchial wash-outs, and in gastric lavage samples due to swallowed pulmonary infiltrates. For the same reason, stool occult blood could be positive.

Lung biopsy is not necessary but highly recommended to differentiate between capillaritis and non-capillaritis. DAH syndromes with pulmonary capillaritis are mostly autoimmune causes including Wegener's granulomatosis, microscopic polyangiitis, Goodpasture's syndrome, etc., while those without pulmonary capillaritis include IPH, Heiner's disease, and certain non-inflammatory cardiovascular disorders. The non-capillaritis DAH syndromes can be further differentiated with blood tests for c-ANCA, RAST tests, and anti-GBM antibodies.[1,3,4]

Supportive treatment in terms of blood transfusion, oxygen and mechanical ventilation is warranted for children experiencing symptomatic anaemia and/or respiratory distress due to significant acute pulmonary bleeding. There are still debates over the most effective treatment for IPH, yet pulse steroid therapy is well-established for controlling severe life-threatening pulmonary bleeding.[1,3,4] Taytard et al suggested pulse methylprednisolone at 300 mg/m^2/day for 3 days.[3] Susarla et al reported on use of intravenous methylprednisolone at 2-4 mg/kg/day every 6 hours or pulse intravenous methylprednisolone at 30 mg/kg (max 1 g) for 3 days.[5]

Upon remission and for disease maintenance, steroid therapy in a regular pulse or regular oral regimen with weaning after disease remission is commonly used for disease control,[1-5,7] with follow-on oral prednisolone at 1 mg/kg/day on daily[3] or alternate-day basis.[5] The largest review article[3] suggested monthly methylprednisolone 300 mg/m^2/day for 3 days per month for initial treatment, with daily oral prednisone added (1 mg/kg/d) for severe situations. Duration of maintenance treatment remains debatable.[3,5,7] Inhaled corticosteroid is recommended by Nusslein et al as a supplementary treatment.[1]

Adjunctive treatment including hydroxychloroquine,[3-5] mycophenolate mofetil,[3] azathioprine,[3-5] methotrexate[5] and cyclophosphamide[1,4,5] are reported to be options for steroid-refractory IPH or patients who cannot tolerate the side effects of steroids. These agents can be administered alone or with steroid therapy. Intravenous immunoglobulin[5] is also a possible adjunct for refractory bleeding.[1,4,5] Evidence has shown that a more aggressive treatment approach allows better survival,[4,5] with improvement in 5-year survival up to 86%[4] as compared to the old figures of 3-5 years' median survival.[1]

In conclusion, IPH is a rare disorder with a variety of presenting symptoms but should be considered as a differential diagnosis for unexplained anaemia. Physicians must be vigilant for development of associated autoimmune diseases and long-term side effects of corticosteroids. Treatment options are variable but mainstay treatment consists of corticosteroid therapy with or without adjuvant immunosuppressants.

Declaration of Interest

The authors report no conflicts of interest.

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