Case Study

PULMONARY HAEMOSIDEROSIS

D Manzini[1]
AC Jeevarathnum[2]
A van Rooyen[3]

1. Registrar in Paediatrics, Steve Biko Academic Hospital, University of Pretoria

2. Fellow in Paediatric Pulmonology, Steve Biko Academic Hospital, University of Pretoria

3. Anatomical Pathologist, Steve Biko Academic Hospital, University of Pretoria

A 2 year 9 month old girl was referred to Steve Biko Academic Hospital (SBAH) from Tshwane District Hospital (TDH) on the 31st of October 2014, with an initial diagnosis of a community acquired pneumonia. Her initial chest x-ray is depicted in Figure 1 showing non-specific interstitial changes with involvement of both lung fields.

HISTORY AND SYMPTOMATOLOGY

The patient had presented to TDH with a 3 month history of cough and shortness of breath. Her cough was dry and non-productive. The parents did not observe any haemoptysis. She had never experienced wheezing and was not nebulised during any of her previous admissions. She had been losing weight and the parents had noticed increasing shortness of breath and fast breathing.

She had had multiple admissions to TDH where she was treated for a community acquired pneumonia. The chest x-rays taken at TDH were unfortunately not available to us. She had completed several courses of antibiotics. The parents reported minimal to no improvement following any of the previous admissions.

RELEVANT HISTORY

The patient has no significant perinatal, family, or surgical history. She had been confirmed to be HIV negative. There was no family history of atopic disease.

In terms of the dietary history, the child was exclusively breastfed from birth until 6 months and subsequently gradually weaned onto solid foods. Significantly, the dairy component of the diet consisted of yoghurt daily, milkshakes weekly, with infrequent ingestion of fresh milk or cheese.

EXAMINATION

No evidence of atopy was noted in this patient. Anthropometry was in keeping with an assessment of moderate acute malnutrition. The patient looked acute on chronically unwell and severe pallor was observed. There was no jaundice or splenomegaly that would have indicated a haemolytic cause for the pallor. The respiratory examination revealed moderate respiratory distress with tachypnoea, nasal flaring, subcostal and intercostal recessions, but no grunting. She was oxygen dependent with nasal prong oxygen running at 2 L/min. Chest auscultation was completely clear. There was no evidence of heart failure and the rest of the examination was normal.

Bedside urine dipstix examination was normal, with no haematuria.

SUMMARY

- 2 year 9 month old infant;
- History of recurrent lower respiratory infections;
- Moderate respiratory distress with an interstitial pattern on chest x-ray;
- Pallor likely to be secondary to an iron deficiency anaemia.

DISCUSSION AND PLAN

Further laboratory investigations confirmed an iron deficiency anaemia with an Hb of 2.2 g/dl (10.8-14.2), MCV of 68.7 fL (70-86), MCH of 13.5 pg (23-31), iron of 2.1 umol/L (9-21.5), ferritin of 18 ug/L (36-84), transferrin of

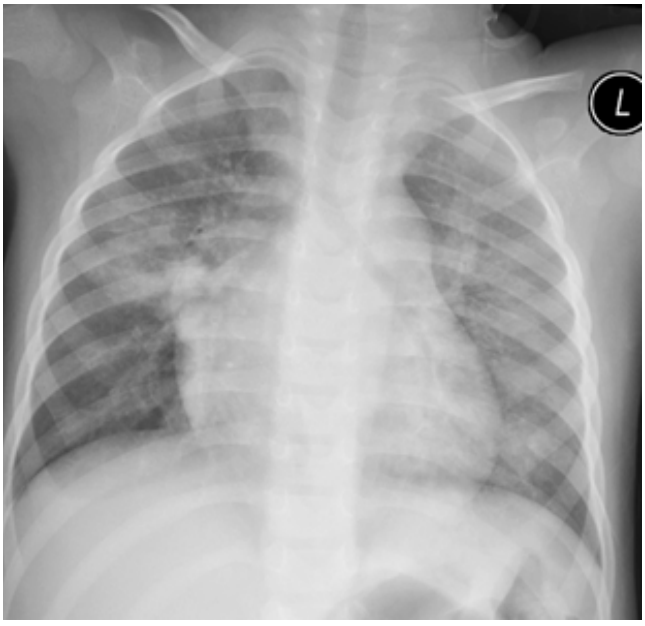


Figure 1: CXR of the patient

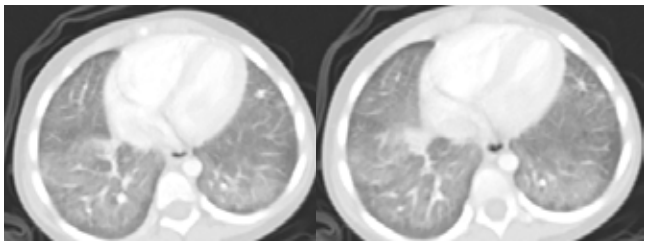


Figure 2: CT scan of the patient

3.30 g/L (1.49-3.82) with a saturation of 3% (15-50%). Reticulocytes were 5.20% (>2 suggests an adequate bone marrow response) and the serum haptoglobin was 0.98 g/L (0.3-2). Stools for occult blood were negative. There was no blood in the urine and no other evidence of glomerulonephritis.

Septic markers were not suggestive of a bacterial infection with a WCC of $8.73x10^9$/L (6-18) and a PCT of 0.1 ug/L (< 0.5 suggests an unlikely systemic bacterial infection).

High resolution CT chest is depicted in Figure 2 which showed diffuse interstitial changes and ground glass opacities.

At this point in time, we considered pulmonary haemosiderosis as a possible cause for the interstitial lung changes and iron deficiency anaemia. Workup for Goodpasture Syndrome including anti-basement membrane antibodies was negative. Auto-immune workup including ANCA for Wegener's granulomatosis was also negative.

A lung biopsy was conducted for diagnostic purposes. Histology revealed alveolar spaces filled with blood and haemosiderin-laden macrophages (proven with iron stain). This confirmed the diagnosis of pulmonary haemosiderosis.

Under dietetic consultation, all cow's milk products were discontinued. The child was commenced on Neocate. The child received pulse treatment with methylprednisone and was also started on Chloroquine. After the dietary dairy exclusions and the pulse methylprednisone, the child was successfully weaned off oxygen and dramatically improved clinically.

ASSESSMENT

Pulmonary haemosiderosis most likely secondary to Heiner Syndrome.

DISCUSSION

Heiner Syndrome refers to an entity of diffuse pulmonary haemorrhage that occurs in association with a severe hypersensitivity to cow's milk in children, most commonly in children between 4-29 months of age.[1,2] In 1962, Heiner described the triad that constitutes the syndrome: iron-deficiency anaemia, haemoptysis, and multiple alveolar infiltrates on chest radiographs.[3]

The incidence of Heiner Syndrome is difficult to determine, as only few reports have been published. As a diagnosis of exclusion, Heiner Syndrome lends itself to misdiagnosis, which could account for the lack of reliable statistics on disease incidence.[2]

The pathology of pulmonary haemosiderosis has historically been classified as primary or secondary. Primary pulmonary haemosiderosis (PPH) is described as encompassing the diagnosis of idiopathic pulmonary haemosiderosis (IPH), Goodpasture Syndrome (anti-basement membrane antibody disease) and Heiner Syndrome.[4] Secondary pulmonary haemosiderosis occurs secondary to another disease process and includes entities such as SLE, Wegener granulomatosis, Henoch-Schönlein purpura and coagulopathies.[4]

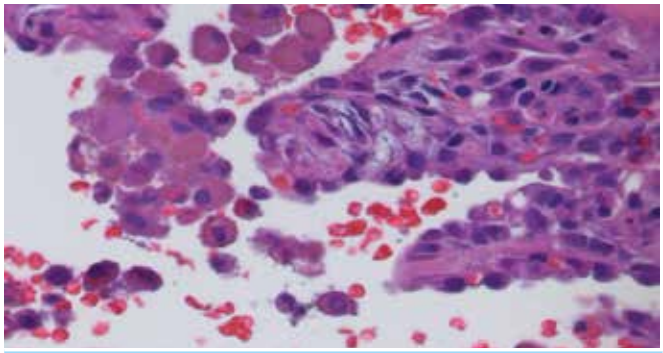
PRESENTATION

The clinical presentation of the syndrome is variable and potentially fatal. The history of ingestion of cow's milk is paramount. In most cases, haemoptysis or haematemesis and dyspnoea are the presenting complaint, either slowly, insidiously or acutely, with severe pulmonary haemorrhage and hypoxaemia. Dyspnoea associated with wheezing is also a notable presentation, which has often been misdiagnosed as asthma. There may also be a history of symptoms of milk intolerance: grossly bloody stools, vomiting, symptoms of gastrointestinal reflux, and upper airway congestion.[3] The spectrum of nutritional presentation ranges from failure to thrive and moderate acute malnutrition to severe acute malnutrition. Anaemia, due to iron deficiency is often present as a result of chronic blood loss and deposition of iron in the lungs and may be severe enough to warrant urgent transfusion of packed cells in the acute presentation.[3]

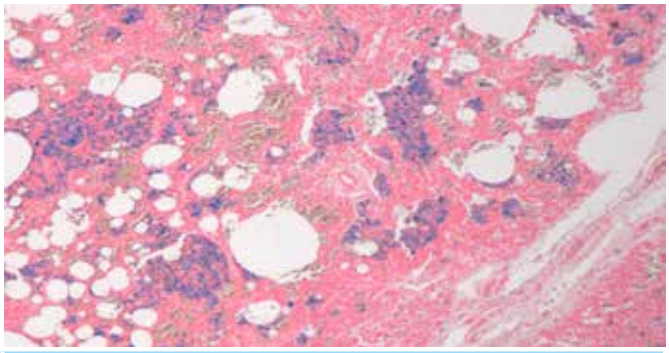
Biochemically there is usually elevation of total serum IgE, peripheral eosinophilia, alveolar deposits of IgE, IgA and C3. Conventional IgE allergy tests to cow's milk are usually negative. However, if available there can be high levels of precipitins to cow's milk protein. Radiologically there is a typical pattern on the chest x-ray: a butterfly or batwing pattern, i.e. symmetrical alveolar infiltrates slanting upwards towards the lateral chest walls.

PATHOPHYSIOLOGY

Heiner syndrome is a non-IgE type of cow's milk allergy. The pathophysiology resulting in the clinical picture of Heiner Syndrome begins with bleeding from alveolar capillaries into pulmonary interstitium and alveolar spaces, with the resulting free haemoglobin being transformed into haemosiderin. Macrophages ingest the haemosiderin (becoming haemosiderin-laden macrophages) and subsequently release pro-inflammatory molecules leading to acute then chronic inflammation with fibrosis if bleeding occurs repeatedly.[2]



H&E Stain X4: High magnification of haemosiderin-laden macrophages. Large cells with cytoplasm filled with brown pigment.[6]



Iron stain: Prussain Blue X4: The Prussian blue confirms the pigment to be haemosiderin by staining blue for iron. The red blood cells do not stain.[6]

Figure 3: Lung biopsy specimen from the patient

DIAGNOSIS

The diagnosis of Heiner Syndrome is essentially a process of the confirmation of pulmonary haemorrhage with its complications of anaemia and haemosiderin-laden macrophages, exclusion of other causes of pulmonary haemorrhage; and improvement of symptoms upon total avoidance of cow's milk (the documentation of precipitating antibodies to cow's milk in the serum being a controversial part of the process). Workup for Goodpasture Syndrome including anti-glomerular basement membrane antibodies and an auto-immune workup including ANCA for Wegener granulomatosis is also indicated.

The suggestive symptomatology; anaemia due to blood loss and eventually due to iron deficiency; failure to thrive; unexplained chronic interstitial radiological changes, evidence of clinical allergy, with elevated levels of precipitating antibodies to bovine milk proteins in serum are highly predictive. The diagnosis is supported by the documentation of clinical and radiological improvement after strict cow's milk avoidance. Within this context, the definitive diagnosis is made by the finding of haemosiderin laden macrophages (siderophages) on broncho-alveolar lavage or lung biopsy.[3]

TREATMENT

The aim of the treatment is to stabilise and arrest the inflammatory process underlying the disorder. Treatment of Heiner Syndrome is basically strict avoidance of cow's milk and any other identified offending food. Initially, treatment is symptomatic, e.g. bronchodilators, antihistamines, systemic or inhaled steroids and iron.[3] If bleeding is severe enough to interfere with air flow, rigid bronchoscopy may be necessary to remove clots, with high pressure mechanical ventilation also an option thereafter.[2]

Immunosuppressive treatment of the acute episode with steroids (2 mg/kg/day prednisolone) is effective in most patients. Long term treatment with high dose steroids for 6 months followed by low doses would ensue. If there is no satisfactory response to immunosuppressive therapy in the acute phase, methylprednisolone as a pulse (30 mg/kg daily for 3 days) or cyclophosphamide (2-3 mg/kg/day) should be given. Other immunosuppressive agents such as chloroquine and azathioprine combined with prednisone have been shown to be effective.[3]

As such, Heiner syndrome should be considered in children with interstitial lung disease and an iron deficiency anaemia.

PROGNOSIS

Unfortunately, the literature on Heiner syndrome is extremely scanty. The long term prognosis and chances of outgrowing the cow's milk protein allergy are largely unknown. In the literature that does exist, relapses have been reported on reintroduction of cow's milk in children as old as 6-8 years. It thus seems that prolonged elimination of cow's milk is warranted and if reintroduction is attempted, it should ideally be under close monitoring in the hospital setting.

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