Case Report

Heiner Syndrome Mimicking Pneumonia with Iron Deficiency Anemia

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ABSTRACT

Heiner Syndrome is an unusual form of pulmonary hemosiderosis mostly caused by cow milk. It presents as iron deficiency anemia, and hypoproteinemia. This clinical case describes a female infant with failure to thrive presenting with cough, low-grade fever, fast breathing with refusal to feed. On examination severe anemia with congestive cardiac failure was found, the cause of which was evaluated. Chest X-ray showed bilateral fluffy infiltrates mimicking pneumonia. Investigations revealed microcytic hypochromic anemia with normal corrected reticulocyte count. Iron deficiency anemia (IDA) was diagnosed. However, the etiology of bilateral fluffy lung infiltrates could not be established in this child. Hence Broncho Alveolar Lavage (BAL) for hemosiderin-laden macrophages and immunoglobulin for cow milk precipitin was done to establish the diagnosis.

Keywords: pneumonia mimicker, cow milk protein allergy (CMPA), iron deficiency anemia, diffuse alveolar hemorrhage (dah), pulmonary hemosiderosis, Heiner syndrome

Heiner Syndrome (HS) is an unusual form of pulmonary hemosiderosis caused by cow milk [1]. It is also known as cow milk-induced rare pulmonary disease in infants and young children [2]. It is distinguished by recurring respiratory tract symptoms, infiltrates that resemble pneumonia on chest radiographs, fever, anaemia, and failure to thrive [3]. Some patients with the syndrome have reported gastrointestinal symptoms such as anorexia, vomiting, diarrhoea, abdominal discomfort, and bloody faeces. These clinical symptoms have been shown to resolve within one to three weeks of stopping cow milk. The disease's variable character usually causes delay in identification and treatment. The existence of precipitating antibodies against cow milk proteins helps to support the diagnosis.

Heiner et al first described the condition in the United States of America (USA) in a group of seven children aged 6 weeks to 17 months who were fed cow's milk and had recurring respiratory symptoms and infiltrates on chest radiographs [1]. Moissidis et al. in the United States found that the most children with this condition were identified between the fourth and twenty-nine months of life [2]. There have been a few further case reports of the disease in the United States, Italy and Turkey. We present the case of a one-year-old female child with the syndrome treated at our hospital.

CASE REPORT

A one-year-old female child weighing 7.8 kg was brought in with complaints of cough persisting for 4 days,low-grade intermittent fever for 1 day, refusal to feed for 1 day, and one episode of nonbilious, nonprojectile vomiting. On initial observation, she exhibited pallor, fast breathing (RR- 66/min), tachycardia (HR- 170/min), and lethargy with response to tactile stimulus. There was no history of wheezing episodes. She was born at term weighing 2.7 kg, with an uneventful perinatal period. Her development and immunization were age-appropriate. She was exclusively breastfed until 3 months, after which complementary feeding started with a deficit of 4 gm of protein and 520 kcal of calories.

Physical examination revealed severe pallor, tachycardia, tachypnea with chest recessions, bounding pulses, cool extremities, a grade 3 short systolic murmur in the apical area, and a liver palpable 3 cm below the right subcostal margin.

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Chest X-ray showed an enlarged cardiac silhouette with a cardiothoracic (CT) ratio of 0.58. Bilateral peripheral fluffy opacities in lung fields mimicking pulmonary edema and pneumonia were evident **[Figure 1]**. Echocardiography ruled out congenital heart disease, and sepsis screen results were negative. She presented with severe microcytic hypochromic anemia (Hb-3.90) and aniso-poikilocytosis.

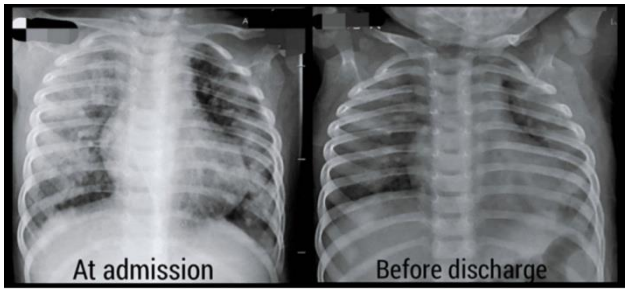

Figure 1: Chest x-ray at the time of admission (left) showing bilateral fluffy infiltrates in all lung zones limited to the periphery compared against initiation of resolution of infiltrates after starting steroids (right).

The corrected reticulocyte count was 0.6% **[Table 1]**. Hemoglobin electrophoresis was normal. The iron profile indicated a normal ferritin level with a total iron binding capacity (TIBC) in the upper normal range and significantly low transferrin saturation **[Table 2]**. Iron deficiency anemia (IDA) was suspected. Urine analysis for hematuria and blood culture for sepsis were inconclusive. Stool examination for routine and occult blood ruled out parasitic infestation and gastrointestinal loss as causes of anemia. Given the severe anemia and congestive cardiac failure, a packed red cell transfusion at 10 ml/kg was administered.

Table 1: Red cell indices at hospitalization and follow-up

Red cell Indices	At admission	On follow up	Normal range
Hemoglobin (g%)	3.90	7.50	11.0-13.0
Mean corpuscular volume (fl)	59.40	76.30	78-82
Mean corpuscular hemoglobin (pg)	22.70	23.80	28-33
Mean corpuscular hemoglobin concentration (%)	38.10	31.20	33-38
Red cell distribution width (%)	23	16	14.5-15.5
Reticulocyte count (%)	5.4	1.3	1-2

fl- femto litre, p – pico gram

After ruling out sources of blood loss, a Direct Coomb's Test was conducted to investigate the possibility of M. pneumonia-associated walking pneumonia with autoimmune hemolytic anemia due to cold agglutinin antibody, but the test was negative.

A detailed dietary history revealed intermittent feeding of cow milk by the grandmother. Diffuse Alveolar Hemorrhage (DAH) secondary to cow milk protein allergy was considered. Bronchoscopy was planned, and bronchoalveolar lavage (BAL) fluid was analyzed for routine studies, Gene Xpert for tuberculosis, and hemosiderin-laden macrophages. Investigations for small vessel vasculitides (anti-neutrophil cytoplasm antibody) were also negative. BAL for hemosiderin-laden macrophages tested positive. IgE titre for cow milk precipitin was elevated at 178.72 KU/L (normal range 0-100 KU/L). Based on these findings, a diagnosis of Heiner's syndrome was made.

Table 2: Iron profile of child at hospitalization

Iron profile	Values	Normal reference range
Serum Ferritin (ng/ml)	62	5-50
Total Iron Binding Capacity (TIBC) (mcg/dl)	345	190-350
Total Body Iron (mcg/dl)	20	37-1702
Serum Transferrin (mg/dl)	196	206-381
Transferrin Saturation (%)	5.8	20-50

mcg- microgram, mg- milligram, ng- nanogram, ml- milliliter, dl- deciliter

Cow milk was eliminated from the child's diet, and oral corticosteroids were initiated at 2 mg/kg/day for 2 weeks, followed by tapering over another 2 weeks. On follow-up, the child showed weight gain and resolution of lung infiltrates. An oral food challenge (OFC) with cow milk is planned, with monitoring of cow milk IgE precipitin titer during follow-up.

DISCUSSION

Heiner syndrome is an uncommon form of primary pulmonary hemosiderosis that is linked to cow milk protein hypersensitivity. It is twice as common in female children, with a mean age of onset between 3.5 and 4.5 years, who are fed cow milk. Symptoms include rectal blood loss resembling microcytic hypochromic anemia, akin to iron deficiency anemia, recurrent pulmonary infiltrates, and hypoproteinemia. These symptoms result from the immunologically mediated production of precipitins/antibodies to cow milk protein.

The condition was first identified and described by Heiner et al. in 1960 in seven children, most of whom presented with chronic respiratory diseases like wheezing and iron deficiency anemia, similar to our case [1]. Moissidis et al., in their review of eight cases, also noted upper respiratory tract symptoms and pulmonary infiltrates on chest X-ray. Three cases had fresh blood in stools, which was absent in our case [2].

Pathological findings may include elevated IgE levels against cow milk precipitins, peripheral eosinophilia, and deposits of IgG, IgA, and C3 in the alveoli. Both Moissidis et al. and Stafford et al. demonstrated milk precipitins in the majority of cases [2,3]. Hemosiderin-laden macrophages in bronchoalveolar lavage were first utilized by Moissidis et al., followed by Koc et al., and reported in case reports by Mourad et al. and Arasi et al. [4,5,6]. This prompted us to perform a bronchoscopy on our patient to identify hemosiderin-laden macrophages and confirm the diagnosis of Heiner syndrome.

Primary treatment involves eliminating cow milk from the diet. Steroids and other immune modulators such as HCQ, azathioprine, and cyclophosphamide may benefit severely ill patients or those who do not respond to cow milk elimination. The use of steroids and other immune modulators is based on the immune-mediated mechanism of the condition, as indicated by case reports from Mourad et al. and Yavuz et al. [4-7]. The optimal route of administration for these drugs remains unclear, as both oral and intravenous modes have been used, and no study compared one over the other [8].

Prognosis varies, ranging from death due to massive pulmonary bleeding to pulmonary fibrosis. Saeed et al. reported on seventeen patients with Heiner syndrome, three of whom died from diffuse alveolar hemorrhage (DAH). Thirteen required long-term immunosuppression due to pulmonary fibrosis, with a five-year survival rate of 86% [9]. Zhang et al. also noted that long-term immunosuppression may improve outcomes for children with this condition, which supported our decision to use steroids in our patient [10].

CONCLUSION

With insufficient information, unusually varied presentation, and lack of diagnostic criteria for this condition, we must suspect Heiner's syndrome in children with unexplained hemoptysis or pulmonary infiltrates, bloody diarrhea, and iron deficiency anemia to avoid long-term pulmonary and growth-related morbidity. Attempting to demonstrate an IgE-mediated mechanism may reassure both parents and the clinician about the diagnosis and potential remission. Follow-up examination is necessary to monitor growth, resolution of symptoms, and improvement of anemia. Cow milk may be gradually reintroduced late, but it's important to always be aware of the possibility of recurrence of the condition.

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