Looking Beyond the Obvious: An Unusual Cause of Iron Deficiency Anaemia

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Abstract Iron deficiency anaemia (IDA) is the most common haematological disorder seen in childhood. While poor intake of iron is the most common cause of IDA, a diligent search must be made to exclude other causes. We present a 5 year old girl who had recurrent hospital admissions for chest infection, radiographic evidence of bilateral pulmonary infiltrates and severe IDA. When she failed to respond to repeated courses of antibiotics, anti tubercular and parenteral and oral iron therapy, a lung biopsy was done which revealed blood and hemosiderophages within the alveoli. Further investigations were suggestive of SLE (dsDNA positivity). A diagnosis of SLE induced alveolar haemorrhage was made and therapy with glucocorticoids was initiated. She has responded well to therapy.

Keywords Iron deficiency anemia IDA · Pulmonary hemosiderosis · Systemic lupus erythematosus (SLE) · Diffuse alveolar hemorrhage (DAH)

Introduction

Iron deficiency anaemia (IDA) is the most common haematological disorder seen in childhood. Though inadequate nutrition is the commonest cause of IDA, every child, especially those more than 24 months of age, presenting

with persistent and non responsive IDA needs to be investigated to identify any other underlying diagnosis [1].

Diffuse alveolar haemorrhage (DAH) is one of the rare, chronic and life threatening condition seen in children and is characterized by hemoptysis, dyspnea, alveolar infiltrates on chest radiograph and varying degrees of IDA [2, 3]. It may occur either primarily as a disease of the lungs or secondary to cardiac, systemic vascular, collagen or renal diseases.

Idiopathic pulmonary hemosiderosis (IPH) is a diagnosis of exclusion and is commonest in children who may or may not have celiac disease [4]. However, before coming to this diagnosis, other causes must be excluded. In this case, SLE was diagnosed and though DAH is known in SLE, it is rare in children and the management and prognosis is different from IPH. The rarity of this disease and the variable clinical course results in many diagnostic as well as therapeutic pitfalls. The aim of this presentation is to highlight the interesting facets of this case and to stress the fact that a persistent search for the cause of IDA in a child will often yield rewarding results.

Case Report

A 5 year old girl, presented to us with recurrent episodes of fever, cough, difficulty in breathing with occasional episodes of haemoptysis and progressive pallor for the previous one and a half years for which she had received multiple courses of antibiotics, anti tubercular therapy (ATT) and two blood transfusions elsewhere. On admission to our centre, she had severe respiratory distress and required oxygen support. Chest radiograph and CT thorax showed right lower lobe consolidation. Blood investigations revealed Hemoglobin (Hb) 5.3 g%, Serum ferritin

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125 ng/dl (normal: 7–140 ng/ml) and serum iron 13 mcg/dl (50–120 mcg/dl). The Mantoux test was positive and the ESR was 65 mm in the first hour. Sputum examination was not done but overnight gastric aspirate analysis for the tubercle bacilli was negative. In view of poor and declining respiratory efforts, she was put on the ventilator and given a packed red cell transfusion. Antibiotic therapy was initiated. A subsequent bronchoscopy and bronchoalveolar lavage was done which was unremarkable and also ruled out a foreign body. A diagnosis of pulmonary tuberculosis with IDA was made and with therapy, she gradually improved and was discharged on a four drug ATT regimen and oral iron therapy. A month later she was better and her Hb had improved to 9.2 g%.

She was admitted for the second time after 3 weeks with similar complaints and recurrence of severe anaemia (Hb 5 g%). As the chest X ray showed marked improvement from earlier, she was given oral antibiotics, another packed cell transfusion and discharged.

After 1 month, she was admitted for the third time with severe cough, fever spikes, respiratory distress along with worsening chest X ray findings. After stabilization, including ventilation, an open lung biopsy was done.

Histopathology of the lesion showed accumulation of hemosiderin laden macrophages in the alveolar spaces and variable proliferation of pneumocytes (Fig. 1). The inter alveolar septae were thickened and had neutrophilic infiltrate. Hemosiderin accumulation was also noted in the vessel walls and interalveolar septae (Fig. 2). Vasculitis as evidenced by neutrophils in the small vessel walls and around damaged vessels was also identified. Further investigations were carried out to identify a secondary cause of DAH including pANCA and cANCA, to rule out

Fig. 1 Lung biopsy with hemosiderin laden macrophages in the alveolar space, thickening of alveolar septae and neutrophilic infiltrate (H and E $\times 100$). *Inset* capillaritis showing neutrophilic infiltration in capillary wall (H and E $\times 400$)

Fig. 2 Hemosiderin deposits in alveolar macrophages, alveolar septae and around blood vessels (Perls stain $\times 100$)

ANCA associated vasculitis and C3, C4 and ANA to rule out collagen vascular disease—all of which were negative. However, the Anti dsDNA test was positive at 54.90 IU/ml (normal <30 IU/dl). A final diagnosis of SLE leading to DAH was made. The renal function tests and urine examination were normal. The ATT was stopped and she was started on oral steroids. She is clinically better at present, 3 months after starting treatment and repeat X rays show complete resolution of the initial findings. Her haemoglobin is steady at 12 g%.

Discussion

Persistent and severe IDA in this child with recurrent chest infections and bilateral alveolar opacities on imaging made us investigate further for a single diagnosis which could explain all the features. Though initial management focused on a commonly encountered explanation viz. pulmonary tuberculosis, subsequent investigations revealed a completely different diagnosis (diffuse alveolar hemorrhage) which, with a different approach, the child responded well.

Diffuse alveolar hemorrhage (DAH) may be an emergency and often life-threatening clinical situation where destruction of the pulmonary microvasculature and extravasation of blood into the alveolar space occurs. Multiple clinical syndromes and conditions may be responsible for DAH, including systemic causes or those limited to the lung. DAH may be with capillaritis or “bland” pulmonary hemorrhage, without vasculitis or capillaritis. The causes of DAH with capillaritis include primary idiopathic small vessel vasculitis like ANCA associated vasculitides (Wegener’s granulomatosis, Churg Strauss syndrome and microscopic polyangiitis) Goodpasture’s Syndrome, and Henoch–Schonlein purpura.

Secondary vasculitis seen in systemic diseases like SLE and rheumatoid arthritis has also been implicated in DAH [5–7]. Coagulopathies, platelet defects, pulmonary infections, pulmonary neoplasms, pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis and toxins such as cocaine and pesticides are also causes of pulmonary hemorrhage. Idiopathic pulmonary hemorrhage is a disease of children and young adults occurring in the 1st to 3rd decades of life. It may be associated with celiac disease, dermatitis herpetiformis, autoimmune hemolytic anemia and sensitivity to cow milk [4]. IPH is a disease of unknown etiology and is a diagnosis of exclusion, reached after other causes of DAH have been excluded. The distinction between the various causes of DAH is made on clinical, radiological and laboratory parameters. Our patient had DAH associated with vasculitis and was dsDNA positive which led to a final diagnosis of iron deficiency anemia secondary to DAH in a patient with SLE.

Pulmonary disease is a common and well documented component of SLE and may rarely signal the onset of disease. DAH may be the initial manifestation of SLE [8]. Other pulmonary manifestations of SLE in childhood include chronic interstitial pneumonitis, acute pneumonia, pulmonary edema, and alveolar overinflation [9]. Pulmonary disease produced by childhood SLE may represent a subgroup of SLE disease and occasional cases have been reported with isolated pulmonary symptoms in the absence of skin and renal involvement and associated poor response to corticosteroids [10].

Glucocorticoids therapy is the treatment of choice and as was initiated in our case. Others immuno-suppressant agents including azathioprine, hydroxy chloroquine, cyclophosphamide and methotrexate have been used with variable results in steroid resistant cases [11]. A further possible line of treatment is plasmapheresis, which removes the immune complexes from the blood in an attempt to reduce the suspected continuing immune damage and may offer an effective and non-toxic treatment for this disease [12].

While two decades ago the mean survival was 3 years, recent data indicates a 5-year survival rate of 86 %. [13]. Ninety percent of patients achieve remission within 6 months [14]. Ten percent of those refractory to standard immunosuppressant therapies are at high risk for sudden death [15]. Serial falls in hemoglobin are indicative of DAH progression [16] while the disappearance of ANCA in a previously positive child is almost always associated

with absence of disease activity [17]. We conclude that DAH should be considered as a differential diagnosis in recurrent unexplained anemia. A high index of suspicion, extensive evaluation for the cause and prompt management can yield vastly rewarding results.

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