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Idiopathic pulmonary hemosiderosis. A case with autoimmune disease in the family

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ABSTRACT

Idiopathic pulmonary hemosiderosis (IPH) is a chronic, recurrent pulmonary disease predominantly affecting children and often having severe outcome. The triad consisting in iron-deficiency anemia, hemoptysis and diffuse pulmonary infiltrates can guide the diagnosis, but the clinical presentation varies greatly, hence the disease can be easily missed initially. The etiology of IPH is still unknown; allergic, environmental or genetic factors have been proposed, but in the past years the autoimmune theory seems to be more evident, especially in cases with long survival. We present the case of a nine year old girl diagnosed with IPH with a family history of autoimmune disease.

Keywords: hemosiderosis, idiopathic, pulmonary, autoimmune

INTRODUCTION

Idiopathic pulmonary hemosiderosis (IPH) is a rare and severe disease that affects especially children and causes recurrent lung bleeding. It can be characterized by the triad iron-deficiency anemia, hemoptysis and diffuse pulmonary infiltrates (1,2). The diagnosis can be difficult, especially in young ages where hemoptysis can lack. In these cases, anemia may steer the diagnosis wrongly through different variants of iron-deficiency anemia, hemolytic anemia or leukemia (1-4). The etiology of the disease is unknown, allergic, environmental or genetic factors being proposed (1). In the last decade many reports designate the autoimmune theory as more evident, especially in cases with long survival (5-8). We present the case of a nine year old girl with a family history of autoimmune disease diagnosed with IPH.

CASE REPORT

A 9-year-old girl presented to our clinic, diagnosed with hypochromic anemia and suspicion of acute lymphoblastic leukemia. The disease started two months before as an upper respiratory tract infection followed by productive cough with blood strips and weight loss. The girl was admitted to the local hospital where hemogram revealed a hemoglobin level of 6.9 g%. She was transfused and received symptomatic therapy. She was then referred to our clinic for further investigation.

Physical examination on admission showed intense skin and mucosal pallor, normal height and weight, dry cough with small amounts of blood, no pulmonary rales and moderate hepatomegaly. The initial hemoglobin level of 6.9 g% dropped at 4.8 g% in 2 days. Leukemia was ruled out by the absence of blasts on the bone marrow aspirate. The peripheral blood smear also showed no blasts, but only signs of a hypochromic regenerative iron deficiency anemia. Moreover, hereditary microspherocytosis was excluded by normal osmotic resistance. Bleeding time and clotting time were normal. The diagnosis of pulmonary tuberculosis was advanced due to presence of hemoptysis, elevated ESR level (80 mm/1 hour) and X-ray showing congestive hil-

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lum on both lungs. The diagnosis was ruled out by negative tuberculin skin test and culture.

Because the family history revealed an autoimmune disorder in a second degree relative (rheumatoid arthritis in a cousin who had been a patient in our clinic in childhood) immunological assays were carried out, but only indirect Coombs test was found weakly positive. Rheumatoid factor, antinuclear antibodies, ANCA, immune electrophoresis and immune complexes were all negative. After 6 days of hospitalization during which the patient received three blood transfusions, she was discharged at the demand of her parents with oral iron supplements, folic acid and vitamin C.

One year later she is readmitted in severe condition, showing intense skin pallor, retrosternal pain, dyspnea, polypnea, inconstant pulmonary crackles, rare cough (the patient is coughing upon insistence of the medical staff) tachycardia, cold extremities and intense thirst. Hemoglobin value was 3.1 g% requiring urgent blood transfusion. Due to the signs of acute hemorrhagic anemia and presence of hemoptysis in the last admission the suspicion of IPH was made. Peripheral blood smear indicated the same elements as in the previous year. In addition, there were signs of extrarenal azotemia and the chest X-Ray developed a "ground glass" aspect (Fig. 1). Anamnesis revealed presence of hemoptysis in small amounts for about two years previous.

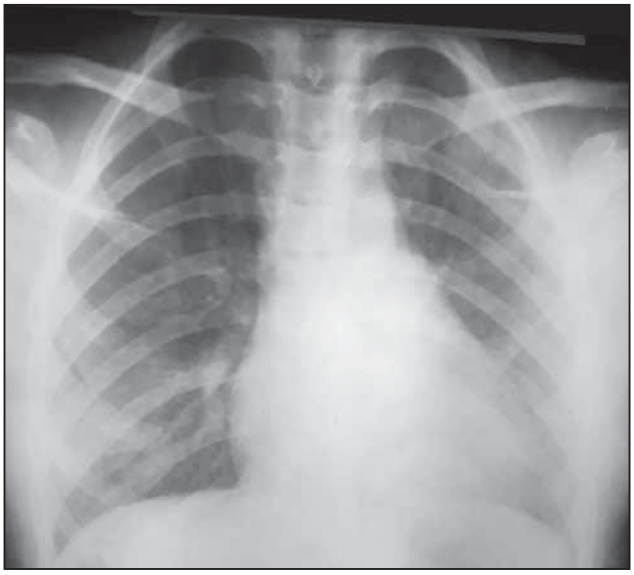

FIGURE 1

The diagnosis of IPH was established by detection of hemosiderin-laden macrophages in sputum (Perls coloration). Treatment was started with cyclophosphamide in 2-3 months cures, corticosteroids and oral iron. Outcome was satisfactory but the patient was lost from the study 4 years after diagnosis. The only information we had regarding the patient after that was through her relative who confirmed entrance into adulthood, even marriage.

DISCUSSIONS

Idiopathic pulmonary hemosiderosis (IPH) is a chronic recurrent pulmonary disease that often has a severe outcome. The average survival time after the onset of symptoms is estimated of 2,5 years (1). The triad iron-deficiency anemia, hemoptysis and diffuse pulmonary infiltrates can guide the diagnosis although hemoptysis is usually missing in infants and small children (1-3,9). Worldwide, reports of over 500 IPH's cases have been described from neonatal period until adulthood, even cases in the same family (sisters/mother-daughter) showing possible genetic, allergic or autoimmune etiology (1,10,11).

Clinical presentation varies greatly, most cases initially presenting as different types of anemia, few of these having associated hemoptysis (1-3,12). In a recent review study made on 107 IPH's patients, only 57% presented hemoptysis while anemia was present in 93.45% of cases (9). In general, few pulmonary signs are described in patients with IPH: cough, hemoptysis and dyspnea (1,9). In adults, where IPH is even rarer than in children, the predominant symptoms are pulmonary (1,8,13).

Apparently, the case seems to be typical for IPH. The patient presented severe anemia (requiring blood transfusions) almost simultaneously with hemoptysis, but the diagnosis of IPH was delayed for a year. A large number of studies report an important delay of diagnosis varying from 1 to 6.3 years (14-17). This characteristic of IPH is due to low clinical suspicion and difficulty of diagnosis. Depending on the dominant feature in the initial presentations, IPH can be wrongly interpreted as different types of anemia (iron-deficiency or hemolytic anemia) or, in case of hemoptysis, as community-acquired pneumonia or pulmonary tuberculosis (2, 18-20).

In the presented case, the anemia was mimicking an iron deficiency although its severity first raised the suspicion of leukemia. The type of anemia was hypochromic, microcytic, with elevated reticulocytes count (varying from 15‰ to 49‰) and low iron level. Hereditary microspherocytosis was also ruled out. IPH can also imitate hemolytic anemia, with an elevated bilirubin level, secondary to hemoglobin absorption from the lung and high reticulocytes number. Nevertheless, it was proven that there is no amplified intravascular hemolysis

(2). Also, the presence of hemoptysis and initial X-ray image led to a presumed diagnosis of pulmonary tuberculosis, which is the most common cause of pulmonary hemorrhages in our area. It is known there is no specific pattern for IPH on chest X-ray. In our case the X-ray image "perfected" in time, revealing an almost typical aspect of ground-glass opacities later on, when the hemorrhages were more profuse. Several other reports show cases of IPH interpreted initially as pulmonary TB and some treated as such (1,20).

Family history of rheumatoid arthritis and the positive Coombs test led to the possibility of an autoimmune anemia. Many other cases diagnosed with IPH reported the presence of intermittent positive Coombs test as well as cold agglutinins, but the latter was not identified in our patient (21,22). It is estimated that cases with survival longer than 10 years have an autoimmune mechanism involved (15-17). Moreover, it has been suggested that 1 out of 4 patients who survive longer than average, develops an autoimmune disorder, usually evolving into rheumatoid arthritis (15-17). New evidence broadens the horizon of future autoimmune pathology, a recent case of IPH was described developing into Sjögren syndrome in adulthood (23).

It is interesting that a pattern or an immunological profile for these patients is not yet established. Studies all over the world report different variants of positive immunological tests in IPH cases varying from Coombs test, to ANA, ANCA, rheumatoid factor, cow's milk allergy or celiac disease antibodies, anti-glomerular basal membrane, even anti-smooth muscle cell or anti ds-DNA antibodies (1,2,15,16). Some studies report the most frequent antibodies found are those positive in vasculitis or systemic diseases, like ANCA, anti-smooth muscle cell or ANA (15). Furthermore, ANCA was even considered a key factor of progression into an immunologic disorder or as sign of severe prognosis (16,24). In our case these antibodies were negative. However, there was no testing for celiac disease at the moment of diagnosis.

CONCLUSIONS

Good response to cyclophosphamide treatment, positivity of Coombs test, long survival time and family history of rheumatoid arthritis make us believe an immunological mechanism was involved. It would have been interesting to asses the correct survival time but in this case it can only be estimated to approximately 8 years from diagnosis. We would like to highlight the importance of the chest X-ray in any unresolved type of anemia even if the initial radiological images show common aspects. A complete set of tests must be carried out at diagnosis and also during follow-up in order to better asses the possibility of developing an autoimmune disorder.

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