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An interesting co-existence of celiac disease and idiopathic pulmonary hemosiderosis: Lane-Hamilton syndrome

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ABSTRACT

Idiopathic pulmonary hemosiderosis is characterized by hemoptysis resulting from recurring alveolar hemorrhage attacks, iron deficiency anemia, and parenchymal infiltrations as seen on chest radiographs. The clinical course may consist of silent and asymptomatic attacks, or it may sometimes exhibit a fulminant course with rapidly developing anemia and hypoxemia. Celiac disease is an autoimmune enteropathy triggered by the consumption of gluten-containing foods in genetically predisposed individuals. Co-existence of idiopathic pulmonary hemosiderosis and celiac disease is defined as Lane-Hamilton syndrome. We describe a case of Lane-Hamilton syndrome with growth and developmental delay; complete remission of pulmonary symptoms was achieved with a gluten-free diet.

Keywords: Idiopathic pulmonary hemosiderosis, celiac disease, anemia, gluten-free diet

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Idiopathic pulmonary hemosiderosis (IPH) is characterized by hemoptysis resulting from recurring alveolar hemorrhage attacks, iron deficiency anemia, and parenchymal infiltrations as seen on chest radiographs [1]. It is generally observed in children, but rarely, may occur in adults. Recurring intra-alveolar bleeding constitutes the pathophysiology of the disease. Reticulonodular infiltrates associated with this bleeding are observed on chest radiographs. Iron deficiency anemia occurs secondary to massive hemoptysis. The etiopathogenesis of the disease is unclear [2, 3]. Vasculitis, connective tissue diseases, various autoimmune diseases, infections, and some drugs can lead to recurring alveolar hemorrhage attacks, while a clinical picture of IPH arises when no underlying cause can be shown. The clinical course may consist of silent and asymptomatic attacks, or it may sometimes exhibit a fulminant course with rapidly developing anemia andhypoxemia. Late complications such as pulmonary fibrosis and cor pulmonale may develop following recurring attacks and adversely affect the course of the disease.

Celiac disease (CD) is an autoimmune enteropathy triggered by the consumption of gluten-containing wheat, rye, barley, and oats in genetically predisposed individuals. It may occur with classic symptoms such as chronic diarrhea, weight loss, growth delay, and malabsorption or with non-gastrointestinal symptoms such as refractory iron deficiency anemia, isolated short stature, osteoporosis, and hepatitis. Intestinal

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injury with inflammation occurs because of specific T cell response to gluten. Co-existence of idiopathic pulmonary hemosiderosis and celiac disease is defined as Lane-Hamilton syndrome. This is a rare condition that generally accompanies symptomatic clinical CD findings [4]. IPH responds well to corticosteroids, while a gluten-free diet can reduce the need for corticosteroids in comorbid IPH-CD [5]. We describe a case of Lane-Hamilton syndrome with growth and developmental delay; complete remission of pulmonary symptoms was achieved with a gluten-free diet.

CASE PRESENTATION

An 8-year-old girl was referred to us due to a hemoglobin (Hb) value of 2.7 g/dL from an external clinic to which she presented with lethargy, respiratory difficulty and occasional hemoptysis over the previous 6 months. The patient's past medical history and her family medical history were unremarkable. Tachycardia (heart rate > 140/min) was noted during physical examination. She weighed 19.3 kg (<3 p) and her height was 112.5 cm (<3 p). Her skin and mucosa were significantly pale. Pronounced rales were present in both hemithoraces at respiratory examination. A 2-3/6 systolic murmur was present. Three centimeters of the liver was palpable. Results of other organ system examinations were normal. Complete blood count values were Hb: 2.7 g/dL, hematocrit (Hct): 12%, erythrocyte mass: 1.2 million/mm3, mean erythrocyte volume (MCV): 54.1 fL, mean erythrocyte concentration: 31.6 g/dL, erythrocyte distribution width: 16.2%, white blood cell (WBC) count: 7300/mm3, and platelet count: 532,000/mm^3. Peripheral smear results showed that granulocytes (58%), lymphocytes (34%), and monocytes (8%) were present. Erythrocyte morphology was compatible with hypochromic microcytic anemia. No atypical cells were observed. Serum iron level was 3 µg/dL, total iron binding capacity was 471 µg/dL, and ferritin was 2.89 ng/dL. Transferrin saturation was 0.6%. Liver and kidney function tests and arterial blood gas analyses results were normal. Activated partial thromboplastin time was 23.6 s, and prothrombin time was 13.5 s. C-reactive protein was 1 mg/L (0-8 mg/L) and erythrocyte sedimentation rate was 12 mm/h. There were no acid-resistant bacilli in sputum. Immunoglobulins (Ig) M, G, A and, serum complements 3 and 4 levels were normal. Anti-nuclear antibody, double-stranded DNA antibody, anti-neutrophil cytoplasmic autoantibodies (p-ANCA and c-ANCA) and anti-glomerular basal membrane antibody test results were normal. Respiratory function tests results were normal. The sweat test using the Macroduct method yielded normal results at 33 mmol/L (0-40: normal, 40-60: repeat test, >60: high). Bilateral basal infiltration was determined using a posterior-anterior chest radiograph (PACR) (Figure 1a). Thoracic tomography revealed a patchwork of bilateral diffuse ground glass densities with irregular

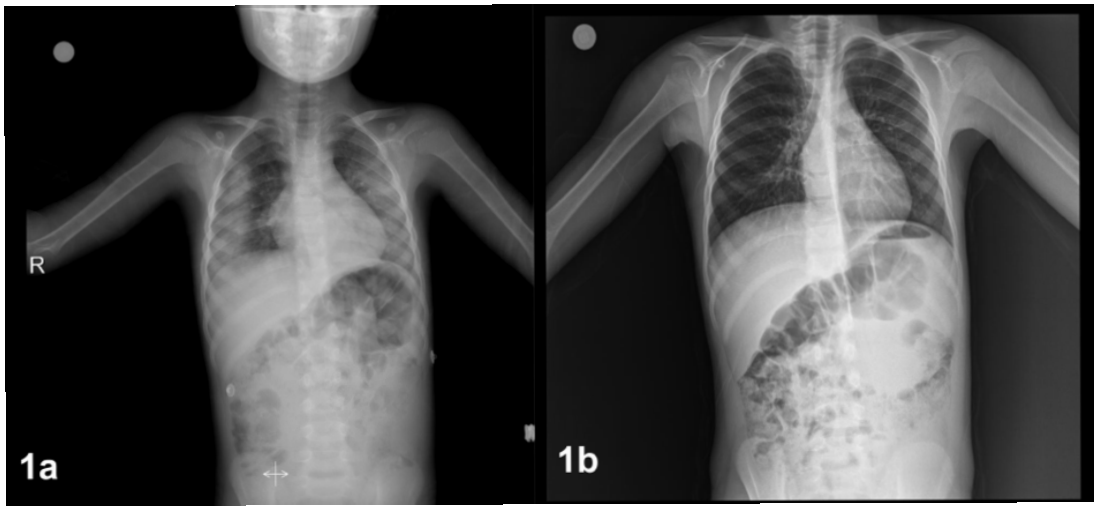

Figure 1. (a) Bilateral basal infiltration on posterior-anterior chest radiograph, (b) Posterior-anterior chest radiograph after gluten-free diet.

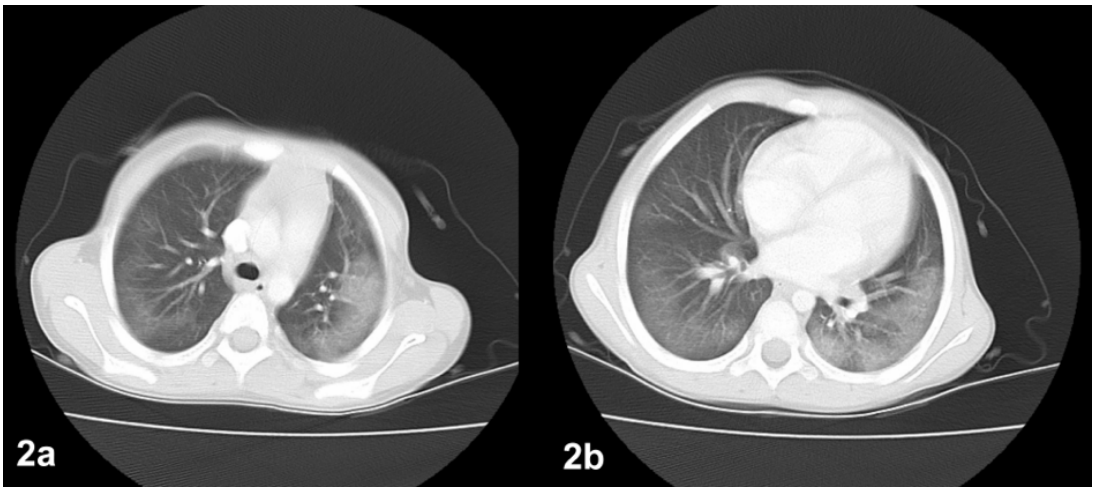

Figure 2. (a, b) Bilateral diffuse ground glass densities with irregular margins in a localization compatible with the vascular tracts and consolidation in the lower lobe of the right lung on thoracic tomography.

margins in a localization compatible with the vascular tracts and consolidation in the lower lobe of the right lung (Figures 2 a and 2b). Erythrocyte suspension was administered three times, and subsequently Hb value was measured to be 12.7 g/dL. Tachycardia attributed to heart failure and liver enlargement was resolved. A bronchoscopy was performed because of the absence of an etiological cause and since the clinical, laboratory, and radiological findings supported pulmonary hemosiderosis. The bronchial mucosa was hyperemic at bronchoscopy, and bronchoalveolar lavage (BAL) fluid was pink in color. The patient also exhibited growth and development delay, and serum celiac antibodies were requested on suspicion of CD accompanying pulmonary hemosiderosis. Anti-tissue transglutaminase IgA (tTg IgA) level was >200 U/ml and anti-endomysial antibody (EMA) level was 1/320 (+). Cytopathological analysis of BAL fluid revealed abundant hemosiderin-bearing macrophages (Figures 3a and 3b). Endoscopic examination revealed millimetric eroded areas covered with exudates on the bulbus duedoni and a scalloped appearance in the folds of the second part of the duodenum. Intense lymphocytic infiltration, total villous atrophy and, and crypt hyperplasia (MARSH 3C) were determined at pathological examination (Figures 4a and 4b). Lane-Hamilton syndrome was suspected in this patient with comorbid pulmonary hemosiderosis and CD, and she was started on a gluten-free diet. Respiratory difficulty improved after transfusion. The existing bilateral basal infiltration improved at PACR performed 14 days after the initiation of iron and B12 supplementation and a gluten-free diet (Figure 1b). At 3-month check-up examination the patient weighed 22.5 kg (10th p) and

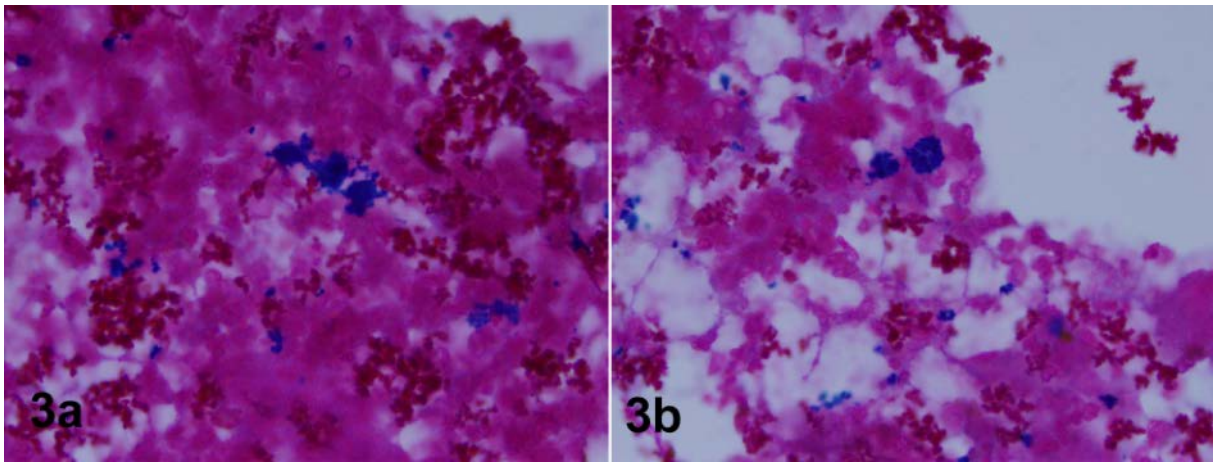

Figure 3. (a, b) Cytopathological analysis of BAL fluid with abundant hemosiderin-bearing macrophages.

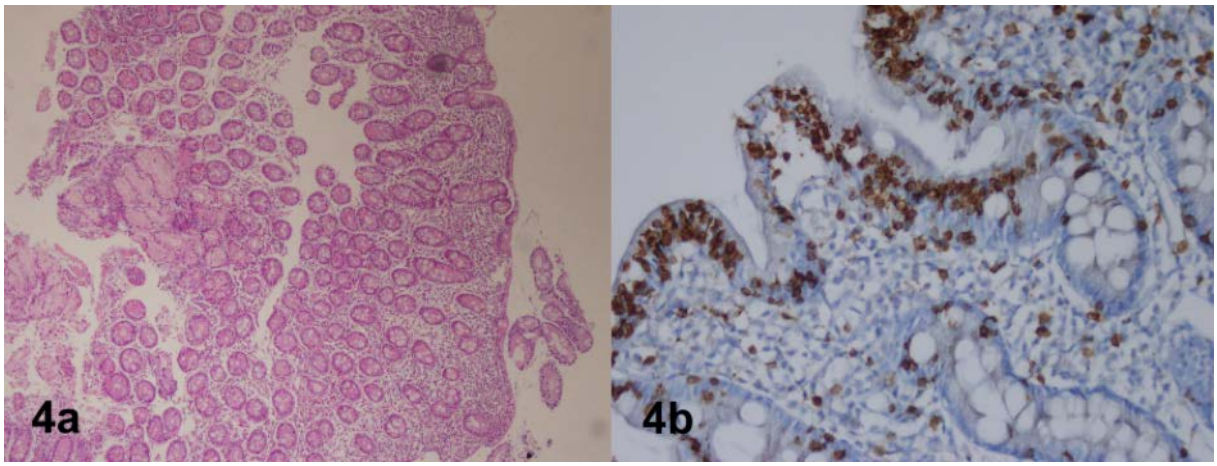

Figure 4. (a, b) Pathological examination of duodenum (Intense lymphocytic infiltration, total villous atrophy and, and crypt hyperplasia).

was 124 cm in height (10thp). Her Hb value was 13.8 g/dL, Hct was 39%, MCV was 84.1 fL, WBC count was 5300/mm3, and platelet count was 332,000/mm3. Her serum iron level was 78 µg/dL, total iron binding capacity was 204 µg/dL, ferritin was 22.19 ng/ml, and tTg IgA was 24.5 U/ml, EMA (-). The patient has been symptom-free at follow-ups at the pediatric hematology and pediatric gastroenterology over the past year.

DISCUSSION

IPH is a rare disease frequently seen in children. Eighty percent of cases appear in the first decade, while 20% can begin in adulthood. There is no marked gender difference, although a male predominance is observed as age increases [6, 7]. Patients generally present with hemoptysis, parenchymal infiltrations at pulmonary radiography and iron deficiency anemia [1, 8].

The etiology of IPH is unclear. The first description of the disease as immunological in nature was made by Steiner in 1954 [9]. Additionally, a good response to immunosuppressive treatment is generally achieved, which suggests that immunological mechanisms are involved in its pathophysiology [10]. Although no immune complex deposition has been shown in the lungs, the presence of immune complex in the circulation in some cases supports the idea of an immunological mechanism being involved in the development of the disease [11]. Recurring hemorrhages resulting from the triggering of unidentified immunological mechanisms cause free iron to be stored in lung tissue. This deposited free iron leads to pulmonary fibrosis via a mechanism similar to fibrosis of the liver in hemochromatosis [12].

CD is characterized by small bowel mucosa injury resulting from cellular and humoral system activation following the consumption of gluten-containing food [13]. The molecular similarity between gluten and nutrition antigens is thought to CD by triggering an immune response. It is generally characterized by diarrhea and growth delay, particularly in childhood. It may appear with non-gastrointestinal symptoms or in milder forms. Transglutaminase 2 (TG2) is a multi-functional protein found in the cell cytoplasm and outside the cell in various tissues. Functional impairment is seen in various organs, including the liver, bowel, lung, kidney and placenta, because of TG2 dysregulation through several mechanisms [14]. TG2 plays a significant role in the pathogenesis of CD by deamination of gluten proteins. anti-tTG IgA used in the diagnosis of CD are 91-100% specific and EMA are 100% specific [11].

The comorbidity of IPH and CD is known as Lane-Hamilton syndrome. This was first described by Bailey, and the focus has been on an immunological etiology since it may also be comorbid with other connective tissue diseases [1, 9, 13]. Perelman *et al*. [15] proposed three hypotheses concerning the comorbidity of IPH and CD. The first is the deposition of immune complexes containing food allergens in the

basal membrane of the alveolar capillaries. The second is the relationship between alveolar basal membrane antigens and anti-reticulin antibodies. The third involves the effect of adenovirus 12, a potential etiological factor in CD, in IPH [15]. Pulmonary hemorrhage attacks have been reported to decrease following gluten-free diet therapy in cases of comorbid IPH and CD. The level of anti-tTG IgA in the circulation decreases with diet therapy, and the patient's clinical findings improve. This suggests that, similar to the immunological mechanism of CD, anti-tTG IgA that form lead to pulmonary hemosiderosis and can trigger fibrosis by impairing the functioning of the TG2 in the lungs. In our case, growth and developmental delay was present in addition to pulmonary hemosiderosis. CD was determined with a small bowel biopsy performed when anti-transglutaminase IgA was positive. Pulmonary hemosiderosis generally responds well to corticosteroids. Because of high long-term recurrence levels, other immunosuppressive agents are also recommended when corticosteroids are insufficient [16]. In addition to cases in which comorbid IPH and CD have been brought under control with a gluten-free diet alone, there are other cases in which steroid therapy has been used together with a gluten-free diet [1]. Complete remission was achieved with a gluten-free diet in our case.

CONCLUSION

In conclusion, CD must be investigated serologically in cases of IPH with growth and developmental delay despite the absence of digestive system symptoms. A positive result for anti-transglutaminase IgA is, to a large extent, diagnostic. Cases with accompanying CD can first be managed with a gluten-free diet before corticosteroid therapy if respiration function tests are normal or close to normal. However, free iron accumulation in the lungs can lead to interstitial fibrosis, and the addition of corticosteroid therapy to a gluten-free diet should be considered in patients with impaired respiratory functions.

Informed consent

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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