

Severe Alveolar Hemorrhage – What’s in it for the Gastroenterologist?

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ABSTRACT

Background: Alveolar hemorrhage is a potentially life-threatening condition which is usually managed by the pulmonologist. When considering its etiology, there is a rare association that sets the disease into the hands of the gastroenterologist.

Case presentation: We report the case of a 48 year-old female who was admitted to the intensive care unit for severe anemia and hemoptysis. On imaging, diffuse pulmonary infiltrates suggestive of alveolar hemorrhage were detected and a diagnosis of pulmonary hemosiderosis was made. She received cortisone therapy and hematologic correction of anemia, with slow recovery. In search of an etiology for the pulmonary hemosiderosis, an extensive workup was done, and celiac disease specific serology was found positive. After confirmation of celiac disease by biopsy, a diagnosis of Lane-Hamilton syndrome was established. The patient was recommended a gluten-free diet and at 6 months follow-up, resolution of anemia and pulmonary infiltrates were observed.

Conclusion: Although the association is rare, celiac disease should be considered in a patient with idiopathic pulmonary hemosiderosis. In our case, severe anemia and alveolar infiltrates markedly improved with glucocorticoids and gluten-free diet.

Key words: alveolar hemorrhage – celiac disease – Lane-Hamilton syndrome.

Abbreviations: APTT: activated partial thromboplastin time; BAL: bronchoalveolar lavage; CD: celiac disease; Cd: crypt depth; GFD: gluten-free diet; GI: gastrointestinal; IEL: intraepithelial lymphocyte; INR: international normalized ratio; IPH: idiopathic pulmonary hemosiderosis; LHS: Lane-Hamilton syndrome; NBI: narrow band imaging; Vh: villous height.

INTRODUCTION

Due to its protean manifestations, celiac disease (CD) can be considered a clinical chameleon. Despite some frequent clinical scenarios (typical malabsorption, chronic iron-deficiency anemia, premature osteoporosis) and some frequent disease associations (type 1 diabetes mellitus, autoimmune thyroid disease), CD can also be hidden among the most uncommon diseases attended by different medical specialties. We report a patient with severe alveolar hemorrhage and pulmonary

hemosiderosis presenting with hemoptysis, severe anemia and diffuse alveolar infiltrates in whom we made a diagnosis of CD. This association of pulmonary involvement (i.e. idiopathic pulmonary hemosiderosis) and CD is also known as the Lane-Hamilton syndrome (LHS). So far, worldwide, no more than 30 cases of LHS have been presented [1, 2]. There is a wide differential diagnosis in patients with pulmonary hemosiderosis, but after exclusion of the most frequent secondary causes, CD screening is recommended [3].

CASE REPORT

A 48 year-old female, smoker, was admitted to the intensive care unit for severe anemia, after acute onset of severe hemoptysis. At presentation, the patient was severely ill, with marked pallor, low oxygen saturation on room air (SpO₂ 75-80%) and a hemoglobin level of 3.6 g/dl. She denied overt genital or gastrointestinal (GI) bleeding, but history was positive for recent hemoptysis. The personal and family

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medical history were unremarkable. Laboratory workup revealed severe microcytic anemia, marked hypocoagulability (high values for prothrombin time, INR and APTT), without evidence of liver disease. Computed tomography (CT) showed diffuse pulmonary sclero-emphysema with pulmonary infiltrates suggestive of alveolar hemorrhage (Fig. 1). The first therapeutic step was the correction of anemia by transfusion of 4 units of packed red blood cells and simultaneous parenteral iron supplementation (ferric carboxymaltose) for hemoglobin target over 8 g/dl, and of coagulopathy corrected with fresh frozen plasma and vitamin K. The procalcitonin test ruled out sepsis and a 3 day pulse-therapy with methylprednisolone was started, followed by tapered oral prednisone. On glucocorticoid therapy and following correction of anemia, the general clinical status of the patient and the alveolar hemorrhage significantly improved. The bronchoscopic examination was unremarkable, without evidence of malignancy; the bronchoalveolar lavage (BAL) revealed frequent mucus, rare red blood cells and numerous siderophages, with a Golde score of 182 (normal values under 25), suggesting a moderate alveolar hemorrhage. Microbiology examinations from the BAL fluid were negative. We proposed a lung biopsy, but the patient refused it.



Fig. 1. CT scan of the thorax: diffuse pulmonary sclero-emphysema with pulmonary infiltrates suggestive of alveolar hemorrhage.

Meanwhile, an extensive panel of immunological tests was performed in search of an etiology for the pulmonary hemosiderosis. Other causes of diffuse alveolar hemorrhage were ruled out: serum quantitative determination of rheumatoid factor, antinuclear antibodies, anti-Ro/La antibodies, anti-dsDNA, perinuclear and cytoplasmic anti-RNP, anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, and alpha-1 antitrypsin were all negative. The serum complement level was normal. Also serologies for HIV, hepatitis B and C, leptospirosis and syphilis were negative. The urine work-up was unremarkable. Cardiology consult and echocardiography were also normal and excluded a cardiac cause for pulmonary disease, or pulmonary hypertension. No medication inducing alveolar hemorrhage and history of drug abuse was noted.

In this setting, we performed the quantitative determinations of CD specific serum autoantibodies that showed positive results (IgA-antitransglutaminase 2 antibodies values over 200 U and anti-endomysium antibodies positive at serum dilution of 1:500). Upper GI endoscopy revealed a nodular

pattern in the duodenal bulb and mucosal fissures in the distal duodenum, changes which were better delineated with the NBI filter (Figs. 2, 3). Multiple biopsies were taken, both from bulb and distal duodenum. Histological examination of correctly oriented formalin fixed, hematoxylin-eosin stained biopsy specimen described mucosal injuries highly compatible with CD: increased intraepithelial lymphocytes (IELs), crypt hyperplasia and villous atrophy with a morphometric measurement of 127 μ m and 257 μ m for the average villous height (Vh) and average crypt depth (Cd), respectively (Vh:Cd =0.49) [4] (Fig. 4). The duodenal frozen biopsies were examined in immunofluorescence for the celiac specific transglutaminase 2-targeted-IgA subepithelial deposits using double staining (for IgA and transglutaminase 2, respectively) [5]. The result was clearly positive (Fig. 5). The intraepithelial inflammation in the bulb as well as duodenal mucosa was further studied using monoclonal antibody staining of frozen sections. Both CD3+ and $\gamma\delta$ T cell receptor bearing IELs densities were highly increased [4] (Table I, Figs. 6, 7).

A final diagnosis of CD associated with pulmonary hemosiderosis was established defining a case of LHS. A gluten-free diet (GFD) was prescribed to the patient, together with a tapered regimen of prednisone. At three months follow-up the patient is doing well, with resolution of anemia (normal hemoglobin level) and coagulopathy and no evidence of recurrent alveolar hemorrhage. The CT scan performed at six months showed marked improvement of the pulmonary lesions (Fig. 8).

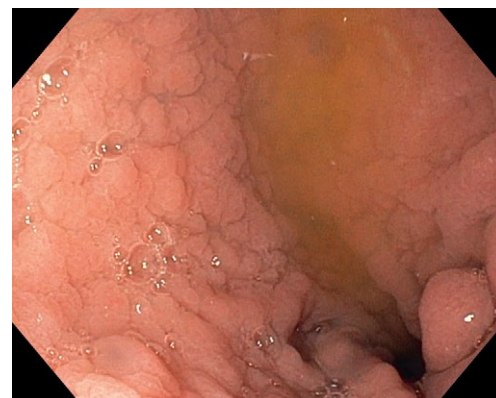


Fig. 2. Upper GI endoscopy (Olympus, Tokyo, Japan): nodular pattern in the duodenal bulb.

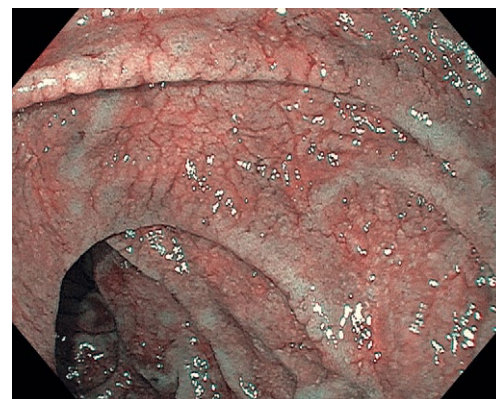


Fig. 3. Upper GI endoscopy (Olympus, Tokyo, Japan) with NBI filter: mucosal fissures in the distal duodenum.

Table I. Density of the CD3+ and $\gamma\delta$ T cell receptor bearing intraepithelial lymphocytes (IELs)

Cells/mm epithelium	CD3	$\gamma\delta$
Bulb	81	29
Duodenum	64	21

Normal values: CD3 = 37 cells/mm epithelium; $\gamma\delta$ = 4.3 cells/mm epithelium

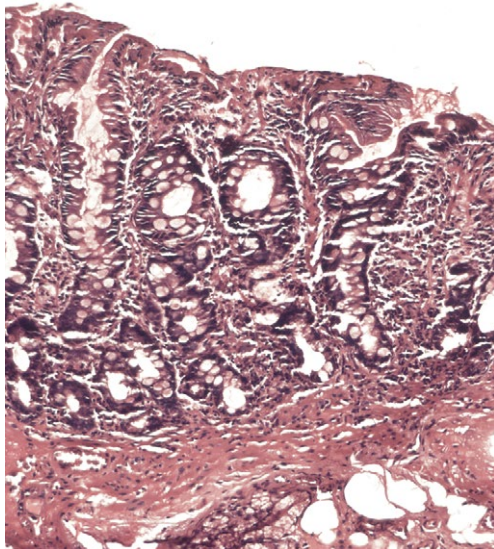


Fig. 4. Small bowel biopsy sample, H&E x5. Crypt hyperplasia and villous atrophy.

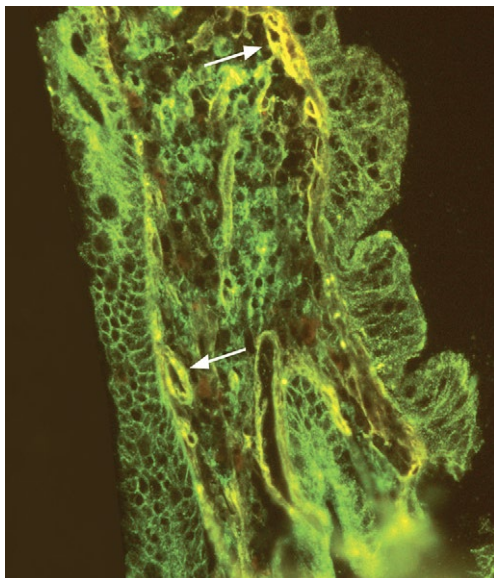


Fig. 5. Small bowel frozen biopsy sample, positive immunofluorescence for the celiac specific transglutaminase 2-targeted IgA subepithelial deposits.

DISCUSSION

Forty-five years after the first description of Lane and Hamilton [6], the syndrome carrying their names is still very rarely encountered in clinical practice. Immunological

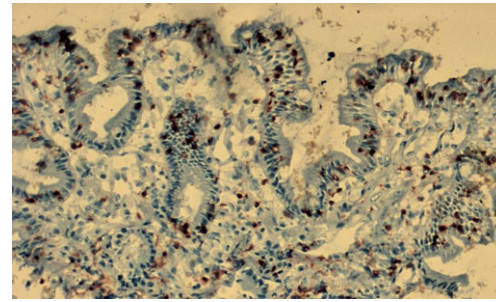


Fig. 6. Small bowel frozen biopsy sample, monoclonal antibody staining: high density of $\gamma\delta$ T cell receptor bearing intraepithelial lymphocytes (IELs).

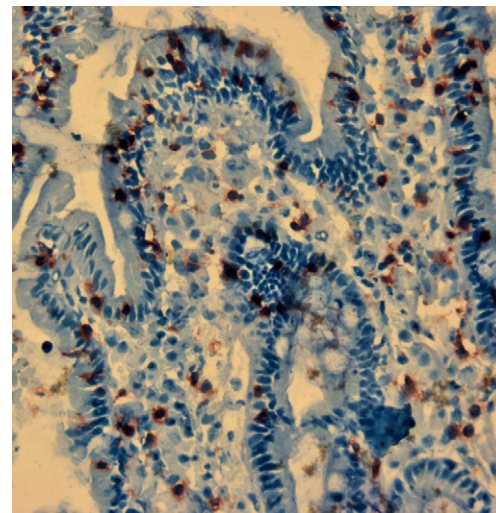


Fig. 7. Small bowel frozen biopsy sample, monoclonal antibody staining: high density of CD3+ T cell receptor bearing intraepithelial lymphocytes (IELs).

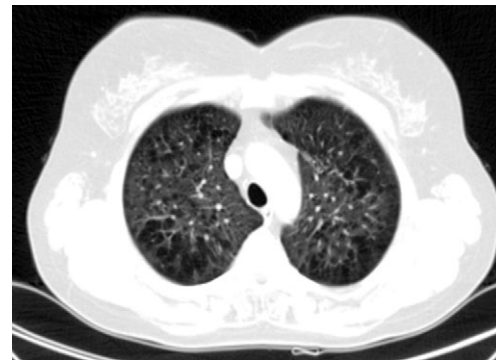


Fig. 8. CT scan of the thorax: improvement of lesions.

mechanisms seem to be the connection between the two diseases which constitute LHS, but the pathogenic link is not clearly known.

Although idiopathic pulmonary hemosiderosis (IPH) has been defined by the triad of hemoptysis (or other respiratory symptoms such as cough or dyspnea), iron deficiency anemia and diffuse pulmonary infiltrates, literature data has reported that not all criteria are seen in patients with this disease [7, 8]. Still, our patient had all three features of IPH, with severe anemia dominating the clinical picture. Idiopathic pulmonary hemosiderosis is a medical emergency, with 14% mortality rate in the acute phase [9].

Although it could have been explained by the hemoptysis, the severe anemia prompted the search of an alternative associated mechanism. Our patient could have had preexisting undiagnosed clinically silent anemia before this acute presentation. Celiac disease is usually thought of in front of a suggestive clinical scenario. Idiopathic pulmonary hemosiderosis is merely such a scenario, but CD serologic screening is recommended in these patients, irrespective of the presence of GI symptoms, as the reported cases of IPH associated with CD were GI symptom-free [10]. This is also the case of our patient, who had no history of GI complaints which could have prompted for a specific workup.

Some authors even recommend performing upper GI endoscopy with duodenal biopsies in all patients with IPH [11, 12]. Searching for CD in such a rare setting is however justified, as the GFD can lead to remission of IPH in some patients and can reduce the need for corticosteroids in others [11, 13, 14]. Although some have questioned the improvement of IPH on GFD by the confounding concomitant use of corticotherapy, the gluten-dependent mechanism and the beneficial effect of GFD are supported by Khemiri et al. [3], who showed that rechallenge with gluten induced relapse in respiratory symptoms.

Our patient greatly improved on corticosteroid therapy and GFD, with dramatical improvement of pulmonary disease and correction of anemia.

CONCLUSION

Although it is a rare disease, idiopathic pulmonary hemosiderosis should prompt for celiac disease screening. In our LHS case, severe anemia improved rapidly with corticotherapy and a gluten-free diet.

Conflicts of interest: None to declare.

Authors' contributions: A.P., C.J. and M.J. conceived and designed the report. D.V.B., A.P. and C.J. drafted the manuscript and searched literature data. C.J. and M.S. were in charge of the clinical management of the patient and prepared the figures. A.P. and K.L. did the histology evaluation. A.P., C.J. and M.J. critically reviewed the manuscript. All authors approved the final version of the manuscript.

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