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CASE REPORT

Lane-Hamilton syndrome: a case report

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Abstract

Idiopathic pulmonary hemosiderosis is an uncommon disease of childhood, manifesting with the triad of recurrent hemoptysis, diffuse parenchymal infiltrates on chest radiographs and iron deficiency anemia. Celiac disease is an enteropathy characterized by life-long intolerance to ingested gluten in genetically susceptible people. In 1971 Lane and Hamilton first described the association of idiopathic pulmonary hemosiderosis with celiac disease and since then a few isolated cases have been reported in literature. We report a child with pulmonary hemosiderosis presenting with hemoptysis, severe anemia, and diffuse alveolar infiltrates in whom we made a diagnosis of celiac disease. In our case, severe anemia and alveolar infiltrates markedly improved with gluten-free diet.

Keywords: Idiopathic pulmonary hemosiderosis. Celiac disease. Lane-Hamilton syndrome. Case report.

Síndrome de Lane-Hamilton: reporte de un caso

Resumo

A hemossiderose pulmonar idiopática é uma doença rara em idade pediátrica, caraterizada por hemoptises recorrentes, infiltrados difusos no parênquima pulmonar na radiografia torácica e anemia ferropénica. A doença celíaca é uma enteropatia caraterizada por intolerância ao glúten em pessoas geneticamente suscetíveis. Em 1971, Lane e Hamilton descreveram o primeiro caso que associava a hemossiderose pulmonar com a doença celíaca e, desde então, um pequeno número de casos tem sido descrito na literatura. Reportamos um caso clínico de uma criança com hemossiderose pulmonar caraterizada por hemoptises, anemia grave e infiltrados difusos no parênquima pulmonar a quem foi diagnosticada doença celíaca. A anemia severa e os infiltrados alveolares resolveram com a introdução de uma dieta isenta de glúten.

Palavras-chave: Hemossiderose pulmonar idiopática. Doença celíaca. Síndrome Lane-Hamilton. Relato de caso.

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Keypoints

What is known

- Idiopathic pulmonary hemosiderosis is an uncommon disease of childhood manifesting with the triad of recurrent hemoptysis, diffuse parenchymal infiltrates on chest radiographs and iron deficiency anemia.
- Idiopathic pulmonary hemosiderosis has been associated with celiac disease in rare cases.

What is added

- Patients with idiopathic pulmonary hemosiderosis should be screened for celiac disease, even if there are no symptoms of gastrointestinal disease.
- A high index of suspicion for pulmonary hemosiderosis should be kept in patients of celiac disease with disproportionately severe anemia.
- Early recognition of Lane-Hamilton syndrome and initiation of treatment with a gluten-free diet may result in disease remission and may prevent progressive pulmonary disease.

Introduction

Although hemoptysis is a rare condition in infants and children, it is potentially life-threatening and may cause significant morbidity. Unless the volume of blood is considerable, hemoptysis may be difficult to detect because younger children, especially infants, swallow their sputum. However, once identified, the source and underlying pathology must be investigated in a systematically manner[1]. The differential diagnosis for hemoptysis is extensive, ranging from relatively common to quite rare conditions. Possible etiologies include infection, bronchiectasis, non-pulmonary bleeding, trauma, coagulopathy, cardiac disease, pulmonary tumor, vascular anomaly, autoimmune disease, and pulmonary-renal syndromes[2,3].

Idiopathic pulmonary hemosiderosis (IPH) is an uncommon disease of childhood, with an incidence varying from 0.24 to 1.23 patients per million children[4,5], manifesting with the triad of recurrent hemoptysis, diffuse parenchymal infiltrates on chest radiographs and iron deficiency anemia[4,5]. Recurrent alveolar bleeding may eventually produce pulmonary hemosiderosis and fibrosis. Diagnosis of IPH requires evidence of diffuse alveolar hemorrhage (DAH) and exclusion of other causes (Table 1)[6].

Celiac disease (CD) is a common immune-mediated enteropathy driven by dietary gluten and related proteins in genetically predisposed individuals. In over half of the patients, CD presents with extra-intestinal manifestations, most commonly short-stature, anemia, delayed puberty, liver abnormalities, dental enamel defects, aphthous stomatitis, myopathy, arthralgias, and synovitis. In the rarest forms CD includes headaches, ataxia, neuropathy, and seizures with bilateral occipital calcifications, osteopenia, and osteoporosis, hyposplenism, infertility, dermatitis herpetiformis, and alopecia. Hemorrhagic events, such as gastrointestinal hemorrhage, hematuria, epistaxis, and hemoptysis are the most uncommon presentations of CD[7-13].

Case report

A 12-year-old healthy girl presented a 6 month not explained/investigated history of intermittent hemoptysis, cough, and upper respiratory tract symptoms. One month before, she was suffering from recurrent and diffuse abdominal pain, fatigue, and dizziness. She was admitted to our paediatric unit due to persistent periumbilical and right iliac fossa pain with 24 hours evolution. She had normal menses and denied epistaxis, black or tarry stools, and easy bleeding. There were no changes in stool patterns, fevers, night sweats, and weight loss. The personal and family medical history was unremarkable. There was no history of close contact with any tubercular patient.

She was in reasonable general health, had moist and discolored mucous membranes, had no jaundice or cyanosis, and breathed normally. Her vital signs were within normal limits, and her SpO2 was 98% on room air. Her weight was 45 kg (50-75 percentile), height 158 cm (50-75 percentile), and body mass index 18kg/m^2 (25-50 percentile). Cardiopulmonary and neurological examination revealed no abnormalities. Abdominal examination revealed localized tenderness and muscular rigidity to the right iliac fossa. She had no skin lesions, joint lesions, peripheral edema, or digital clubbing.

Lab investigations showed: severe microcytic, hypochromic anemia (Hb = 6 g/dL); total leukocyte count 10.93 × 10^9/L with 73.3% polymorphs and 18.9% lymphocytes; platelet count 205 × 10^9/L. Coagulation profile, renal and liver function tests were normal.

Table 1. Causes of diffuse alveolar hemorrhage

Disorders with capillaritis	Disorders without capillaritis	
	Cardiovascular causes	Non-cardiovascular causes
– Granulomatosis with polyangiitis (Wegener) – Microscopic polyangitis – Systemic lupus erythematosus – Goodpasteurs disease – Henoch-Schönlein purpura – IgA nephopathy – Behçet syndrome – Cryoglobulinemia – Drug-induced capillaritis – Idiopathic lung-kidney syndrome – Idiopathic pulmonary capillaritis	– Mitral stenosis – Pulmonary veno-occlusive disease – Arteriovenous malformation – Pulmonar lymphangioleiomyomatosis – Pulmonary hypertension – Pulmonary capillary hemangiomatosis – Chronic heart disease – Pulmonary infarction	– Idiopathic pulmonary hemosiderosis – Heiner syndrome – Celiac disease – Coagulopathies – Hematopoietic cell transplantation

Sedimentation rate was 6 mm/hour, C-reactive protein 0.10 mg/dL. The mean corpuscular volume was 60.9 fL, reticulocyte count 1,25 %, serum iron 8 μg/dL, total iron-binding capacity (TIBC) 413 μg/dL, ferritin 23.5 ng/mL. The peripheral smear examination showed hypochromic microcytic anemia. Urine examination did not reveal albuminuria or hematuria.

Computed tomography (CT) revealed an ileocecal appendix, approximately 10mm wide, with same slight densification of the surrounding fat. Moreover, there were signs of a ground glass appearance of the lung bases with unspecific features. Suspicion of acute appendicitis led to the patient's transfer to the Pediatrics Surgery Observation Unit. When the patient was admitted, an abdominal ultrasound was performed that also suggested the diagnosis. In addition, chest radiograph showed bilateral diffuse alveolar infiltrates.

Red blood cells transfusion was performed before laparoscopic appendectomy, which confirmed an acute appendicitis's initial stages.

Additional studies revealed unremarkable vitamin B12, folate, haptoglobin, and uric acid levels. Antinuclear, anti-neutrophil cytoplasmic (p-ANCA and c-ANCA), and rheumatoid factor were negative. C3 and C4 levels were normal. Serologic tests for Epstein-Barr virus, cytomegalovirus, and parvovirus B19 were negative.

During her stay at the hospital, the patient remained hemodynamically stable, in sustained apyrexy. She recovered from the fatigue, and dizziness and did not show any signs of bleeding during the hospitalization.

She was given parenteral iron supplementation - Hg 7.7g/dL on the discharge date. She was discharged home after 5 days, with instructions to complete parenteral iron supplementation (200 mg elemental iron per infusion, three infusions, every 2 days).

A pulmonary CT was performed after discharge, which revealed bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities suggestive of hemosiderosis or hemorrhage (Figs. 1, 2 and 3). Lung function tests were within the normal range. Sputum examination for bacteria and mycobacteria was negative. IGRA test and allergology studies were negative. There were also no signs of hemosiderin, but the sample showed a small amount of blood.

Tissue transglutaminase IgA (TTGA) titer was 2400 U/mL (normal: < 10 U/mL) and anti-deamidated gliadin titer was 220 U/mL (normal: < 7 U/mL). A duodenal biopsy revealed total villous atrophy and intense lymphocyte and plasmocyte infiltration at lamina propria consistent with a diagnosis of CD (type 3C in Marsh Classification). Thus, a gluten-free diet was initiated.

Within six months, there was resolution of the pulmonary lesions in the pulmonary CT. Based on this, a final diagnosis of Lane-Hamilton syndrome was made. Due to the favorable clinical evolution of the patient, a bronchoscopy was considered unnecessary.

After two years of follow-up, the patient is doing well, without anemia, and no evidence of recurrent alveolar hemorrhage. During this period, an improvement of gastrointestinal symptoms, weight and height gain, and a reduction of antibody titer was reported (Table 2).

Discussion

The association of IPH with CD was initially identified in a young adult by Lane and Hamilton in 1971, who proceeded to call it the "Lane-Hamilton syndrome". This is an extremely rare condition, therefore there is a limited number of case reports of this syndrome in the literature[5,8-9]. Several retrospective

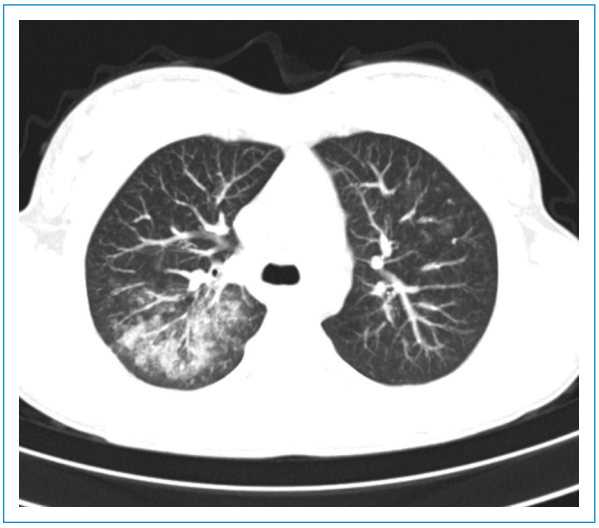

Figure 1. Bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities.

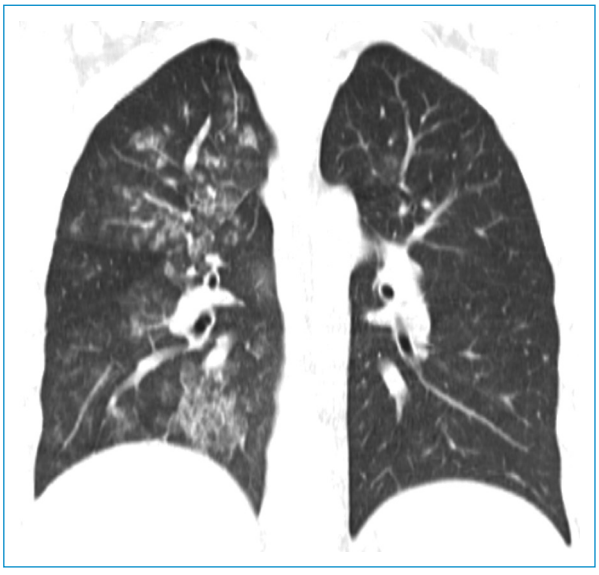

Figure 2. Bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities.

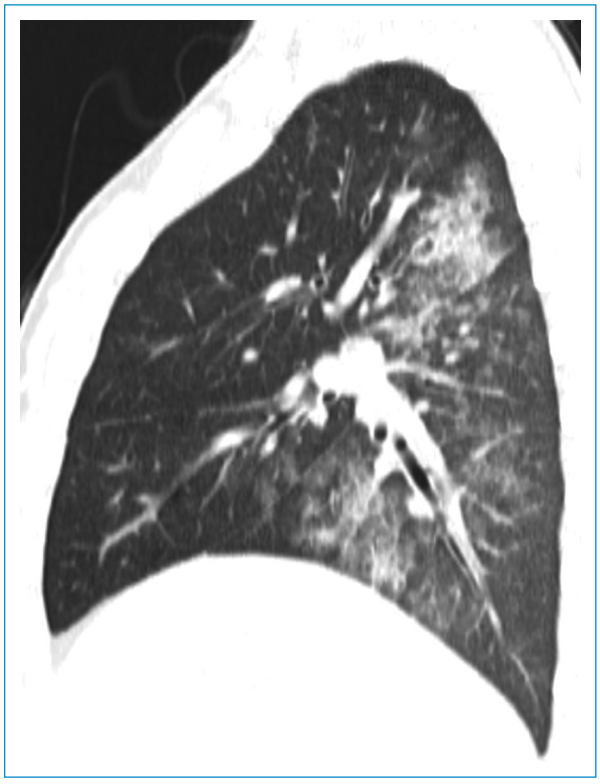

Figure 3. Bilateral diffuse alveolar infiltrates over middle and lower zones and ground glass opacities.

Table 2. Clinical evolution

	Admission	2 years of follow-up
Weight	45 kg (50-75 percentile)	61 kg (75-90 percentile)
Body mass index	18 kg/m^2 (25-50 percentile)	24 kg/m^2 (75-90 percentile)
Hemoglobin	6 g/dL	13.4 g/dL
Tissue transglutaminase IgA	2400 U/mL	44 U/mL
Anti-deamidated gliadin	220 U/mL	4.3 U/mL

observational studies have reported the prevalence of celiac antibodies in pediatric patients with IPH[8]. Remarkably, only half of these children presented gastrointestinal symptoms in addition to recurrent hemoptysis[2,10].

Lane-Hamilton syndrome has been considered an association of two different disease entities, but whether there is a unifying mechanism in the pathogenesis of both disease entities is currently unknown[8]. Hemosiderosis in celiac disease is likely to occur due to the deposition of immune complexes involving an auto-antigen like gluten on the alveolar basement membrane or to direct reaction between the antigen of alveolar basement membrane and an antibody like the anti-reticulin one[6]. Additionally, a specific strain of adenovirus has been proposed as another pathogenic mechanism[5]. Thus, while it is commonly suggested that LHS represents the overlap of two separate disease processes, IPH and celiac disease,

others have suggested that LHS should be considered as a single disease entity[2].

In Lane-Hamilton syndrome, a gluten-free diet (GFD) is the mainstay of therapy. The clinical importance of this diagnosis is that a significant improvement can be obtained with GFD not only in intestinal but also in pulmonary symptoms. IPH can be a difficult disease to treat, and previous studies suggest that the treatment is often complicated by frequent recurrences and sometimes the development of end-stage lung disease requires lung transplantation. However, in Lane-Hamilton syndrome, the use of GFD can result in partial or complete cessation of lung hemorrhage, reduce the need for blood transfusions and steroid therapy, and leads to radiological improvement in most individuals, as seen in this case[8,10-12]. For those who do not respond to a gluten-free diet, immunosuppressive therapy may be necessary. The typical first-line immunosuppressive treatment for IPH are systemic steroids. Additional treatment options include hydroxychloroquine, cytotoxic agents, or a combination of one of these medications with systemic steroids[2]. Long-term nutritional follow-up is also important; it has been reported that poor adherence to the diet can reactivate respiratory and gastrointestinal symptoms[11,13]. Lane-Hamilton syndrome results in significant morbidity and mortality once recurrent alveolar hemorrhage may result in progressive pulmonary fibrosis if left untreated[8,14,15].

In conclusion, a high index of suspicion for celiac disease should be kept in patients with pulmonary hemosiderosis, especially with disproportionately severe anemia in spite of absence of gastrointestinal symptoms and vice-versa. Therefore, all patients diagnosed with IPH should be screened for CD by serologic assays, which are very sensitive, and any respiratory illness associated with aggravation of anemia should prompt a pulmonologist to actively look for hemosiderosis. This can be safely and non-invasively done by histopathological examination of sputum/induced sputum for hemosiderin laden macrophages and a gluten-free diet alone can lead to remission of the pulmonary symptoms.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Zaidi SJ, Schweig L, Patel D, Javois A, Akhter J. A novel approach to the diagnosis and treatment of hemoptysis in infants: A case series. Pediatric Pulmonology. 2018;53:1504–9.
2. Ostrom K, et al. Index of Suspicion. Pediatrics in Review. 2014;35:396.
3. Kamienska E, Urasinski T, Gawlikowska-Sroka A, Glura B, Pogorzelski A. Idiopathic Pulmonary hemosiderosis in a 9-year-old girl. European Journal of Medical Research. 2009;14:112-15
4. Keslin O, et al. Unusual Presentation: Pulmonary Hemosiderosis with Celiac Disease and Retinitis Pigmentosa in a Child. Pediatric Pulmonology. 2011;46:820–23.
5. Sethi G, Singhal K, Puri A, Mantan M. Benefit of Gluten-Free Diet in Idiopathic Pulmonary Hemosiderosis in Association with Celiac Disease. Pediatric Pulmonology. 2011;46:302–5.
6. Singhal, et al. Hemoptysis in patients of celiac disease with disproportionately severe anemia: tip of the iceberg?. Multidisciplinary Respiratory Medicine. 2013;8:25.
7. Reed A et al. Lane-Hamilton Syndrome: An Illustration of Extraintestinal Manifestations of Celiac Disease. Clinical Pediatrics. 2020;1-4.
8. Saha B, Saha S, Bonnier A, Saha B. Association between idiopathic pulmonary hemosiderosis and celiac disease in pediatric patients: A scoping review of the literature over the past 50 years. Pediatr Pulmonol. 2022;57:1127-44.
9. Nacaroglu HT, et al. Association of Celiac Disease with Idiopathic Pulmonary Hemosiderosis; Lane Hamilton Syndrome. Iranian Journal of Pediatrics. 2015;25:e3312.
10. Agarwal S, et al. Lane-Hamilton Syndrome: Rare Association of Idiopathic Pulmonary Hemosiderosis with Celiac Disease. Tropical Gastroenterology. 2018;39:28-56.
11. Santos J, et al. Pulmonary hemosiderosis associated with celiac disease: improvement after a gluten-free diet. Jornal Brasileiro de Pneumologia. 2012;38:412-14.
12. Testa M, et al. Hemorragia pulmonar asociada a enfermedad celíaca. Archivos Argentinos de Pediatría. 2012;110:e72-76.
13. Pichardo C, Muinos W, Brathwaite C, Hernandez E. Pulmonary Hemosiderosis Associated With Celiac Disease: Lane Hamilton Syndrome. Journal of Pediatric Gastroenterology and Nutrition. 2017;64:5.
14. Panda P, Siranga R, Kaur K, Sood R. Lane Hamilton Syndrome. The Indian Journal of Pediatrics. 2018;85:699.
15. Popp A, et al. Severe Alveolar Hemorrhage – What's in it for the Gastroenterologist?. Journal Gastrointestinal Liver Diseases. 2016;4:555-8.