

# Triple Diagnosis of Crohn's Disease, Celiac Disease, and Eosinophilic Esophagitis in a Child With Siderius-Hamel Syndrome

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## ABSTRACT

Siderius-Hamel syndrome is a rare condition characterized by intellectual disability and distinct facial features. Crohn's disease-related eosinophilic esophagitis (EoE) has been reported; however, an association between celiac disease and EoE remains controversial. We present a case of a child with Siderius-Hamel syndrome who had characteristic findings of all these conditions—Crohn's disease, celiac disease, and EoE—an occurrence that to our knowledge has not been reported previously. The purpose of this report is to make physicians aware of this rare occurrence, so that it can be kept in mind while evaluating a patient with Siderius-Hamel syndrome presenting with gastrointestinal complaints.

## INTRODUCTION

Siderius-Hamel or Siderius X-linked mental retardation syndrome is a rare condition and only a few families with this condition have been described in the literature.<sup>1-6</sup> Crohn's disease-related eosinophilic esophagitis (EoE) has been reported; however, the association between celiac disease and EoE remains controversial.<sup>7,8</sup> There is an increased risk of autoimmune conditions, such as Crohn's disease, ulcerative colitis, and celiac disease, in patients with EoE, with possible shared genetic etiology between ulcerative colitis and EoE.<sup>9</sup> We describe the first reported case of a child with Siderius-Hamel syndrome, who had characteristic findings of all 3 conditions—an occurrence that, to our knowledge, has not been reported previously.

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## CASE REPORT

An 11-year-old white boy with Siderius-Hamel syndrome presented to the gastroenterology clinic for abdominal pain and constipation for 1 month. He was diagnosed with Siderius-Hamel syndrome at 5 years of age based on mild intellectual disability; developmental delay; dysmorphic features, including arched eyebrows, hypertelorism, broad nasal bridge, and thin upper lip; and identified PHF8 mutation on the genetic test. For gastrointestinal

symptoms, he was treated with laxatives and had improved stool frequency and consistency, though abdominal pain persisted. Two weeks later, he developed nonbloody diarrhea, which persisted after discontinuing the laxatives. Pertinent negatives include dysphagia, odynophagia, food impaction, hematochezia, and weight loss or growth problems.

Laboratory investigations showed abnormal celiac serology with elevated tissue transglutaminase IgA of 16.8 U/mL (normal range 0-14.9 U/ml), antigliadin IgA of 72.2 U/ml (normal range 0-14.9 U/ml), antigliadin IgG of 27.2 U/ml (normal range 0-14.9 U/ml) and anti-endomysial IgA of 1:10 (normal < 1:10). IgA level was normal at 185 mg/dL (normal range 50-330 mg/dL). Complete blood count, comprehensive metabolic panel, and inflammatory markers also were normal. Stool infectious studies were negative. An esophagogastroduodenoscopy (EGD) showed mild linear furrowing of the esophagus (Figure 1a) and duodenal bulb erythema. Colonoscopy was remarkable for mild erythema, erosions, and exudates in the terminal ileum. The colon and cecum appeared grossly normal. EGD biopsies detected up to 20 eosinophils per high-power field (HPF) in both the distal and proximal esophagus (Figure 1b, 1c) as well as duodenitis with increased intraepithelial lymphocytes (approximately 39/100 enterocytes) and mild villous blunting (Figure 2a). Colonoscopy biopsies showed chronic active

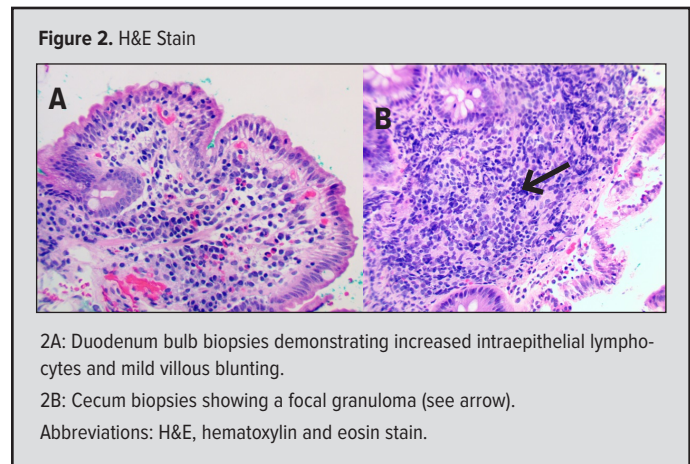
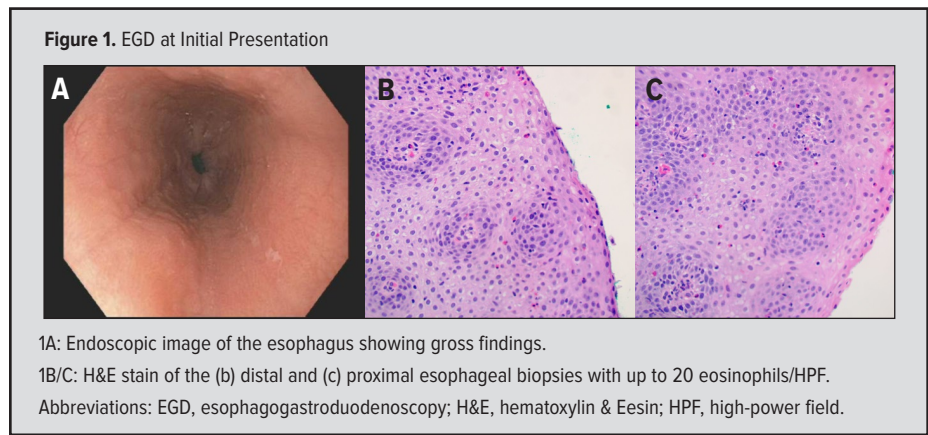
ileitis and chronic active colitis with a focal granuloma (Figure 2b), confirming the diagnosis of Crohn's disease. Computed tomography enterography revealed a normal small bowel.

The patient was started on a strict gluten-free diet and treated with oral prednisone 40 mg daily and subcutaneous methotrexate 15 mg weekly, due to the patient's inability to swallow pills. Steroids were gradually tapered off over a period of 6 weeks. To establish the diagnosis of EoE, a follow-up EGD almost 3 months

after treatment with high-dose proton pump inhibitor (omeprazole 20 mg twice daily) was performed, which showed worsening esophagitis (marked linear furrowing and mucosal edema) (Figure 3a). Biopsies revealed > 30 eosinophils per HPF in both distal and proximal esophagus (Figure 3b, 3c), findings consistent with EoE. Duodenal biopsies showed improved intraepithelial lymphocytes (approximately 21/100 enterocytes) and no villous atrophy. In addition to gluten-free diet, a milk and soy elimination diet was recommended. To identify additional food allergens, the patient was referred to the Allergy and Immunology Department. Rapid allergo sorbent test was negative. Skin prick test could not be performed as the patient was noncooperative. At 3-month follow-up, abdominal pain and diarrhea resolved while on injectable methotrexate and gluten-free diet. Follow-up celiac serology was normal. Stool calprotectin was normal at 22.0 mcg/g, although baseline stool calprotectin at initial diagnosis was not done. The patient had poor adherence to the elimination diet; therefore, a third EGD to assess response to treatment with dairy and soy elimination diet for EoE was not done until family reported dietary adherence for at least 3 months. A third EGD was done 9 months after the second EGD and showed improved linear furrowing in the distal esophagus with normal appearing proximal esophagus. Biopsies revealed up to 25 eosinophils per HPF and up to 15 eosinophils per HPF in distal and proximal esophagus, respectively. Duodenum biopsies showed worsening duodenitis (increased intraepithelial lymphocytosis and villous blunting, which was not seen on the second EGD). We suspect that the finding on third EGD could be related to poor adherence to the dairy and soy elimination, and gluten-free diet. The patient continues to remain under our follow-up, and the importance of strict compliance to the dietary elimination has been discussed.

## DISCUSSION

Celiac disease is a Th1-mediated autoimmune disease triggered by ingestion of food containing gluten in genetically susceptible individuals.<sup>10</sup> EoE is a Th2-mediated inflammatory disorder triggered by exposure to dietary allergens leading to the invasion of the esophageal mucosa by eosinophils, T lymphocytes and mast cells.<sup>11</sup> Celiac disease and EoE are 2 immune-mediated conditions

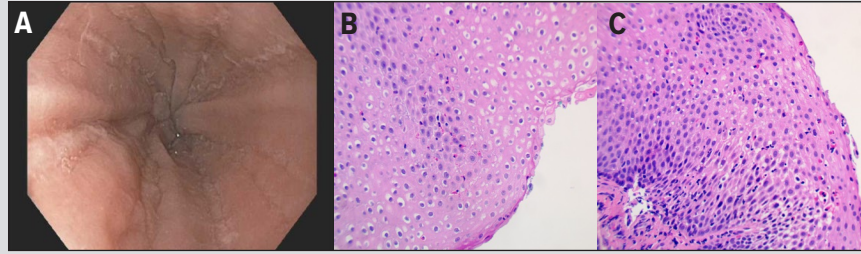


that affect the upper gastrointestinal tract, in response to dietary triggers. Elimination of food triggers can lead to clinical as well as histological improvement in both conditions.<sup>12</sup> The coexistence of EoE and celiac disease in the same patient was first described by Shah et al in 2006.<sup>13</sup> In recent years, multiple studies have assessed whether an association exists between celiac disease and EoE in children, with variable results.<sup>7,8</sup> Most recently, Hommeida, et al, found no increased risk of EoE in children with Crohn's disease in the largest cohort study and meta-analysis to date.<sup>14</sup>

Crohn's disease is a predominantly Th1-mediated chronic inflammatory condition of the gastrointestinal tract. Patients with celiac disease have an increased risk of developing Crohn's disease compared to the general population.<sup>15</sup> Active Crohn's disease can be associated with increased esophageal eosinophilia,<sup>16</sup> therefore it was not clear at first if it was primary EoE or Crohn's-related esophageal eosinophilia. However, based on the distinct endoscopic appearance and finding of esophageal eosinophilia, which worsened on follow-up EGD despite the use of proton pump inhibitors, primary EoE appeared more likely. It is difficult to conclude if persistent esophageal eosinophilia despite treatment of Crohn's disease is due to primary EoE, as clinical implications of mucosal eosinophils in inflammatory bowel disease are still being researched.<sup>17</sup>

It has been shown that patients with Crohn's disease can have

**Figure 3.** Follow-up EGD on High-Dose Proton Pump Inhibitors



**3A:** Endoscopic image of the esophagus showing gross findings.

**3B/C:** H&E stain of the distal (b) and proximal (c) esophagus demonstrating > 30 eosinophils/HPF.

Abbreviations: EGD, esophagogastroduodenoscopy; H&E, hematoxylin and eosin; HPF, high-power field.

low positive levels for anti-tissue transglutaminase (tTG) antibodies; however, antiendomysial antibodies are reported to be detectable only in celiac disease.<sup>18,19</sup> Our patient also had mildly elevated tTG IgA; however, the presence of abnormal anti-endomysial IgA, antigliadin IgG and IgA, and histopathology findings, all went in favor of celiac disease. Celiac genetics also could be considered in this patient; however, based on the above-mentioned findings, clinical response and normalization of celiac serology, as well as histological improvement on gluten-free diet, confirmed the diagnosis of celiac disease. Therefore, celiac genetics was not determined necessary.

Siderius X-linked mental retardation syndrome is characterized by cleft lip, cleft palate, and distinctive facial features, including long face, sloping forehead, broad nasal bridge, supraorbital bridge, and upslanting palpebral fissures, and is caused by mutation in PHF8, which encodes a chromatin remodeling protein with putative transcription factor activity.<sup>1-5</sup> Thus far, not a single case of Siderius X-linked mental retardation syndrome with this combination of autoimmune conditions has been reported. Since the PHF8 gene is being linked with regulation of immune activity,<sup>20,21</sup> it is possible that modification of the PHF8 influenced the development of immune-mediated diseases, rather than our finding being a mere coincidence.

## CONCLUSION

This case highlights a rare occurrence between 3 distinct gastrointestinal conditions—Crohn's disease, eosinophilic esophagitis, and celiac disease—in a patient with Siderius X-linked mental retardation syndrome. Additional studies are necessary to assess the relationships between the development of these conditions and PHF8 activity.

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