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Case Report

Very early-onset inflammatory bowel disease: Novel description in glycogen storage disease type Ia

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ABSTRACT

Although inflammatory bowel disease is a well-described feature of glycogen storage disease type Ib, it has been reported in only a small number of individuals with glycogen storage disease type Ia (GSDIa). We describe, to our knowledge, the first patient with GSDIa and very early-onset inflammatory bowel disease (VEO-IBD). Larger studies are needed to better understand this possible association, elucidate the mechanism of VEO-IBD in GSDIa, and inform management.

1. Introduction

Glycogen storage disease type Ia (GSDIa) is caused by biallelic variants in *G6PC1* leading to loss of glucose-6-phosphatase function. Because there are deficits of both glycogenolysis and gluconeogenesis , emergent hypoglycemia is the most significant cause of early mortality. The phenotypic spectrum includes hepatomegaly, hepatic adenomas with malignant potential, kidney disease, lactic acidosis, hypertriglyceridemia, elevated serum uric acid, impaired platelet function, pulmonary hypertension, and osteoporosis among numerous other sequelae [1]. These symptoms are also common to glycogen storage disease type Ib (GSDIb) due to biallelic *SLC37A4* variants. GSDIb, unlike GSDIa, is associated with neutropenia [1], which is a consistent feature of inflammatory bowel disease (IBD) in patients with GSDIb [2]. Although not as common as in GSDIb, IBD has been described in GSDIa previously, as discussed below. We report the first case, to our knowledge, of a patient with very early-onset inflammatory bowel disease (VEO-IBD) and GSDIa with no other etiology of VEO-IBD identified.

2. Case description

A 4-year-old boy was diagnosed with GSDIa at age 6 months. He experienced metabolic acidosis shortly after birth and had recurrent admissions with hypoglycemia and lactic acidosis. Genetic testing showed a maternally inherited pathogenic variant (c.247C>T; p.Arg83Cys) and a paternally inherited variant of uncertain significance (VUS) (c.1034T>C; p.Leu345Pro) in the *G6PC1* gene. The VUS appears to be novel and does not appear to have been reported in the scientific literature, disease-associated databases such as ClinVar, or large population studies such as the Genome Aggregation Database (gnomAD). Other missense variants have been reported nearby in exon 5 (p.Val338Phe and p.Ile341Asn). Computational prediction tools and conservation analysis provide conflicting expectations regarding an impact to protein function and this information is not sufficient to prove or rule out pathogenicity. Although the variant was felt to meet criteria of a VUS, it was thought to more likely be pathogenic than benign as it is novel, near other disease-associated variants, and in the compound heterozygous state with a pathogenic variant.

The patient had placement of a gastrostomy tube at age 8 months, was fed by frequent boluses of cornstarch, and received feeding therapy. Continuous glucose monitoring was utilized, and he had bolus feeding every 2 to 3 h during the day and continuous overnight feeding. He established care at Duke around 19 months of age and at that time was receiving 30 g cornstarch mixed with 4 oz Nutramigen every 2 h. He had 8–10 bowel movements daily with many having a chalky consistency, and it was felt it may have reflected undigested cornstarch. He was transitioned to 15 g cornstarch mixed with 5.5 oz Nutramigen every 2 h via G-tube. With the reduction in cornstarch, his bowel movements were reported by parents as more normal. At age 25 months, he was growing well although weight was above goal. His dietary regimen was adjusted

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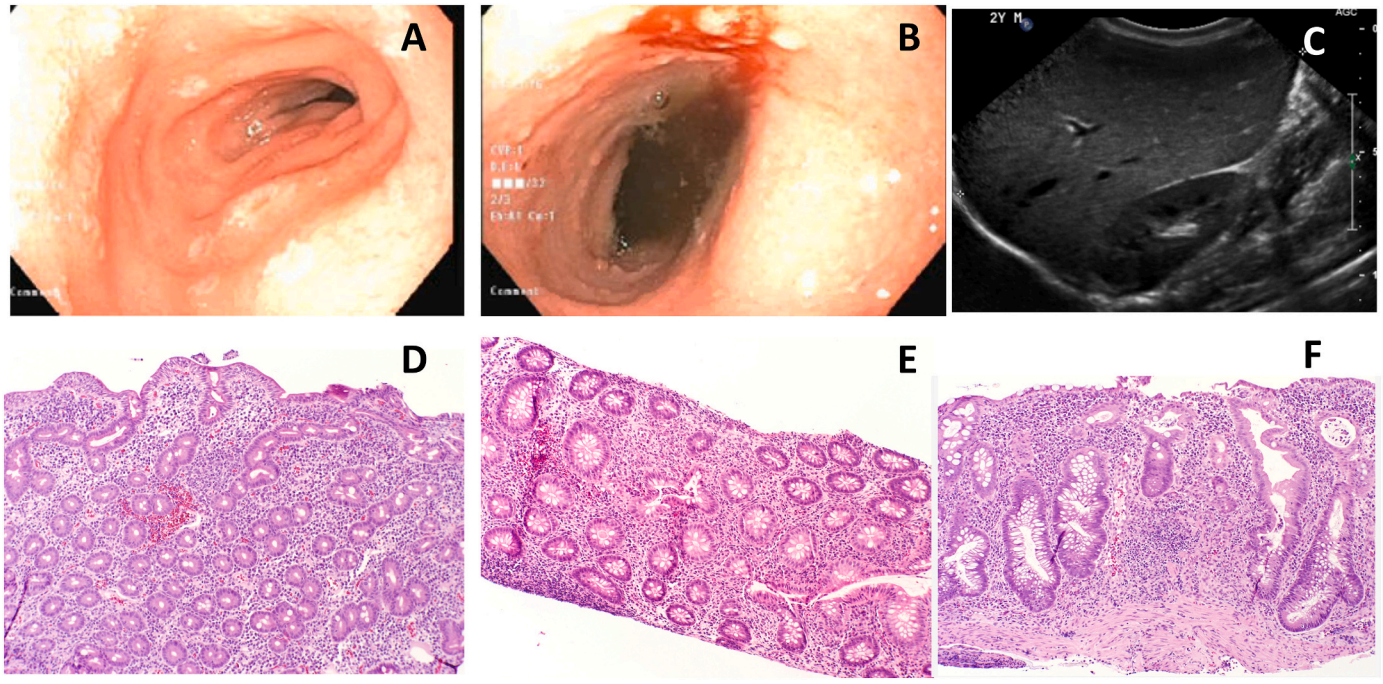

Fig. 1. Upper endoscopy demonstrated esophagitis, diffuse mild inflammation of the stomach, and erythematous duodenal mucosa with white plaques (Panel A shows the duodenal bulb). Colonoscopy demonstrated diffuse moderate inflammation characterized by erythema, friability, and shallow ulcerations in the rectum, sigmoid colon, descending colon, transverse colon, and ascending colon (Panel B shows the descending colon). Panel C shows a longitudinal view of the liver on ultrasound, demonstrating hepatomegaly, mild coarsening of hepatic parenchyma, and diffuse increase in hepatic echogenicity but no evidence of focal hepatic masses or adenomas. Panel D demonstrates histopathology of duodenal mucosa with severe villous blunting, increased inflammatory cells in the lamina propria, and crypt hyperplasia. Panel E demonstrates histopathology of the cecum with cryptitis (intraepithelial neutrophils) and crypt abscess (collection of neutrophils within the crypt) consistent with active colitis. No chronic mucosal injury is seen. Panel F shows histopathology of the sigmoid/rectum with features suggestive of chronic mucosal injury (crypt architecture disarray and basal plasmacytosis) and active colitis. These findings are consistent with a chronic active colitis and concerning for IBD.

to increase cornstarch mixed with formula at bedtime to 31 g (7.88 g per hour) to extend sleep time if possible. At 33 months, it was explained that his parents had separated, and dietary regimen varied depending on the home he was in (bolus feeding at one parent's home while the other had a component of continuous feeding). However, the different feeding schedules did not seem to affect metabolic control as evidenced by improving lipid panel and no acidosis and overall glucose control being satisfactory. Frequent bowel movements also improved with Vivonex formula. Based on his excellent growth and labs, his cornstarch and bolus feeds were adjusted over the years. Metabolic control of his GSDIa has been very good. Laboratory values suggest good metabolic control. At age 2-years-old, labs showed lactate 3 mM, uric acid 4.2, LDL 106, and triglycerides 206. His growth continued to be excellent.

He developed abdominal pain and bloody diarrhea at 40 months of age. Laboratory studies were noteworthy for iron deficiency anemia, elevated fecal calprotectin >1000 μg/mg, and absence of enteric pathogens on stool testing. Endoscopic evaluation demonstrated inflammatory changes in the esophagus, stomach, and duodenum with severe villous blunting of the duodenal mucosa on histopathology (Fig. 1). Colonoscopy revealed diffuse inflammatory changes throughout the colon with sparing of the cecum and terminal ileum. Histopathology showed chronic active colitis in all colonic segments and severe villous blunting in the terminal ileum without chronic inflammation. CT enterography did not reveal small bowel inflammation. His clinical constellation was felt to be consistent with chronic inflammatory bowel disease suggestive of indeterminate colitis with a diagnosis of VEO-IBD made at age 42 months. The patient underwent molecular testing for evaluation of 18 genes implicated in primary immunodeficiencies (Mayo Clinic Autoinflammatory Primary Immunodeficiency Gene Panel) with no variants reported. Exome sequencing was also performed with no variants reported other than the known *G6PC1* variants. Based on this evaluation, it was felt that the cause of VEO-IBD was likely related to GSDIa. Growth remained above the 50th percentile; although the percentiles for height and weight decreased following diagnosis, growth was still good. From around age 44 months to 48 months old, he was off cornstarch and received continuous Vivonex feeds.

The patient was followed closely by gastroenterology with expertise in VEO-IBD. His clinical course was marked by aggressive inflammatory bowel disease refractory to treatment with corticosteroids, methotrexate, infliximab, and vedolizumab. He required temporary diverting ileostomy and is now stable and in clinical remission on combination therapy with ruxolitinib and canakinumab after ileostomy reversal. Neither of these medications are conventional therapies for IBD but are used in VEO-IBD.

3. Discussion

VEO-IBD, characterized by onset before six years of age, may be associated with more aggressive disease compared to individuals with later onset IBD [3]. Approximately 6–15% of pediatric patients with IBD present with VEO-IBD [4]. Individuals with VEO-IBD may be more prone to indeterminate colitis, as illustrated by the patient in this case report. Monogenic causes of VEO-IBD have been previously described in over 50 genes, including genes implicated in primary immunodeficiencies, encompassing approximately 15–20% of patients with VEO-IBD [3]. Additionally, environmental exposures have been suggested to contribute to VEO-IBD risk [3]. This is particularly notable when considering individuals with VEO-IBD who have a concurrent inborn metabolic disorder necessitating the use of cornstarch to maintain euglycemia. Additionally, individuals with VEO-IBD have been suggested to have a higher IBD polygenic risk score [5].

IBD has been previously described in individuals with GSDIb [6–7].

The relationship between the two conditions has been attributed to neutropenia and/or neutrophil dysfunction [8]. Granulocyte colony-stimulating factor has been used to improve IBD in GSDIb [9]. However, there is a paucity of literature that describes IBD in individuals with GSDIa. There was a previous report of five individuals with GSDIa who developed IBD [10], but none of these individuals were diagnosed with IBD in early childhood or met the diagnostic criteria of VEO-IBD. The authors recognize that there are not screening guidelines in place for IBD among individuals with GSDIa [10]. They also note that IBD in individuals with GSD1a appeared to differ from IBD in the general population in that remission was achieved with only aminosalicylic acid treatment [10]. As more individuals with concurrent IBD and GSD1a are described, the course of IBD in individuals with GSD1a is likely to be better characterized. Certainly, the patient described in this report with VEO-IBD and GSD1a has a significantly different clinical course than individuals reported previously with both IBD and GSD1a. Lastly, it is noteworthy that in a study of fifty patients with GSDIa without IBD symptoms that eleven individuals (22%) had findings of IBD based on serologic, genetic, and inflammatory markers [11]. These authors raise three possible explanations for IBD in GSDIa: effects of cornstarch, that glucose-6-phosphatase deficiency increases the likelihood of developing IBD, and that genetic or epigenetic predisposition may concurrently predispose to IBD and GSDIa in some populations [11].

The data available in the literature and the observations in this case raise the possibility of IBD and/or VEO-IBD being part of the phenotypic spectrum of GSDIa. We agree with others [11] that there remains a possibility that chronic use of cornstarch to prevent hypoglycemia may contribute to gastrointestinal symptoms in this cohort of patients in the presence of additional risk factors. However, many individuals with GSDIa take cornstarch, but IBD does not appear common. This patient was initially on extremely high doses of cornstarch and had very good metabolic control and improvement of bowel symptoms when reduced. After development of symptoms of VEO-IBD, the patient had persistence of gastrointestinal symptoms even while not on cornstarch.

This is, to our knowledge, the first case of VEO-IBD characterized in a patient with GSDIa with other causes of VEO-IBD excluded. Given the rarity of both conditions and previous literature acknowledging clinical presentation of IBD in older patients with GSDIa as well as serologic findings of IBD in patients with GSDIa and expression of *G6PC1* in the intestinal mucosa, we suggest that IBD and VEO-IBD may be part of the GSDIa phenotype. Until more data are available, we recommend caution in evaluating whether VEO-IBD is part of the GSDIa phenotype. Whether this is an association due to intrinsic loss of glucose-6-phosphatase function or whether this finding is confounded by high doses of cornstarch or other factors such as modifier genes or epigenetic contributions is a matter that warrants future study. Better understanding the mechanism of IBD in GSDIa will likely inform management decisions for these patients.

Declaration of Competing Interest

None.

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