

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Very Early Onset of Inflammatory Bowel Disease in a Patient With Long-Segment Hirschsprung's Disease

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ABSTRACT

Hirschsprung's disease (HSCR) is a congenital defect caused by impaired development of the enteric nervous system. Inflammatory bowel disease has an increased prevalence in patients with HSCR. We describe the clinical course of a patient with long-segment HSCR who, at the age of 12 months, developed diffuse intestinal inflammation most clinically consistent with very early onset inflammatory bowel disease. We further explore previous studies that implicate the underlying neuroenteric abnormalities in HSCR as possible explanations for this patient's intestinal immune and inflammatory dysregulation.

INTRODUCTION

Hirschsprung's disease (HSCR) is a congenital defect of the enteric nervous system caused by the impaired migration, proliferation, differentiation, and survival of enteric nervous system progenitors. After surgical repair, 2%–35% of patients have been reported to develop Hirschsprung-associated enterocolitis (HAEC), an inflammatory condition diagnosed based on clinical symptoms of abdominal distension, fever, diarrhea, and sepsis and known histological features.^{1,2} Multiple studies additionally document an association between the development of inflammatory bowel disease (IBD) in patients with HSCR, with one recent study demonstrating a prevalence of IBD in patients with HSCR of 2.7% compared with 0.7% in patients without HSCR matched for age and sex.^{3,4} Although the pathogenesis of both HAEC and IBD is poorly understood, they both are assumed to derive from mechanisms involving the microbiome and mucosal immune response and may represent a spectrum of inflammatory diseases. We describe a patient with long-segment HSCR who developed diffuse intestinal inflammation most consistent with very early onset IBD (VEOIBD).

CASE REPORT

Our patient had long-segment HSCR with a transition in the jejunum at 72.5 cm proximal to the ileocecal valve. He underwent a diverting jejunostomy at 12 days of life, followed by resection of the ileum and a colectomy at 3 months of age. Subsequently, he was dependent on total parenteral nutrition and enteral feeds via a gastrostomy tube. His family history was only notable for a paternal grandmother with ulcerative colitis. At 12 months old, he developed several episodes of bright red blood per rectum in the absence of any other clinical symptoms. Flexible sigmoidoscopy showed mild edema, ulceration, and friability of the rectal stump. Pathology revealed diffuse lymphoid hyperplasia with patchy cryptitis most consistent with diversion colitis. Budesonide enemas were initiated.

Over the following 2.5 weeks, rectal bleeding persisted and therapy was changed to hydrocortisone enemas and enteral antibiotics for small intestinal bacterial overgrowth. Jejunostomy output increased, which progressed to the development of melena and hematemesis over a period of 2 weeks. Esophagogastroduodenoscopy and flexible sigmoidoscopy were notable for severe acute gastritis with ulceration and reactive changes, moderate acute duodenitis with focal ulceration and reactive changes, mild focal acute enteritis in the jejunum, and large intestine with reactive crypts with lymphoid hyperplasia (Figure 1). Gastric, duodenal, and jejunal biopsies showed varying degrees of acute inflammation without any identifiable infection. He was started on enteral budesonide and

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Figure 1. Esophagogastroduodenoscopy showing (A) the gastric mucosa, (B) duodenal mucosa, and (C) colonic mucosa.

sucralfate. He continued on hydrocortisone enemas and antibiotics for bacterial overgrowth. However, bloody output persisted, resulting in multiple transfusions. Intravenous (IV) pulse steroids were initiated with rapid clinical improvement. Repeat esophagogastroduodenoscopy and flexible sigmoidoscopy performed after 7 days of IV steroids showed marked improvement, and the patient was discharged on an oral steroid taper.

Attempts to wean oral steroids over the ensuing months led to the recurrence of symptoms, resulting in multiple admissions during which the patient required several days of IV pulse steroids. Five months after initial symptom onset and failure to achieve remission on steroid monotherapy, infliximab was initiated with marked clinical improvement. Methotrexate was added 2 months later because of continued high jejunostomy output, with the thought that dual immunosuppressive therapy would be more effective. Weaning off these medications started 10 months after initial symptom onset. The patient was in full clinical remission of all medications 27 months after initial symptom onset. Seven months after discontinuation of immune-modulating medications and biologics, he continued to be in clinical remission.

Multiple subspecialty services were involved in this patient's evaluation and management. Whole exome sequencing (WES) was significant for a maternal and patient rearranged during transfection proto-oncogene gene variant of unknown significance, which has been described in patients with HSCR.⁵ WES was additionally revealing for a single recessive lipopolysaccharide-responsive and beige-like anchor protein gene variant of unknown significance, which was inherited paternally. Although this gene is associated with common variable immunodeficiency, it was not determined to be related to his underlying clinical phenotype per immunogenetic evaluation.⁶ Whole exome sequencing otherwise showed no abnormalities in known IBD pathway genes. Immunology workup was nonrevealing for an underlying primary immune dysregulation disorder, and rheumatologic evaluation was not concerning for systemic autoimmune etiologies of intestinal inflammation such as Bechet's disease, sarcoidosis, or antineutrophil cytoplasmic antibodies-associated vasculitis.

DISCUSSION

This case describes a patient with long-segment HSCR who at 12 months old developed severe, generalized IBD-like intestinal inflammation, most consistent with a diagnosis of VEOIBD. HAEC was not thought to be responsible for his clinical presentation because he failed to respond to numerous courses of antibiotics.

Although multiple studies link HSCR and IBD, we have found no previous documented cases of VEOIBD in a patient of this age with HSCR. Interestingly, these studies demonstrated that the prevalence of IBD is higher in male patients and patients with long-segment HSCR.^{3,4,7} They also observed a higher prevalence of Crohn's disease than ulcerative colitis in these populations. Genetics has a role in the development of IBD, and this patient has a grandparent with a diagnosis of ulcerative colitis, although the grandparent did not have any genetic variants associated with IBD on WES.

Both HSCR and IBD have multifactorial etiologies that are not fully understood. However, studies focused on the pathophysiology of HAEC demonstrate the importance of the enteric nervous system on overall intestinal homeostasis, mucosal barrier function, innate immunity, and the intestinal microbiome.² Similarly, IBD is assumed to derive from a combination of host-gut microbiome interactions and abnormal intestinal innate immunity.³ These similar mechanisms provide insight into why HSCR is associated with a spectrum of intestinal inflammatory diseases.

There is a dearth of literature regarding the treatment for IBD in the setting of HSCR. We describe a unique case of VEOIBD in a patient with long-segment HSCR who successfully reached full clinical remission with the off-label use of infliximab, methotrexate, and steroids and has remained in remission, off therapy for 8 months. Continued efforts in understanding and recognizing the clinical presentation, disease course, and management of patients with HSCR who develop IBD will allow us to gain further insights into the unique pathways that link these 2 conditions together.

DISCLOSURES

Author contributions: Both authors contributed equally to this manuscript. K. Whitfield Van Buren is the article guarantor.

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Informed consent was obtained for this case report.

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REFERENCES

- 1. Carneiro PMR, Brereton RJ, Drake DP, Kiely EM, Spitz L, Turnock R. Enterocolitis in Hirschsprung's disease. *Pediatr Surg Int.* 1992;7: 356-60.
- 2. Austin KM. The pathogenesis of Hirschsprung's disease-associated enterocolitis. *Semin Pediatr Surg.* 2012;21:319–27.

- Löf Granström A, Granström AL, Amin L, Arnell H, Wester T. Increased risk of inflammatory bowel disease in a population-based cohort study of patients with Hirschsprung disease. J Pediatr Gastroenterol Nutr. 2018;66:398–401.
- Nakamura H, Lim T, Puri P. Inflammatory bowel disease in patients with hirschsprung's disease: A systematic review and meta-analysis. *Pediatr Surg Int.* 2017;34:149–54.
- Heanue TA, Pachnis V. Enteric nervous system development and hirschsprung's disease: Advances in genetic and stem cell studies. *Nat Rev Neurosci.* 2007;8(6):466–79.
- Alkhairy OK, Abolhassani H, Rezaei N, et al. Spectrum of phenotypes associated with mutations in LRBA. J Clin Immunol. 2016;36(1):33–45.
- Levin DN, Marcon MA, Rintala RJ, Jacobson D, Langer JC. Inflammatory bowel disease manifesting after surgical treatment for Hirschsprung disease. J Pediatr Gastroenterol Nutr. 2012;55:272–7.

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