



An Unusual Hiccup: Severe Singultus as a Symptom in Ulcerative Colitis

Anas Zaher, MD¹, Amneet K. Hans, MD², and Dana J. Lukin, MD, PhD, FACP²

¹Department of Medicine, New York Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY

²Jill Roberts Center for Inflammatory Bowel Disease, Division of Gastroenterology and Hepatology, New York Presbyterian Hospital, Weill Cornell Medicine, New York, NY

ABSTRACT

Inflammatory bowel disease encompasses a group of chronic inflammatory conditions associated with both intestinal and extra-intestinal manifestations. We present a 26-year-old man with a history of ulcerative colitis who presented with a disease exacerbation associated with severe intractable hiccups. We report a unique clinical symptom associated with severe ulcerative colitis and the diagnostic dilemma associated with this presentation. This case highlights the importance of recognizing unusual symptoms that can be associated with inflammatory bowel disease exacerbations and demonstrates the therapeutic potential of effective therapy of the underlying inflammatory disease.

KEYWORDS: ulcerative colitis; hiccups; inflammatory bowel disease

INTRODUCTION

Inflammatory bowel disease (IBD) is associated with both intestinal and extraintestinal manifestations. We present a 26-year-old man with a history of ulcerative colitis (UC) who presented with a UC flare and severe intractable hiccups. We report a unique clinical symptom associated with severe UC and the diagnostic dilemma associated with this presentation. This case highlights the importance of recognizing unusual symptoms that can be associated with IBD exacerbations and demonstrates the therapeutic potential of effective IBD therapy.

CASE REPORT

A 26-year-old man with left-sided UC presented to the emergency department for intractable hiccups and left-sided abdominal pain. He was diagnosed with UC 6 years earlier and was treated with balsalazide, which he self-discontinued after 1 year. Two years after diagnosis, he started experiencing hiccups, which were managed with metoclopramide and chlorpromazine with marginal benefit. He achieved mild improvement with levetiracetam and gabapentin. It was unclear whether the patient had an UC exacerbation during this period. He remained off UC therapy until 2 months before his current presentation, when he experienced the return of bloody diarrhea, abdominal pain, and severe, persistent episodes of hiccups. Colonoscopy showed moderately severe left-sided UC. Upper endoscopy revealed gastritis for which he was started on pantoprazole. There was no evidence of Crohn's disease. Prednisone 60 mg daily and mesalamine enemas 4 g nightly were started with no improvement in gastrointestinal symptoms or hiccups. Infectious stool studies were negative. The patient was evaluated in 4 separate emergency departments for severe, intractable hiccups. Computed tomography (CT) of the chest, magnetic resonance imaging of the brain, and laboratory tests were unremarkable.

On presentation, the patient reported progression of severe, persistent hiccups during sleep with difficulty breathing and vomiting. He reported worsening abdominal pain and diarrhea on prednisone 40 mg. His vital signs were remarkable for tachycardia and a fever of 38.1°C. He was ill-appearing with generalized abdominal tenderness. Laboratory test results were notable for a hemoglobin of 12.5 g/dL (normal 13.8–17.2 g/dL), a normal white blood cell count, C-reactive protein (CRP) 3.6 mg/dL (<0.3 mg/dL), and albumin 2.7 g/dL (normal 3.4–5.4 g/dL). Gastrointestinal pathogen panel was positive for *Salmonella* for which a 5-day course of

azithromycin was initiated. Chest x-ray was clear. CT of the abdomen/pelvis revealed pancolonic wall thickening and mucosal enhancement. On day 3 of hospitalization, flexible sigmoidoscopy was performed because of persistent diarrhea and showed severe inflammation in the rectum and sigmoid colon, with small ulcers, friability, and spontaneous hemorrhage, consistent with Mayo Score 3 UC (Figure 1). The patient was started on intravenous methylprednisolone 30 mg twice daily and infliximab 5 mg/kg that day. Given persistent hiccups, he was evaluated neurology. They requested a magnetic resonance imaging of the brain and cervical spine, both of which were unremarkable. Gabapentin was increased, and baclofen was continued. Over the next 2 days, the patient demonstrated clinical improvement, with less abdominal pain and bowel frequency. Interestingly, his hiccup frequency and severity decreased as well. Two days after the infusion, because of a partial response but with an uptick in hiccups, a second infliximab 5-mg/kg dose was given. Five days after the first dose of infliximab, CRP improved to 0.7 mg/dL. Hiccups improved gradually over this time, and he was discharged with a prednisone taper with complete resolution of hiccups and UC symptoms. Three months after the presentation, he discontinued hiccups medications and reported no return of hiccups. His CRP remained normal, and he is maintained on infliximab 5 mg/kg every 8 weeks.

DISCUSSION

A hiccup (singultus) is an involuntary, spasmodic inspiration that abruptly ceases when the glottis closes. Hiccups remain a medical enigma and serve no identifiable physiologic function.¹ They are caused by contractions of the diaphragm and can be brought on by any process that alters the afferent, central, or efferent parts of the reflex arc.² Most hiccups are self-limited; however, intractable hiccups are rare and typically associated with central nervous system disorders, gastrointestinal diseases, or cardiovascular disease.

Common causes of hiccups include central nervous system disorders including stroke and infections, vagus and phrenic nerve disorders such as goiter or foreign-body irritation, gastrointestinal disorders including gastritis, pancreatitis,

pancreatic or gastric cancer, gallbladder disease, inflammatory bowel disease, colorectal cancer, and esophagitis.³⁻⁵ Toxic metabolic factors such as alcohol and drug reactions, post-operative effects, and psychogenic factors such as stress contribute to hiccups as well.³ Uncommon associations have been reported with gastrointestinal disorders, including colonic ulcers and pancreatitis; however, an association between hiccups and IBD has not been previously described.⁶⁻⁸ When evaluating a patient with hiccups, an early CT scan of the head, chest, and abdomen can be performed to detect any abnormalities along the vagal and phrenic nerves in addition to standard laboratory tests and imaging. An upper gastrointestinal endoscopy may be helpful to examine the upper digestive tract, and if no cause is identified, further tests such as esophageal manometry and a 24-hour pH-impedance reflux study may be considered.^{9,10}

Therapy for persistent hiccups should be directed at the underlying cause of the condition. In addition to empiric proton pump inhibitors, additional pharmacological treatments focus on targeting dopaminergic and GABAergic receptors;¹¹ however, our patient had limited response to these agents. Given the lack of neurological or extraluminal findings, the intractable hiccups were suspected to have a gastrointestinal association. This was supported by rapid and complete symptom resolution of hiccups and previously oral corticosteroid-refractory UC symptoms after starting infliximab, a monoclonal antibody targeting tumor necrosis factor—alpha, which reduces the inflammatory response.⁶ The exact mechanism underlying the relationship between IBD and hiccups remains unclear but may be related to neuronal irritation from the acute inflammatory process occurring in the colon adjacent to the peridiaphragmatic area, such as left-sided UC. Alternatively, a systemic inflammatory response or other noninflammatory symptoms related to IBD exacerbation could drive hiccups.

To the best of our knowledge, this is the first reported association of intractable hiccups with severe ulcerative colitis. This case demonstrates the need to consider atypical etiologies for hiccups with a thorough evaluation for potential medical and neurologic causes and treatment directed at the underlying driver of symptoms.

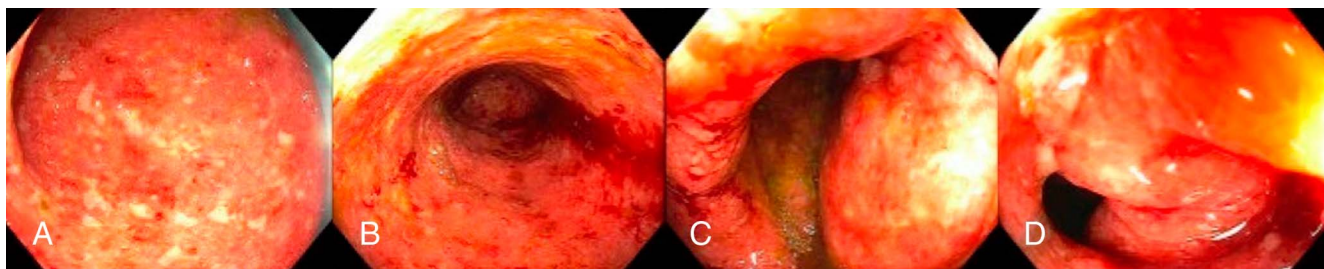


Figure 1. Flexible sigmoidoscopy images demonstrating Mayo 3 colitis of the sigmoid colon (A, B) and rectum (C, D). Inflammation is observed in a continuous and circumferential pattern from the anus to the sigmoid colon, characterized by changes in blood vessel appearance, erosions, friability, granularity, mucus, and shallow ulcerations.

DISCLOSURES

Author contributions: A. Zaher: manuscript drafting, chart review and data abstraction, and manuscript revision. AK Hans: manuscript drafting and manuscript revision. DJ Lukin: manuscript drafting, manuscript revision, and is the article guarantor.

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Informed consent was obtained for this case report.

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