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Case Proceedings

A Masking Effect: A Case of Initial Presentation of Ulcerative Colitis After Discontinuing Growth Hormone Therapy

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Background: The inflammation and repair of the intestinal mucosa in inflammatory bowel disease (IBD) involve a complex interplay between innate, adaptive immune responses, and hormones. This may explain the relapsing clinical course of the disease.

Methods: We present the first reported case of a patient presenting their initial flare of ulcerative colitis immediately after discontinuing growth hormone (GH) therapy, suggesting treatment with GH or growth factors may prevent the development of IBD.

Results: This is a case of a 13-year-old female with a history of GH deficiency, presenting with an 8-week history of abdominal pain, blood-stained diarrhea, and fecal calprotectin greater than 8000 mcg/g, 2 weeks after discontinuing GH therapy. The patient subsequently underwent an esophagoduodenoscopy and colonoscopy with biopsies showing histological features consistent with ulcerative colitis.

Conclusions: The finding of withdrawing GH or growth factors therapy potentially unmasking IBD in this patient raises a question of whether growth factors can inhibit the development of IBD and suggests beneficial effects of treatment with GH or growth factors as adjuvant therapy for IBD.

Lay summary

In a case of a 13-year-old patient with a history of growth hormone deficiency, she developed ulcerative colitis symptoms shortly after stopping treatment which supports the hypothesis that growth hormone may benefit inflammatory bowel disease patients as an adjuvant therapy.

Key Words: IBD, inflammatory bowel disease treatment, ulcerative colitis, growth hormone use in IBD, adjuvant therapies of IBD, growth factors in IBD

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic recurrent inflammation of the gastrointestinal tract. The pathogenesis behind IBD is not well understood and is likely related to immune system disorders and imbalances between inflammatory mediators. Growth factors have antioxidant and anti-apoptotic properties aside from stimulating cellular differentiation. For example, epidermal growth factor (EGF) has been shown to ameliorate the effect of oxidative stress on the intestinal mucosa. Villa et al. demonstrated that pre-ischemic administration of intraluminal EGF significantly protects against intestinal ischemia-reperfusion injury in rats.[1]; in a similar ischemia model, Arda-Pirincci et al.[2] demonstrated partially recovered intestinal mucosa architecture in rats treated with intraperitoneal EGF versus untreated rats.

Growth retardation has been recognized as a complication associated with IBD in pediatrics. It is reported to have an incidence at diagnosis ranging between 15% to 40% in Crohn's disease (CD) and 3% to 10% in ulcerative colitis (UC).[3]

The addition of growth hormone (GH) in treating children with established IBD has been previously studied.[4–6]

Case Presentation

A 13-year-old female presented from an outside facility with complaints of vague, intermittent, suprapubic abdominal pain, fatigue, and an abnormal fecal calprotectin of greater than 8000 ug/g. She also endorsed occasional blood-stained diarrhea but denied weight loss, fever, or skin rashes. Her past medical history included Kawasaki disease and GH deficiency. She was recently noted to have severe iron deficiency anemia believed to be secondary to menorrhagia (requiring blood and iron transfusions). Her home medications include ferrous sulfate and montelukast. She had a history of GH deficiency, treated with daily GH injections (1.8 mg) for 6 years, which was discontinued 2 weeks before the onset of symptoms, as the patient had achieved her expected height. The patient was pale on examination, with a height-for-age consistent with the 25th percentile. Significant laboratory findings included a white blood cell count 14.3 k/

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cm³, hemoglobin 10 gm/dL, platelet 506 k/μL, MCV 74.8 fL, C-reactive protein (CRP) 2.68 mg/dL, serum iron 9 ug/dL, percent iron saturation 3%, and ferritin 3 ng/mL. Other potential causes of acute colitis including infection were ruled out. esophagoduodenoscopy and colonoscopy showed erythematous gastric mucosa, congested mucosa at the appendiceal orifice, and contiguous nonbleeding ulcerated mucosa of the rectum, sigmoid colon, descending colon, and splenic flexure (Figure 1). The biopsy reading showed mild-to-moderate acute inflammation, crypt architectural distortion, and increased chronic inflammatory cells in the lamina propria consistent with IBD (Figure 2). The patient was treated with prednisone twice daily. The patient reported significant improvement in abdominal pain, and mesalamine was added to her medications on the 2-week follow-up clinic visit.

Discussion

Ulcerative colitis is characterized by idiopathic chronic inflammation and ulcerations in the rectum in 95% of the cases and may present as continuous mucosal ulcers extending to involve other aspects of the colon. The inciting causes of the inflammatory cascade in IBD are not well understood. The treatment of IBD is directed at blocking factors involved in the inflammatory cascade with steroids, immune-modulating therapies, biologics, and small molecular agents. Growth factors have been shown to promote the renewal of epithelial and immune cells, enhance wound healing, mucosal integrity, and potentially modulate inflammation.[7] Growth factors help maintain mucosal barrier integrity by promoting colonic epithelial cell's survival and inhibiting NF-kB activation by activating the Signal Transducer and Activator of Transcription Factor 5b (STAT5b).[8]

Han et al.,[8] using a 2,4,6-trinitro-benzene sulfonic acid-induced colitis (TNBS) model in STAT5B deficient mice, demonstrated that GH administration reduced colonic inflammation induced by TNBS in the control group of mice, causing a decrease in the severity score, while the effect of GH was blocked in STAT5b deficient mice. Kara et al.,[9] using a similar TNBS-induced colitis model in mice, showed more serious intestinal damage in the TNBS-only-treated mice group compared to TNBS plus GH-treated group, with no damage found in saline-only-treated sham group.

Another study by Han et al.[10] in null mice with colitis discovered that GH increases the interaction of Src homolog 2 domain-containing protein tyrosine phosphatases (SHP2) with the glycoprotein 130 receptor, which negatively regulates the activation of Constitutive Signal Transducer and Activator of Transcription, STAT 3 (a protein that has been shown to promote chronic inflammation in IBD). Williams et al.,[11] using a dextran sodium sulfate (DSS)-induced colitis model in transgenic mice overexpressing GH (MT1-bGH-TG) to determine whether increased plasma GH levels alter inflammation or crypt damage induced by the colitis, found that DSS induced similar colonic injury in the transgenic mice overexpressing GH and wild-type (WT) control groups; however, more transgenic MT1-bGH-TG mice survived than WT mice, and by recovery day 7, transgenic MT1-bGH-TG mice had less inflammation and crypt damage than WT mice, as well as improved survivability.

Our patient has a history of GH deficiency and has received GH supplements for 6 years. Her symptoms of UC presented after a short interval, 8 weeks, after discontinuing the GH therapy. Growth hormone has an average half-life of 20–30 minutes with a biological half-life of 9–17 hours. The possibility that our patient had IBD manifesting as growth failure cannot be ruled out. Short stature is a known complication of IBD in pediatrics. A retrospective study by Rinawi et al.[12] in 291 Crohn's and 125 UC patients discovered a mean height *Z*-score lower than the control group, especially in males and those diagnosed before puberty. Growth retardation has been reported in less than 10% of patients with UC. The growth delay in IBD has been attributed to severe malnutrition due to malabsorption secondary to intestinal inflammation, anorexia, and metabolism related to systemic inflammation, particularly in CD.[3] Others have suggested GH resistance or deficiency as a possible cause of short stature seen in some patients with IBD. According to Tenore et al.,[13] IBD patients may present with growth failure preceding abdominal symptoms by some years. This study further reported that 8 out of 10

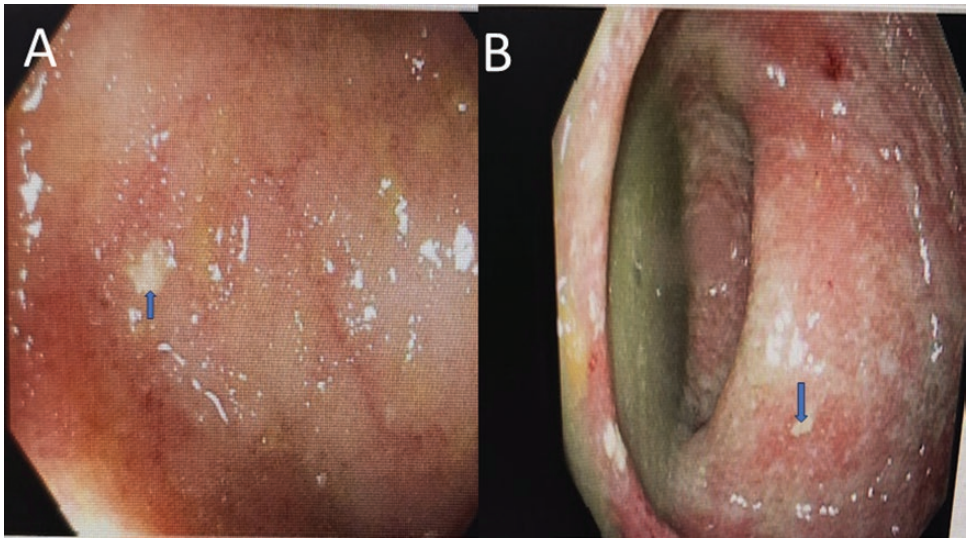

Figure 1. A, Ulcer in the terminal ileum (black arrow). B, Ulcerated rectal mucosa (black arrow).

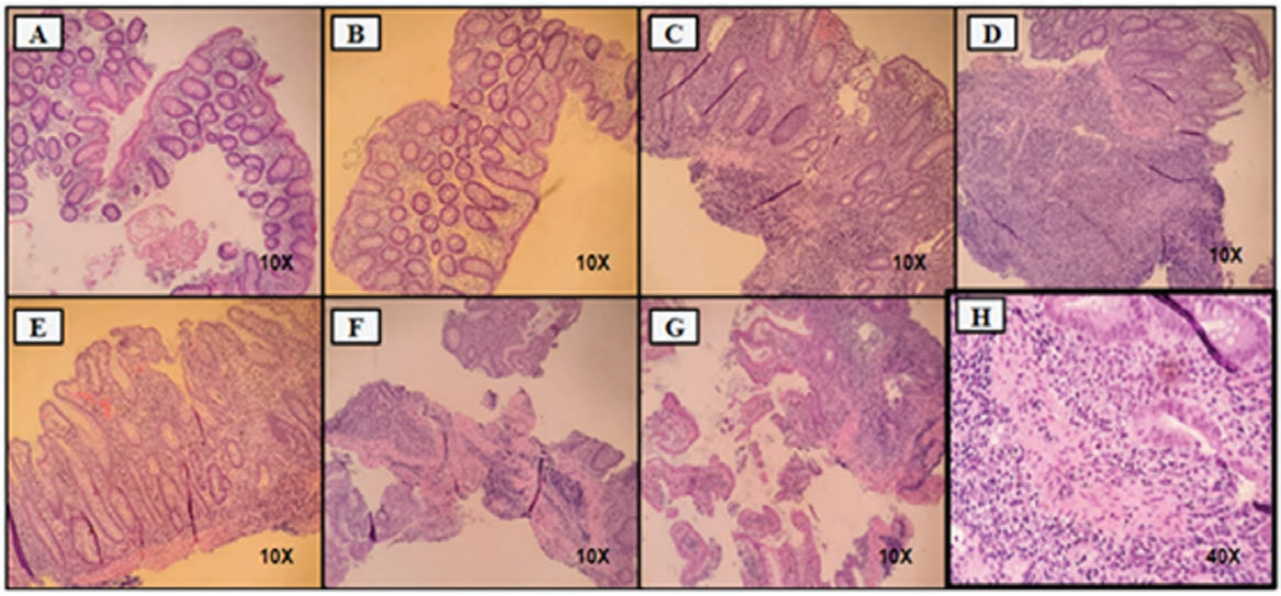

Figure 2. Hematoxylin and Eosin (H&E) stains of colonoscopy biopsies from cecum (A), transverse colon (B), appendiceal orifice (C), splenic flexure (D), descending colon (E), sigmoid colon (F), rectum (G), splenic flexure higher power (H). Panels (A, B) demonstrate unremarkable colonic mucosa. While panels (C–H) display biopsies from the appendiceal orifice, splenic flexure, descending colon, sigmoid colon, and rectal biopsies show superficial fragments of colonic mucosa with mild-to-moderate acute inflammation (*black arrows*), crypt architectural distortion (*red arrows*), and increased chronic inflammatory cells in the lamina propria (*black boxes*). There is no granulomatous inflammation, dysplasia, or malignancy. Panels (A–G) were taken at 10X magnification. Panel (H) was taken at 40X magnification. These histologic findings are consistent with inflammatory bowel disease.

patients with documented IBD and a history of decreased growth velocities had a mean basal GH higher than the control population, concluding that growth failure in IBD is not necessarily due to GH deficiency alone. A similar finding was also reported by Tietjen et al.[14] However, Wong et al.[15] reported a contrary finding in 28 patients with IBD, 4 of which showed biochemical evidence of GH deficiency, 5 had a normal serum response, and 11 had evidence suggesting GH resistance.

This patient presented with short stature years before developing intestinal symptoms of IBD and was successfully treated with GH for short stature for 6 years.

The onset of our patient's first IBD flare following discontinuation of GH supports previous studies on the anti-inflammatory effects of growth factors in IBD. A double-blind and placebo-controlled study by Slonim et al.[5] in patients with moderate-to-severe CD showed that the use of a GH dose of 5 mg/day subcutaneously for 1 week, followed by 1.5 mg/day maintenance dose for 4 months was superior to placebo in reducing disease severity. In a randomized, double-blind control clinical trial by Sinha et al.[16] involving 24 patients with mild-to-moderate UC treated with 5 µg of EGF enema, 10 out of 12 treated with EGF enema and mesalamine were in remission after 2 weeks compared to 1/12 in the control group treated with only mesalamine. In a randomized control trial by Denson et al.[6] involving 20 patients with active CD receiving steroids 12 weeks after the initiation of 0.075 mg/kg of GH in half of the patients, 65% of those on GH achieved clinical remission compared to 20% of steroid only control group.

Improvement noted in subjects treated with growth factors is attributed to the anti-inflammatory effects. The effect of GH has also been noted with improved intestinal adaptation in short gut syndrome, occasionally seen in complicated IBD patients. In a study by Iannoli et al.,[17] New Zealand rabbits with mid-duodenal ileal resection who were treated with GH (0.2 mg/kg/day) and EGF (1.5 pg/kg/h) for 7 days showed enhanced nutrient transport with an increase in microvillus height from 25% to 35%.

Growth factors cause the proliferation of both normal and malignant cells, and the possibility that treatment with growth factors may increase the risk of tumor occurrence in predisposed subjects may be an area of concern regarding the therapeutic use of growth factors in IBD.[18] However, none of the study trials reported cancer development in treated individuals during its use. GH therapy is the standard of care treatment for short stature secondary to GH deficiency. Further studies may need to be done in humans to support its efficacy as a therapy in IBD patients.

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Author Contributions

X.V. and T.M. evaluated the patient and presented the case to O.U., who did a literature review and wrote the manuscript. D.S. did a literature review and contributed to the discussion. The manuscript was then submitted to T.N., A.S., and X.V., who edited and made changes before submission.

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Conflicts of Interest

None to disclose.

Data Availability

Data not publicly available.

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