

Concurrent Ulcerative Colitis and Neurofibromatosis Type 1: The Question of a Common Pathway

William Adams, MD,^a Lisa Mitchell, DO,^a Roberto Candelaria-Santiago, MD,^b Jody Hefner, DO,^a Joseph Gramling, MD^a

Patients with neurofibromatosis type 1 (NF1) are prone to the development of gastrointestinal stromal tumors, which may present clinically with hematochezia, obstruction, or abdominal pain. These symptoms are also commonly associated with the presentation of ulcerative colitis (UC). Within the past 5 years, there have been 2 reports of concurrent NF1 and UC and a common pathophysiologic pathway involving mast cells has been postulated. We present the case of a 15-year-old boy with a known history of NF1 who presented with 3 months of hematochezia and loose stools. A colonoscopy revealed pancolitis and histology demonstrating acute cryptitis, focal crypt abscesses, and architectural distortion consistent with UC. Due to the paucity of reported cases, the findings of both diseases in the same individual could reasonably be discounted as coincidence. However, in light of increasing reports of concurrent NF1 and UC, advances in characterizing the microenvironment within neurofibromas, and recent findings regarding potential shared genetic susceptibility, it is increasingly possible that the proposed common pathway is accurate. Our case adds to the literature and underscores the need for further investigation.

Two cases of concomitant neurofibromatosis type 1 (NF1) and ulcerative colitis (UC) have been described in recent literature.^{1,2} These findings are unique, given that the most common gastrointestinal complication in patients with neurofibromatosis is a stromal tumor. A common pathogenetic pathway to explain the relationship between NF1 and UC involving mast cells has been proposed on the basis of altered mast cell signaling observed in neurofibromas as well as current studies implicating mast cell dysregulation in the development of UC. Here we report the case of a 15-year-old boy with known plexiform-type NF1 who presented with bloody diarrhea. After thorough clinical evaluation, colonoscopy, and biopsy, he was found

to have UC. Literature regarding our understanding of the mast cell's role in NF1 and UC, as well as evidence supporting a potential common pathway, is also discussed.

CASE REPORT

A 15-year-old boy presented to the pediatric gastroenterologist with 6 weeks of episodic loose stools and hematochezia 3 to 4 times a day. He reported 1 episode of fecal incontinence. He also reported being awakened from sleep by the urge to stool twice in the previous few weeks. He denied any recent dietary changes, illnesses, travel, fever, abdominal pain, trauma, or vomiting. His past medical history was significant for plexiform NF1 with primary involvement of his right pelvis that required a right

abstract

Departments of^aPediatrics, and^bPathology, Madigan Army Medical Center, Tacoma, Washington

Dr Adams performed the literature search and drafted the initial manuscript; Dr Mitchell performed the initial evaluation of the patient, and reviewed and revised the manuscript; Dr Candelaria-Santiago prepared, stained, and evaluated tissue samples, and reviewed and revised the manuscript; Dr Hefner followed up with the patient, and reviewed and revised the manuscript; Dr Gramling performed the initial evaluation of the patient to include the esophagogastroduodenoscopy, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to W. Aaron Adams, MD, Department of Pediatrics, Madigan Army Medical Center, 9040 Jackson Ave, Tacoma, WA 98431. E-mail: william.a.adams2.mil@mail.mil

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distal femur and proximal tibia epiphysiodesis due to leg length discrepancy. He had no family history of NF1 or inflammatory bowel disease (IBD).

On physical examination he had a soft, nondistended, nontender abdomen with normal bowel sounds, no masses, and no hepatosplenomegaly. Perirectal and digital rectal examinations were normal. His skin had multiple diffuse café-au-lait macules, axillary and inguinal freckling, and multiple subcutaneous masses. Baseline laboratory data were obtained, including a complete blood count and complete metabolic panel, which were significant only for microcytic anemia. Inflammatory markers obtained were mildly elevated with an erythrocyte sedimentation rate of 39 mm per hour (0–15 mm/h) and C-reactive protein of 1.8 mg/dL (0–0.5 mg/dL).

Esophagogastroduodenoscopy and ileocolonoscopy were performed. The gastric antrum had mildly erythematous mucosa indicating moderate inflammation, whereas the duodenum, gastric fundus, and esophagus were normal in appearance. Biopsy of the gastric antrum showed nonspecific focally active gastritis. The remaining biopsies in the esophagus, gastric fundus, and duodenum were normal. The mucosa throughout the colon was diffusely congested, erythematous, inflamed, and ulcerated (Fig 1). Biopsies were obtained throughout the colon and 1 medium-sized nonbleeding polyp was excised. Microscopic analysis showed active chronic crypt destructive colitis and architectural distortion and surface erosion (Fig 2A), acute cryptitis (Fig 2B), and focal crypt abscesses (Fig 2C) in the cecum, ascending, transverse, descending, sigmoid colon and rectum. Biopsy samples from the terminal ileum were normal. Immunohistochemical staining for CD117 (also known as mast cell growth factor receptor

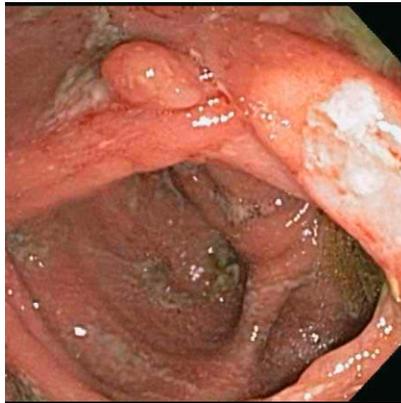


FIGURE 1
Colonoscopy photograph showing polyp and congested, inflamed colonic mucosa.

or c-kit) demonstrated notably increased expression in the colonic mucosa (Fig 3). Additional laboratory studies obtained after the colonoscopy included *Clostridium difficile* polymerase chain reaction, QuantiFERON-TB Gold (Cellestis Limited; Melbourne, Australia), and bacterial stool cultures, which were all negative.

Given the colonoscopy and biopsy results, UC was diagnosed and the patient was started on oral prednisone, 5-aminosalicylic acid, and omeprazole. He was seen for follow-up 48 hours after colonoscopy and his hematochezia had resolved but the loose stools continued. At his 6-week follow-up, he was no longer having hematochezia or diarrhea, and was started on a steroid taper.

DISCUSSION

NF1 is an autosomal dominant genetic disorder affecting 1 in 3000 to 4500 individuals.^{3,4} Patients present with a constellation of symptoms that include café-au-lait spots, neurofibromas, Lisch nodules, axillary freckling, and often developmental delays. NF1 is the result of a mutation in the tumor suppressor gene *NF1* located on chromosome 17 that codes for neurofibromin, a protein that regulates the Ras GTPase signaling

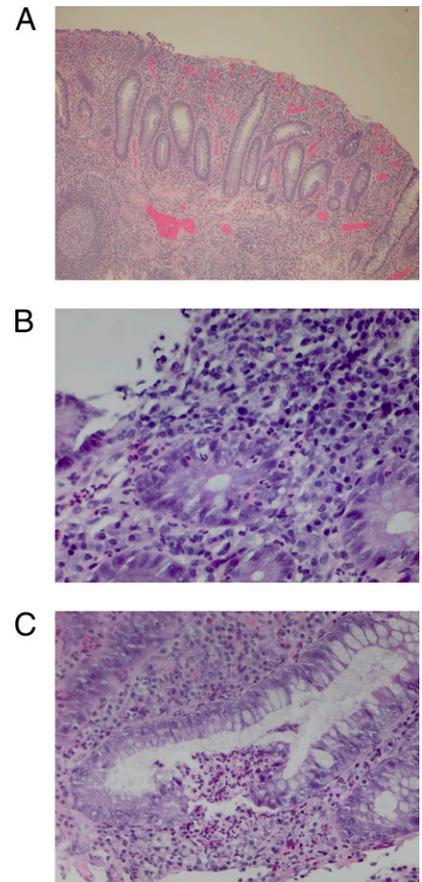


FIGURE 2
Photomicrographs of colon tissue samples demonstrating the following: A, mucosal surface erosion and distortion of normal crypt architecture (hematoxylin-eosin [H&E] $\times 2$); B, cryptitis with granulocytic infiltration into the crypt walls (H&E $\times 40$); and C, crypt abscess with granulocytes within the glandular lumen (H&E $\times 40$)

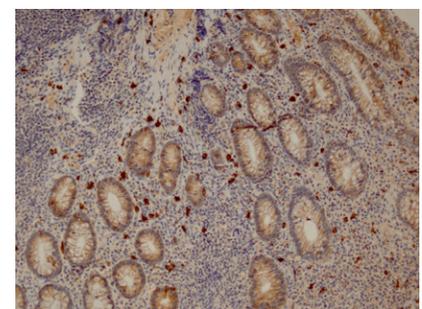


FIGURE 3
Photomicrograph of CD117/c-kit-stained colonic mucosa sample highlighting significantly elevated expression of CD117 in the colonic mucosa and the lamina propria ($\times 40$).

protein involved in cell survival and division.^{5,6}

The development of cutaneous and internal neurofibromas is a characteristic feature of NF1.⁷ Neurofibromas are composed of Schwann cells, fibroblasts, degranulating mast cells, and vascular cells.⁸ The activation, proliferation, and regulation of mast cell function in patients with NF1 has been of increased interest to researchers in recent years. Results of some studies indicate that Schwann cells in patients with NF1 regulate mast cell degranulation. This cell-to-cell interaction is mediated through the cell surface cytokine receptor known as c-kit.^{9–11} Schwann cells in patients with NF1 express higher levels of c-kit compared with normal Schwann cells.¹² It is known that more mast cells are recruited and activated in plexiform than in encapsulated neurofibromas, but that increased mast cell signaling is seen in both NF1 tumor types.¹³ However, this increased mast cell recruitment may not be limited to the microenvironment of neurofibromas. In one animal study, mice lacking the *NF1* gene were shown to have increased numbers of peritoneal and cutaneous mast cells as well as enhanced mast cell proliferation and survival.¹⁴ Baratelli et al² demonstrated markedly increased expression of CD117/c-kit in colonic mucosa samples from their patient with concurrent NF1 and UC, demonstrating the increased presence of mast cells there. We were able to replicate this finding in our own patient (Fig 3).

Altered mast cell function also seems to play a role in the pathogenesis of UC. One of the more widely accepted theories for the evolution of UC is that immune dysregulation in the gastrointestinal tract results in an abnormal proinflammatory milieu that compromises the intestinal lumen barrier. Bacterial antigens are then able to penetrate the

intestinal mucosa triggering the cyclical inflammatory chain reaction responsible for the symptoms of UC.¹⁵ Degranulating mast cells are involved in this process through the release of proinflammatory cytokines that alter the physiology of the gastrointestinal microenvironment, resulting in increased epithelial barrier permeability.^{16,17} The authors of some studies have reported that the interplay between nerves in the intestinal mucosa and mast cells results in mast cell degranulation and could be the initiating immune dysregulator that sets in motion the inflammatory cycle of UC.^{18,19} Normal intestinal barrier function seems to be the result of balanced pro-IBD and anti-IBD mast cell mediators.¹⁵ Disrupting this balance, whether by infection, allergy, or genetic susceptibility, could cause IBD. The altered cell signaling in patients with NF1 may tip the scale in favor of the pro-IBD mast cell mediators, thus placing patients with NF1 at higher risk of developing UC.

Given that the incidence of NF1 is 1 in 3000,³ and the incidence of UC is 21 in 100 000, the odds of a single patient having both diseases is ~1 in 15 000 000 if they are assumed to be unrelated coincidental events.^{3,20} Currently, there are no studies directly linking NF1 and UC, but as more cases of concurrent UC and NF1 accumulate, a correlative role beyond coincidence becomes more likely. Genome-wide association studies have analyzed the genomes of patients with IBD by comparing them with healthy controls and have demonstrated nearly 100 susceptibility loci for IBD, 47 of which are for UC. Some of these loci have shared susceptibility with multiple sclerosis, rheumatoid arthritis, vitiligo, celiac disease, ankylosing spondylitis, Behcet, and many other diseases.²¹ The most current estimation of undiscovered genetic susceptibility for UC is 84%,²¹ which underscores both the

deficiency of accurate epidemiologic data on disease overlap, as well as the vast amount yet to be learned about the genetic contribution to disease.

CONCLUSIONS

Our case adds to the literature on concurrent UC and NF1, lending credence to the idea that this association may not be a coincidence and that there may be a common pathophysiological pathway that links the 2 diseases. Current literature supports a role for altered mast cell function in the pathogenesis of both diseases. Although these cases could still represent incidental findings, this seems less likely as more cases accumulate. New genome-wide association studies have shown susceptibility loci linking UC with other diseases, and many other loci have yet to be discovered.

Further investigation is needed concerning the microenvironmental regulation of mast cells in patients with NF1, the role of mast cells in the pathogenesis of UC, and continued genome-wide association studies for shared disease. Future breakthroughs in this area will guide our understanding and treatment of both diseases.

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ABBREVIATIONS

IBD: inflammatory bowel disease
NF1: neurofibromatosis Type 1
UC: ulcerative colitis

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