Inflammatory Bowel Disease and Primary Sclerosing Cholangitis in a Pediatric Patient With Neurofibromatosis Type 1

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ABSTRACT

We describe a case of a 15-year-old adolescent boy with neurofibromatosis type 1 who presented with inflammatory bowel disease and primary sclerosing cholangitis. The literature available on the association of neurofibromatosis type 1 with inflammatory bowel disease is limited to 7 clinical case reports, and none had comorbid primary sclerosing cholangitis. We present a review of the published literature on this rare association and add the findings of our patient.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic condition secondary to a mutation on chromosome 17. The protein involved is neurofibromin, which participates in the Ras signaling pathway, functioning as a tumor suppressor. Gastrointestinal complications of NF1 include constipation, gastrointestinal neurofibromas, or schwannomas, and rarely, gastrointestinal stromal tumors. We describe a case of a 15-year-old adolescent boy with NF1 who presented with inflammatory bowel disease and primary sclerosing cholangitis (IBD-PSC). The literature available on the association of NF1 with IBD is limited to a small number of case reports, and none had comorbid PSC.¹–⁶ We present a review of the published literature on this rare association and add the findings of our patient.

CASE REPORT

The case involves a 15-year-old adolescent boy who was diagnosed with NF1 in infancy. He has comorbid autism spectrum disorder, functional constipation, and a stable left optic glioma. There is a family history of Crohn’s disease in the maternal great-uncle. The patient presented with a 5-month history of diarrhea, weight loss, and abdominal cramping with a recent onset of bloody stools. He was passing 5–8 stools per day (Bristol type 7) mixed with blood (<50% of stool volume) and experienced nocturnal stooling at least once per week. His Pediatric Ulcerative Colitis Activity Index was 55 at presentation.

At presentation, numerous café-au-lait spots were noted throughout the skin, along with axillary, inguinal freckling, and multiple small neurofibromas on his face. His abdomen was soft and nontender with no hepatosplenomegaly. A rectal examination revealed no erythema, skin tags, or fissures. The initial workup included a normal hemoglobin (141 g/L), elevated inflammatory markers—erythrocyte sedimentation rate 66 U/L and C-reactive protein 13.4 mg/L—and mildly elevated liver enzymes—alanine aminotransferase (ALT) 41 U/L, gamma glutamyl transferase 80 U/L, aspartate transaminase (AST) 29 U/L, alkaline phosphatase level 110 U/L with normal synthetic liver function—bilirubin 0.41 mg/dL, international normalized ratio 1.1, and albumin 3.5 g/dL. A bowel ultrasound demonstrated mild large bowel wall thickening with hypervascularity and subtle wall thickening involving the common bile duct (Figure 1). Magnetic resonance cholangiopancreatography demonstrated mild beading most prominently in the proximal common bile...
duct and proximal right and left hepatic ducts (Figure 1). Magnetic resonance enterography suggested normal small bowel enhancement and thickness. His antinuclear Ab was positive to a titer of 1:160, antiliver-kidney microsomal/antismooth muscle Ab was negative, and IgG was 25. The patient’s hepatitis B/C serologies, ceruloplasmin, alpha-1-antitrypsin, and celiac serology were negative. Repeat liver enzymes were improved before the initiation of steroids (ALT 40 U/L, gamma glutamyl transferase 29 U/L, and AST 29 U/L), and decision was made not to undergo liver biopsy and instead follow liver enzymes over time. His IBD serologies revealed a positive anti-PR-3 antibody (344 CU) and positive ASCA (26 KEU/L). Fecal calprotectin was 707 mg/kg.

The patient underwent upper endoscopy and colonoscopy. His upper endoscopy was normal, and his colonoscopy revealed pancolitis (Mayo type 2) with normal-appearing terminal ileum. Pathology demonstrated chronic proctocolitis with moderate activity, absence of ileal involvement, and absence of granulomas (Figure 2). Immunohistochemical staining for c-kit protein showed an increase of mast cells (MCs) in the patient’s colon compared with the normal control (Figures 2). There were up to 50 MC per high power field in the cecum, compared with 20 per high power field in the control. A diagnosis of IBD favoring ulcerative colitis (UC) (Paris classification E4S0) with PSC was made, and the patient was started on oral steroids (1 mg/kg for 2 weeks followed by a taper), 5-aminosalicylic acid, and ursodiol. On follow-up after 3 months, his steroids were tapered off and he was in clinical remission (Pediatric Ulcerative Colitis Activity Index 0) on 5-aminosalicylic acid alone with normal liver enzymes (ALT 12 U/L and AST 12 U/L).

DISCUSSION

We share a rare case of IBD-PSC with NF1 in a 15-year-old adolescent boy with an increase in MC on histopathology. A review of the literature demonstrates 7 cases (4 female and 3 male) previously reported.1–6 Five cases received a diagnosis of UC, and 2 a diagnosis of Crohn’s disease. The mean age of onset of disease was 36 years, with only 2 cases reported in the pediatric age group.2,3 Both previous pediatric cases presented as UC and had evidence of increased MC proliferation on immunohistochemistry. There have been no reported cases where PSC is comorbid with both IBD and NF1.

Mendelian gene disorders such as NF1 can increase the risk of developing complex diseases such as UC (relative risk 1.58).7 MC are immune cells that secrete several cytokines on degranulation and express various receptors and ligands on their surface and had been hypothesized as the center point of the pathway involved in this association. Schwann cells in patients with NF1 have increased secretion of c-kit ligand, which increases the migration and degranulation of MC to tissue including the GI tract.8 Degranulation of MC leads to the release of proinflammatory cytokines, which is suggested to alter the gastrointestinal milieu and trigger inflammation in patients with IBD.9 Baratelli et al proposed that increased MC activation in NF1 predisposes to the development of IBD and demonstrated increased MC presence in the colonic mucosa of a patient with NF1 and UC.3 This increased MC presence was replicated by Adams et al, strengthening the possibility of a pathogenesis involving MC pathway.2 In our case, MCs are also increased throughout the colon; further mechanistic

Figure 1. (A) Sonographic image along course of common hepatic/bile duct demonstrates wall thickening and luminal caliber changes and (B) coronal MRCP 3D image demonstrates mild beading of biliary duct at hepatic confluence.

Figure 2. (A) Left colon biopsy showing features of inflammatory bowel disease—crypt distortion, crypt microabscess, plasmacytosis, Paneth cell metaplasia (arrowhead). Hematoxylin phloxine saffron stain at 200× magnification; (B) cecal biopsy shows colitis and increased mucosal mast cells by CD117 immunohistochemistry (100× magnification) and (C) normal control colon shows normal mast cell density by CD117 immunohistochemistry (100× magnification).
studies are needed to confirm this association. Similar to IBD, abnormalities in MC have also been hypothesized in the pathogenesis of PSC. MC-derived histamine can stimulate biliary proliferation and fibrosis, and previous studies had revealed an increase in c-kit ligand and MC numbers in patients with PSC, with therapeutic benefits shown on inhibition of MC in animal models.10–14 We were unable to obtain a liver biopsy in our case.

Our case is the first to report PSC comorbid with NF1 and IBD. This interesting trifecta of conditions highlights the need for further research into the link between MC proliferation, NF1, and IBD-PSC and the possibility for preventative or treatments for patients at a higher risk of developing these inflammatory disorders because of Mendelian gene disorders such as NF1.

DISCLOSURES
Author contributions: E. Lehan wrote the article and reviewed the literature. T. Wang, D. Soboleski, A. Acker, and M. Kehar edited the article and reviewed the literature.

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