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Intractable Diarrhea in Two Brothers: Late Diagnosis of Tufting Enteropathy in Adolescence

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Case Presentation and Evolution

Two brothers aged 17 and 19 had been followed in our Pediatric Gastroenterology clinic for over 14 years for complaints of intractable diarrhea of uncertain etiology. Both brothers had 5–6 watery stools per day without emesis, abdominal pain, melena, or hematochezia. They experienced no nocturnal bowel movements and reported some improvement in stool output with fasting. Stool output did not improve during a trial of hydrolyzed or elemental enteral formulae. The brothers were maintained with a regular diet in which concentrated sweets were avoided, and were supplemented with parenteral nutritional support 4 days/week. Both brothers were developmentally appropriate for age and were attending high school. There was no known family history of diarrhea, autoimmune conditions, or other major medical issues. Their medications included loperamide, cyproheptadine, iron, and vitamins C and D. At ages 17 and 19, the brothers were at the 25th and 4th percentile for weight and the 20th and 6th percentile for height, respectively.

Extensive diagnostic evaluation had been performed throughout the course of their childhood. Negative studies included infectious stool studies; there were no known travel or abnormal exposures. Both brothers had normal serum inflammatory markers, Hgb, platelet count, endomysial antibody assay, and anti-tissue transglutaminase IgA assays (with normal quantitative serum IgA). Immunodeficiency evaluation had also been unrevealing, including negative HIV screening, normal T and B cell subsets, normal immunoglobulin levels, and appropriate post-vaccination titers for pneumococcus, diphtheria, and tetanus. Both siblings had normal hemoglobin A1c levels and no thyroid, parathyroid, or adrenal disease. Fecal elastase, serum cationic trypsinogen, sweat chloride, and pancreatic secretin stimulation tests were normal in both brothers, providing no support for the diagnosis of exocrine pancreatic insufficiency. Multiple endoscopies and colonoscopies over a 13-year period were normal other than nonspecific mild villous blunting in a subset of duodenal biopsies. Periodic acid-Schiff staining and electron microscopy revealed no evidence of microvillous inclusion disease. The younger brother's duodenal biopsies when tested for disaccharide activity revealed alactasia with normal α -glucosidase activity with histologically normal villi. The

older brother's biopsies initially demonstrated alactasia, also with histologically normal villi, although 8 years later generalized disaccharidase deficiency accompanied by villous blunting was reported. LactoTYPE testing (Prometheus Laboratories, Inc.) revealed a C/C-13910 variant, associated with lactase non-persistence and predisposition to lactose intolerance in adults. Abdominal ultrasound, fluoroscopic upper GI, and abdominal CT scanning revealed no evidence of adrenal or pancreatic mass to suggest a vasoactive intestinal peptide (VIP) secreting mass; no abnormal lymphatic morphology, bowel dilation, or pseudo-obstruction were reported.

Further evaluation demonstrated fat malabsorption with increased fecal fat by staining (>100 droplets per high powered field) and abnormal 72 h quantitative fecal fat (7.2 and 5.1 g, respectively, with approximately 10 g/day fat intake). In the absence of exocrine pancreatic insufficiency, concern for possible primary bile acid malabsorption secondary to the absence of ileal bile acid transport was raised [1]. Yet, fecal bile acid output was normal for both brothers, excluding this diagnosis. Further genetic testing was performed with identical HLA typing noted in both brothers. Blood and tissue samples were negative for enteric anendocrinosis, with duodenal enteroendocrine cells normal in number and with no mutation of the neurogenin-3 gene identified [2]. Exome sequencing of >25,000 genes comparing both brothers and their parents revealed identical mutations in the epithelial cell adhesion molecule gene (EPCAM) in the brothers. Retrospective review of prior intestinal biopsies, including multiple additional H&E sections and immunohistochemical staining for EPCAM, demonstrated focal, subtle epithelial disorganization that was not evident when reviewed initially, with complete loss of EPCAM expression. These results were considered consistent with the definitive diagnosis of congenital tufting enteropathy (Fig. 1).

Discussion

Congenital tufting enteropathy, also known as intestinal epithelial dysplasia, is a form of congenital enteropathy with autosomal recessive inheritance that typically initially manifests as severe intractable diarrhea in the first days of life. The condition is quite rare, with prevalence estimated to be 1/50,000–100,000 live births in Western Europe [3]. Tufting enteropathy is a form of intractable diarrhea of infancy (more recently labeled severe protracted diarrhea) defined as diarrhea lasting longer than 2 weeks, onset of symptoms prior to 3 months of age (newer guidelines state <2 years of age), with negative infectious stool studies, and evidence of malabsorption and malnutrition requiring parenteral support to maintain adequate nutritional status [4, 5]. The diagnosis is confirmed histologically with typical features including disorganization of surface enterocytes into “tufts,” often accompanied by villous atrophy of variable severity [3].

Mutations in the EPCAM gene at chromosome 2p21 have been identified as the underlying cause of congenital tufting enteropathy [6]. EPCAM, involved in cellular communication and cell adhesion, interacts with the tight junction protein claudin-7, connecting with the actin cytoskeleton via α -actinin [7, 8]. EPCAM is primarily known for its potential contribution to tumorigenesis, with reported increased cell surface expression in malignancies of the intestinal tract, breast, and kidney [6]. Mice with EPCAM mutation exhibited decreased expression of tight junction proteins, increased intestinal permeability,

and decreased ion transport [9]. Loss of immunohistochemical staining for EPCAM in intestinal tissue is specific to congenital tufting enteropathy, with normal staining in patients with celiac disease, inflammatory bowel disease, chronic granulomatous disease, giardiasis, and microvillus inclusion disease [10]. Detailed knowledge of how the EPCAM mutation contributes to the pathogenesis of congenital tufting enteropathy awaits further study.

Our cases are unique in that the brothers were diagnosed with congenital tufting enteropathy in adolescence rather than in infancy. A thorough evaluation for multiple causes of intractable diarrhea had been considered, including infection, immune dysregulation, cystic fibrosis and pancreatic insufficiency, disaccharidase deficiency, structural abnormalities, malignancy, and congenital enteropathies. Most cases of congenital tufting enteropathy are diagnosed based on clinical features and intestinal histology in infancy or early childhood. Nevertheless, histologic findings can be focal or subtle, increasing the challenge of diagnosing the condition and in our cases delaying diagnosis until thorough genetic testing was obtained. Given that the histologic findings typical of congenital tufting enteropathy can be subtle or imperceptible with routine evaluation, immunohistochemical staining of duodenal biopsies for EPCAM is a promising way to improve diagnostic yield [11, 12]. Congenital enteropathies including tufting enteropathy should be considered in atypical cases of intractable diarrhea even in adolescence. Retrospective review of biopsy materials with additional immunohistochemical staining may lead to a definitive diagnosis, as it did in these cases.

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Key Messages

- Congenital enteropathies including tufting enteropathy should be considered in adolescents and adults with intractable diarrhea and an otherwise negative evaluation, despite previously normal intestinal mucosal histopathology.
- Immunohistochemical staining of intestinal biopsies for loss of normal EPCAM expression can help to identify congenital tufting enteropathy with subtle abnormalities.

Fig. 1.
H&E staining of duodenal biopsies showing subtle enterocyte tufts (a, b).
Immunohistochemical staining for EPCAM in normal intestine control (c) and duodenal biopsy of tufting enteropathy (d)