Case History

This is a case of a 4 month old male infant from the Middle East, who was born at term with a birth weight of 3 kg. On day of life 14, the infant was taken to a hospital in the family’s home country, with a history of loose, mucoid, nonbloody stools and non-bloody emesis several times a day, along with persistent poor feeding and failure to thrive, with a weight of 2.7 kg. There is no parental history of consanguinity. The patient’s 5 year old brother also has a history of diarrhea since infancy and was started on hyperalimentation with total-parental-nutrition (TPN), while his five sisters are all reported to be healthy. No source of infection was found during the hospital admission. A course of high-caloric formula was tried, along with a trial of hydrolyzed formula, but neither was successful. After three weeks, TPN was started and a central line was placed, with two subsequent line infections. The family presented to our hospital for further evaluation of both boys’ failure to thrive and diarrhea after a diagnosis of congenital tufting enteropathy (CTE) was made at an outside institution in the old brother; however, slides were not available for our review. Esophagogastroduodenoscopy was performed with biopsies which was non-revealing with a normal esophagus, normal antrum, body of the stomach, and fundus, and normal duodenal bulb, 2nd portion of the duodenum, and distal duodenum. Flexible sigmoidoscopy of the rectum and sigmoid colon appeared to be normal and biopsies were taken of the left colon. Biopsies of the duodenum, stomach, and left colon are provided. A confirmation of the diagnosis in the brother and a new diagnosis of CTE was made in the patient. Transplant evaluation was initiated with subsequent diagnostics tests performed (chest x-ray, EKG, echocardiogram, and abdominal and retroperitoneal ultrasounds), which were within normal limits without signs of TPN induced liver cirrhosis and thus were listed only for
small bowel transplantation at this time. The two brothers are also undergoing genetic screening to determine their CTE mutation.

**Diagnosis**

Congenital Tufting Enteropathy (CTE), also known as Intestinal Epithelial Dysplasia, is a rare intractable congenital diarrhea of neonatal/early infancy period, usually presenting around 2-3 weeks of life, with distinct morphologic features and a newly described genetic basis of the disease. The clinical history is one of protracted watery diarrhea, of a secretory type, usually presenting in the neonatal period (<28 days) which is unresponsive to changes in diet or bowel rest. Treatment includes cessation of enteral feeding and nutrition replacement with total parental nutrition (TPN) with most needing subsequent transplantation.

Complete epidemiologic data are not fully elucidated, given the only recent discovery of the genetics of disease; however, it has been suggested by Goulet *et al.* to be between 1/50,000 to 1/100,000 live births in Western Europe, where the largest group of patients are being treated at the Necker-Enfants Malades Hospital in Paris, France (1). Certain ethnic groups have increased risk of disease including those of Arabic origin (Middle-East, Turkey, and North Africa) in which a founder effect at the *EPCAM* locus has been demonstrated in seven families from the Arabic peninsula, with other ethnic groups showing similar and variant mutations (2).

**Pathologic features**

There is variable villous atrophy, from complete to sub-total, with reactive crypt hyperplasia. The pathognomonic biopsy features show clusters of crowded surface cells, aggregated in clusters of so-called “tufts,” along with scattered detached single cells sitting right above the surface. These abnormal surface enterocytes display decreased apical cytoplasm, imparting a tear-drop shape. The microvillous brush border is intact, albeit focal disruption right around the tufts, which has been previous demonstrated on transmission electron micrograph (EM). However, the advent of
a diagnostic immunohistochemical stain (*infra vida*) has superseded the utility of EM. There are no cytoplasmic vesicles containing microvilli/dense granules, as is seen in microvillous inclusion disease (MVID). There is no inflammatory damage, including no increase in intraepithelial lymphocytes, as is seen in celiac disease. There is also an absence of acute inflammation and normal lamina propria cellularity. It is important to note that acute infectious/ischemic enteritis/colitis may often display focal “pseudotufting;” but the admixed inflammation is not a feature of CTE. Furthermore, there is no significant crypt damage/apoptoses to suggest autoimmune enteropathy, which can be confirmed with negative circulating auto-enterocyte antibodies. There are also normal numbers of neuroendocrine cells to rule out enteroendocrine cell dysgenesis (ECD); of note, villus alterations are not typical in ECD, which usually presents with normal histology.

The crypt hyperplasia of CTE is typically mild with some descriptions of possible abnormal regeneration with branching and dilatation (i.e. ‘pseudocystic’ formation), although these secondary crypt changes are related to the degree of surface damage and atrophy and are not diagnostic features alone. With the recent discovery of the genetic basis of the disease, immunohistochemistry has provided new diagnostic utility. The MOC-31 (EpCAM) antibody shows complete absence of membranous epithelial staining throughout the endodermal gastrointestinal tract (e.g. stomach to rectum), with retained staining in the squamous mucosa/epidermis (2-3).

**Background**

The first patient with CTE was described clinically in 1978 by Davidson *et al.*, but it was not until 1994, after which Reifen *et al.* compiled this and two other cases, was the term “tufting enteropathy” first coined. The first patient described by Davidson *et al.* was a female infant who presented at one week of life with a protracted watery diarrhea and a family history of a brother.
who had died at 22 months from protracted diarrhea of infancy. This child also died 18 months from severe diarrhea. The other two other children in the case-series, both TPN-dependent, were still alive at 6 and 8.5 years of age. These original three cases were described as having variable villous atrophy with focal epithelial tufts of closely packed enterocytes with apical rounding of the plasma membrane. The adjacent epithelium and lining of the crypts were without apparent abnormalities. There was no inflammatory damage. The microvilli were normally formed, with slight disorganization of the brush border around the tufted surface; however, no inclusion bodies or secretory granules were present by EM. Extensive clinico-pathologic investigation, including immunophenotyping of T and B cells, assessment of autoantibodies (i.e. anti-enterocyte, ANA, anti-SMA, anti-mitochondrial antibodies), sweat chloride testing, Schilling test with intrinsic factor, and an anatomic screen of the small intestine with barium x-ray, did not indicate any other known etiology of the protracted diarrhea of infancy. While the pathognomonic histological changes in these original cases were present only in the small bowel, subsequent studies have shown similar tufting histology also present in the colon. A better descriptive term of intestinal epithelial dysplasia (IED), has been introduced; however, tufting enteropathy appears to be engrained into the vernacular, and as the official OMIM term (entry number 613217), CTE remains the current recognized diagnostic term.

Genetic basis of disease

Sivagnanam et al. were the first group to identify the disease causing gene of CTE as EpCAM on chromosome 2p21, in Gastroenterology 2008 (OMIM 185535; GenBank accession number: NM_002354). Sivagnanam et al. sequenced two Mexican-American cousins (non-consanguinity) with CTE along with their unaffected siblings and parents using SNP genotyping and found a unique 6.5-Mbp haplotype of homozygous SNPs on short arm of chromosome 2 in the two cousins. Direct sequencing of the 12 known genes expressed in the intestine in this region (2p21) then revealed a homozygous G>A substitution at the donor splice site of exon
4/intron 5 in the *EpCAM* gene (c.491+1G>A), while unaffected family members showed a heterozygous mutation, thus revealing an autosomal recessive pattern of inheritance.

Sivagnanam *et al.* (2008) identified two additional variant mutations, including homozygous substitution at exon 4 acceptor splice site (c.427-1G>A) in a Native-Canadian patient with consanguinity of the great grandparents. The other was in a Russian patient without a history of consanguinity, showing a heterozygous substitution in exon 3 (c.200G>A) which resulted in a missense mutation (C66Y) responsible for encoding the extracellular functional domain (Epidermal growth factor 2). All patients present in the neonatal period and these mutations retained the C-terminal part of the EPCAM protein (6). Sivagnanam *et al.* (2010) group subsequently identified a novel nonsense mutation in a patient within a consanguineous family, involving a homozygous substitution in exon 3 (c.412 C>T), resulting in a premature stop codon (7). Salomon *et al.* identified two mutations with founder effect at the *EPCAM* locus in seven consanguineous families from the Arabic peninsula (Kuwait and Qatar), one of which was a novel mutation (2). The previously described homozygous single base pair insertion in exon 5 (c.498insC) with frameshift and premature truncation (Q167Pfsx21) (8) was present in five families. With implementation of a mathematic algorithm, the mutation was estimated to be introduced in this population around 190 generations or 5000-6000 years prior. Al Mayouf *et al.* originally described this c.498insC mutation in four Saudi patients with concomitant chronic polyarthritis (8). The novel homozygous splice site mutation alters the acceptor splice site of exon 5 (IVS4-2A→G) and was calculated to be a younger mutation, introduced only about 40 generations prior. Both of these mutations cause a premature stop codon with protein product lacking half of the extracellular domain, as well as the whole transmembrane and cytoplasmic domains. Interestingly one family had compound heterozygous mutations involving both of the described mutations (c498insC/IVS4-2A→G). Most recently, Ko *et al.* also described a compound heterozygous mutation in two Korean siblings. The mutation carried by the mother had been previously described as the donor splicing site mutation in exon 4/intron 5.
(c.491+1G > A) and the father carried a novel nonsense mutation in exon 3 (c.316A>T, p.Lys106X).

**Molecular pathology transformed into diagnostic use**

The *EPCAM* gene mapped to 2p21 consists of 10 exons. The EpCAM protein product belongs to the family of Cell Adhesion Receptors and is a glycoprotein expressed on most epithelial cell membranes. This family of receptors has been recognized as having an important role cellular adhesion, as EpCAM co-localizes with E-cadherin at cell-cell junctions and interacts with the tight junction protein claudin-7. Previous work has shown an abnormal deposition of laminin and heparin sulfate proteoglycan in the enterocyte basement membrane, an increase in the number and length of the desmosomes between enterocytes, as well as an abnormal distribution of α2β2 integrin (9-11). The epithelial-to-mesenchymal interactions play a role in intestinal cell development and differentiation in the maintenance of the crypt-villus axis. Furthermore, EpCAM is also thought to mediate cell-cell communication via recruitment of α-actins and may be important in the cellular signaling, migration, proliferation, and cell differentiation. The mouse model of CTE shows inactivation of the transcription factor Elf3 with marked reduction in transforming growth factor β type II receptor (TGF-β RII), which is an inducer of intestinal epithelial differentiation. Alterations in EpCAM may then result in both disrupted associations with α-actins, E-cadherin, claudin-7, and other cellular components to disrupt cellular differentiation, cell-cell communication, and cell adhesion, all of which may have a role in the phenotypic abnormalities of enterocyte malabsorption of CTE (1, 9-15).

Sivagnanam *et al.* did additional confirmatory studies in one of Mexican-American patients with RT-PCR, showing a 66-bp in frame deletion of the mRNA, which while not likely to affect the translation of the C-terminal portion of the protein, did decrease both the protein expression (Western blot) and tissue expression (IHC) of EpCAM protein, as compared to normal and
inflammatory bowel controls. The affected patient still retained both adequate E-cadherin (intestinal epithelium control) and actin (total protein control) expression by Western blot. Furthermore, immunofluorescence was performed on formalin-fixed paraffin embedded tissue (FFPE) tissue of all five affected patients using the antibody 323/A3 (epitope maps to the N-terminal, first part of epidermal growth factor-like domain of EpCAM, encoded by exon 2). The results of all five patients, including the one patient without a described mutation, showed negative fluorescent staining of the enterocytes, as compared to the strong epithelial staining of controls, which included both age-matched unaffected subjects and one inflammatory bowel disease patient. Of note, the English-Italian patient without an identified mutation did have both clinicopathologic features and absence of IHC staining which strongly supported the diagnosis of CTE; his older age and absence of a known mutation suggests he has a more cryptic mutation in the promoter or intronic regions of the EPCAM gene.

Extrapolating from fluorescent immunohistochemical (IHC) staining, bright-field IHC with peroxidase-labeled antibodies on FFPE should also demonstrate the diagnostic complete absence of EpCAM staining in cases of CTE. Ranganathan et al. demonstrated the diagnostic utility of MOC-31/EpCAM antibody staining in the largest series to date, which was presented at Society for Pediatric Pathology (SPP) meeting in Milwaukee, September 2011 (3). MOC-31 (EpCAM) antibody staining (at dilution of 1:50, purchased from the Cell Marque Corporation, Rocklin, CA) was performed on both cases of CTE and variety of control samples. The 15 cases of CTE (13 of which had FFPE tissue) were compared with 30 control tissues, which comprised of microvillous inclusion disease (n=2), autoimmune enteropathy (n=16), allergic enteritis (n=1), celiac disease (n=2), allograft bowel (n=1), adenoviral enteritis (n=2), EBV enteritis (n=3), and Crohn’s disease (n=3). All control tissues demonstrated a strong, crisp membranous epithelial staining of the enterocytes, while all the CTE cases (n=13) showed complete absence of staining in all tissue sections, regardless of site (i.e. stomach, small bowel, colon), both in the
presence or absence of tufting. Two of CTE cases had confirmatory mutations by genetic sequence analysis of the *EPCAM* gene. Salomon *et al.* also showed lack of monoclonal antibody IHC staining for EpCAM antibody (323/A3 mouse IgG1, Acris Antibodies GmbH®, Montlucon, France). Both studies showed the complete absence of the membranous EpCAM/MOC-31 staining without background/cytoplasmic staining in cases of CTE, which corresponds to mutations in *EPCAM* gene. Thus IHC staining with MOC-31/EpCAM antibody is of diagnostic utility in the ruling in CTE and excluding other etiologies of protracted diarrhea of infancy.

**Associated phenotypic features with CTE**

Various case reports have suggested associated phenotypic features with CTE, including dysmorphic features, choanal atresia, skeletal dysplasias, chronic arthritis, and nonspecific punctuated keratitis. Some of these features, including the skeletal and joint features, may present some years after the initial early infancy diagnosis of CTE. Of note, many of the described hair abnormalities are likely attributed to an abnormal nutritional status (i.e. vitamin deficiency or history of chronic TPN) rather than representing true disease (i.e. no evidence of trichorrhexis nodosa). Furthermore, Sivagnanam *et al.* recently published a case report of syndromic tufting enteropathy harboring the *SPINT2* (19q13.2) mutation, which is the same mutation seen in congenital sodium diarrhea (16). The patient was previously described by Bird *et al.* in relation to the family case series of an 8 year old boy with CTE, choanal atresia, ophthalmologic, hematologic, and hair abnormalities (17). This now 10-year-old boy did not have a known *EPCAM* mutation but was screened for the *SPINT2* mutation, as the associated features of choanal atresia and corneal erosions has also been described in congenital sodium diarrhea (CSD) with *SPINT2* mutations (18). CSD is a protracted diarrhea of infancy with hyponatremia, metabolic acidosis, and a severe secretory diarrhea with high fecal sodium loss. Intestinal biopsies show non-specific changes but may reveal a mild to moderate villous atrophy.
without evidence of tufting. While only one case report has been described with tufting morphology and a \textit{SPINT2} substitution mutation (c.488A>G) in exon 7, it raises the possibility that the subset of so-called ‘CTE with choanal atresia, ophthalmologic, and other associated features’ may represent a unique genetic alteration with a converging genetic-phenotypic pathway. However, it does stress the importance of performing MOC-31 immunostaining, an inexpensive alternative to genetic testing. If staining shows a normal pattern of retention, further investigation with \textit{SPINT2} mutational analysis may be warranted to better classify these cases.

As with many discoveries in medicine, we may learn that additional mutations may cause an overlapping phenotype of CTE. The following is a summary of the current cases of CTE described in the literature with additional associated features.

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Description</th>
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<tr>
<td>Abely et al. 1998</td>
<td>2</td>
<td>2 yo full-term boy of nonconsanguineous parents, short stature, microcephaly, large nose, hypertelorism, blepharophimosis, larger/posterior rotated ears, micrognathia, flat supraorbital ridge, high-sloping forehead, psychomotor retardation, eczematous skin lesion, wooly hair but non-diagnostic of trichorrhexis nodosa, sacral malformation (Dubowitz-like syndrome)</td>
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<tr>
<td>Al-Mayouf et al. 2009*</td>
<td>2</td>
<td>2.5 yo former premature (35 wk) girl of nonconsanguineous parents and no external dysmorphisms with active arthritis of small and large joints with tenosynovitis and radiographic changes of chronic arthritic changes</td>
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<tr>
<td>Bird et al. 2007^</td>
<td>3 (siblings)</td>
<td>8 yo full term boy of nonconsanguineous parents with bony choanal atresia, corneal scarring and chronic corneal inflammation, episodic fevers and cytopenia with normal bone marrow, abnormal dry fizzy hair, mild micrognathia, bilateral preauricular pits, single transverse palmar creases, prominent nasal bridge, elongated philtrum and thin vermilion of upper lip, bifid uvula, chronic otitis media, normal cognition. 2 years later found to have a homozygous mutation in the \textit{SPINT2} gene (16).</td>
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<tr>
<td>Preterm sister (36 wks) born after above proband with bilateral choanal atresia, micrognathia, high/broad nasal root, elongated philtrum and thin vermilion of upper lip, posterior rotated ears, photophobia and corneal inflammation and drainage, 2 wk old sister of above proband who died five years before brother’s birth from severe dehydration from diarrhea, status post bilateral choanal atresia repair at day 9 of life. Eye discharge</td>
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died at 5 years old with liver cirrhosis complications.

El-Matary et al. 2007  N=1  6 yo full-term girl with generalized skeletal dysplasia (in range of parastreemmatic dwarfism without kyphoscoliosis), Coomb’s positive hemolytic anemia and thrombocytopenia with negative autoantibody screen, including anti-enterocyte antibodies

Ko et al. 2010*  N=2 (siblings)  3 month old full term girl with a broad nasal bridge and micrognathia, oligoarticular juvenile rheumatoid arthritis, concomitant wooly and easily removable hair that resolved with zinc and selenium supplementation and negative circulating autoantibodies.

Proband brother, full term, Broad nasal bridge, micrognathia, folate and vitamin B12 deficiencies.

Roche et al. 2010  N=10  Ophthalmic functional disorders since the first months of life, with superficial punctate keratitis and conjunctivitis. N=1 with alacrima and cataract. N=5 asymptomatic conjunctival hyperemia

*Those cases with tufting enteropathy with confirmed EPCAM mutations. ^See text for re-classification of genetic basis of disease.

Differential diagnosis

Intractable diarrhea of infancy was coined by Dr. Avery and colleagues in 1968 (with the current preferred term of protracted diarrhea) and describes a severe diarrhea in neonates and infants (less than 1 year old), lasting greater than 3 weeks and unresponsive to changes in oral intake. These diarrheas have typically carried a high mortality rate but with earlier pathologic diagnosis and prompt induction of aggressive therapies including total parental nutrition (TPN), immunosuppressive management for certain disorders, and/or transplantation if medical management fails, it is hoped that the mortality rate will continue to decline. Many of the congenital protracted diarrheas now have a genetic basis which allows for an earlier diagnosis. The differential diagnosis neonatal protracted diarrhea with villus alterations includes CTE, microvillous inclusion disease (MVID), autoimmune enteropathy/IPEX syndrome, syndromic protracted diarrhea of infancy, and congenital defects of ion absorption (i.e. Congenital Sodium and Chloride Diarrheas). The congenital defects of ion absorption often present with an antenatal history of polyhydramnios and while there may be mild villous alternations, often there no specific abnormalities. Osmotic diarrhea results from an increased osmotic load or non-
measured ion (i.e., Cl−, Mg2+) and resolves with bowel rest. There is a high fecal ion gap (i.e. >50), in contrast to the low osmotic gap (<50) typical of the secretory diarrheas. Congenital carbohydrate transport and/or enzyme disorders are examples of osmotic diarrheas which result in increased lactate formation from bacterial fermentation.

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<tr>
<th>Osmotic Diarrhea</th>
<th>Secretory diarrhea</th>
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<td>Congenital defects of ion absorption (sodium and chloride diarrhea)</td>
<td>Bacterial enterotoxins</td>
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<td>Disaccharidase deficiency</td>
<td>Congenital tufting Enteropathy</td>
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<td>Lysinuric protein intolerance</td>
<td>Autoimmune Enteropathy</td>
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<td>Abetalipoproteinemia</td>
<td>Microvillous inclusion disease</td>
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<td>Neuroendocrine cell dysplasia</td>
<td>Congenital immunodeficiency</td>
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<td>Gluten-sensitive enteropathy</td>
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<td>Syndromic Diarrhea of Infancy</td>
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In MVI disease, there is severe villus atrophy without significant crypt hyperplasia. Special stains (i.e. PAS and the CD10 immunohistochemical stain) to highlight the brush border demonstrate an absence of a crisp brush border and rather highlight the abnormal accumulation of cytoplasmic granules at the apical periphery. The diagnosis is confirmed by electron microscopy (EM) which demonstrates an absent or markedly reduced small, stubby apical microvilli with cytoplasmic vesicles containing microvilli and/or electron dense granules. There is a mutation in the myosin 5B gene (*MYO5B*) at chromosome 18q21, which encodes a protein involved in the recycling of endosomes. The mutation is thought to cause an abnormal intracellular transport, assembly, and differentiation of the Golgi-derived microvilli vesicles which then results in defective brush-border assembly.

Enteroendocrine Cell Dysgenesis shows no significant villous atrophy or inflammation by H&E but does demonstrate a significant crypt depletion of neuroendocrine cells, both in the small intestine (0-4/50 hpf vs. normal 145/50 hpf) and colon (0-4/50 hpf vs. normal 85/50 hpf), with a neuroendocrine immunostain (i.e chromogranin); however, the stomach retains normal numbers of endocrine cells. Point mutations have been detected in the neurogenin-3 gene (*NEUROG3*)
at chromosome 10q22.1. Mutations result in an arrest of endocrine cell development in the small intestine and colon. How this leads to malabsorption is not yet fully elucidated. Endocrine cells may be needed to co-localize with factors important for nutrient assimilation and absorption (i.e. hepatocyte nuclear factor (HNF1)) or play a role in normal development of absorptive cells.

Autoimmune Enteropathy (AIE) shows villous atrophy with inflammation and epithelial damage including numerous crypt apoptoses and variable crypt hyperplasia. The diagnosis is confirmed with indirect immunofluorescence (i.e. patient's circulating anti-enterocyte antibodies (IgG>IgM or IgA) react with control enterocytes) and shows a linear staining pattern along the apex and baso-lateral border of normal enterocytes. The genetics and pathogenesis is multifactorial and some cases associated with the IPEX syndrome (immunodysregulation, polyendocrinopathy, and enteropathy) result from a mutation of the FOXP3 gene at Xp11.23-Xq13.3. The Foxp3 protein is normally responsible for immune homeostasis in regulatory CD4+/CD25+ T cells so its loss or dysfunction leads to immunodysregulation. Other less common associations with AIE include Usher syndrome (hyperinsulinism with enteropathy and hearing loss) and autoimmune polyendocrinopathy (Addison disease and/or hypoparathyroidism), candidiasis, and ectodermal dysplasia with a genetic aberration in the AIRE gene at 21q22.3.

Other infantile diarrheas that one must also keep in mind include syndromic protracted diarrhea of infancy which shows moderate villus atrophy without inflammation and is associated with a low birth weight, mild mental retardation, dysmorphic features (i.e. prominent forehead, broad nose, hypertelorism) trichorhexis nodosa, and immunodeficiency. Milk and soy protein intolerance will result in villous atrophy with inflammation, including eosinophils. Protracted infectious enteritis and/or ischemia may produce a pseudotufting pattern which should be distinguished from CTE by presence of acute inflammation and retained staining of MOC-31. Gluten sensitive enteropathy, also known as celiac disease, shows a variable degree of villus atrophy with inflammatory damage and increased numbers of intraepithelial T-lymphocytes
(>25-30/100 enterocytes vs. normal of < 20 lymphocytes per 100 enterocytes), and regenerative crypt hyperplasia, after consumption of wheat gluten or related rye and barley proteins. Typical presentation is seen after the neonatal period and the diagnosis is confirmed with serum antibodies (ie. antigliadin, anti-tissue transglutaminase (tTG-IgA, IgG), anti-endomysial (EMA-IgA, IgG antibodies). The pathogenesis and genetics are multifactorial, influenced by both environmental and genetic factors (i.e. haplotypes HLA-DQ2 and HLA-DQ8).

Rarely Hirschsprung disease may present with diarrhea rather than constipation. Finally Munchhausen syndrome by proxy should clinically be ruled out only after other osmotic and secretory diarrheas with normal morphology have been clinically excluded.

In summary, CTE is one of the protracted diarrheas of infancy which presents in the early neonatal period requiring prompt diagnosis with histologic and immunohistochemical evaluation in order to direct therapy with early hyperalimentation and thus prevent un-do work-up or unnecessary treatment. Genetic screening for \textit{EPCAM} mutations is available which may be of importance in rare cases with tufting morphology but retention of MOC-31 staining, especially in the context of syndromic features, including choanal atresia. Furthermore, these rare cases may warrant screening for \textit{SPINT2} mutations, which may be a new unrecognized variant of protracted diarrhea of infancy with tufting morphology.
References:


