A rare cause of congenital diarrhea in a Turkish newborn: tufting enteropathy

Dilek Kahvecioğlu[1], Duran Yıldız[1], Atilla Kılıç[1], Banu İnce-Alkan[2], Ömer Erdeve[1], Zarife Kuloğlu[3], Begüm Atasay[1], Arzu Ensari[2] , Resul Yılmaz[4], Saadet Arsan[1]

Divisions of [1]Neonatology, and [3]Pediatric Gastroenterology, Department of Pediatrics, and [2]Department of Pathology, Ankara University, Faculty of Medicine, Ankara, and [4] Department of Pediatrics, Gaziosmanpaşa University Faculty of Medicine, Tokat, Turkey
E-mail: dileksaracoglu@yahoo.com

SUMMARY: Kahvecioğlu D, Yıldız D, Kılıç A, İnce-Alkan B, Erdeve Ö, Kuloğlu Z, Atasay B, Ensari A, Yılmaz R, Arsan S. A rare cause of congenital diarrhea in a Turkish newborn: tufting enteropathy. Turk J Pediatr 2014; 56: 440-443.

Tufting enteropathy is an autosomal recessive congenital enteropathy presenting with early-onset severe intractable diarrhea. It presents with watery diarrhea that develops in the first days after birth and persists despite bowel rest. Growth is impaired, and most patients require total parenteral nutrition. The histological characteristic of tufting enteropathy is the presence of epithelial tufts. We hereby present a patient who was referred to our neonatal intensive care unit because of chronic diarrhea and diagnosed with tufting enteropathy according to histological examination. To the best of our knowledge, the newborn case presented here is the first one reported from Turkey. As TE is a very rare disease, it should be considered in patients with continuing diarrhea beginning in the first days of life.

Key words: tufting enteropathy, congenital diarrhea, newborn.

Tufting enteropathy (TE), also known as intestinal epithelial dysplasia, is an autosomal recessive congenital enteropathy presenting with early-onset severe intractable diarrhea. Only a few cases have been reported since 1994 when it was first described by Reifen et al.[1-7]. It is a very rare condition, with the prevalence of the disease being estimated at around 1/50,000-1/100,000 in Western Europe. Mutations in the epithelial cell adhesion molecule (EpCAM) gene on chromosome 2p21 have been recently identified in patients with TE as the responsible genetic abnormality. Surface expression of EpCAM is necessary for cell proliferation/stem cell renewal and differentiation in intestinal mucosa. Mutations in the gene cause defective differentiation of the enterocytes together with abnormalities in the epithelial tight junctions[7].

Tufting enteropathy presents with watery diarrhea that develops in the first days of life and persists despite bowel rest. Growth is impaired, and most patients require total parenteral nutrition (TPN). It is a life-threatening condition, causing electrolyte imbalance and dehydration. It causes protein-energy malnutrition, irreversible damage to the bowel and liver damage, which progresses to end-stage cirrhosis. Intestinal transplantation has been used to treat TE in some patients with intestinal failure. The histological characteristic of TE is the presence of epithelial tufts composed of closely packed enterocytes with rounding of the apical plasma membrane, which results in a teardrop configuration. The epithelium looks disorganized, with tufts, buds or small papillae dropping off into the lumen—features that are most prominent at the villous tip[8].

We hereby present a patient who was referred to our neonatal intensive care unit (NICU) because of chronic diarrhea due to TE.

Case Report

A 3800 g male newborn of 38 weeks gestation was born to a 25-year-old mother by cesarean section after an uneventful pregnancy. He did not require any resuscitation in the delivery room and was discharged on the 1st day. On the postnatal 4th day, he was admitted to the hospital for watery diarrhea (10 times a day)

and poor oral intake. He failed to tolerate either breast milk or formula. Although hydration treatment was conducted, his diarrhea persisted. He was referred to our NICU on the postnatal 33rd day for further evaluation.

There was consanguinity between the parents, and family history revealed the death of another brother at one month of age because of persistent diarrhea. Three of his cousins died of unknown causes during the infancy period. His mother did not suffer from polyhydramnios during her pregnancy. On physical examination, cachectic appearance, respiratory insufficiency and hepatomegaly were recorded. His body weight was 2.3 kg (< 3rd percentile for his age), and he had no dysmorphic facial features. Laboratory tests revealed anemia (Hb: 6.9 g/dl), thrombocytopenia (86000/L), leukocytosis (35800/L), impairment of renal and liver function (blood urea nitrogen: 68 mg/dl, creatinine: 0.93 mg/dl, aspartate transaminase: 421U/L, aspartate aminotransferase: 340 U/L, gamma glutamyl transpeptidase: 66 U/L), severe hypophosphatemia (0.5 g/dl) and increase in acute phase reactants on admission. His oral intake was stopped, and 400 ml/kg/day intravenous TPN and antibiotic treatment were started. Stool output was up to 190 g/day despite bowel rest and TPN. Stool examination demonstrated that the pH was 5, in addition to reducing substance positivity. Moreover, microscopic evaluation showed fat globules in the stool. On the other hand, stool tests for pathogens and stool Na^+ concentration (70 mmol/L) were unremarkable. Although phosphorus supplementation was started on admission, his hypophosphatemia persisted, and sudden cardiac arrest occurred on the postnatal 35th day.

Postmortem full-thickness intestinal biopsy from the jejunal wall was performed. Microscopically, there was mild to moderate villous atrophy and crypt hyperplasia with little inflammation in the lamina propria. The surface epithelium was irregular, particularly at the villous tips, with small buds or tufts formed by groups of enterocytes. A PAS (periodic acid-Schiff) stain and CD10 immunohistochemistry revealed irregularities in the brush border over the epithelial tufts. Small groups of enterocytes were floating in the lumen near the surface (Figs. 1 and 2). These findings were compatible with TE.

Discussion

Tufting enteropathy is an autosomal recessive congenital disorder resulting from mutations in the EpCAM gene on chromosome 2p21 that lead to abnormal development of the intestinal mucosa. It is characterized by severe intestinal failure, requiring parenteral nutrition and small bowel transplantation in some cases[7]. EpCAM functions as a typical adhesion molecule and is connected to the actin cytoskeleton. EpCAM interacts directly with claudin 7, a protein required for the formation of tight junctions, implying a role for EpCAM in cellular adhesion[1]. Guerra et al.[9] suggested that loss of mTrop1/EpCAM caused TE in a mouse model. Although it is a very rare condition, TE is generally observed on the island of Gozo near Malta and in Arabic-origin families[8].

Tufting enteropathy usually presents with diarrhea within the first days of life, as observed in our patient. Stool volume ranges between 100 and 200 ml/kg per day. The disease is a combination of both secretory and osmotic diarrhea, as in our patient. There is no history of polyhydramnios in pregnancy, which is important in differential diagnosis. Most patients have consanguineous parents and affected siblings, some of whom die during the first months of life from severe diarrhea of unknown origin[8].

Only a few cases have been reported with phenotypic abnormalities. Choanal atresia, esophageal atresia, imperforate anus, non-specific keratitis and Dubowitz syndrome have been reported in relation to the disease[1]. None of these features were observed in our case. Roche et al.[6] described 15 cases with TE, 10 of whom had punctuate keratitis. Our patient died 2 days after referral to our NICU, and although we could not perform an ophthalmic examination, his eye appearance was normal. Matary et al.[2] described two cases of TE with skeletal dysplasia and Coomb's (+) anemia. Our patient also had anemia; however, the Coomb's test was negative. All physical and laboratory evaluations showed that our case was a nonsyndromic one.

Histological abnormalities in TE are villous atrophy, disorganization of the surface epithelium and basement membrane abnormalities. Villous

atrophy is present in all patients but may be variable in severity. The characteristic finding on biopsy is the presence of "tufts," which comprise surface enterocytes with focal crowding. Electron microscopy has demonstrated distruption of desmosomal and integrin-mediated contacts between enterocytes [8]. An increase in the number and length of the desmosomes between enterocytes and an abnormal distribution of α2β2 integrin have been observed in pathological studies of TE, which suggests that changes in cell-cell adhesion play a role in the pathogenesis of the disease [4].

Other intractable congenital diarrhea syndromes, such as microvillus inclusion disease, congenital chloride diarrhea, congenital sodium diarrhea, glucose-galactose malabsorption, autoimmune enteropathy and syndromic diarrhea, should be considered in the differential diagnosis. Congenital chloride diarrhea or congenital sodium diarrhea can easily be distinguished from TE by the absence of polyhydramnios and blood and stool electrolyte assessment[8]. Our patient's mother did not suffer from polyhydramnios during her pregnancy, and the patient did not have either hyponatremia or hypochloremia. TE can be distinguished from microvillus inclusion disease, autoimmune enteropathy and syndromic diarrhea by histologic evaluation of biopsy specimens. All of the above entities may also show varying degrees of villous/crypt abnormalities, and all lack the epithelial tufts characterizing TE. Microvillous inclusion disease shows complete or partial loss of the brush border together with vacuoles in the apical cytoplasm of the enterocytes revealed by abnormal PAS or CD10 stains. Patients with autoimmune enteropathy and/or syndromic diarrhea may have diminished goblet cells, increased intraepithelial lymphocytes and inflammation in the lamina propria in biopsy specimens[8].

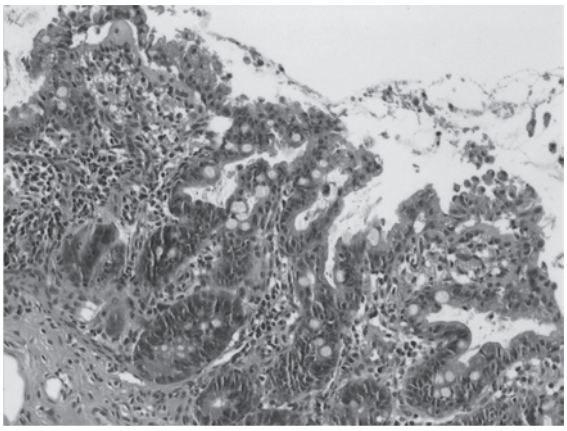

Fig. 1. Irregular surface epithelium with small buds or tufts formed by groups of enterocytes. (H&E X20)

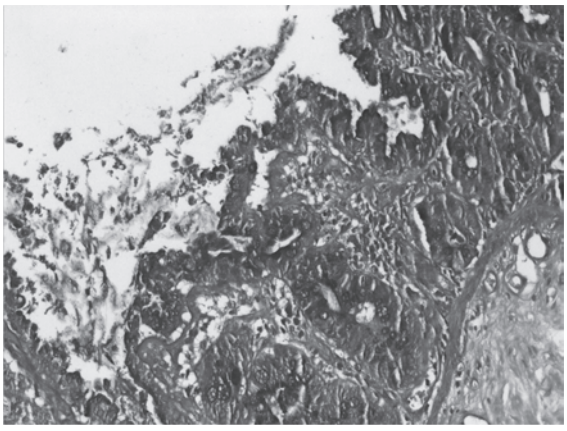

Fig. 2. PAS stain showing irregularities in the brush border over the epithelial tufts. (PAS X20)

Although most patients require long-term parenteral nutrition, Lemale et al.[3] reported 3 cases out of a total of 7 patients with TE who were permanently weaned off parenteral nutrition. The authors could not find any association between histological lesions in duodenal biopsies and clinical outcomes. Those patients with irreversible intestinal failure are candidates for intestinal transplantation. Because of the high mortality rate in transplantation, intestinal transplantation should be considered only in patients with such complications of TPN as life-threatening sepsis and extensive thrombosis[8,10]. The long-term prognosis is variable and mortality is high in patients with severe intestinal disease and liver failure[8].

In conclusion, to the best of our knowledge the newborn case presented here is the first one reported from Turkey. As TE is a very rare disease, we suggested that it should be considered in patients with continuing diarrhea beginning in the first days of life. We suggest that the results of future investigations regarding the molecular basis of the disease may aid in offering prenatal diagnosis for TE.

REFERENCES

1. Bird LM, Sivagnanam M, Taylor S, Newbury RO. A new syndrome of tufting enteropathy and choanal atresia, with ophthalmologic, hematologic and hair abnormalities. Clin Dysmorphol 2007; 16: 211-221.
2. El-Matary W, Dalzell AM, Kokai G, Davidson JE. Tufting enteropathy and skeletal dysplasia: is there a link? Eur J Pediatr 2007; 166: 265-268.
3. Lemale J, Coulomb A, Dubern B, et al. Intractable diarrhea with tufting enteropathy: a favorable outcome is possible. J Pediatr Gastroenterol Nutr 2011; 52: 734-739.
4. Patey N, Scoazec JY, Cuenod-Jabri B, et al. Distribution of cell adhesion molecules in infants with intestinal epithelial dysplasia (tufting enteropathy). Gastroenterology 1997; 113: 833-843.
5. Reifen RM, Cutz E, Griffiths AM, Ngan BY, Sherman PM. Tufting enteropathy: a newly recognized clinicopathological entity associated with refractory diarrhea in infants. J Pediatr Gastroenterol Nutr 1994; 18: 379-385.
6. Roche O, Putterman M, Salomon J, et al. Superficial punctate keratitis and conjunctival erosions associated with congenital tufting enteropathy. Am J Ophthalmol 2010; 150: 116-121.
7. Sivagnanam M, Mueller JL, Lee H, et al. Identification of EpCAM as the gene for congenital tufting enteropathy. Gastroenterology 2008; 135: 429-437.
8. Goulet O, Salomon J, Ruemmele F, de Serres NP, Brousse N. Intestinal epithelial dysplasia (tufting enteropathy). Orphanet J Rare Dis 2007; 2: 20-26.
9. Guerra E, Lattanzio R, La Sorda R, et al. mTrop1/Epcam knockout mice develop congenital tufting enteropathy through dysregulation of intestinal E-cadherin/β-catenin. PLoS One 2012; 7 doi:10.1371.
10. Balzar M, Bakker HA, Briaire-de-Bruijn IH, Fleuren GJ, Warnaar SO, Litvinov SV. Cytoplasmic tail regulates the intercellular adhesion function of the epithelial cell adhesion molecule. Mol Cell Biol 1998; 18: 4833-4843.