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Case Report

A Novel Homozygote EpCAM Gene Mutation in Turkish Neonate with Tufting Enteropathy

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Abstract

Congenital tufting enteropathy is characterized by intractable watery diarrhea, weight loss, malnutrition and growth retardation in newborn. It is a rare autosomal recessive disorder which is caused by mutations in the gene encoding human epithelial cell adhesion molecule (EpCAM). The diagnosis is based on a combination of clinical signs, histological findings and genetic tests that identify a mutation in the EPCAM gene. We report a Turkish neonate with congenital tufting enteropathy presenting to the emergency department with severe watery diarrhea and weight loss. He was diagnosed as having congenital tufting enteropathy based on his clinical signs and genetic analysis. He was fed by total parenteral nutrition and carbohydrate-poor formula. Despite fact that it is often difficult to find the etiology of conditions that cause congenital diarrhea, clinical suspicion and genetic analysis might be helpful in making the diagnosis of congenital tufting enteropathy.

Key words*: congenital diarrhea, tufting enteropathy, epithelial cell adhesion molecule, infant*

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Introduction

Congenital tufting enteropathy (CTE), also called intestinal epithelial dysplasia, is characterized by severe and intractable diarrhea in newborn. Its incidence is estimated as 1/50,000–100,000 live births in western Europe, although the cases were reported higher in the Middle East due to the high degree of consanguinity (1). Histologically, CTE is characterized by abnormalities in the intestinal epithelium, including villous atrophy, crypt hyperplasia, and focal epithelial tufts (2). It is caused by a disease-related mutation in the gene encoding human epithelial cell adhesion molecule (EpCAM, MIM# 185535) (3). The gene defects in affected newborn usually presents with electrolyte imbalance, severe dehydration, impaired growth and weight loss (4). Most cases generally requires parenteral nutrition and in some severe cases small bowel transplantation can be required (5-6). It is important to manage parenteral nutrition and electrolyte supplements to acquire adequate caloric and fluid intake for normal growth and development (7).

Case

A term male neonate weighing 3210 g, 50 cm long, with a normal Apgar score was born by C/S (cesarean section) from a 31-year-old mother. In the family history, the parents were first consanguineous. Mother had FMF (familial mediterranean fever) (heterozygot, double gene) and lactose intolerance. In addition, the mother had no history of polyhydramnios in whom pregnancy follow-up was performed regularly.

The newborn was admitted to the emergency room 1 week after birth with complaints of diarrhea, severe dehydration and vomiting. Watery diarrhea was described after each feeding. He required admission to the neonatal intensive care unit due to dehydration and poor feeding with 20% weight loss. The patient could not tolerate breast milk or standard formula. Despite adequate hydration treatment, his diarrhea continued. On physical examination was remarkable for sunken fontanellea and distended abdomen. There was no dysmorphic findings. Blood analyses showed metabolic acidosis with pH 7.07 and base excess -20, sodium (Na+) 140 mmol/L, potassium (K+) 5.7 mmol/L, and chloride (Cl-) 121 mmol/L. The stool test was initially within normal limits. Both abdominal X-ray and ultrasound revealed moderate dilated intestinal loops and bowel distension. Watery diarrhea and metabolic acidosis led to a suspicion of congenital diarrheal disorders. Hence, additional laboratory studies including genetic test and endoscopic evaluation were carried out: His

stool electrolytes were as follows: Na+ of 43 (ref: 20–30) mmol/L, K+ of 45 (ref: 55–65) mmol/L and Cl- of 27 (ref: 5–20) mmol/L, (Increased osmotic gap: 110 mOsm/kg). Osmotic diarrhea was initially considered after the evaluation of electrolytes within normal limits and anyon gap. Upper gastrointestinal (GI) endoscopy and colonoscopy revealed no abnormality. However, duedonal biopsy revealed villous atrophy, focal clumping of surface epithelial cells, crypt hyperplasia, slight decrease in goblet cells, slight increase in intraepithelial lymphocytes. In genetic analysis, it was identified a homozygous mutation in the EPCAM gene: c.325C>T (p.Gln109Ter). The patient was treated with total parenteral nutrition (TPN). Diffrent types of formula were tried for the patient. He moderately tolerated low-carbohydrate formula. At three months of age, he is currently receiving TPN treatment and has diarrhea 4–5 times per day.

Discussion

Since the first case report of CTE was published by Reifen et al. in 1994 (2). More than 200 cases of CTE have been reported in the world. (4). The first case of tufting enteropathy in Turkey was reported by Kahvecioğlu D, et al. in 2014 (8).

Just like other congenital causes of diarrhea, CTE is a rare autosomal recessive disease that causes protracted watery diarrhea, abdominal distention, and repeated vomiting, leading to severe dehydration (3). Although the disease has a congenital onset, late presentation in adolescence has rarely been described (9). Our patient's complaints of severe watery diarrhea, abdominal bloating and recurrent vomiting occurred immediately after birth.

The etiology of congenital diarrhea is often difficult to establish, the diagnosis of CTE is based on clinical symptoms, histopathological findings and genetic analysis. It is characterized by recognition of villus atrophy and crypt hyperplasia of the intestinal epithelium. Focal epithelial tufts are typically found in the duodenum and jejunum (3-10). Lais Pegas et al. reported a newborn with CTE and they found the epithelial tufts in the terminal ileum and partial villous atrophy in duodenum (11). On the other hand, Bosaleh et al. found that duodenal and rectal biopsies of a patient diagnosed with CTE were normal (12). In our case, increased intraepithelial lymphocytes and villous atrophy were evident in the duodenum, while colon biopsies were within normal limits (Figure 1).

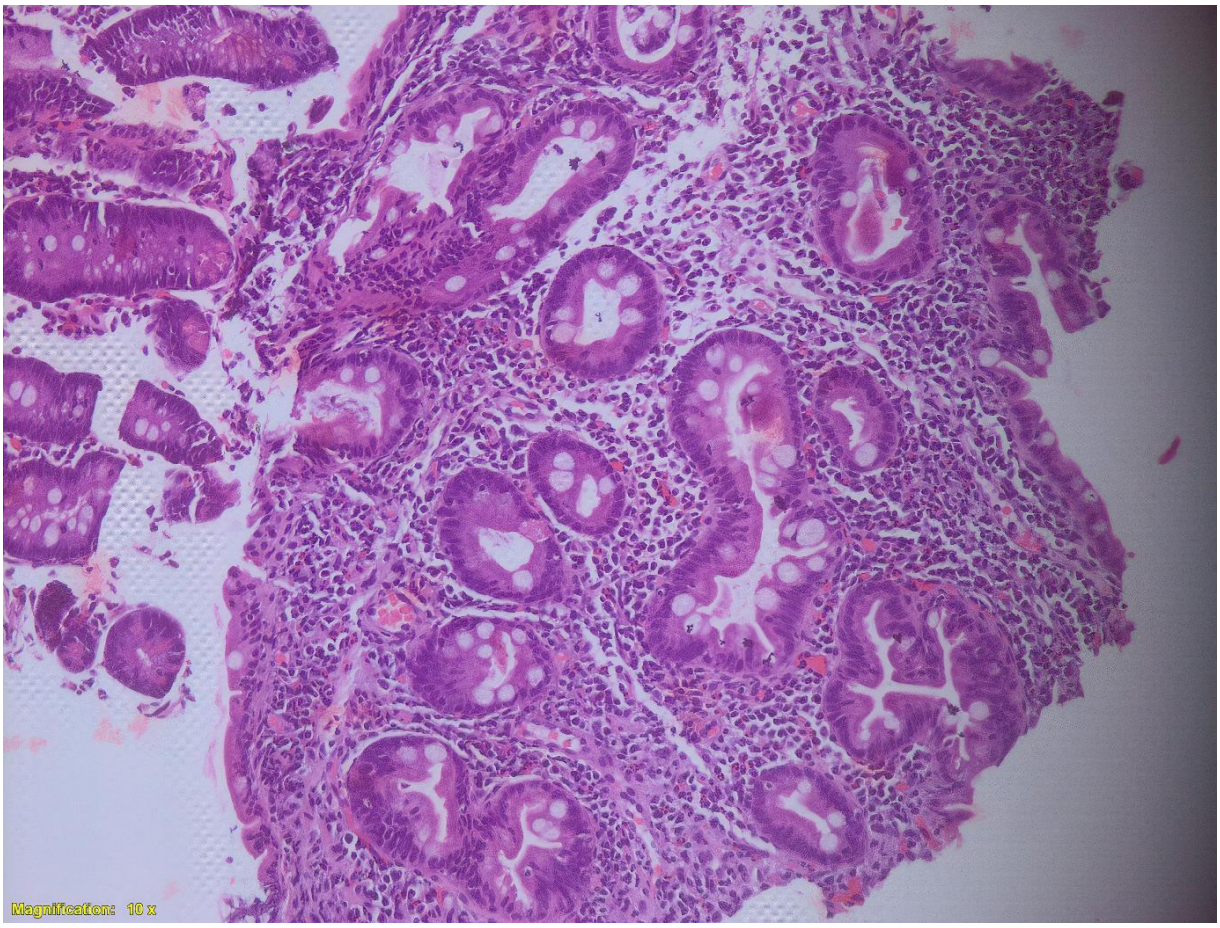

Figure 1. Severe villous atrophy and mixt inflammatory infiltrate in the lamia propria and epithelial tufts (H&E x 20)

Since the EpCAM gene was identified for tufting enteropathy, nearly 120 cases of tufting enteropathy with molecularly confirmed have been reported in the world (13). In 2008, Sivagnanam et al. (3) discovered EpCAM mutations in the epithelial cell cause CTE. Since then, more than 100 EpCAM variants have been identified (13). Furthermore, mutations in the serine peptidase inhibitor Kunitz type 2 (SPINT2, MIM# 605124) have been shown to be associated with syndromic CTE. Extraintestinal symptoms such as choanal atresia and ophthalmological findings represent syndromic forms of CTE (14-15). Moreover, mutations in the EPCAM gene have been shown to be associated with Lynch syndrome (16). We detected a homozygous c.325C>T (p.Gln109Ter) nonsense mutation in the EPCAM gene without phenotypic syndromic appearance in our patient. The variant was classified as "likely pathogenic" according to ACMG (American College of Medical Genetics and Genomics) guidelines. This variant has not been previously submitted to ClinVar (17). We found a novel point mutation in the EpCAM gene.

Prevention of malnutrition is the most important step in the management of CTE. There is no any specific formula for the disease. Furthermore, almost all patients require parenteral nutrition. Intestinal transplantation can be life-saving in cases where treatment fails. (5). We started treatment with parenteral nutrition and carbohydrate-poor formula. Our patient, who partially gained weight, is followed up by the pediatric gastroenterology clinic.

In conclusion, CTE is a rare inherited condition that can be difficult to diagnose and treat at any age. This is the first case report of novel homozygous mutation in EPCAM.

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Conflict of Interest

No conflict of interest was declared by the authors.

Author Contributions

Concept – E.S., S.N.N.; Design - E.S., K.A., S.N.N.; Supervision – K.A., E.S.; Funding – S.E., H.M.; Materials – S.E., H.M.; Data Collection and/or Processing - S.N.N., E.S.; Analysis and/or Interpretation – E.S., K.A., S.N.N; Literature Review – S.N.N., K.A.; Writing – S.N.N., E.S., K.A.; Critical Review – K.A., E.S. S.N.N.; Other – S.E., H.M.

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