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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Combined Immunodeficiency With Inflammatory Bowel Disease in a Patient With TTC7A Deficiency

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ABSTRACT

Tetratricopeptide repeat domain-7A (TTC7A) deficiency causing combined immunodeficiency with inflammatory bowel disease (IBD) is rare. This case report alerts physicians to the possibility of TTC7A deficiency causing combined immunodeficiency with IBD and also highlights some of the current treatment options. We describe a 19-year-old patient with a compound heterozygote *TTC7A* mutation causing combined immunodeficiency, IBD, and multiple intestinal atresia. Compound heterozygote *TTC7A* mutations are known to cause combined immunodeficiency and IBD. Although rare, clinicians should be alerted to this variant and should understand the general approach to treatment.

INTRODUCTION

Familial multiple intestinal atresia (MIA) is most commonly an autosomal recessive disorder with or without combined immunodeficiency. However, several reports have recently described patients who present with compound heterozygous mutations in the tetratricopeptide repeat domain-7A (*TTC7A*) gene, detected by whole exome sequencing. *TTC7A* codes for a TTC7A and plays a role in epithelial cell growth, polarity, and differentiation in the gastrointestinal tract and thymus gland.[1,2] The manifestations of this disease result in MIA, inflammatory bowel disease (IBD) with epithelial defects, apoptosis and strictures, and severe combined immunodeficiency. To our knowledge, there are only 5 other case reports of disease onset in early adulthood, and this particular case was associated with a compound heterozygote mutation in the *TTC7A* gene (*TTC7A* of p.L823P in exon 20 c.T2468C from the paternal allele) and a mutation in complement factor I (*CFI*) gene (p.R167Kc.500G>A in exon 4 from the maternal allele). The patient was heterozygous for the *CFI* mutation, which encodes CFI, a serine proteinase regulating the deleterious cytotoxic and proinflammatory activity of the complement pathway.[3] Individuals with compound heterozygous pathogenic variants are prone to recurrent respiratory, urinary tract, ear, and skin infections.[3]

CASE REPORT

A 19-year-old woman with a history of repeated *Klebsiella* infections was hospitalized in February 2016 with abdominal pain, nausea, vomiting, and bloody diarrhea. Positive findings on physical examination included gross abdominal distention and diffuse tenderness to light and deep palpation. Laboratory testing revealed low serum levels of immunoglobulin (Ig) G (142 mg/dL), IgA (28 mg/dL), and IgM (16 mg/dL); low vaccine titers for tetanus (received 1 year before); and positivity for cytomegalovirus (CMV). Additional laboratory investigation demonstrated negative results for DQ2/8, antibodies to transglutaminase, IgA, endomysial antibodies, and human immunodeficiency virus. Stool cultures for bacteria, ova and parasites, and viral etiologies were negative. Computed tomography at that time demonstrated enteritis with regions of multiple, thickened, enhancing loops of the small bowel, with narrowing and alternating regions of prestenotic dilatation from the terminal ileum to the duodenum. Additionally, colitis

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extended from the ascending to the distal transverse colon. Colonoscopy and esophagogastroduodenoscopy with push enteroscopy demonstrated ulcerated mucosa at the ileocecal valve, with narrowing at the terminal ileum that was not able to be passed. Histopathology of colonic biopsies revealed CMV inclusions, with jejunal biopsies showing focal villous atrophy, foveolar metaplasia, focal chronic active inflammation, and ulceration with regenerative changes consistent with IBD. She demonstrated an initial improvement in her clinical symptoms and was then transitioned to sirolimus, infliximab, and a slow prednisone taper before discharge for presumed combined immunodeficiency with IBD. She also received weekly intravenous immunoglobulin for immunodeficiency and was treated for CMV colitis with ganciclovir.

She was subsequently readmitted to an outside hospital and transferred to our center 18 days later with severe abdominal pain, *Klebsiella pneumoniae*, and *Enterococcus faecalis* bacteremia. Her immunosuppressive therapy was discontinued in the setting of her bacteremia, and she was treated with antibiotics. Computed tomography re-demonstrated multiple, dilated, fluid-filled small bowel loops with a collapsed distal colon, with evidence of complete small bowel obstruction (Figure 1). The differential diagnosis at that time included IBD, common variable immunodeficiency, familial Mediterranean fever, and hemophagocytic lymphohistiocytosis (HLH). Her ferritin was 217.3 ng/mL, and her peripheral smear and bone marrow biopsy were not consistent with HLH or familial Mediterranean fever.

Given this patient's combined immunodeficiency with IBD presentation, whole exome sequencing was performed, with the patient having a pathogenic heterozygous mutation (p.L823c.2468T>C) from the paternal allele of the *TTC7A* gene. Additionally, she had a heterozygous mutation (p.R167Kc.500G>A) from the maternal allele of the *CFI* gene of uncertain significance. She underwent an exploratory laparotomy with resection of the strictures in the jejunum and ileum, appendectomy, and enteroenteric anastomosis with end ileostomy. On histopathology, there was chronic active enteritis with ulceration and acute inflammatory exudate, pyloric gland metaplasia, and regenerative epithelial change that was negative for granulomas, dysplasia, or CMV inclusion bodies. On additional staining, there was extensive neural hyperplasia of the superficial submucosa and lamina propria, with loss of glands in an area of ulceration in the jejunum and ileum (Figure 2). The patient was diagnosed with a compound heterozygous *TTC7A* mutation causing combined immunodeficiency associated with IBD. Nearly 36 months after completing intestinal rehabilitation, the patient is currently receiving *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole. She is undergoing intestinal transplantation evaluation, and RhoA kinase inhibitor therapy is being considered as a therapeutic option.

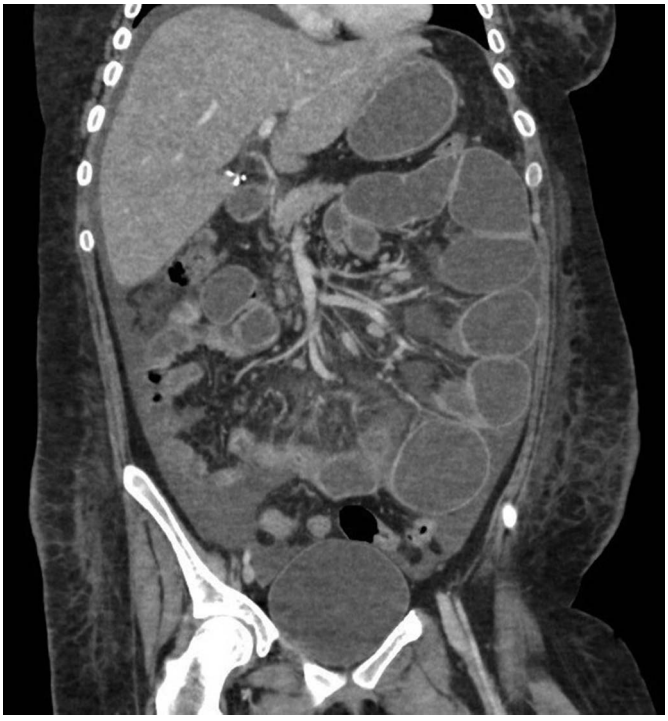

Figure 1. Abdominal and pelvic CT with intravenous contrast demonstrating multiple, dilated, fluid-filled small bowel loops with a collapsed distal colon. These findings confirmed complete small bowel obstruction.

DISCUSSION

Hereditary MIA is a rare cause of intestinal obstruction associated with a profound combined immunodeficiency.[2]

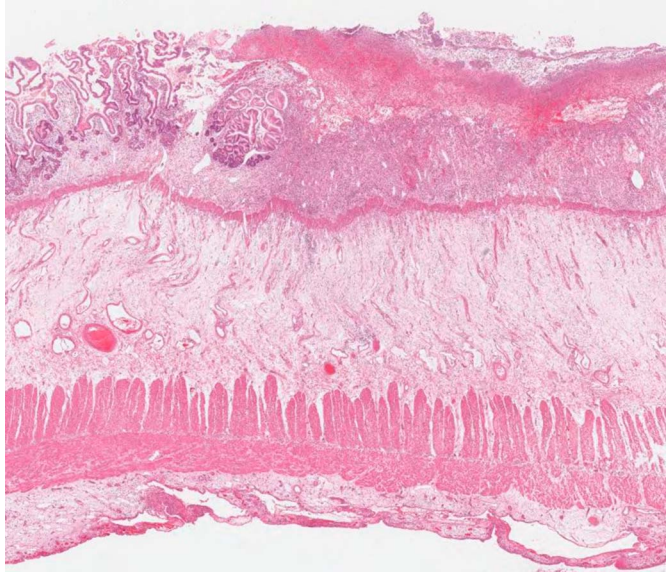

Figure 2. Low-power, full-thickness image from the ileal resection showing chronic active enteritis (top left) with ulceration and inflammatory exudate (top right).

Mutations in the *TTC7A* have been described previously, and our patient has a characteristic variant that has been identified in previous studies.[1,2,4,5] Pathogenic variants in the *TTC7A* gene are associated with autosomal recessive intestinal diseases including hereditary MIA and early-onset IBD.[5–7] Individuals with *TTC7A* pathogenic homozygotic variants often die in infancy or early childhood, although survival into adulthood has been reported in heterozygotic individuals with the early-onset IBD phenotype.[4–6] Our patient had a mutation in exon 20 pLeu823Pro (CTG>CCG):c.2468T>C of the *TTC7A* gene paired with a pArg167Lys (AGA>AAA):c.500G>A mutation in exon 4 of the *CFI* gene, and to our knowledge, this represents the sixth reported case of a compound heterozygote *TTC7A* deficiency mutation causing combined immunodeficiency with IBD.[3–5] Intestinal atresias are not associated with polygenetic IBD and hence are likely attributable to the underlying genetic variant in this patient. Given the significant morbidity and mortality associated with this condition, clinicians should be aware of this diagnosis and its treatment options, which are currently limited. The main treatment options that have been identified include steroids, azathioprine, methotrexate, cyclosporine, sirolimus, tacrolimus, tumor necrosis factor-α antagonists,[8–11] and hematopoietic stem cell transplant.[11] The RhoA kinase inhibitor (Y-27632) in vitro has demonstrated the ability to potentially reverse disturbed intestinal epithelia and thymic thymocytes,[12,13] and it is currently being explored as a treatment option.[10,13]

DISCLOSURES

Author contributions: DT Broome and A. Young wrote the manuscript. H. Torbic, S. Krishnan, M. Rizk, and F. Rieder edited the manuscript. I. Gordon and K. Lai provided pathology slides and figure legends for the manuscript. DT Broome is the article guarantor.

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Informed patient consent was obtained for this case report.

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