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Authors

Chan, Alvin
Mulatinho, Milene
Iskander, Paul
et al.

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CASE REPORT | PEDIATRICS

Maternal Uniparental Disomy 14 (UPD14) Identified by Clinical Exome Sequencing in an Adolescent with Diverticulosis

Alvin P. Chan, MD, MPH[1], Milene Mulatinho, PhD[2], Paul Iskander, MD[3], Hane Lee, PhD[2], Julian A. Martinez-Agosto, MD, PhD[4,5], and Joanna Yeh, MD[1]

[1]*Division of Pediatric Gastroenterology, Department of Pediatrics, University of California, Los Angeles, Los Angeles, CA*
[2]*Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA*
[3]*Department of Radiology, University of California, Los Angeles, Los Angeles, CA*
[4]*Division of Medical Genetics, Department of Pediatrics, University of California, Los Angeles, Los Angeles, CA*
[5]*Department of Human Genetics, University of California, Los Angeles, Los Angeles, CA*

ABSTRACT

Pediatric diverticular disease is extremely rare, with most cases associated with connective tissue disorders. We report an adolescent boy with syndromic features who presented with acute complicated sigmoid diverticulitis. Clinical exome sequencing analysis detected a 6.5-Mb region of homozygosity on chromosome 14, consistent with partial maternal uniparental disomy. Analysis of this region did not identify rare homozygous variants but included several imprinted genes that were candidates for the observed phenotypes. The pediatric clinical presentation of diverticulosis in this patient has not been previously described in maternal uniparental disomy of chromosome 14 and adds to the phenotypic spectrum of the syndrome.

INTRODUCTION

Acute diverticulitis is a condition characterized by inflammation or infection of small outpouchings along the intestinal tract. Although common in the elderly due to age-related changes in intestinal wall compliance, diverticulitis is extremely rare in the young, with most pediatric cases linked to genetic syndromes associated with connective tissue defects, including Ehlers-Danlos syndrome, Marfan syndrome, and Williams-Beuren syndrome.[1,2] Given its low prevalence in younger patients, acute diverticulitis is rarely considered on the differential diagnosis for acute abdominal pain. This report discusses the presentation and management of pediatric diverticular disease, while also highlighting a pediatric case of diverticulosis/diverticulitis that has not previously been described in maternal uniparental disomy of chromosome 14.

CASE REPORT

A 15-year-old boy with mild dysmorphic features and learning disabilities was admitted for acute-onset abdominal pain, nausea, and vomiting. His postnatal history included premature birth at 29 weeks of gestational age with a prolonged neonatal intensive care unit course due to intrauterine growth restriction, hypotonia, and poor feeding. His medical history was significant for short stature, precocious puberty, obesity, type 2 diabetes mellitus, inguinal hernia requiring multiple repairs, constipation, and hyperparathyroidism/hypercalcemia secondary to primary parathyroid adenoma that resulted in parathyroidectomy at age 14 years.

On initial presentation, the patient was hemodynamically stable but moderately distressed with generalized abdominal tenderness, with rebound and guarding, and abdominal distention. Preliminary laboratory testing revealed leukocytosis with bandemia (white

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Correspondence: Alvin P. Chan, MD, MPH, Division of Pediatric Gastroenterology, Department of Pediatrics, University of California, Los Angeles, 757 Westwood Plz, B711 RRUMC, Los Angeles, CA 90095-7419 (alvinchan@mednet.ucla.edu).

blood cell, 12.1 × 10^9/L; bands, 12%) and elevated C-reactive protein (3.4 mg/dL). Contrast computed tomography (CT) imaging demonstrated thickening of the sigmoid colon with adjacent fat stranding and multiple sigmoid diverticula with large local abscess with a small collection of air suggestive of loculated perforation (Figure 1).

On admission, a catheter was placed to drain the abscess. Broad-spectrum antibiotics such as vancomycin, cefepime, and metronidazole were empirically started, but later switched to piperacillin-tazobactam monotherapy as inflammatory markers downtrended. The etiology of the colonic perforation was suspected to be from diverticulosis; however, given the rarity of this condition in adolescents, other etiologies, including infection, tumor, and inflammatory bowel disease, were investigated. Blood cultures and gastrointestinal pathogen polymerase chain reaction panel were negative. Specific markers for gastroenteropancreatic neuroendocrine tumors were assessed and normal. Additional laboratory studies after discharge revealed normal fecal calprotectin and negative inflammatory bowel disease serology panel.

The patient spent 6 weeks in the hospital and completed the remaining 2 weeks of antibiotics and catheter drainage at home. In total, the patient underwent 8 weeks of antibiotics targeting Gram-negative and anaerobic bacteria and 8 weeks of percutaneous abscess drainage. When the drain was finally removed, repeat imaging with magnetic resonance enterography showed resolved abscess, persistent sigmoid thickening with subtle stranding in the surrounding fat compatible with healing perforation, and scattered small diverticula throughout the ascending, transverse, and sigmoid colons. The small diverticula were again seen on contrast barium enema study at 6-month follow-up (Figure 2). The patient did not have any further symptoms at his 6-month follow-up visit.

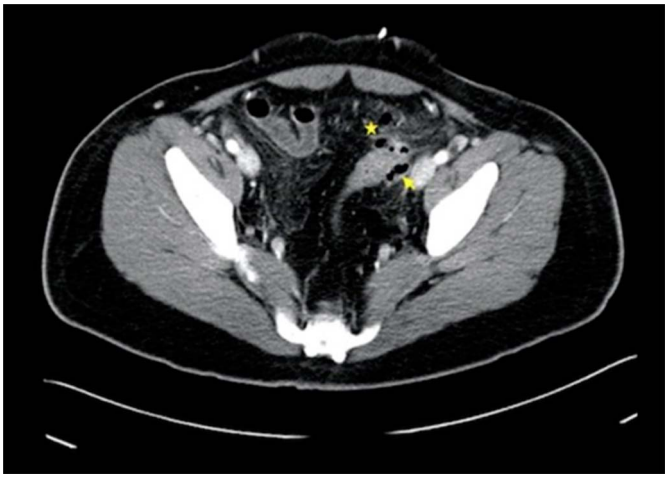

Figure 1. Abdominal computed tomography showing few sigmoid diverticula (arrow) associated with significant colonic wall thickening, fat stranding, and local abscess measuring 6.1 × 2.7 × 2.9 cm (star).

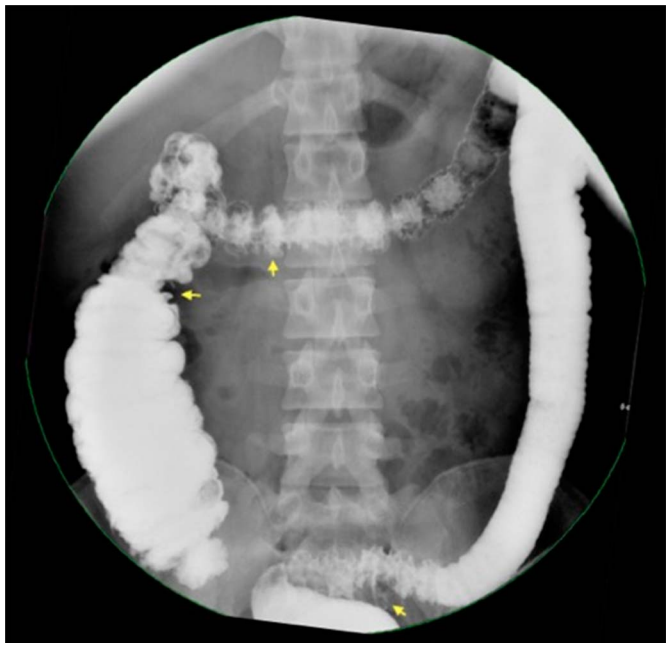

Figure 2. Barium enema contrast study showing scattered small diverticula in the ascending, transverse, and sigmoid colons (arrows) and diffuse lack of haustra and smooth-appearing mucosa in the descending colon suggestive of chronic inflammation.

DISCUSSION

Diverticular disease in pediatrics is rare. The clinical manifestation of the disease is variable, with the classic features of fever, leukocytosis, and left lower quadrant abdominal pain present in only less than one-third of young patients. Laboratory investigations are nonspecific, but may reveal leukocytosis and elevated inflammatory markers. CT is the preferred modality for diagnosis, with typical findings including presence of diverticula, colonic wall thickening, extraluminal air, and abscess formation. Management of acute diverticulitis is generally nonoperative with bowel rest, antibiotics, and abscess drainage if present. Surgery may be indicated for hemodynamic instability, failure to antibiotic or drainage therapy, or recurrent episodes.[3,4]

In our patient, despite early evidence favoring acute diverticulitis, the case was a diagnostic challenge because diverticulitis is not only uncommon in pediatrics, but it also resembles many other conditions. Inflammatory bowel disease, specifically Crohn's disease, was considered because of its association with abscesses and bowel wall thickening, but the acute onset of symptoms and absence of weight loss and bloody stools were not consistent with the diagnosis. The normal fecal calprotectin and negative inflammatory bowel disease serology panel provided further evidence against inflammatory bowel disease. Infectious etiologies were also considered, but laboratory studies were negative for a comprehensive list of gastrointestinal pathogens. Acute appendicitis may mimic sigmoid diverticulitis, but the appendix was normal on CT imaging. Finally, given the patient's previous history of the parathyroid adenoma, there was concern for pituitary and gastroenteropancreatic neuroendocrine tumors

associated with multiple endocrine neoplasia type 1, but these were ruled out based on normal neuroendocrine markers. Only after the exclusion of these other causes was the diagnosis eventually established.

Given the clinical presentation of diverticulosis and history of recurrent inguinal hernia repairs in this patient, a defect in connective tissue was suspected. Trio clinical exome sequencing was requested to identify any gene variants associated with connective tissue diseases at risk of diverticulosis, but none were found. However, a 6.5-Mb region of homozygosity was detected on chromosome 14 involving the 14q32.2->q32.33 region. The sequencing data from the trio were consistent with all variants in this region of homozygosity being only inherited from the mother with no evidence of a paternal deletion, consistent with partial maternal unipaternal disomy. These findings were confirmed using a polymerase chain reaction–based clinical uniparental disomy test. No rare homozygous variants were identified in the dissomic region, but several maternally imprinted genes, such as *MEG3* and *MEG8*, were candidates for mediating the observed phenotypes.

Temple syndrome, or maternal uniparental disomy of chromosome 14, is a rare chromosome 14q32 imprinting disorder, associated with a characteristic phenotype that includes hypotonia, motor delay, feeding difficulties, early puberty, small hands and feet, short stature, and obesity.[5,6] Although many of the patient's clinical features are seen in Temple syndrome, diverticulosis has not previously been reported in patients with Temple syndrome. Given the rarity of both pediatric diverticulosis and Temple syndrome, we speculate that alterations in connective tissue may be an unrecognized feature of Temple syndrome that warrants further investigation.

However, one point worth mentioning is our patient's previous history of parathyroid adenoma. As our patient experienced constipation for most of his life, we recognize that his long-standing constipation, likely from hypercalcemia associated with hyperparathyroidism, may have at least contributed to the formation of diverticula seen throughout his colon.

As future research continues to reveal genetic and lifestyle factors contributing to pediatric diverticular disease, we believe that this case highlights the importance of considering acute diverticulitis on the differential diagnosis of any adolescent with an underlying genetic syndrome who presents with acute abdominal pain due to potential complications with delays in treatment.

DISCLOSURES

Author contributions: AP Chan drafted the manuscript and is the article guarantor. M. Mulatinho, H. Lee, and JA Martinez-Agosto analyzed and interpreted the exome sequencing data and performed phenotypic evaluations. P. Iskander interpreted the images. J. Yeh supervised the case. All authors critically reviewed and approved the final version of the manuscript.

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