ACG CASE REPORTS JOURNAL

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Listeria monocytogenes Meningitis After Treatment With Infliximab in an 8-Year-Old Pediatric Patient With Crohn's Disease

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ABSTRACT

Anti-tumor necrosis factor-alpha agents are used for the treatment of inflammatory bowel disease. Central nervous system infections are rare adverse effects of these medications, and to the best of our knowledge, there are only 2 case reports from the pediatric patient population. We report a case of an 8-year-old patient with Crohn's disease who developed *Listeria* meningitis while on infliximab.

INTRODUCTION

Human tumor necrosis factor-alpha (TNF-α) is a large family of proinflammatory proteins and receptors, which plays an important role in immune regulation.[1] The role of increased TNF-α production in Crohn's disease (CD) is well studied.[2] Anti-TNF-α antibodies are believed to neutralize the TNF-α, thus acting as an anti-inflammatory agent.[3] Infliximab is a genetically engineered chimeric immunoglobulin anti-TNF-α that is administered intravenously. Patients on anti-TNF-α therapies such as infliximab can be at an increased risk of opportunistic infections such as *Listeria monocytogenes*.

CASE REPORT

An 8-year-old girl with attention-deficit hyperactivity disorder and growth failure presented with chronic abdominal pain, diarrhea, and rectal bleeding. There was a family history of CD in her mother. The physical examination showed pallor and abdominal tenderness. The endoscopy and colonoscopy were significant for ulceration in the duodenum and patchy inflammation throughout the colon (Figure 1). Histology showed chronic inflammatory changes in the colon (Figure 2). She was diagnosed with CD based on the aforementioned findings. She was initially started on intravenous steroids. Because of poor response, induction therapy with infliximab was initiated. Symptoms resolved after the first induction dose of infliximab (5 mg/kg), and she was discharged home. She received her second infusion (5 mg/kg) 2 weeks later.

Preinfusion laboratory results, including complete blood count and comprehensive metabolic panel, were unremarkable. Two days after the uneventful second infusion, she presented to the emergency department with severe headaches, fever, and lethargy. The patient disclosed having milk and cheese (pasteurized) over the past few days before her presentation. Her physical examination was significant for tachycardia and neck rigidity. Septic workup was initiated. Blood, urine culture, and cerebrospinal fluid (CSF) studies were obtained. Complete blood count showed leukocytosis ($13.7 \times 10^3/\mu L$) with 65% neutrophils. C-reactive protein was elevated to 54.5 mg/L, and the sedimentation rate was 35 mm/h. CSF studies showed decreased glucose (56 mg/dL), elevated protein (99 mg/dL), and pleocytosis (white blood cells 1,640/μL). CSF Gram stain showed 4+ white blood cells but no organisms. She was started on empiric antibiotics that included ceftriaxone and vancomycin. Both blood and CSF culture grew *L. monocytogenes* at 48 hours of collection. The antibiotics were changed to ampicillin (200 mg/kg/d) and gentamicin (6 mg/kg/d) followed by an improvement in her symptoms. She was continued on a tapering dose of prednisone for CD. She completed 21 days of intravenous antibiotics. A month

ACG Case Rep J 2021;8:e00624. doi:10.14309/crj.0000000000000624. Published online: July 9, 2021

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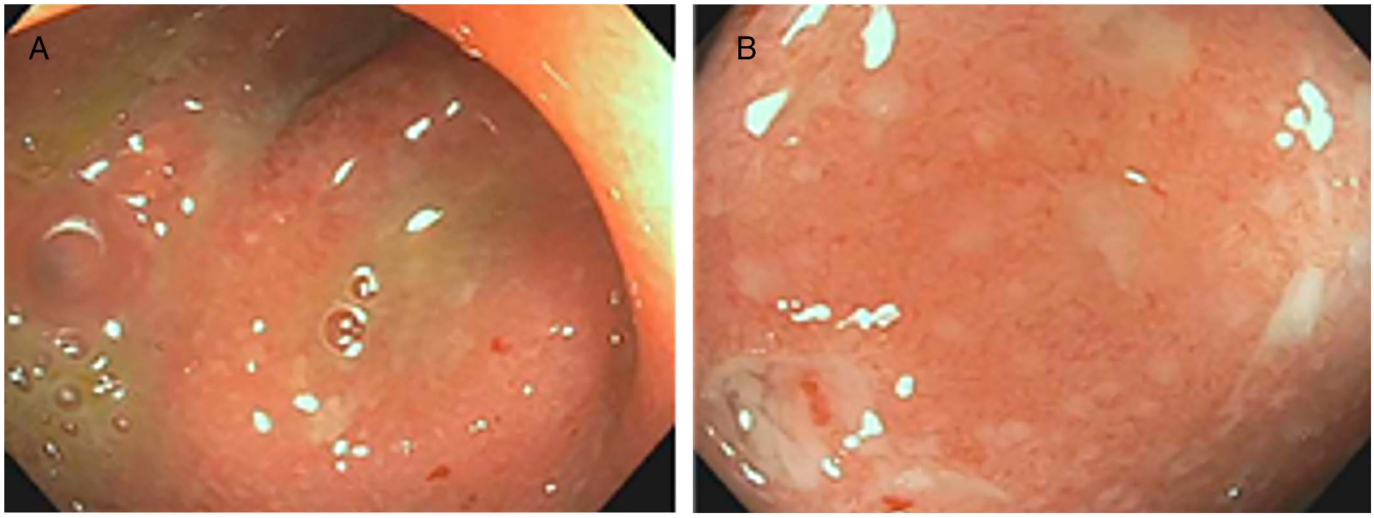

Figure 1. Endoscopic appearance of the colonic mucosa showing severe inflammation with altered vascularity, friable mucosa, and aphthous ulceration in the (A) sigmoid colon and the (B) cecum.

after completing the antibiotics, she was started on methotrexate because parents wanted to avoid biologic therapy. On follow-up visits, no long-term sequelae of meningitis or gentamicin treatment were noted. The patient had no microbiome study. However, she had recurrence of severe gastrointestinal symptoms despite methotrexate treatment for 2 months. Subsequently, she was started on vedolizumab. For 6 months into follow-up, she has been tolerating the combination therapy with methotrexate and vedolizumab and remains asymptomatic.

DISCUSSION

Although anti-TNF-α agents such as infliximab and adalimumab are considered effective therapeutic agents in irritable bowel disease (IBD) management, they are associated with many adverse effects.[4] The common adverse effects including nausea, upper respiratory tract infections, sepsis, reactivation of latent tuberculosis, and invasive opportunistic infections have been reported.[5] Although the exact mechanism is not clear, the downregulation of immune system is considered the underlying etiology.[5] Among opportunistic infections, invasive infections involving the central nervous system are considered rare.[6]

Listeria monocytogenes is a Gram-positive rod that exists in soil, water, and plants and grows in anaerobic conditions.[4] Human transmission is mainly through ingestion of contaminated food such as soft cheese, undercooked meat, milk, and vegetables.[6] In immunocompetent individuals, the infection usually presents as acute febrile gastroenteritis, whereas in elderly and immunocompromised population, the invasive infections such as meningitis and septicemia are common presentations.[6]

Our review of literature showed that the cases of *Listeria* meningitis in patients with IBD, treated with anti-TNF-α, were predominantly reported in the adult population. The Food and Drug Administration adverse event reporting system received 26 cases of invasive *Listeria* infections including sepsis, bacteremia, endophthalmitis, and meningitis.[7] Another review study suggested that 43 cases were associated with anti-TNF-α treatment. Among total cases, 41 were adults while 2 were teenagers. The most common indication for anti-TNF-α treatment was rheumatoid arthritis (n = 23) followed by IBD (n = 15) and Still disease (n = 1).[8] We found 2 cases of *Listeria* meningitis in the pediatric IBD patients who received anti-TNF-α therapy. Kamath et al presented a case of a 17-year-old girl who was

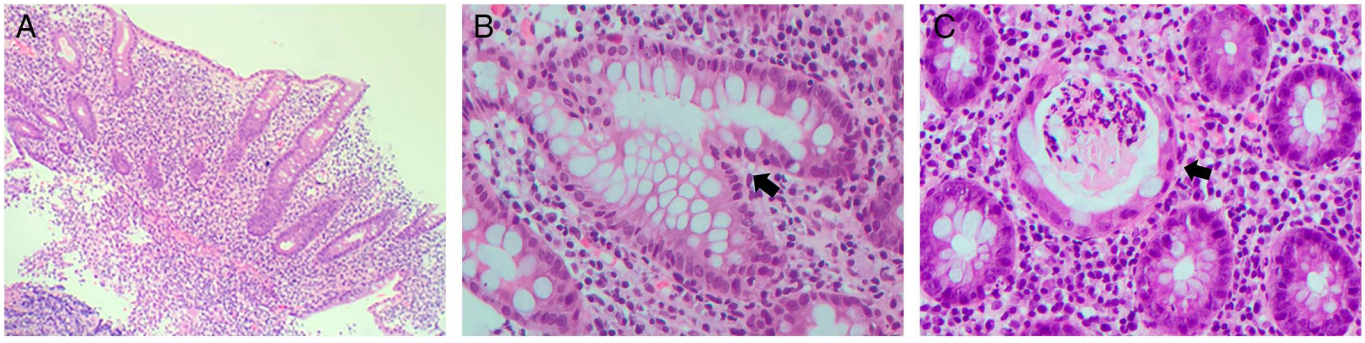

Figure 2. Hematoxylin and eosin–stained sections of the colonic mucosa showing (A) lamina propria with crypt architectural distortion, (B) bifurcation (arrow), and (C) active colitis demonstrated by crypt abscess (arrow) in the setting of chronic inflammatory bowel changes.

treated with infliximab, mesalamine, 6-mercaptopurine, and prednisone for CD. Three days after her first infliximab infusion, she was diagnosed with *Listeria* meningitis. The infection was treated with appropriate antibiotics. She had no neurological sequelae.[6] The second case was reported by Chaung et al who presented a case of 17-year-old boy with ulcerative colitis. Five days after his first infliximab infusion, the patient presented with emesis and abdominal pain and later developed fever, hypotension, and headache. He was diagnosed with *Listeria* meningitis and treated with antibiotics. His hospital follow-up showed that he developed vertigo likely because of gentamicin toxicity.[4]

These cases and our case report suggest the importance of the patient education and high index of suspicion for the invasive *Listeria* infection. Our patient might have been exposed to *Listeria* because of milk or cheese intake. These infections, although treatable, could lead to high morbidity and mortality, prolong hospitalization and complications secondary to antibiotics treatment. Although anti-TNF-α agents play an important role in the treatment of IBD, their use can increase the risk of opportunistic central nervous system infections such as with *Listeria* species. Patient education should include avoiding exposure to uncooked meat, soft cheese, unpasteurized milk, and unhygienically handled ready-to-eat food(s). A high index of suspicion is required for early diagnosis and treatment to avoid the mortality and long-term complications of such infections.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. A. Rana is the article guarantor.

Financial disclosure: None to report.

Previous presentation: This case was presented at the North American Society for Pediatric Gastroenterology Annual Meeting; October 16-19, 2019; Chicago, Illinois.

Informed consent was obtained for this case report.

Received July 20, 2020; Accepted March 30, 2021

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