



Adult Intestinal Toxemia Botulism in a Patient With Crohn's Disease

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ABSTRACT

Adult intestinal toxemia botulism (ITB) is a rare illness that can be fatal if not recognized. ITB can occur when botulinum neurotoxin-producing clostridia colonize the intestine. Underlying intestinal abnormalities associated with dysbiosis are likely a prerequisite for colonization. Dysbiosis seems necessary for spore germination and neurotoxin production. Botulism neurotoxins are the most lethal poisons known and are classified into 7 serotypes: A through G. The clinical presentation consists of cranial nerve abnormalities and descending flaccid paralysis. Prompt recognition and treatment with botulism antitoxin and supportive measures is often successful, but delayed recognition can be fatal. In this study, we present a case of a 40-year-old woman with Crohn's disease who developed ITB. This is the first case in literature to report adult intestinal botulism from *Clostridium botulinum* producing toxin B and F in the same patient.

INTRODUCTION

Botulism is a neurological illness characterized by severe bulbar weakness and paralysis secondary to neurotoxin-producing clostridia.¹ Most patients present with blurred vision, diplopia, dysphagia, dysarthria, and generalized weakness.¹ Botulism incidence is very low with less than 200 reported cases in the United States every year.² There are 4 main types of botulism, classified based on the route of exposure. Infant botulism is the most common in the United States (70%–75%) and occurs when toxin-producing clostridia colonize an infant's intestinal tract. Foodborne botulism occurs after ingestion of preformed toxin (20%–25%). Wound botulism (5%–10%) occurs with *Clostridium botulinum* colonization of a wound. Adult intestinal toxemia botulism (ITB) is rare, accounting for <1% of botulism cases in the United States.² ITB was first reported in 1980.³ Its pathogenesis is similar to infant botulism where *C. botulinum* colonizes the gastrointestinal (GI) tract and produces neurotoxin. An intact intestinal microbiota resists colonization with *C. botulinum* and prevents spore germination. Disruption of normal intestinal microbiota or mucosal defenses in patients with a history of bowel resection, inflammatory bowel disease (IBD), or achlorhydria predispose patients to ITB.^{4,5} Once produced in the intestine, botulism neurotoxins are absorbed in the small intestine, enter the intestinal lymphatic system, and enter the systemic circulation.

CASE REPORT

A 40-year-old woman with Crohn's disease (CD) presented with a 10-day history of generalized muscle weakness, dysphagia, diplopia, and dysarthria. There was no vomiting, abdominal pain, diarrhea, constipation, fever, numbness, headache, urine retention, or back pain. The patient was afebrile, normotensive, and the heart and respiratory rates were normal. Neurological examination revealed absent pupillary reflexes bilaterally, muscle weakness, and absent deep tendon reflexes in the proximal and distal muscles of the 4 extremities. Light touch and proprioception sensations were intact.

The medical history was significant for ileocolonic CD diagnosed 27 years ago and multiple bowel resections related to fistulas and abscesses. When the patient was 13 years old, she had resection of 32 cm of small bowel and cecum for small bowel obstruction, with resultant end-to-end ileocolonic anastomosis. Histopathology of resected bowel confirmed CD diagnosis. Fifteen years later, the

patient needed a second small bowel resection for a small intestinal abscess and a bowel perforation. After the second small bowel resection, the patient did not follow with gastroenterology and declined CD maintenance therapy for fear of the risks associated with immunosuppressive therapy. Three months before presentation, the patient underwent a third resection of 100 cm of small bowel for a small bowel "ileal-ileal" fistula and abscess refractory to percutaneous drainage, resulting in a diverting loop ileostomy. The patient agreed to start immunosuppressive therapy after the third ileal resection surgery for CD. Three weeks before this presentation, she received the first 2 induction doses of infliximab 5 mg/kg (week 0 and 2) for active small intestinal disease evident by contrast-enhanced cross-sectional imaging.

The patient was admitted to the medical ward with neurology consulting. Brain magnetic resonance imaging and lumbar puncture were normal. On hospital day 2, she developed rapidly progressive muscle weakness and subsequent respiratory distress. Negative inspiratory forces declined to indicate poor respiration muscles function and respiratory failure. The patient was intubated and mechanically ventilated. Guillain-Barré syndrome (GBS) and myasthenia gravis (MG) were suspected based on the clinical presentation, and the patient was started on intravenous (IV) immunoglobulin and methylprednisone 1 g/d. MG-specific antibodies including acetylcholine receptor (AChR-Ab), muscle-specific tyrosine kinase (MuSK-Ab), and low-density lipoprotein receptor-related protein 4 were negative. Electromyogram identified myopathic features suggestive of MG. Over the following days, despite the addition of methotrexate, cyclophosphamide, and additional doses of IV immunoglobulin, the patient did not improve. She developed complete paralysis of the upper and lower extremities, severe ophthalmoplegia with inability to open eyes, inability to speak, and persistent respiratory failure. Given the lack of clinical improvement with GBS and MG treatments, an alternative diagnosis was sought.

Botulism was suspected because of its similar clinical presentation to MG and GBS. Stool polymerase chain reaction for *C. botulinum* was sent and returned positive for *C. botulinum* toxin B and F genes on hospital day 51. The center of disease control was contacted, and antitoxin therapy in the form of IV heptavalent botulinum antitoxin was administered on hospital day 52. Within 4 days, the patient started to improve, open her eyes, and move her extremities. Botulism was confirmed with the mouse bioassay test performed on a stool sample at Minnesota Department of Health Laboratory and was positive for toxin B and F of *C. botulinum*. In the mouse bioassay test, mice were injected with the presumed botulism toxin obtained from the stool sample provided by the patient with and without botulism antitoxins. Mice were then observed for signs of botulism. Over the following weeks, she had a remarkable recovery with the help of physical, occupational, and speech therapies. Eighty days after hospitalization, she was able to speak, ambulate with assistance, and the tracheostomy tube was removed.

A 2-week regimen of oral metronidazole and IV penicillin G, a prolonged course of oral vancomycin 500 mg 4 times daily for 6 weeks, in addition to probiotic therapy, was initiated to eradicate *C. botulinum*.

DISCUSSION

Acute flaccid paralysis, normal sensation, and the absence of fever constitute the triad of botulism regardless of the subtype.^{1,5} The neurotoxin of *C. botulinum* is the most potent bacterial toxin known to humankind and is responsible for the clinical presentation of botulism. In addition to *C. botulinum*, human disease can occur from toxins by other clostridia species (*C. butyricum* and *C. baratii*). ITB, also known as enteric infectious botulism or adult intestinal toxemia, is an extremely rare form of botulism with less than 35 reported cases in medical literature.^{4,6} This type of botulism is similar to infant botulism (the most common type of botulism) by in vivo neurotoxin production after infection with *C. botulinum*, unlike foodborne botulism where pathogenesis occurs from exposure to preformed neurotoxin.⁴ Although this form of botulism can occur in patients with no identifiable risk factors, 16 cases of ITB have been reported in patients who had distorted GI anatomy, gastric or bowel resection, or endoscopy.^{3,6-16} Twelve of these patients were women, and the age of presentation ranged between 33 and 79 years. The time to diagnosis was less than 3 days in 50% of cases. *C. botulinum* type A was the culprit toxin in 7 cases, type B in 3, and type F in 1 case. *C. baratii* type F toxin was reported in 5 cases.^{3,6-16}

The pathogenesis of ITB is unclear, but the association of altered GI anatomy, IBD, and resultant colonization of clostridia and ITB suggests the interplay of dysbiosis, altered immune, and inflammatory responses in the pathogenesis of this condition. Only 3 ITB cases with altered GI anatomy had an associated diagnosis of IBD were reported in the literature.^{12,16} Because of the rarity of ITB and the relatively high prevalence of IBD and small bowel resection, the development of ITB cannot be attributed solely to altered anatomy, antibiotic therapy, bowel inflammation, and immunosuppression despite reported association. Other unidentified risk factors are likely contributing to ITB pathogenesis. Diagnosis can be made by demonstration of toxigenic *C. botulinum* in blood or stool and/or *C. botulinum* toxin in the serum in patients with compatible clinical presentation.⁴ The long time to ITB diagnosis in our patient is attributed to the rarity of ITB and the similar clinical presentation to MG. Our patient received a total of 2 doses of anti-tumor necrosis factor therapy before ITB diagnosis. However, the use of anti-tumor necrosis factor therapy was only reported in our case and was not reported in the published ITB cases associated with IBD.^{12,16}

Our case is unique by the fact that *C. botulinum* toxin testing came back positive for both toxin B and F, which to the best of our knowledge has not been reported. The presence of *C. botulinum* toxin F in addition to toxin B in our patient may have

contributed to the severe clinical presentation. This can be supported by the severe clinical presentation of the only published case with available clinical information of *C. botulinum* toxin F.¹⁵ However, the delayed recognition of ITB likely contributed to the severe clinical course as well. In addition, the presence of both toxin B and F did not influence the decision to give botulinum antitoxin. Of note, our patient did not report ingestion of canned foods, and there was no evidence of surgical wound infection to suggest foodborne or wound botulism, respectively. There are no formal practice guidelines for the treatment of ITB because of the paucity of data. Early recognition and prompt treatment with antitoxin may improve clinical outcomes and shorten the length of hospitalization.^{4,6,17,18} Antibiotic treatment with metronidazole and penicillin, whole bowel irrigation with polyethylene glycol, and probiotic therapies were implemented in many case series.^{5,6} Although rare, unexplained motor neuron paralysis in a patient with underlying intestinal abnormalities should prompt clinical consideration of ITB.

DISCLOSURES

Author contributions: M. Abdallah wrote the manuscript. K. Rank and S. Keely edited the manuscript. M. Abdallah and D. Anderson reviewed the literature. B. Vaughn revised the manuscript for intellectual content, approved the final manuscript, and is the article guarantor.

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