

Hospital-acquired intestinal toxemia botulism in a newly diagnosed adult colon cancer patient

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ABSTRACT

This manuscript reports a case of intestinal toxemia botulism in an adult with recently diagnosed metastatic colon cancer in whom botulism symptoms began 23 days after hospital admission. Representing the rarest form of botulism presentation in clinical practice, this infectious disease may have developed due to a cluster of predisposing factors that favored *Clostridium botulinum* colonization and the endogenous production of neurotoxins, among which are previous use of broad-spectrum antibiotics and colon changes related to the development of the neoplasia. This case highlights the importance of considering intestinal toxemia botulism in the differential diagnosis of a patient presenting with symmetrical descending flaccid paralysis, since immediate treatment with botulinum antitoxin may improve clinical outcomes.

KEYWORDS: Adult intestinal toxemia botulism. Neuropathy. Intestinal colonization. Diagnosis. Neuromuscular junction. Symmetrical descending flaccid paralysis. *Clostridium botulinum*.

INTRODUCTION

Botulism is a paralytic neurotoxin-induced disease caused by *Clostridium botulinum*¹⁻³. This clinical entity is capable of affecting individuals at any age¹. Classically, botulism has an acute presentation⁴, and its spectrum includes four main types of naturally occurring disease, numbered as follows: intestinal (or hidden) infection with *in situ* production of toxins; this is most commonly reported in infants (I), than in adults (II); wound botulism (III); the disease caused by contaminated food, the so-called foodborne botulism (IV) which is characterized by the ingestion of preformed toxins^{2,3,5,6}. Two other forms of the disease are represented by (V) iatrogenic botulism, during the use of botulinum toxin either for therapeutic or cosmetic indications, and (VI) inhalation botulism, caused by aerosolized toxins^{7,8}. Adult intestinal toxemia botulism (II), also called infant-like botulism⁹, is the rarest form¹⁰, characterized by the ingestion of spores, their intestinal germination and the intraluminal production of neurotoxins^{1,9,11,12}.

Typically characterized by bilateral cranial neuropathy followed by descending flaccid symmetric paralysis and potential ventilatory impairment, the differential diagnosis of botulism can be challenging, as the disease may share some features with several other clinical entities. Moreover, the differential diagnosis includes some atypical clinical presentations of botulism itself^{4,8,13}. Considering the high

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mortality rates related to this form of botulism, ranging from 40-50% in untreated cases¹³, prompt diagnosis is crucial for the specific treatment with the antitoxin, besides the supportive care^{4,8,10,13}.

Herein we report a case of sporadic adult intestinal toxemia botulism initiated after a 23-day hospitalization period, in a patient admitted due to a recently diagnosed colon cancer.

CASE REPORT

A 63-year-old Brazilian man was hospitalized due to severe symptomatic anemia (hemoglobin level of 4 g/dL). His previous clinical history revealed no known comorbidities, no wounds or recent skin infections, and no regular use of any medication.

Computed tomography images showed irregular wall thickness in the hepatic angle of the colon suggestive of primary tumor, with a mass extending longitudinally by 13 cm, with areas of necrosis. The right lobe of the liver had undergone secondary enlargement due to the presence of a large, heterogeneous and hypovascular expansive formation on the liver surface measuring 12.0 x 15.5 x 10.5 cm, and at least three other similar hepatic lesions, presumably metastatic. Furthermore, bilaterally randomly distributed pulmonary nodules with soft tissue densities were found, associated with paratracheal, subcarinal, right pulmonary hilum and left gastric chain lymph nodes enlargement. The endoscopic study revealed a stenotic lesion in the second portion of the duodenum, with tumor characteristics, and

fragments were collected for anatomopathological study. Colonoscopy showed a great vegetative stenotic lesion on the right flexure of the colon, which was biopsied. As both endoscopic biopsies were described as inconclusive, an ultrasound-guided biopsy of the hepatic lesion was performed, leading to the diagnosis of metastatic adenocarcinoma that had probably originated in the colon. This result has motivated the chemotherapy with 5-fluorouracil and leucovorin.

After fourteen days of hospitalization, the patient started fever, hypotension responsive to intravenous fluids and sinus tachycardia. The diagnosis of sepsis with undefined focus was then established, with the administration of broad-spectrum antimicrobial therapy (piperacillin associated with tazobactam), with fast recovery. Nine days later, the patient presented with abdominal pain, prostration, vomiting, frontal headache, dizziness, blurred vision, photophobia and difficulties in speaking. Within a 24-hour interval, he progressed with anarthria and bilateral ophthalmoparesis and ptosis, followed by agitation and respiratory distress finally progressing to cardiac arrest in pulseless electrical activity, probably due to hypoxemia. Cardiopulmonary resuscitation was successfully performed for five minutes, with the need of intubation and maintenance in mechanical ventilation. Subsequently, a brain computed tomography revealed no signs suggestive of intracerebral expanding lesions, or ischemic and hemorrhagic stroke. In addition, lumbar puncture did not show significant alterations (Figure 1).

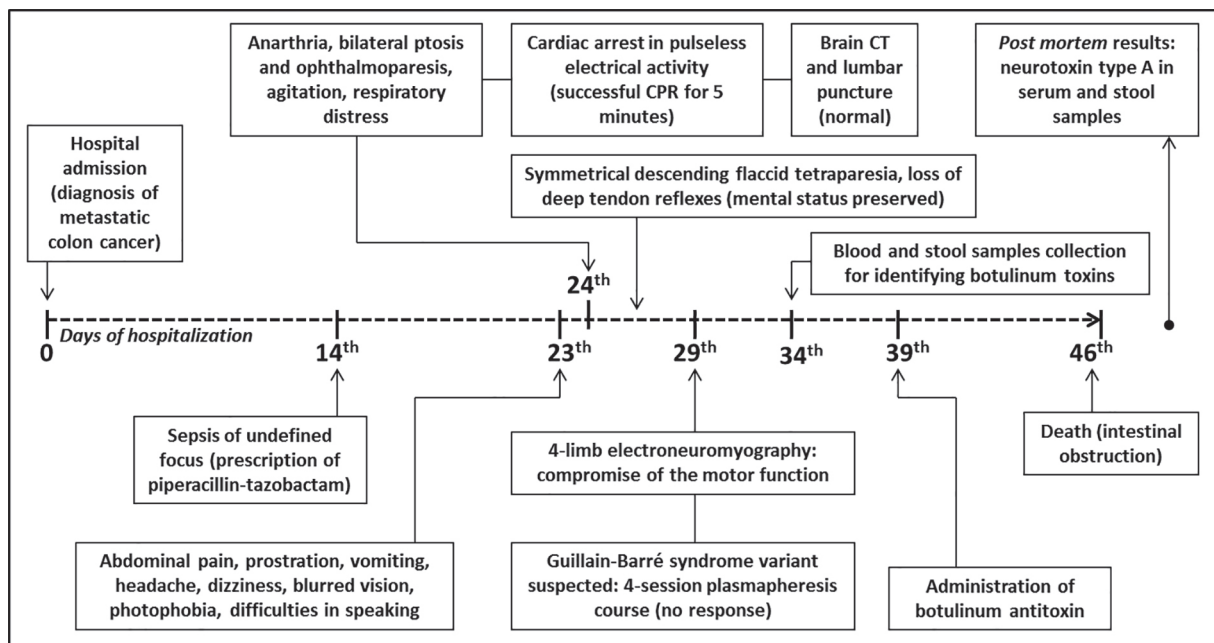


Figure 1 - Representative sequence of events in the reported case reported since hospital admission. CPR: cardiopulmonary resuscitation CT: computed tomography.

As soon as sedation was suspended, the patient regained consciousness, obeying simple commands such as moving hands and feet. From this moment, the neurological examination progressively deteriorated, with development of symmetrical descending flaccid tetraparesia and loss of deep tendon reflexes, with the consciousness status still preserved. Mechanical ventilation was maintained as the patient did not show signs that allowed extubation. A four-limb electroneuromyography, performed five days after the onset of symptoms, revealed intense myopathic findings evidenced by the high recruitment of motor units, with slight incremental response. Neither signs of acute or chronic denervation nor sensitive alterations were observed. Regarding the nervous conduction, the compound muscle action potentials (CMAPs) were found reduced in the proximal muscles, with M waves of low voltage, showing impairment of motor function.

Considering the possibility of a variant of the Guillain-Barré syndrome, a 4-session course of plasmapheresis was performed, without any improvement concerning the neurological pattern. As the clinical presentation could also be associated with adult intestinal toxemia botulism, blood and stool samples were collected for specific neurotoxins identification, with the botulinum antitoxin only available sixteen days after the onset of symptoms, which was then administered. Sequentially, the patient developed intestinal obstruction and progressive worsening in renal function, evolving to death forty-six days after hospital admission (Figure 1). *Post-mortem* examination showed botulinum neurotoxin type A both in serum and stool samples, by the bioassay method with intraperitoneal inoculation of mice (the standard method for detecting these toxins^{5,7}, because of its high sensitivity and specificity^{6,8}).

DISCUSSION

The clinical report described herein brings a case of adult intestinal colonization by *C. botulinum*, secondary to the intestinal germination of spores and intraluminal production of neurotoxins, progressing to intestinal toxemia botulism, an even rarer condition^{1,9,10,12,14}.

Pathophysiologically, botulinum neurotoxins, some of the most potent of all natural toxins known^{6-8,15}, bind to receptors in the presynaptic membrane of neuromuscular junctions^{2,5} leading to the irreversible blockage of exocytosis of acetylcholine in the synaptic cleft⁸, also affecting the sympathetic and parasympathetic nervous systems². Thus, autonomic signs and symptoms may be present⁴, such as constipation, dry mouth, postural hypotension, pupillary alterations and urinary retention^{1,2,11}.

The pathophysiological sequence of events observed in botulism leads to symmetric cranial nerve impairment in the early stages, clinically manifested by dizziness, blurred or double vision, difficulties in speaking and swallowing, followed by descending symmetrical weakness of voluntary muscles (initially in the upper limbs and sequentially in the lower limbs), possibly involving respiratory distress and the need of ventilatory support^{2,5}. Mentation and sensory systems are not usually affected, although cases of sensory impairment have been reported².

When it comes to adults, intestinal toxemia botulism is described as a diagnostic challenge¹⁰, with only a few cases reported worldwide. Indeed, this rarity may contribute to possible delays in adequate diagnosis and the establishment of proper treatment¹².

In the current case, we were able to rule out foodborne botulism because this condition has a relatively short incubation period (3-5 days)⁵ or even shorter, from two to 24 hours⁴, and the patient had been hospitalized for 23 days when symptoms appeared. Moreover, the patient did not present any other evidence of ingestion of contaminated food or a wound source of toxins. Finally, there were no concomitant cases at the hospital, making the possibility of a form of botulism other than the intestinal toxemia very unlikely.

Under normal conditions, ingested spores are eliminated without germinating or producing toxins, so that in most cases the disease does not manifest⁵. Intestinal toxemia botulism in adults is a variant of the childhood botulism, as the spores found it easier to proliferate in the presence of gastrointestinal abnormalities. In the case reported here, the patient had been diagnosed with probable metastatic colon cancer, one of the different gastrointestinal conditions cited in the literature that may favor the colonization of *C. botulinum*. Other predisposing abnormalities are bowel surgery, inflammatory bowel disease⁹, achlorhydria or recent antibiotic treatment^{2,11,12}, and possibly anatomical abnormalities such as Meckel's diverticulum¹. Most of these examples are well-recognized conditions that can disrupt the balanced competition between the normal bowel flora and the normally fastidious *Clostridia* species, in favor of the latter^{5,10}. Considering the possibility of sporadic botulism in a patient without a clear compatible history of food or wound source of botulinum toxins, the identification of excretion of toxins in stool samples is a critical determinant for the diagnosis⁵. Actually, the diagnosis of intestinal toxemia botulism depends on the repeated identification, for prolonged periods (from 2 to 119 days, according to previous reports), of viable *C. botulinum* or neurotoxins in clinical samples, besides clinical features that suggest this infection¹². Despite the fact that in the current report only

one set of samples was positive for *C. botulinum* toxins, considering that the patient died soon after the first samples collection (the results for confirmation were released *post-mortem*), no other form of botulism seems plausible.

The standard treatment for botulism is based on the early administration of the trivalent (A, B and E) botulinum antitoxin¹³. The antitoxin must be administered soon after clinical suspicion of botulism made⁸, since even mouse bioassays may not confirm the diagnosis, justifying why waiting for laboratory confirmation to initiate treatment is described as a serious mistake¹⁴.

In summary, the present case, a rare occurrence of intestinal toxemia botulism in an adult patient, reinforces the importance of considering the possibility of botulism as a differential diagnosis in patients with symmetric cranial nerves impairment and descending symmetrical weakness. Undoubtedly, early diagnosis, supportive care and the administration of botulinum antitoxin are crucial for achieving better clinical outcomes.

AUTHORS' CONTRIBUTIONS

Lucas José Sá da Fonseca: literature review, manuscript draft, English review; Diogo Couto de Carvalho, Helena Providelli de Moraes, Izabela Dayany França Feitosa, Gil Pereira Neto and Rodrigo Vasconcellos Vilela: clinical history review, manuscript draft, literature revision; Breno Franco Silveira Fernandes and Rodrigo Santiago Gomez: manuscript draft, final review of the manuscript; Vandack Nobre: manuscript draft, English review, final review of the manuscript.

CONFLICT OF INTERESTS

None.

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