

## Case Report

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# Toxic Megacolon leading to bowel perforation: A rare adverse effect of bortezomib

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### Abstract

Bortezomib is a chemotherapeutic drug used in the treatment of multiple myeloma and amyloidosis. The major dose-limiting adverse effect is neuropathy. Although rare, autonomic involvement of the gastrointestinal tract, can present with ileus. We report a compelling case highlighting the association between Bortezomib initiation and development of life-threatening toxic megacolon.

**Keywords:** Toxic Megacolon; Bowel perforation; Bortezomib (Velcade).

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### Introduction

Bortezomib (brand name Velcade) is an antineoplastic agent that inhibits proteasomes which regulate protein homeostasis within the cell. Specifically, it reversibly inhibits chymotrypsin-like activity at the 26s proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis [1]. It has been a mainstay for management of Multiple Myeloma for over a decade with significant improvement in overall survival [2]. Common adverse events are well documented and include peripheral neuropathy, headache, diarrhea, constipation, vomiting, and rash. Case reports have documented rare cases of bowel obstruction secondary to paralytic ileus [3-5]. Although the mechanism for these side effects remains poorly studied, it is postulated to be due to autonomic neuropathy. These events are typically managed with discontinuation of the medication and standard bowel obstruction management with complete reversal of symptoms. Unfortunately, this was not enough in our patient, so we present a case of Bortezomib induced toxic megacolon with colonic perforation requiring colectomy, which to our knowledge has not yet been reported in the literature.

### Case presentation

A 64-year-old female presented with complaints of sudden

onset severe back pain, constipation, and lethargy for a couple of days. Her past medical history was significant for well controlled hypertension on bisoprolol and recently diagnosed Immuno-globulin G lambda multiple myeloma. She was recently started on the initial phase of subcutaneous Bortezomib and Lenalidamide systemic chemotherapy and had received two doses of Bortezomib. On presentation, she was noted to be febrile (temperature of 40°C), minimally responsive, and with clinical signs concerning of an acute abdomen. Initial laboratory work-up revealed leukopenia with white blood cell count of 2400cell/ml, and an absolute neutrophil count of 800 cell/ml along with lactic acidosis and elevated inflammatory markers. Except a hyponatremia of 124 mg/dL; all electrolytes were within normal limits including calcium. Blood cultures were positive for Methicillin Sensitive Staphylococcus Aureus (MSSA) for which broad spectrum antibiotics were started. A Computed Tomography (CT) angiography of the chest and abdomen revealed diffuse colonic distention extending from the ascending colon to the sigmoid colon, with irregular wall thickening at the point of transition in the sigmoid colon concerning for obstruction. Within hours, the patient became hemodynamically unstable and required intubation with mechanical ventilation along with vasopressor and inotropic support for septic shock. She underwent an emergent laparotomy with intraoperative findings of

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a massively enlarged colon without evidence of ischemia or obstruction grossly suggestive of toxic megacolon. A total colectomy with an end ileostomy was performed. Surgical pathology revealed no malignancy, negative CMV immunostaining, no evidence of pseudo-membrane, absence of septic emboli, benign lymph nodes, and no chronic inflammatory changes. Fecal material was appreciable in the peri-colonic fat suggestive of perforation. Hospital course was complicated by acute renal insufficiency and hospital acquired pneumonia. She received an extended course of antibiotics for MSSA bacteremia postulated to eventuate from bowel flora translocation. Patient eventually required percutaneous tracheostomy for long-term weaning from mechanical ventilation due to chronic debilitation from multiple myeloma. She was eventually decannulated and clinically improved.

### Discussion

There is reasonable suspicion that this event was caused by Bortezomib, as other etiologies typically considered such as infection, recent abdominal surgery or excessive opioid use without an appropriate bowel regimen were not present in our patient's history. Additionally, her presentation was similar to other published case reports as it was soon after initiation of treatment rather than following several doses. It is unclear why her presentation was so severe, and while there are theories that ileus in these patients is secondary to autonomic neuropathy, our patient did not have any risk factors for predisposing neuropathy that may have led to this worsened presentation. Regardless of cause, it is important to look to how we may mitigate this in our future patients. Progress has already been made in the field, as studies done in the early days were able to identify IV bortezomib as more likely to dispose to adverse GI effects without being more efficacious than the subcutaneous preparation, leading to this method now being preferred [6]. Our patient was on the subcutaneous dose of Bortezomib given twice weekly, which is a common dosing regimen typically over four 42-day cycles before transitioning to weekly doses later in the treatment course. One approach that is being explored is an initial dose of once per week which was shown in a small study to decrease the rate of paralytic ileus without compromising efficacy [7]. This may be an option for patients at higher risk for paralytic ileus such as those with renal insufficiency or on long term opioids which are both common scenarios for our Multiple Myeloma patients, and if larger studies can confirm no loss of efficacy this regimen may be considered for all patients in the future [8].

CT scan of the abdomen with IV contrast showing diffuse colonic distention extending from the ascending colon to the sigmoid colon. Within the sigmoid colon at the area of transition there is irregular circumferential wall thickening with a few polypoid projections. There are nondilated loops of small bowel visualized. There is no pneumatosis or free air.

**Operative findings:** Massively enlarged colon, but without evidence of ischemia or perforation. There was no evidence of a mechanical obstruction.



Figure 1:



Figure 2:

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