Neutropenic Enterocolitis: A Rare Complication of Sacituzumab Govitecan

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Keywords
Colitis · Chemotherapy · Neutropenia

Abstract
Neutropenic enterocolitis (NE) is a rare form of inflammatory colitis seen in severely neutropenic patients. Patients with NE typically have severe neutropenia (absolute neutrophil count [ANC] <500/mm³) in the setting of exposure to cytotoxic chemotherapy. Taxanes have traditionally been associated with NE, but there has been a growing amount of literature, linking a variety of other chemotherapeutic agents. Sacituzumab govitecan (SG) is a novel antibody-drug conjugate comprising a topoisomerase I inhibitor component conjugated to an antibody targeting human trophoblast cell-surface antigen 2 (Trop-2). SG is approved for the treatment of unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) and urothelial cancer. We report a case of NE in a patient with mTNBC receiving SG and its successful management. Prompt diagnosis and management of NE in such patients can be potentially lifesaving.

Introduction
Neutropenic enterocolitis (NE) involves the development of potentially life-threatening bowel wall necrosis in a severely neutropenic patient. Patients with an absolute neutrophil count (ANC) <1,000/mm³ are at increased risk, but NE typically occurs in patients with ANC <500/mm³ [1]. The pathogenesis of NE is poorly understood. It is hypothesized that cytotoxic chemotherapy damages the integrity of the gut mucosa and permits translocation of luminal...
microorganisms into the bowel wall. In immunosuppressed patients, the subsequent infection and its dissemination are often poorly controlled, leading to potentially fatal complications [2]. Histologic evaluation of the bowel in NE is characterized by areas of necrosis, infiltrating microorganisms, hemorrhage, ulceration, and edema [2]. Clinical signs and symptoms can include fever, abdominal pain, abdominal distention, diarrhea, gastrointestinal hemorrhage, hypotension, and tachycardia [3, 4]. Findings on abdominal imaging such as bowel wall thickening on computerized tomography (CT) or ultrasound can facilitate diagnosis [5]. Complications from NE include bowel ischemia, bowel perforation, sepsis, and disseminated intravascular coagulation [2, 6, 7]. NE has a high mortality rate that has been reported to exceed 50% [8]. The diagnosis of NE is often challenging, and prompt evaluation and management can be lifesaving [2]. Chemotherapy-induced NE is a relatively rare complication of treatment in a cancer patient. It has been commonly reported in patients with hematologic malignancies and stem cell transplant patients receiving myeloablative chemotherapy regimens [9]. NE has also been associated with the use of cytotoxic chemotherapy for the treatment of solid tumors, particularly with the use of Taxane-based regimens (paclitaxel and docetaxel) [9, 10]. We report a case of diagnosis and successful management of NE in a 57-year-old female patient with metastatic breast cancer receiving treatment with SG.

Case Report

The patient is a 57-year-old woman with stage IIIB (ER [estrogen receptor] negative, PR [progesterone receptor] negative, HER-2 [human epidermal growth factor receptor-2] negative) invasive ductal adenocarcinoma of the right breast at the time of initial diagnosis. She was treated with neoadjuvant chemotherapy consisting of dose-dense doxorubicin and cyclophosphamide (4 cycles), followed by right breast lumpectomy, and adjuvant radiation therapy. Three months after the completion of adjuvant radiotherapy, she had recurrence of cancer in the right breast along with lung metastasis. She received several lines of cytotoxic chemotherapy for metastatic disease including capecitabine, nab-paclitaxel, and gemcitabine. Following disease progression on these agents, she was started on SG. The first dose of SG was administered intravenously (IV) at 10 mg/kg. The patient's baseline hematologic parameters were within normal limits: white blood cell count (WBC) 5,000/mm³ (reference range: 3,700–10,500/mm³); ANC 3,081/mm³ (reference range: 2,188–8,206/mm³); hemoglobin 14.2 g/dL; and platelet count of 336,000/mm³.

Twelve days after the initiation of SG, the patient presented to the emergency department with 3 days of progressively worsening abdominal pain and vomiting. She was afebrile (temperature of 36.8°C) and hypotensive (blood pressure of 96/69 mm Hg). Physical exam revealed diffuse abdominal tenderness, most significant in the epigastrium and right upper quadrant, with minimal guarding and no rebound tenderness. Laboratory evaluation was notable for an ANC of 409/mm³ (reference range: 2,188–8,206/mm³) and WBC count of 1,100/mm³ (reference range: 3,700–10,500/mm³); ANC 3,081/mm³ (reference range: 2,188–8,206/mm³); and platelet count of 336,000/mm³. CT scan of the abdomen with intravenous contrast showed edematous wall thickening of the ascending colon (Fig. 1–3). Blood cultures and stool antigen testing (including Clostridium difficile toxin and antigen screen) were negative for an infectious source. A clinical diagnosis of NE was made.

During her hospitalization, she was put on bowel rest and received IV rehydration therapy, along with broad-spectrum antibiotics (IV cefepime 2 g every 8 h and oral metronidazole 500 mg every 8 h). The patient's neutropenia improved without the use of growth factor
support agents (Table 1). Serum sodium improved to 132 mEq/L with intravenous hydration. Hyponatremia was attributed to hypovolemia from diarrhea and low oral intake. She improved clinically with normalization of her hemodynamic parameters by hospital day 3. She was able to tolerate an oral diet on hospital day 4. On day 5 of hospitalization, the patient was discharged.

**Fig. 1.** Axial view of edematous wall thickening of the ascending colon indicative of colitis measuring 12 mm (yellow arrow).

**Fig. 2.** Coronal view of edematous wall thickening of the ascending colon indicative of colitis (yellow arrow).

**Fig. 3.** Fat stranding of the omentum indicative of inflammation (yellow arrow).
Case Reports in Oncology

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DOI: 10.1159/000525351

Home. Oral antibiotic therapy was continued to complete a total of 14 days of treatment. In the outpatient setting, she was successfully re-challenged with SG. She received cycle 2 of SC 19 days after hospitalization. The dose of SC was reduced from 10 mg/kg to 7.5 mg/kg, and granulocyte colony-stimulating factor (G-CSF) was administered prophylactically. The patient received a total of 3 additional cycles of SG with prophylactic G-CSF and did not experience recurrence of severe neutropenia or abdominal symptoms. Treatment with SC was subsequently stopped due to disease progression.

Discussion

Sacituzumab govitecan is an antibody-drug conjugate consisting of an anti-Trop-2 antibody conjugated with SN-38, an active metabolite of irinotecan and a topoisomerase I inhibitor [11]. Trop-2 is a transmembrane Calcium channel transducer that is heavily expressed in breast cancer tissue and in other tumors [12]. The expression of Trop-2 is associated with an unfavorable prognosis in advanced breast cancer [13]. Binding of the antibody component of SC to Trop-2 facilitates targeted delivery of the anti-neoplastic agent SN-38 to tumor cells. In the phase 3 randomized control trial (ASCENT), SG monotherapy showed improved objective response rate (35% vs. 5%), progression-free survival (5.6 vs. 1.7 months), and overall survival (12.1 vs. 6.7 months) when compared with other single-agent chemotherapies (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with mTNBC [14]. SG use was associated with an increased incidence of treatment-related adverse events when compared to single-agent chemotherapy including grade 3 or higher neutropenia (51% vs. 33%), diarrhea (10% vs. <1%), and febrile neutropenia (6% vs. 2%) [14]. While there is an increased incidence of neutropenia and gastrointestinal symptoms (diarrhea), with SC, the occurrence of NE is rare. Neutropenic colitis has been reported to occur in 0.5% of the patients receiving SG [15].

Early recognition and prompt intervention are crucial towards improving outcomes in NE. Despite the availability of published literature on the occurrence of NE in cancer patients, there is a lack of consensus on an established diagnostic criterion. Proposed criteria incorporate both subjective and objective findings in the absence of alternative etiologies that could result in gastrointestinal injury. Symptoms indicative of NE may include fever, abdominal pain/cramping, abdominal distention, diarrhea, and/or gastrointestinal bleeding in a neutropenic patient. Supportive radiographic findings include presence of bowel wall thickening on ultrasound or CT scan [8, 9]. Treatment approach typically addresses management of febrile neutropenia and signs and symptoms of inflammatory or infectious colitis [16]. Management strategies incorporate bowel rest, electrolyte repletion, and fluid resuscitation with the consideration of parenteral nutrition for patients with prolonged periods of dietary restriction [17]. Empiric treatment with broad-spectrum antibiotics is indicated due to the potential for translocation of luminal gut microorganisms into the bowel wall or the bloodstream resulting from the bowel ischemia or necrosis. The choice of empiric antibiotic therapy is often similar to agents utilized in the management of neutropenic fever in cancer patients. The most commonly utilized intravenous agents include piperacillin-tazobactam, cefepime, ceftazidime, or an antipseudomonal carbapenem (imipenem or meropenem) [18]. Considering gastrointestinal involvement in NE, the addition of anaerobic

Table 1. Absolute neutrophil count during hospitalization (reference range: 2,188–8,206/mm³)

| Day     | Day 2  | Day 3  | Day 4  | Day 5  |
|---------|--------|--------|--------|--------|
| Day 1  | 409/mm³| 464/mm³| 2,345/mm³| 2,850/mm³| 2,590/mm³|
antibiotic coverage is important, such as using piperacillin-tazobactam or using cefepime in combination with metronidazole. NE can also be complicated by fungal infections such as fungal infiltration of bowel wall or overt fungemia. Amongst fungal microorganisms, *Candida* spp is the most common species involved in NE [19]. Antifungal therapy should be strongly considered in patients in whom neutropenic fever persists for greater than 3–5 days. The use of hematopoietic growth factors in NE is controversial, as there is a lack of prospective randomized data. The potential utility of growth factors in NE can be extrapolated from clinical experience in cancer patients with neutropenic fever. Growth factor support can be considered in patients who are high-risk for infection-associated complications or who have additional risk factors such as expected prolonged (>10 days) and profound (<100/mm³) neutropenia, age >65 years, pneumonia, hypotension, sepsis syndrome, or invasive fungal infection [18, 20]. Surgical intervention is typically avoided in cancer patients with marked neutropenia or thrombocytopenia. Select patients with NE can be considered for surgery with complications such as bowel perforation, persistent gastrointestinal bleeding after resolution of thrombocytopenia and coagulopathy, or continued clinical deterioration despite aggressive medical management [21, 22]. Our patient was treated with conservative management and successfully discharged after a 4-day hospitalization with resolution of her symptoms. She was successfully rechallenged with three additional cycles of SG. Subsequent doses of SG were administered at a reduced dose (7.5 mg/kg) along with prophylactic growth factor support. She did not have recurrence of NE with additional therapy with SG.

**Conclusion**

NE is a rare but potentially fatal complication of chemotherapy and must be considered in a cancer patient presenting with abdominal symptoms in the setting of severe neutropenia. Diagnosis can be challenging and is based on symptoms, laboratory findings, and imaging results. NE should be considered in the differential diagnosis of a cancer patient receiving SG therapy who presents with severe neutropenia and abdominal symptoms. After successful treatment of NE, such patients can be safely rechallenged with SG with dose reduction and addition of prophylactic growth factor support.

**Statement of Ethics**

This case report did not meet the threshold of research per the University of Iowa Institutional Review Board standards and thus did not require ethics approval. Written informed consent was obtained from the patient’s next of kin for publication of this case report and any accompanying images, as the patient is now deceased.

**Conflicts of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

There were no funding involved in the development of this case review.
Author Contributions

Dr. Adam Prescott, MD; Dr. Aditya Ravindra, MD; and Dr. Asad Javed, MBBS: offered substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; provided final approval of the version to be published; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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