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Case Report

Ischemic Colitis Associated with Paclitaxel and Carboplatin Combination

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Keywords
Ischemic colitis · Chemotherapy complications · Paclitaxel · Carboplatin

Abstract
A 62-year-old white female with a history of early-stage triple-negative breast cancer on a combination of carboplatin and paclitaxel in the adjuvant setting presented with lower gastrointestinal bleeding. She tolerated 4 cycles of dose-dense adriamycin/cyclophosphamide with no major symptoms. After 6 cycles of weekly paclitaxel in combination with carboplatin every 3 weeks, she presented with diarrhea and lower gastrointestinal bleeding. Colonosopic examination showed erythema and inflammation in the splenic flexure, descending colon, and sigmoid colon consistent with ischemic colitis. Pathology favored the same diagnosis. She was treated conservatively with intravenous fluids and bowel rest. Chemotherapy was held for 2 weeks and resumed after recovery without carboplatin. She was able to tolerate the remaining 6 cycles of paclitaxel with no recurrence of her symptoms.

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Background

Paclitaxel (Taxol) is one of the cornerstone chemotherapies in treating breast cancer. It is often used as part of combination chemotherapy in the adjuvant setting and can be used as a single agent in the metastatic setting. Adverse reactions include alopecia, peripheral neuropathy, nausea, vomiting, diarrhea, and mucositis. The combination of carboplatin and paclitaxel is often used in triple-negative breast cancer, especially in the neoadjuvant setting, as some studies showed benefit in terms of complete pathologic response [1]. Using this combination in the adjuvant setting is controversial. The BR003 is a clinical trial investigating the benefit of adding carboplatin to the standard chemotherapy in the adjuvant setting (NCT02488967). It is hypothesized that adding carboplatin in the adjuvant setting may add some benefit, but it is possible that it may increase side effects and intolerability. In this case, the patient was not able to tolerate the combination, but was able to tolerate single-agent paclitaxel after recovery. This suggests the possibility of added toxicity with the combination.

Case Presentation

A 62-year-old white female with a history of hypertension, which is well controlled, was found to have a new irregular density with microcalcifications on screening mammogram. Biopsy showed invasive mammary carcinoma of the ductal type. Tumor was grade 3, ER negative, PR negative, and HER2-neu negative by immunohistochemistry staining. She was diagnosed with stage IIA (T2, N0, M0) breast cancer. She has never smoked and has no history of drinking.

She underwent lumpectomy with sentinel lymph node biopsy. Her tumor measured 3.2 cm with negative margins. Lymph node biopsy was negative. She met the criteria for adjuvant chemotherapy treatment. She was enrolled in clinical trial BR003. The trial investigates the benefits of adding carboplatin to the standard chemotherapy in patients with triple-negative breast cancer in the adjuvant setting. She was planned to receive dose-dense adriamycin/cyclophosphamide for 4 cycles followed by weekly Taxol for 12 weeks plus carboplatin every 3 weeks for 4 cycles. She received 4 cycles of adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles with pegfilgrastim support. She was then started on paclitaxel 80 mg/m^2 with carboplatin adjusted for an area under the curve of 6 mg/mL/min.

She tolerated 6 cycles of weekly Taxol as well as 2 doses of carboplatin with the exception of mild neuropathy and mild cytopenia. Three days after her cycle 6 of Taxol, the patient presented to the emergency room with abdominal cramping and diarrhea for 1 day prior to admission. She also reported multiple episodes of large amounts of bright red blood with bowel movements. Her symptoms were associated with generalized weakness and fatigue. She denied any fever, chills, nausea, or vomiting. Evaluation upon hospitalization revealed stable vital signs with no fever. Abdominal examination revealed mild diffuse tenderness with no guarding or rebound tenderness.

Laboratory examination revealed normal white blood cells with absolute neutrophilic count of 6.9 ×10^9/L, hemoglobin of 9.4 g/dL, and platelet count of 83 × 10^9/L. Chemistry profile was remarkable for potassium of 3.3 mEq/L. Stool for occult blood was positive. Stool PCR testing was negative for multiple organisms including *Campylobacter*, *Clostridium difficile* (toxin A/B), *Salmonella*, *Yersinia enterocolitica*, enteroaggregative *E. coli*, enteropatho-

genic *E. coli*, enterotoxigenic *E. coli*, *Cyclospora cayetanensis*, *Entamoeba histolytica*, *Giardia lamblia*, adenovirus, rotavirus A, and *Cryptosporidium*. Abdominal X-ray showed no evidence of bowel obstruction or ileus. The patient underwent colonoscopic evaluation, which revealed moderately severe ischemic colitis in the splenic flexure, descending colon, and sigmoid colon (Fig. 1). The cecum, ascending colon, transverse colon, and rectum appeared normal. These findings, along with the lack of significant cardiovascular risk factors and previous events, suggested that her condition is likely related to chemotherapy. Pathology showed acute colitis, favoring ischemic colitis (Fig. 2, Fig. 3).

The patient was treated with intravenous fluid hydration and bowel rest. Her diarrhea as well as her abdominal cramps resolved within 3 days. She was discharged home and her chemotherapy was held for 2 weeks. After carefully reviewing the literature, the patient was offered to continue on single-agent paclitaxel, with close monitoring after explaining the possibility of relapse. Single-agent weekly paclitaxel was resumed and carboplatin was discontinued. She was able to tolerate the remaining 6 cycles of weekly paclitaxel well.

Discussion

Ischemic colitis is a rare complication of cytotoxic chemotherapy. The more frequent gastrointestinal toxicities of chemotherapy include nausea, vomiting, diarrhea, and infectious complications, especially in the setting of neutropenia. Taxane-based chemotherapy (docetaxel and paclitaxel) has been associated with various types of colitis. *Clostridium difficile*-associated pseudomembranous colitis is more common [2]. Neutropenic colitis is another less common entity. Cases of ischemic colitis in the absence of neutropenia and infectious etiologies are rare but few are reported in the literature. Ischemic colitis related to the combination of carboplatin/paclitxael was previously reported [3, 4]. Paclitaxel is an antimicrotubule agent that exerts its antineoplastic effect through halting mitosis. The mechanism by which it causes ischemic colitis is poorly understood. It is postulated that it exerts this effect through direct effect on mucosal cells. It is also reported to have an antiangiogenic effect in mice [5]. However, there are no reported cases of ischemic colitis with single-agent paclitaxel. In a case series using docetaxel, one case of ischemic colitis out of six was reported with its use as a single agent. The rest of the cases in this case series of ischemic colitis was observed more with the combination of docetaxel with other agents such as vinorelbine, pamidronate, and cyclophosphamide [6].

This case report suggests that combining a taxane, such as paclitaxel, with another agent, such as carboplatin, may rarely increase the risk of developing ischemic colitis. It does not appear that paclitaxel used as a single agent is as likely to cause this rare complication.

Statement of Ethics

The patient's informed consent was acquired prior to publication of the case. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflict of interest.

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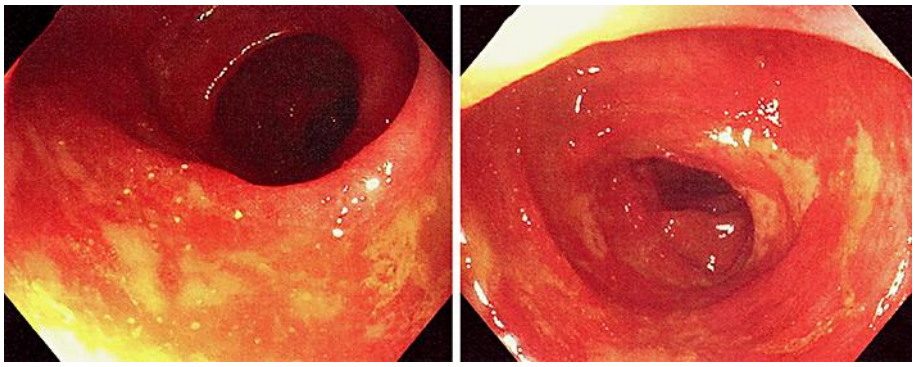

Fig. 1. Splenic flexure colitis.

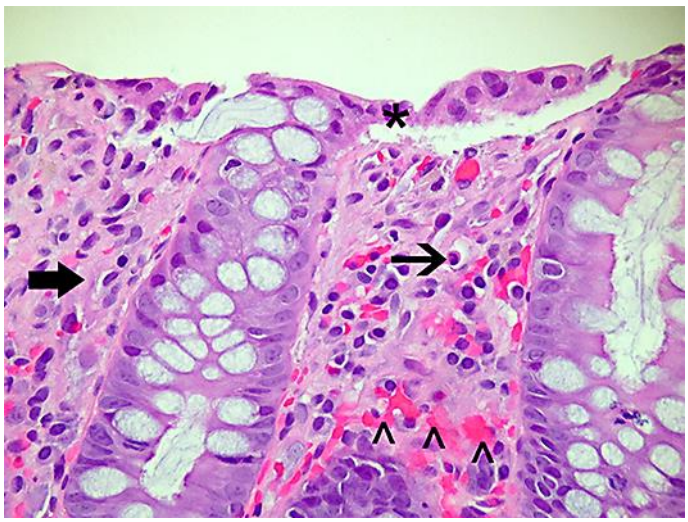

Fig. 2. Histopathological changes suggestive of ischemic colitis characterized by thinned, attenuated surface epithelium (asterisk), increased fibrosis shown by dense eosinophilia of the lamina propria (thick arrow), neutrophil of focal acute inflammation (thin arrow), and focal hemorrhage (carets at lower part of photomicrograph) (400× magnification).

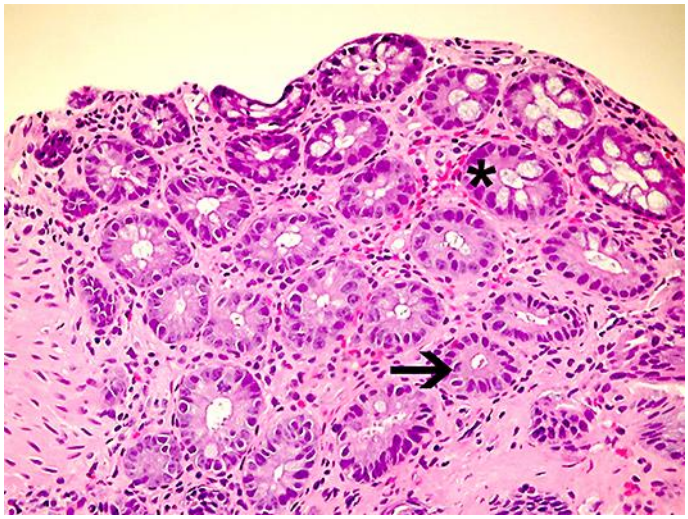

Fig. 3. Histopathological changes suggestive of ischemic colitis characterized by smaller crypts with loss of goblet cells (arrow), compared to more normal crypt with intact goblet cells (asterisk) (200× magnification).