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Case Report

Taxane-Induced Upper Gastrointestinal Bleeding

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Keywords
Gastrointestinal bleed · Chemotherapy · Breast cancer · Taxane

Abstract
Docetaxel is a taxane, which is a class of chemotherapy agent used in the treatment of multiple malignancies. It is known to have gastrointestinal side effects which can range from mild symptoms such as nausea and diarrhea to more severe complications such as neutropenic enterocolitis. In the current literature, taxanes have not been described to cause upper gastrointestinal bleeding and melena. Here, we present a case of a 54-year-old woman with breast cancer who developed dizziness, fatigue, and melena after receiving chemotherapy. Esophagogastroduodenoscopy revealed diffuse gastric erosions as well as ulceration and linear superficial lesions in the duodenum; biopsies from these sites showed taxane-induced toxicity. Her bleeding resolved with medical therapy and subsequent removal of docetaxel from her chemotherapy regimen. This case identifies upper gastrointestinal bleeding as a previously undescribed side effect of docetaxel therapy. Recent docetaxel use should be included in the differential diagnosis for upper gastrointestinal bleed, and diagnosis should lead to consideration of cessation of docetaxel or substitution with another chemotherapeutic agent.

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Background

Taxanes are chemotherapeutic agents whose use is widespread in treating malignancies of the esophagus, stomach, breast, lung, bladder, prostate, and ovary. The gastrointestinal toxicities commonly associated with taxane therapy include nausea, vomiting, mucositis, and diarrhea. Rarely, lower gastrointestinal bleeding and colonic perforation secondary to neutropenic enterocolitis and ischemic colitis have both been reported as complications of taxane-based chemotherapy [3]. Here, we present a case of upper gastrointestinal bleeding secondary to taxane toxicity diffusely involving the stomach and the second portion of the duodenum in the absence of neutropenia. To the best of our knowledge, this complication has not been previously reported to be associated with taxane toxicity in the literature.

Case Report

A 54-year-old woman with recently diagnosed early-stage breast invasive ductal carcinoma presents with recurrent episodes of melena following her chemotherapy infusions. She was diagnosed after a routine mammogram picked up microcalcifications in her right breast, and subsequent biopsy revealed invasive ductal carcinoma which was estrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor 2 positive. She was initiated on the chemotherapy regimen of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) planned every 3 weeks for 6 cycles; she additionally received dexamethasone for premedication and granulocyte colony stimulating factor to reduce the risk of developing febrile neutropenia. She initially tolerated her first cycle well but developed persistent diarrhea 7 days after her first infusion. Five days later, she developed melenic diarrhea that was associated with dizziness for which she presented to a local emergency department; she denied any vomiting, fevers, chills, or abdominal pain during this time. Her medical history was negative for peptic ulcer disease and alcohol abuse. However, she had been intermittently taking ibuprofen for the past 3 months, which had increased recently to approximately 400 mg of ibuprofen a day. On admission, she was afebrile and normotensive, and her abdominal exam was negative for any tenderness, but her hemoglobin was noted to drop from 11.7 g/dL to 8.4 g/dL (reference range 12.0 g/dL–15.5 g/dL) in the first 18 h of her inpatient stay. Her white blood cell count was elevated to 17.5×10^3 cells/mcL (reference range 4.1×10^3 cells/mcL–10.9×10^3 cells/mcL) with a neutrophilic predominance. The patient had been started on intravenous proton-pump inhibitor (PPI) therapy at 40 mg twice a day empirically in the emergency department, and she underwent inpatient esophagogastroduodenoscopy which revealed a nonbleeding post-bulbar ulcer in the duodenum. The ulcer was subsequently biopsied and was negative for *H. pylori*. Her melena resolved by hospital day 2 and was discharged on oral PPI therapy. She stopped taking NSAIDs, and she remained asymptomatic aside from developing some alopecia until her second cycle of TCHP chemotherapy.

Less than 24 h after her second chemotherapy infusion, she had several episodes of black stools that were initially well formed in consistency that progressively became loose and concurrently experienced dizziness and palpitations; she did not experience any abdominal pain, nausea, nor did she have any emesis. She was compliant with her PPI therapy since discharge. She was then directly admitted to our hospital, where physical exam was notable for conjunctival pallor and frank melena on digital rectal exam, but her abdominal exam elicited no tenderness with palpation and was otherwise unremarkable. On laboratory studies, her hemoglobin was critically low at 6.5 g/dL (reference range 12.0 g/dL–15.5 g/dL), trending down from 8.2 g/dL in the oncology clinic the day before despite being transfused 2 units of packed red blood cells during that visit. She additionally had a leukocytosis

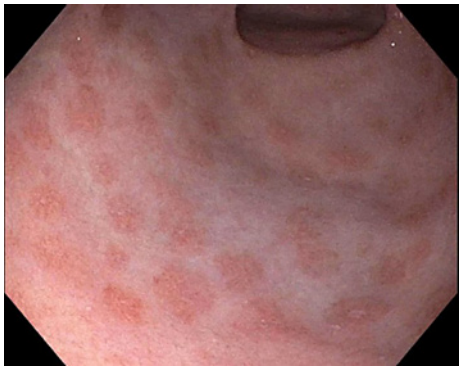

Fig. 1. Stomach, scattered gastral erosions.

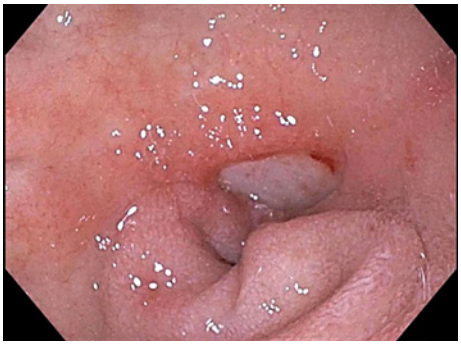

Fig. 2. Clean-based ulcer in the first part of the duodenum.

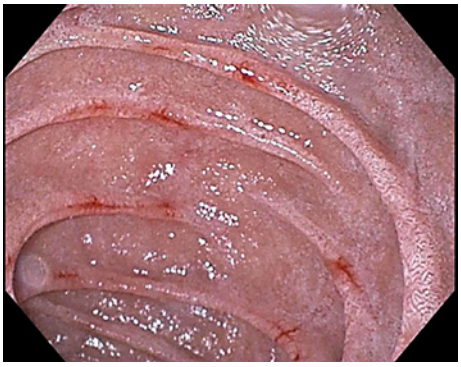

Fig. 3. Linear superficial lesions in the second portion of the duodenum.

to 19.91 × 10^3 cells/mcL (reference range 4.1 × 10^3 cells/mcL–10.9 × 10^3 cells/mcL) with a normal differential distribution. Another urgent inpatient esophagogastroduodenoscopy was performed which showed scattered gastric erosions (Fig. 1) as well as the previously characterized clean-based ulcer in the superior aspect of the post-bulbar area (Fig. 2) and furthermore showed multiple oozing linear superficial mucosal breaks that circumferentially involved the majority of the second portion of the duodenum (Fig. 3). The source of the patient's melena was deemed to be from these prominent mucosal lesions in the second portion of the duodenum which exhibited signs of recent bleeding, as the ulcer in the first portion of the duodenum had a stable appearance with no high-risk stigmata. Biopsies were obtained at all 3 sites and underwent review by pathology. At low magnification, the cells in the proliferative compartment appeared hyperchromatic with numerous mitotic arrest results in several readily apparent mitoses, many seen as ring forms. However, these histo-

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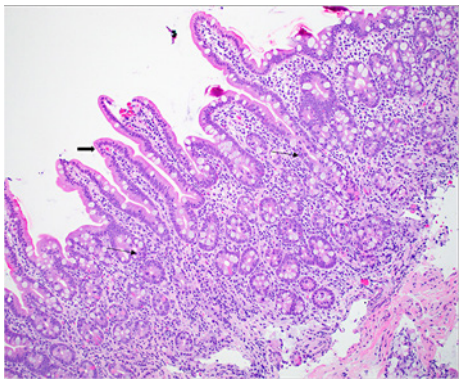

Fig. 4. H&E low-power view of biopsy from mucosal break from the second portion of the duodenum shows hyperchromatic nuclei and numerous mitotic figures at the proliferative compartment (→); however, the surface epithelium shows complete maturation (◗).

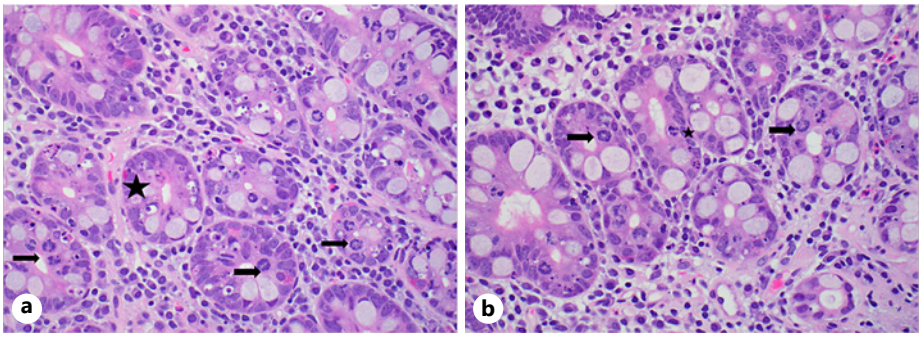

Fig. 5. A, **B** H&E high-power view of the biopsy from the oozing lesions of the second portion of the duodenum shows numerous ring mitosis (◗) and apoptotic bodies (★).

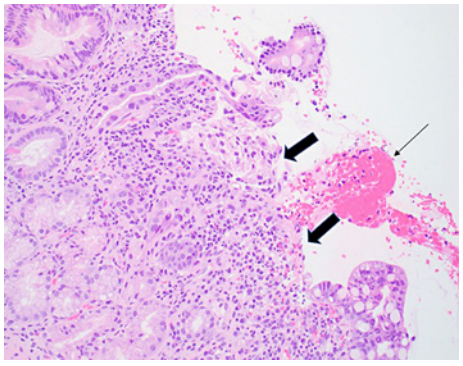

Fig. 6. H&E high-power view of the biopsy from the second portion of the duodenum showing mucosal breaks/ulceration (◗) in the setting of taxane toxicity with focal erosion and hemorrhage (→).

logic changes are confined to the proliferative compartment, and the biopsy displays epithelial surface maturation (Fig. 4). On a higher microscopic magnification, the main striking histologic features were ring mitoses and prominence in apoptosis (Fig. 5 A, B). These findings, seen in all 3 biopsies, were compatible with taxane toxicity. Focal hemorrhaging was observed with the mucosal breaks seen on the duodenal biopsies (Fig. 6). No evidence of *Helicobacter pylori* infection was seen.

The patient's melena resolved on PPI therapy alone. Subsequent stool culture did not grow any pathogenic organisms, and stool studies were negative for *Shigella*, *E. coli* O157, *Salmonella*, and *Campylobacter*. Docetaxel was removed from her next chemotherapy infusion which she tolerated well. She subsequently had taxanes re-introduced into her chemotherapy regimen at

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her next cycle in the form of weekly paclitaxel. She did not report any further GI bleeding and completed her adjuvant chemotherapy successfully. The patient underwent surveillance endoscopy approximately 1.5 weeks after completing paclitaxel therapy, almost 4 months after the previous endoscopy. It showed a normal appearing esophagus and duodenum; however, multiple dispersed erosions were seen in the gastric body with stigmata of recent bleeding. Her hemoglobin was stable at 10.9 g/dL 9 days after the surveillance endoscopy, and she has not required any blood transfusions since docetaxel was removed from her chemotherapy regimen.

Discussion

Taxanes are thought to induce changes in the gastrointestinal epithelium by binding to microtubules, which promotes their polymerization [1]. These microtubule polymers can be visualized under electron microscopy as ringed mitoses, as seen in the biopsies from our patient. The gastrointestinal toxicities commonly associated with taxane therapy include nausea (34–42%), vomiting (22–23%), stomatitis (26–53%), and diarrhea, and there have been several case reports of neutropenic enterocolitis and ischemic colitis. Common skin manifestations include alopecia (56–76%) and nail changes (11–41%) and like gastrointestinal toxicities are also due to the direct cytotoxic effects of taxanes [5]. With regard specifically to combination therapy of docetaxel with carboplatin, trastuzumab, and pertuzumab as per the TCHP protocol, the most common side effects are neutropenia (25.1%), diarrhea (15.5%), febrile neutropenia (15.1%), and anemia (11%). Other side effects of docetaxel include infusion reactions, fluid retention, pneumonitis, fatigue, lacrimal duct stenosis, and peripheral neuropathy [4]. Taxane toxicities typically resolve following cessation or dose reduction of the medication except for peripheral neuropathy, which can persist long following discontinuation of chemotherapy. These toxicities are dose dependent and may have a delayed presentation in patients following infusion. For example, neutropenic enterocolitis can present 2–13 days following docetaxel infusion. There are emerging data suggesting that patients with gene variants in proteins involved in the metabolism of taxanes such as ABCB1, CYP3A4, and CYP3A5 are at higher risk of developing taxane toxicities; however, data are still inconclusive [2]. Within administration regimens of taxanes, weekly administered paclitaxel is associated with less toxicity than docetaxel administered at 3-week intervals [6]. Furthermore, the purported mechanism of docetaxel-induced GI toxicity is p53 independent, whereas paclitaxel appears to induce apoptosis in the GI epithelia [1, 7]. For these reasons, the patient presented in this report was switched to weekly paclitaxel.

Since there have been no previously described cases of upper gastrointestinal bleeding secondary to taxane-induced duodenitis, this patient received the standard of care for nonvariceal upper gastrointestinal bleeding which comprised packed red blood cell resuscitation, PPI therapy, and upper endoscopy, although docetaxel was omitted from her next chemotherapy cycle. Appropriate PPI therapy, which is typically 12 weeks in duration, generally heals over 90% of peptic ulcers given that their aggravating factors such as nonsteroidal anti-inflammatory drug use and *H. pylori* are removed or treated, respectively. Regarding conventional duodenal ulcers and duodenitis, repeat surveillance endoscopy is typically not performed due to their low risk of association with enteric malignancy. The abdominal pain, nausea, emesis, and other symptoms associated with duodenal ulcers resolve with successful treatment with appropriate acid suppressive therapy, and persistence of symptoms may be suggestive of refractory disease. In patients with refractory peptic ulcer disease, the risk for complications such as gastrointestinal bleeding, perforation, and gastric outlet obstruction is approximately 2–3% yearly. With continued PPI therapy and re-introduction of weekly paclitaxel in lieu of docetaxel, she has had no further episodes of gastrointestinal bleeding.

This case illustrates a previously undescribed side effect of gastropathy and duodenopathy causing gastrointestinal hemorrhage associated with docetaxel administration. Our findings will help expand our understanding of the potential complications that can occur with docetaxel therapy. Prompt diagnosis obtained through endoscopic biopsy and medical intervention followed by adjustment of the chemotherapy regimen helped this patient receive successful treatment of her breast cancer without further complication from gastrointestinal bleeding.

Acknowledgments

We would like to recognize all the contributors in this case report. In addition, special thanks are due to all the patients at the Norris Comprehensive Cancer Center, especially the subject of this case report, who have privileged us with their care.

Statement of Ethics

The study is exempt from ethics committee approval as it is a report of a single case; no special protocol was followed, and the patient received the standard of medical care. The subject of the case report has given her written informed consent to publish this case.

Conflict of Interest Statement

Dr. Irene Kang discloses Bristol Myers Squibb (consulting fee) and Puma Biotechnology (consulting fees and speakers bureau) as potential conflicts of interest.

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Author Contributions

Yao Liu and Brent Hiramoto wrote and revised the manuscript; they contributed equally and share first authorship. Janet Kwok reviewed and revised the manuscript and holds second authorship. Ahmad Ibrahim and Sergei Tatsichev performed the pathology figures and analysis; they share third authorship. Irene Kang and Rushabh Modi reviewed and revised the manuscript; they share senior authorship.

Data Availability Statement

All data relevant to the case presentation are available as part of the article and no additional source data are required.

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