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Case Report

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A Case of Pneumatosis Intestinalis With Pneumoperitoneum as a Potential Delayed Adverse Effect of Capecitabine

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Abstract

Ileitis and colitis are known complications of capecitabine when used in patients with gastrointestinal cancers. However, to our knowledge, pneumatosis intestinalis (PI) has not previously been reported with this medication. We present a patient with breast cancer, without any metastases to the gastrointestinal tract, who presented with persistent diarrhea 4 weeks after discontinuing adjuvant capecitabine, which was found to be due to PI. As she had no other risk factors or identifiable causes, her PI was attributed to a delayed reaction to capecitabine. This case highlights the need to consider PI earlier in the differential diagnosis in patients with breast cancer who present with unexplained diarrhea after recent discontinuation of capecitabine.

Keywords: Capecitabine; Pneumatosis intestinalis; Intestinal perforation

Introduction

Capecitabine is an oral pyrimidine analog prodrug used for the treatment of metastatic breast cancer as a single agent or in combination. Ileitis, colitis, and bowel perforation have been reported as complications of capecitabine in patients with gastrointestinal (GI) malignancies while actively receiving the medication [1-4]. However, to our knowledge, pneumatosis intestinalis (PI) has not previously been reported with this medication. Herein, we present what to our knowledge is the first case of PI as a delayed adverse reaction after therapy with capecitabine for breast cancer.

Case Report

A woman in her 70's was diagnosed with right-sided, intraductal grade 3 triple-negative stage III breast cancer and treated with neoadjuvant chemotherapy consisting of doxorubicin, cyclophosphamide, and paclitaxel. Five months after beginning her neoadjuvant therapy, she underwent a mastectomy, and adjuvant therapy with capecitabine was initiated 3 months after her surgery. One week after the end of the first 21-day cycle, she presented to her oncologist with nausea and severe watery diarrhea. Her outpatient evaluation included stool ova and parasites, *C. difficile* stool antigen, and colonoscopy, all of which were negative. Based on her apparent intolerance, capecitabine was discontinued. It was decided that she would not receive additional adjuvant therapy, and because of that decision, genetic testing for dihydropyrimidine dehydrogenase (DPD) mutations was not ordered. DPD is the principle enzyme required for 5-flourouracil (5-FU) metabolism and 3-5% of patients have a mutation leading to partial deficiency that can lead to acute and early-onset toxicity, which would need to be considered if she relapsed and required additional chemotherapy.

Four weeks after discontinuing capecitabine, the patient presented to the emergency department due to continued diarrhea. Her vital signs were: blood pressure (BP) 115/66 mm Hg; heart rate 89/min; respiratory rate 18/min; temperature 97.8 F; and pulse ox 98% on room air. Her physical examination was unremarkable, and her abdomen was normal. Due to prerenal azotemia she was admitted to the hospital and treated with intravenous fluids and anti-diarrheal medications. The morning after admission, she noted abdominal discomfort and a computed tomography (CT) scan of the abdomen/pelvis was ordered, which revealed extensive PI and free intraperitoneal air. She was taken to the operating room that night, and when the surgeons entered the abdomen, they were met with a rush of air consistent with pneumoperitoneum. PI and thickening were present in 4 feet of the jejunum, and there was a 1 cm area of inflamed jejunum that was presumed to be the site of perforation. No bowel was resected as there was no obvious perforation, her post-operative course was unremarkable, and her diarrhea resolved.

Discussion

PI is the presence of gas within the wall of the bowel and has multiple synonyms, including pseudopneumatosis, intestinal emphysema, and bullous emphysema of intestine [5]. In a study of ninety-seven patients with a CT diagnosis of PI, the location of pneumatosis was as follows: 46% colon, 27% small bowel, 5% stomach, and 7% both small and large bowel

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[6]. PI is classified as either primary (idiopathic) or secondary, with the latter making up about 85% of all PI cases. Causes of secondary PI classically include: 1) Mechanical irritation or increased intra-abdominal pressure such as surgery, trauma, colonoscopy; 2) Respiratory disease such as chronic obstructive pulmonary disease (COPD); 3) Bacterial overgrowth producing gas in the intestine lumen, which penetrates the luminal wall through damaged mucosa; and 4) Chemotherapy, as the associated mucositis causes distortion of the bowel wall integrity and increases permeability. Patients with PI may be asymptomatic, but common symptoms include abdominal pain (53%), distention (42%), nausea and vomiting (14%), and bloody stool (13%) [7].

In general, the diagnosis of PI can be made via endoscopy or radiography. On plain radiographs of the abdomen, the classic finding is grape-like clusters or honeycomb-shaped radiolucencies along the wall of the intestine [7]. CT scans, as used in our patient, can also establish the diagnosis, determine the underlying etiology, and evaluate for associated complications. The management of PI depends upon the severity. Emergent laparotomy is indicated for PI presenting with any one of the following: signs of peritonitis, acidosis with PH < 7.3, lactate > 2.0 mg/dL, or portal venous gas. Conservative management is recommended for asymptomatic patients.

Case reports associate PI with patients actively receiving chemotherapy including vincristine, fluorouracil, and platinum alkylating agents, but it has not been reported as a delayed reaction [8, 9]. In our case, the patient received capecitabine, an oral pyrimidine analog prodrug that is hepatically metabolized to 5-FU and commonly used to treat multiple malignancies including breast cancer. Diarrhea is a common adverse effect, and while it has been reported to continue for up to 5 days after discontinuation, capecitabine typically poses little risk for continued toxicity beyond this point. In patients with colon cancer, capecitabine-associated ileitis and colitis have been reported, but to our knowledge capecitabine-associated large bowel perforation has not [1-4]. This case is unique because, to our knowledge, it is the first to associate capecitabine with PI and breast cancer, and only the third case of capecitabine associated bowel perforation in a patient treated for breast cancer. Our patient did not have any tumor burden on the bowel, and the previous reports of perforation were during active treatment with the drug, whereas our patient presented nearly 4 weeks after discontinuing the medication [10]. This late presentation is unexpected based on the mechanism and half-life of less than 1 h. This case demonstrates the need to consider PI in patients treated with capecitabine within the past month who present with persistent diarrhea without other apparent clinical causes.

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Conflict of Interest

We have no conflict of interest or relationship to disclose.

Informed Consent

Not applicable.

Author Contributions

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