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Case Report

Capecitabine-Associated Terminal Ileitis

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Colorectal cancer · Capecitabine · Fluoropyrimidine · Terminal Ileitis · Diarrhea · Adverse event

Abstract
Capecitabine is an oral fluoropyrimidine used as adjuvant and palliative chemotherapy in patients with colorectal cancer. Diarrhea is a well-known side effect of capecitabine and 5-fluorouracil agents. We present a case with terminal ileitis as a rare adverse event of capecitabine treatment. Capecitabine-induced terminal ileitis is likely to be underreported. It should be considered more often as a cause of severe and atypical complaints of diarrhea during treatment with capecitabine or other 5-fluorouracil agents.

Introduction

Capecitabine is an oral fluoropyrimidine, which is the chemotherapy backbone in adjuvant and palliative systemic treatment in patients with colorectal cancer. Gastrointestinal adverse events are common during capecitabine treatment, mostly consisting of nausea and diarrhea. In this paper, we present a rare case of capecitabine-associated terminal ileitis.

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Case Report

A 69-year-old woman without any comorbidities underwent a sigmoid resection for an adenocarcinoma of the sigmoid colon (pT3N2). According to the Dutch guidelines, adjuvant chemotherapy was started 5 weeks after surgery with CAPOX, consisting of capecitabine and oxaliplatin every 3 weeks. Before start, dihydropyrimidine dehydrogenase genotype testing was performed without signs of DPD deficiency.

Shortly after the start of chemotherapy, she had complaints of nausea and a reduced appetite. After 2 weeks, she developed watery stools (without blood) twice daily. The diarrhea worsened to 4–6 times daily during the following days at which loperamide was administered. Three weeks after the start of chemotherapy, she was hospitalized. Physical examination revealed a moderately ill patient with normal vital functions. No abnormalities were found on examination of the heart and the lungs. Upon examination of the abdomen, lively bowel sounds were found, and the abdomen was distended but not tender at palpation. Digital rectal examination revealed no abnormalities. Also, examination of the skin and extremities showed no abnormalities.

The laboratory results showed a hemoglobin level of 8.3 mmol/L (reference 7.5–10.0), thrombocytes 300/nL (reference 150–400), leukocytes 6.0/nL (reference 4.0–10.0), and a C-reactive protein of 83 mg/L (reference <6), with normal liver biochemistry and kidney function. The following days, the diarrhea worsened to a frequency of 12 times a day, and intravenous fluids were administered. Stool cultures were negative for pathogenic bacteria and protozoa. A colonoscopy with biopsy showed an ileitis with superficial but extensive ulceration in the terminal ileum (Fig. 1). Magnetic resonance enterography showed a 5-mm wall thickening of the terminal ileum over a distance of more than 15 cm. More proximal in the ileum, a second area of wall thickness was found over a distance of 7 cm. We discontinued the CAPOX treatment and started budesonide 9 mg once daily. The diarrhea and nausea decreased in the following weeks. After 4 weeks of budesonide use, adjuvant treatment was continued with FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) every 2 weeks. The complaints of nausea and diarrhea resumed mildly (grade 1) during FOLFOX therapy, and therefore we continued budesonide. After 3 cycles of FOLFOX, she decided to discontinue the adjuvant treatment because she was suffering from a vital depression. The budesonide was discontinued after cessation of the chemotherapy without signs of recurrence of ileitis.

Discussion

Diarrhea is a well-known, dose-dependent side effect of the treatment with capecitabine. The diarrhea usually starts at the end of the second or in the third week, is mostly mild, recovers after a few days with sometimes a necessity of treatment with anti-motility agents such as loperamide. Grade 3–4 diarrhea occurs in 11.4% of patients treated with capecitabine monotherapy [1]. In contrast, in patients with a DPD deficiency the diarrhea starts often within the first week and is life threatening [2].

Oxaliplatin can also cause diarrhea but typically starts early after administration within 3–4 days and resolves after 1–2 days without any intervention. In patients treated with the

combination of capecitabine and oxaliplatin, grade 3–4 diarrhea occurs in approximately 18% of cases [1, 3].

Capecitabine-induced diarrhea is caused by acute injury to the intestinal mucosa, which leads to loss of the epithelium [4]. By inducing a mitotic arrest of the crypt cells, the ratio of immature secretory crypt cells to mature villous enterocytes increases, leading to a higher volume of fluid leaving the small bowel that goes beyond the absorptive capacity of the colon, causing clinically significant diarrhea [4, 5].

In the current case, the complaints of diarrhea started within 2 weeks after the first administration of chemotherapy and worsened over time, needing further diagnostic tests, which revealed a terminal ileitis. Terminal ileitis has been previously reported in 8 cases (Table 1) [6–11]. Yet, the pathophysiology and the management of capecitabine-induced terminal ileitis remain unclear. Of the 9 reported cases, all received intravenous fluids, 2 received parenteral nutrition and 7 received antibiotics. Our patient was the only one treated with steroids. Because steroids seem to be contra-indicated in case of mucositis, we believe steroids should be given only after performing colonoscopy with biopsy revealing a clear diagnosis of ileitis.

Considering the cancer treatment, in 5 cases capecitabine was permanently discontinued; in 2 of these cases, a different type of chemotherapy was started, and in 3 cases no chemotherapy was resumed at all. In none of the cases was capecitabine re-administered at the same dose; in 2 cases, capecitabine was restarted at a reduced dose, and in 1 case capecitabine was replaced by 5-fluorouracil (FOLFOX).

If continuation of treatment is desired, patient and tumor characteristics should be taken into account. In a palliative setting, toxicity is an important factor influencing quality of life. Therefore, in case of capecitabine-induced terminal ileitis, resuming capecitabine in a palliative setting seems to be an inconsistent decision. In an adjuvant setting, the absolute risk reduction of relapse has to be weighted against the risk of toxicity. Hence, a re-challenge with a dose reduction of capecitabine or other 5-fluorouracilagents might be a valid option.

An alternative treatment option could be S1, which is an oral fluoropyrimidine only registered for use in a palliative setting that includes three different agents: tegafur, gimeracil, and oteracil. S1 is associated with a significantly lower incidence of hand-foot syndrome compared with capecitabine, with comparable efficacy [12].

Another oral cytotoxic agent named trifluridine-tipiracil (TAS-102) is an oral fluoropyrimidine with a different mechanism of action, which is registered for patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapy [13, 14]. Trifluridine is a thymidine-based nucleic acid analogue; the triphosphate form of trifluridine interferes with DNA synthesis and inhibits cell proliferation. Tipiracil is a potent thymidine phosphorylase inhibitor, which prevents the rapid degradation of trifluridine, resulting in an increased trifluridine exposure [14]. Its associated toxicities are gastrointestinal and hematologic, but in contrast to capecitabine, the gastrointestinal toxicities with trifluridine-tipiracil were almost all grade 1 and 2 with only few grade ≥3 events [13, 14].

Conclusion

Terminal ileitis should be considered more often when the pattern of diarrhea and other complaints are not typical for capecitabine-induced mucositis. Continuing chemotherapy treatment with alternative fluoropyrimidines is an option.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have nothing to disclose.

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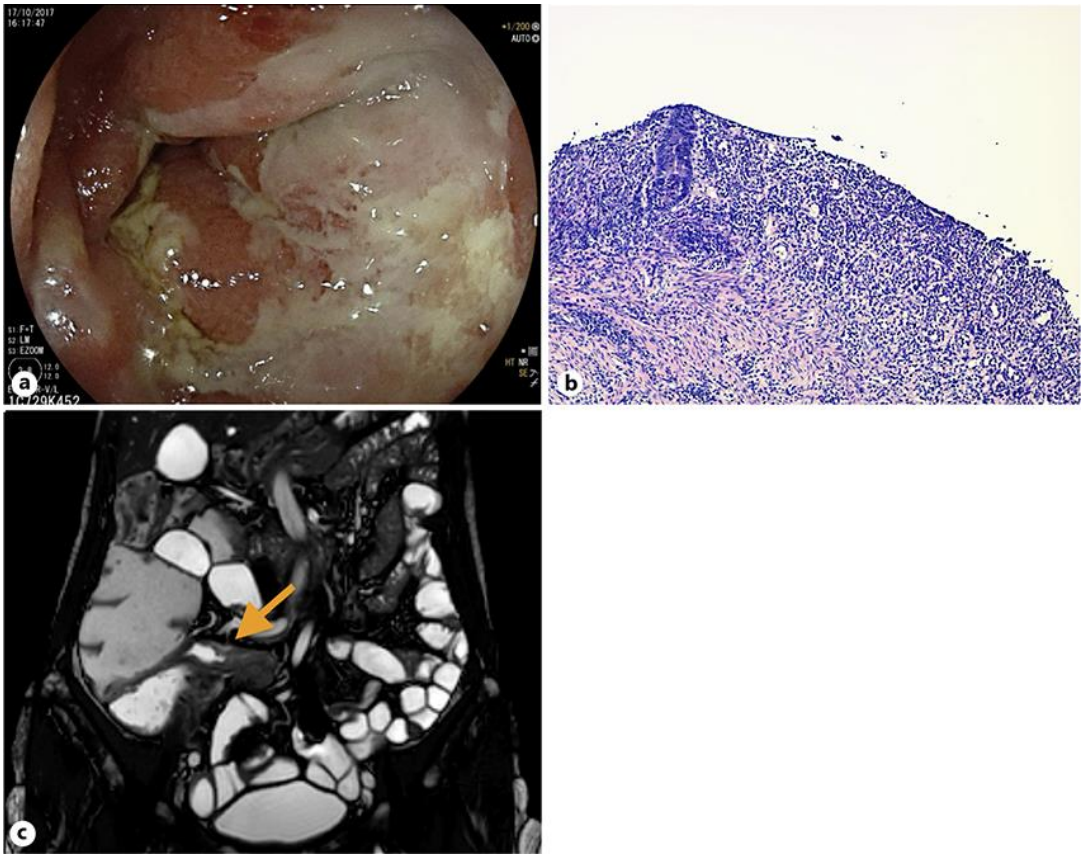

Fig. 1. Diagnostic findings. **a** Terminal ileitis at colonoscopy. **b** Extensive inflammation of the small intestine at pathological review of the biopsy. **c** MR enterography showing a distention of the colon and thickening of the terminal ileal loop (arrow).

Table 1. Earlier reports on capecitabine associated terminal ileitis

	First author [Ref.], year	Patient	Oncologic treatment	Clinical description	Diagnostic findings	Acute management	Anticancer treatment
1	Radwan [6], 2012	Male 67 years Colon carcinoma	Adjuvant Capecitabine	After cycle 2: Diarrhea Lower abdominal discomfort Reduced appetite	CT scan: suggestive of acute ileitis DPyD: unknown	Intravenous fluids Antibiotics	Capecitabine permanently discontinued No further chemotherapy was started
2	Barton [7], 2006	Male 54 years Colon carcinoma	Adjuvant Capecitabine	After cycle 3: Diarrhea Abdominal cramps	Stool cultures: negative Colonoscopy: ulcerative ileitis with eosinophilic infiltrates DPyD: unknown	Parenteral nutrition Antibiotics	Unknown
3	Bouma [8], 2011	Male 73 years Colon cancer with liver metastases	Palliative Capecitabine Oxaliplatin Bevacizumab	After cycle 3: Diarrhea Nausea Abdominal pain Fever	CT scan: circumferential edema of the terminal ileum suggestive of acute ileitis DPyD: not tested	Intravenous fluids Antibiotics	Capecitabine, oxaliplatin and bevacizumab continued at a reduced dose
4	Al-Gahmi [9], 2012	Male 65 years Metastatic rectum carcinoma	Palliative Capecitabine Oxaliplatin	After 12 days: Diarrhea Abdominal pain Fever Emesis	Colonoscopy: isolated ulceration of the terminal ileum with eosinophilic infiltrates DPyD: no mutation	Intravenous fluids Antibiotics	Capecitabine was continued at a reduced dose
5	Mokrim [10], 2014	Female 66 years Metastatic breast cancer	Palliative Capecitabine	After 14 days: Diarrhea Fever Emesis Severe alteration performance status	Stool cultures: negative CT scan: submucosal edema of the distal ileum with abnormal thickening of its wall Colonoscopy with biopsy: inflammatory changes in the ileal mucosa DPyD: mutation DPYD*5,6	Intravenous fluids Antibiotics	Capecitabine permanently discontinued Treatment with exemestane and everolimus was started 4 months later
6	Mokrim [10], 2014	Female 67 years Metastatic breast cancer	Palliative Capecitabine	After cycle 2: Diarrhea Fever Reduced appetite Fatigue	Stool cultures: negative CT scan: partial thickening of the terminal ileal loop DPyD: no mutation	Intravenous fluids Antibiotics	Capecitabine permanently discontinued
7	Lee [11], 2015	Female 61 years Colon cancer with liver/lung metastases	Palliative Capecitabine-irinotecan-bevacizumab	After cycle 4: abdominal pain right lower quadrant Diarrhea Vomiting Fever	CT scan: extensive submucosal edema at the terminal and middle part of the ileum DPyD mutation: unknown	Intravenous fluids Antibiotics G-CSF	One week after discharge, irinotecan and bevacizumab were resumed Capecitabine was permanently discontinued
8	Lee [11], 2015	Female 59 years Sigmoid colon cancer	Adjuvant Capecitabine	After start, diarrhea grade 1, after 3th cycle sudden worsening of diarrhea (grade 4) and mucositis (grade 3)	CT scan: diffuse submucosal edema in a long segment of the distal ileum to the terminal ileum Cultures (blood, stool and urine): negative DPyD mutation: unknown	ICU admission Total parenteral nutrition Inotropic support Electrolyte replacement	Capecitabine was permanently discontinued
9	Van Hellemond, 2018	Female 69 years Sigmoid colon cancer	Adjuvant Capecitabine-oxaliplatin	Diarrhea from start of chemotherapy	Colonoscopy: terminal ileitis MR enterography: distention of the colon and thickening of the terminal ileal loop DPyD: no mutation	Loperamide Intravenous fluids Electrolyte replacement Budesonide	Treatment was switched to FOLFOX

CT, computed tomography; DPyD, dihydropyrimidine dehydrogenase; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin.