Diagnostic Snapshot

Can You Diagnose the Cause of This Patient's Diarrhea?

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Author's disclosure of conflicts of interest are found at the end of this article.

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Abstract

This article will review the case of a 53-year-old female with a diagnosis of metastatic esophageal cancer receiving treatment on a clinical trial protocol combining chemotherapy/immunotherapy with FOLFOX and nivolumab, who presents to the clinic with 2 weeks of progressively worsening diarrhea. She experienced up to 12 loosely formed to watery bowel movements that were brown in color, not malodorous, and did not float. She also experienced associated abdominal pain and cramping, but denied fever, malaise, nausea, or vomiting. Vital signs were stable. Labs and CT chest, abdomen, and pelvis did not reveal a definitive cause. Dietary modification with a bland diet and loperamide did not significantly improved her symptoms.

HISTORY

Ms. D is a 53-year-old female with a past medical history of migraines, Graves' disease, gastroesophageal reflux disease, and now metastatic distal esophageal adenocarcinoma. She initially noticed progressive dysphagia and eventually developed abdominal pain. A magnetic resonance imaging scan of her abdomen showed numerous hepatic masses suspicious for metastatic disease and an encapsulated lesion within the right humerus. An esophagogastroduodenoscopy revealed an ulcer with atypical glands in the distal esophagus/gastroesophageal junction, and biopsies revealed moderately to poorly differentiated adenocarcinoma.

Ms. D enrolled in a front-line clinical trial for metastatic adenocarcinoma of the distal esophagus and was treated with FOLFOX (5-FU, leucovorin, oxaliplatin) and FOLFIRI (5-FU, leucovorin, irinotecan) and nivolumab (Opdivo). 2,000 mg/m^2 of infusional 5-FU was administered over 48 hours as well as IV oxaliplatin at 70 mg/m^2 and IV nivolumab at 240 mg biweekly on a 14-day cycle. She received 9 cycles with responsive disease before oxaliplatin was held due to neuropathy. She then received 4 cycles of only infusional 5-FU and nivolumab.

CHIEF COMPLAINT

Ms. D presented to clinic for a scheduled toxicity evaluation on D1 cycle 14 per protocol complaining of around 14 days of new, persistent diarrhea. She initially started having about 4 loose to watery bowel movements that were brown, not floating, and not malodorous. For 3 to 4 days she noticed up to 12 daily bowel movements, which were associated with cramping and abdominal pain. She took loperamide, which did not improve her symptoms. She reported increased fatigue for the past 8 days but had a good appetite and denied nausea or vomiting. She denied any recent travel, abdominal distension, fever, or malaise.

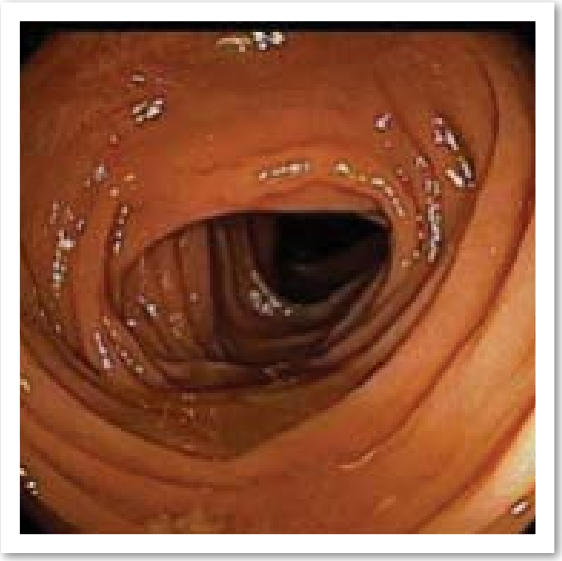

Figure 1

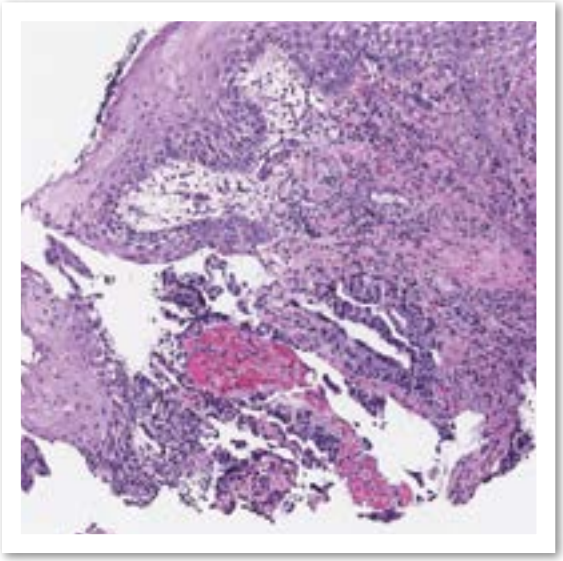

Figure 2

At this point, she was started on loperamide and was instructed to consume a BRAT diet, or a generally bland diet consisting of easily digestible foods such as bread, rice, applesauce, and toast. After 1 week, her diarrhea improved, but she continued to have 4 to 6 loose to watery bowel movements daily with a strict modified diet and up to 16 bowel movements if her diet deviated.

PHYSICAL EXAM AND DIAGNOSTIC WORKUP

On initial exam, Ms. D appeared fatigued but vital signs were normal and she was afebrile. She continued to have oral mucositis, which began approximately 2 months prior and was thought to be toxicity to 5-FU. There were hyperactive bowel sounds and her abdomen was not tender to palpation and not distended. Stool sample for *Clostridium difficile* testing was submitted but not analyzed by the lab because the patient's sample contained formed stool. Laboratory studies including complete blood count and complete metabolic panel were unremarkable.

After a week on the BRAT diet and loperamide with improvement but not resolution of her symptoms, a CT of the chest, abdomen, and pelvis with contrast was ordered and revealed treated hepatic metastases without evidence of mucosal edema within the bowel. Colonoscopy was conducted and as seen in Figure 1, the entire examined colon appeared normal. Random biopsies were taken such as the one seen above in Figure 2 to confirm the diagnosis. These revealed colon mucosa with lymphoplasmacytosis in the lamina propria, increased crypt epithelial apoptotic figures, and focal surface epithelial injury in the transverse, descending, sigmoid colon, and rectum.

DIFFERENTIAL DIAGNOSIS

WHAT IS THE CORRECT DIAGNOSIS FOR MS. D?

A. Immune-mediated colitis

B. Infectious diarrhea

C. Pancreatic enzyme asynchrony or insufficiency

D. Drug- or chemotherapy-induced enteritis or colitis

SEE BACK FOR ANSWER

WHAT IS THE CORRECT DIAGNOSIS FOR MS. D?

A. Immune-mediated colitis (correct answer)

B. Infectious diarrhea

C. Pancreatic enzyme asynchrony or insufficiency

D. Drug- or chemotherapy-induced enteritis or colitis

A **Immune-Mediated Colitis.** Expanding U.S. Food & Drug Administration (FDA) approvals for checkpoint inhibitors targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), as well as programmed cell death receptor protein 1 (PD-1) and its ligand PD-L1 have increased the use of these therapies in the National Comprehensive Cancer Network (NCCN) Guidelines. There is currently FDA approval for use of anti–PD-1 agents in upper gastrointestinal malignancies in the second- or third-line setting. Additionally, many clinical trials are studying their efficacy as single-agent therapies and in combination with other drugs like cytotoxic chemotherapies and targeted therapies.

Nivolumab, along with pembrolizumab (Keytruda), are both anti–PD-1 agents. Immune-related adverse events (irAEs) usually occur within weeks to 3 months after the initiation of therapy; however, cases of the first onset of an irAE have been documented as late as 1 year after discontinuing therapy (Haanen et al., 2017). High-grade toxicities are reported less frequently from either anti–PD-1 agents compared with anti–CTLA-4 agents. However, both classes can cause gastritis, enteritis, and colitis. Diarrhea is more commonly associated with anti–CTLA-4 therapy (27%–54%), although only 8% to 22% experience colitis (Gupta, De Felice, Khanna, & Loftus, 2015). There is less data demonstrating gastrointestinal irAEs associated with anti–PD-1 agents, but most studies have showed that the majority of patients who have diarrhea or colitis are grade 1 to 2, or less than 7 stools daily over baseline. In ATTRACTION-3, the authors compared biweekly nivolumab to chemotherapy for refractory esophageal squamous cell carcinoma. Of the 209 participants who received nivolumab, 10% experienced grade 1 to 2 diarrhea, 1% experienced grade 3 diarrhea, and no patients experienced grade 4 diarrhea (Kato et al., 2019).

Diagnosis of grade 1 and sometimes grade 2 diarrhea can often be made based on symptoms alone after ruling out infectious causes. Colonoscopy with biopsies is considered the gold standard for diagnosis of grade 3 to 4 colitis. However, the histologic findings are fairly unspecific and can mimic other disease processes with acute or chronic mucosal inflammation (Gonzalez et al., 2017). An irAE should be considered in any patient known to be taking a PD-1/PD-L1 inhibitor with a clinical presentation of diarrhea. This diagnosis can be confirmed with biopsies showing mucosal inflammatory changes.

B **Infectious Diarrhea.** Infectious diarrhea, especially *Clostridium difficile* colitis, is a common problem in patients with cancer due to the high rate of hospitalization and use of antibiotics. There is also chemotherapy-induced intestinal damage that can facilitate the proliferation of *Clostridium difficile*. However, this is less likely the cause in this scenario due to the lack of other associated signs or symptoms, including low-grade fever, nausea, abdominal pain, anorexia, pus or mucus in the stool, or leukocytosis. *C. diff* testing was attempted; however, the stool sample was not analyzed by the lab because the sample provided was formed and not watery. If the colonoscopy was undiagnostic, we would have considered repeating testing for *C. diff* colitis.

C **Pancreatic Enzyme Asynchrony/Insufficiency**. This is not likely because Ms. D's symptoms would often be associated with consumption of fatty meals and would normally improve with initiation of a controlled diet. This would be diagnosed clinically based on symptoms, including belching, abdominal cramping, and steatorrhea with pale, floating stools that may appear greasy.

D **Drug- or Chemotherapy-Induced Diarrhea**. This is a common side effect of fluoropyrimidines such as 5-FU due to several mechanisms, includ-

ing acute damage to intestinal mucosa leading to diarrhea. This was less likely the cause in Ms. D's case because FU-induced diarrhea is usually schedule-dependent and most common in the first 3 to 5 days following treatment. Ms. D's diarrhea was not improving several days after treatment but was instead getting worse even a couple weeks after her last dose.

MANAGEMENT

Patients who experience immune-mediated colitis should be counseled on the importance of maintaining adequate oral hydration. According to the NCCN Guidelines, grade 1 gastrointestinal toxicities can be addressed with symptomatic care and close monitoring. Treatment should be suspended for grade 2, and if symptoms do not revert back to grade 1, corticosteroids may be administered. Grade 3 or 4 toxicities warrant suspension of treatment and initiation of high-dose corticosteroids, which should be tapered over 4 to 6 weeks. Some refractory cases may require infliximab treatment or other immunosuppressive therapy. Generally, permanent discontinuation of checkpoint inhibitors is recommended with grade 4 toxicities.

Ms. D completed the steroid taper and systemic therapy was discontinued. She has been followed on clinical observation for the past 26 months without disease progression or another irAE.

Disclosure

The author has no conflicts of interest to disclose.

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