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CASE REPORT | COLON

Gastrointestinal Bleeding in a Patient With Gastric Lymphoma, Tuberculosis Enteritis, and Cytomegalovirus Enteritis

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ABSTRACT

Bleeding from the small bowel can be challenging to identify by endoscopic or radiographic evaluation. We present the case of a patient with incompletely treated latent tuberculosis and medical history of T-cell lymphoma who developed gastrointestinal bleeding because of concurrent Burkitt lymphoma, tuberculosis enteritis, and cytomegalovirus enteritis. The interplay of these 3 diagnoses is discussed.

INTRODUCTION

The small bowel is the site of 5%–10% of gastrointestinal bleeds, which are often difficult to identify by standard endoscopic or radiographic evaluation.[1] Immunodeficient patients such as those with gastrointestinal malignancies like Burkitt lymphoma (BL) of the gut are susceptible to reactivation of latent tuberculosis (TB), which can subsequently affect the gut. Cytomegalovirus (CMV) colitis should also be considered in immunosuppressed patients.[2] This case report discusses how these seemingly disparate diagnoses can co-occur and cause gastrointestinal bleeding.

CASE REPORT

A 68-year-old man from Ecuador with a remote history of natural killer T-cell lymphoma of the nasal cavity and kidney status postchemotherapy and radiation, peripheral T-cell lymphoma status post chemotherapy and autologous stem cell transplant (SCT), and latent TB presented with weight loss, fatigue, and cough. On examination, he was cachectic and had diffuse rhonchi in the lung bases. Thoracic computed tomography (CT) showed areas of focal cavitation, numerous centrilobular nodules, and calcified lymph nodes. Sputum cultures positive for acid-fast bacilli (AFB) and positive *Mycobacterium tuberculosis* polymerase chain reaction (PCR) test confirmed active TB infection. He began treatment with rifampin, isoniazid, ethambutol, and pyrazinamide.

A week into his hospital stay, while the patient was undergoing workup for TB, the patient developed melena. His laboratory work indicated iron deficiency anemia with a hemoglobin of 5.0 from a baseline of 9.5 g/dL, mean corpuscular volume of 71.5 fL, iron of 4.5 μg/dL, transferrin saturation of 1%, and ferritin of 143 ng/mL. Esophagogastroduodenoscopy (EGD) showed a 12 mm cratered, clean-based duodenal ulcer without bleeding, which was not biopsied. There was also gastric mucosal atrophy and erythema in the antrum. Colonoscopy revealed diverticulosis in the sigmoid colon and evidence of a previous cecectomy with ulceration of the ileocolonic anastomosis but showed no active bleeding. The details of the patient's previous surgery are unknown; however, he previously had abdominal lymphadenopathy from T-cell lymphoma, which encased the mesenteric vessels. Biopsies showed nonspecific inflammation with a mature lymphocytic infiltrate near the anastomosis and granulation tissue, but no evidence of T-cell lymphoma. Gastric antrum biopsy showed a reactive gastropathy and focal active inflammation with intestinal metaplasia in the antrum. He was treated with proton-pump inhibitors and transfusions of packed red blood cells.

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Abdominal and pelvic CT angiography obtained the following day revealed a 4 cm segment of terminal ileum with wall thickening and mucosal hyperenhancement and thickened folds in the distal jejunum. Stool AFB culture and *Mycobacterium tuberculosis* PCR were both positive, indicating a probable diagnosis of TB enteritis manifested by the duodenal and anastomotic ulcerations seen endoscopically. Bleeding subsided after initiation of rifampin, isoniazid, ethambutol, and pyrazinamide; however, therapy was interrupted 2 weeks into treatment because of transaminitis. After various attempts to restart therapy, alternative therapy with rifampin, levofloxacin, and amikacin was initiated 2 weeks later. Abdominal and pelvic CT enterography obtained 3 days into the alternative treatment because of recurrent episodes of melena showed a short segment of terminal ileitis and a new 40 cm segment of proximal jejunal wall thickening. Repeat colonoscopy also obtained at this time showed nonbleeding ulcerations at the ileocolonic anastomosis worse than the last evaluation. These findings were consistent with interruption of TB therapy. The patient began prednisone as adjunctive therapy and bleeding initially subsided.

A push enteroscopy was performed 2 months after the initial EGD because of recurrent melena despite appropriate therapy for TB. A 60-mm infiltrative lesion with ulcerated bases and 3 similar smaller lesions were identified on the anterior stomach along with jejunal ulceration (Figure 1). These exophytic, infiltrative lesions were new findings compared with the previous EGD. There was no significant pathology in the duodenum. Jejunal ulcer biopsies showed severe acute inflammation and large cells with inclusions that were highlighted by CMV immunostains, consistent with CMV enteritis (Figure 2). Stains for AFB were also positive. Biopsies of the stomach lesions revealed ulcerative oxyntic mucosa with atypical lymphoid infiltration (Figure 3). The malignant cells were CD20 positive (+), CD10+, Bcl6+, MUM1+, and Bcl-2 negative (−), and the Ki-67 proliferative index was approximately 90% (Figure 4). Epstein Barr Virus (EBV) in situ hybridization and *Helicobacter pylori* staining (cresyl violet) were negative. Fluorescent in situ hybridization studies revealed a c-Myc rearrangement in the absence of Bcl-2 and Bcl-6 rearrangements. These findings were consistent with a diagnosis of BL. Chemotherapy initiation was delayed until after the patient had received 2 weeks of ganciclovir therapy for CMV. He was continued on therapy for TB and began treatment with R-CHOP.

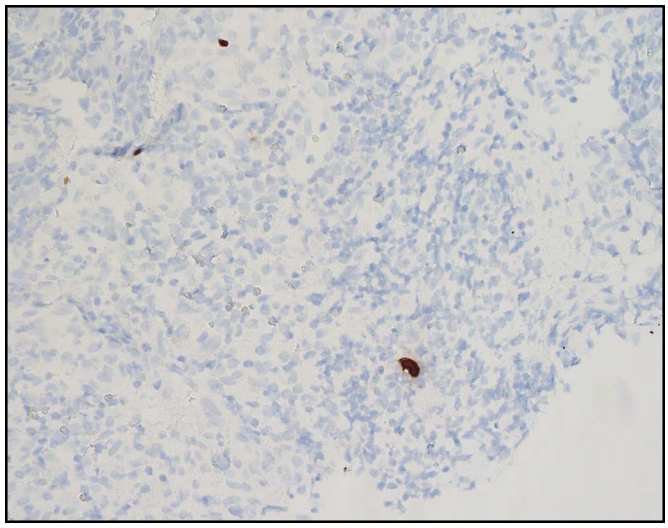

Figure 2. Jejunal biopsy showing occasional enlarged cells with inclusion bodies typical of CMV. Immunohistochemical staining for CMV highlighted CMV infected cells. CMV, cytomegalovirus.

DISCUSSION

Chronic EBV infection plays a role in some cases of Africa endemic and immunodeficiency-associated BL. Interestingly,

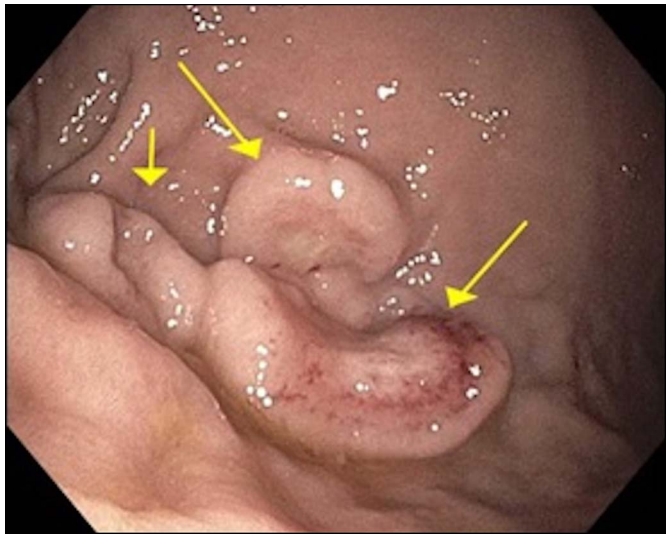

Figure 1. A 60 mm infiltrative lesion with ulcerated bases and 3 similar smaller lesions on the anterior stomach (arrows) identified via push enteroscopy.

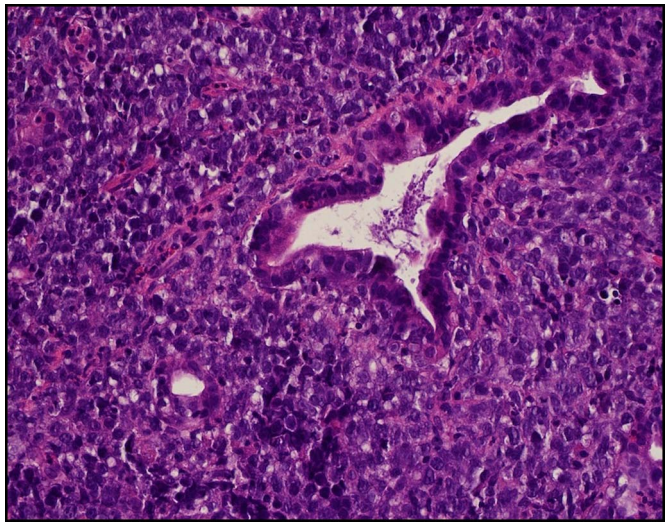

Figure 3. Stomach ulcer biopsy showed a dense infiltrate composed of large lymphoid cells, which effaced the normal gastric mucosal architecture.

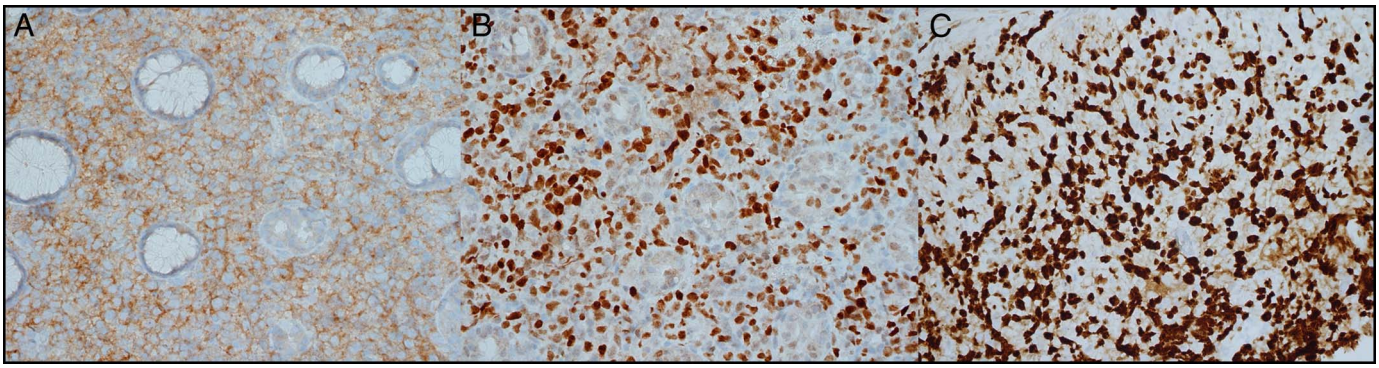

Figure 4. Malignant cells were of germinal center origin as evidenced by (A) CD10+ markers, (B) Bcl-6+ markers, and (C) Ki-67.

this patient had a history of EBV-positive natural killer T-cell lymphoma and EBV-negative peripheral T-cell lymphoma, presenting now with a new EBV-negative high-grade lymphoma of B-cell origin. This could suggest the presence of germline or somatic mutations in the lymphoid or hematopoietic precursors predisposing him to lymphoid neoplasms. Patients with BL typically present with extranodal disease, most frequently in the abdomen.[3] The stomach is the most common site of extranodal involvement (27%), followed by the small and large intestines.[4] The immunodeficiency-associated subtype of BL is usually seen in patients with human immunodeficiency virus (HIV).[3] Notably, this patient was HIV negative.

The basis for this patient's presentation was likely immunosuppression secondary to BL, which led to reactivation of latent TB and increased his susceptibility to CMV infection. Moreover, this patient's history of malignancy and history of autologous SCT likely contributed to his immunosuppression. Secondary solid tumor and lymphoproliferative malignancies are a well-known late complication of SCT.[5] The ulcerations observed endoscopically were likely manifestations of both TB and CMV enteritis. Synergy between these 2 entities along with the lesions from his malignancy likely led to the persistent bleeding despite adequate treatment for TB. Some studies have shown that patients infected with TB are up to 3 times more likely than those without TB to be coinfected with CMV.[6] TB has also been demonstrated to promote CMV reactivation in infected individuals by acting on CMV-specific T-cells and cytokines to aid reactivation.[7] There is also evidence to suggest that CMV coinfection can facilitate conversion from latent to active TB.[8] The incidence of TB in malignancy is highest in non-Hodgkin lymphomas such as BL.[9]

TB involves the bowel in less than 5% of cases in the United States.[11] Intestinal TB can mimic malignancies or IBD, which contributes to diagnostic delay and mismanagement.[12] Common endoscopic findings include ileal or ileocecal disease, nonconfluent involvement of the colon, and nodular mucosa with ulceration.[13,14] Tuberculous peritonitis and lymphadenitis are also commonly seen.[14] Spread to the bowel is usually hematogenous or via swallowing infected sputum from primary pulmonary TB.[15] Intestinal TB presents with abdominal pain, distension, and ascites but can present as gastrointestinal bleeding when jejunal ulceration is present.[16] The diagnosis is made by a combination of radiographic, endoscopic, and histopathologic data; however, there is no gold standard. Biopsy sometimes yields typical caseating granulomas, but laparotomy has a greater tissue yield than endoscopic biopsy.[15,17] The diagnosis can also be made by positive TB culture or PCR results or by clinical suspicion combined with improvement following treatment.[13]

Similar endoscopic findings between IBD and intestinal TB have led to the development of prediction models to differentiate them. These models use location of disease, pulmonary involvement, and TB laboratory tests to distinguish Crohn's disease from intestinal TB with an accuracy of over 90%.[18,19] Identifying ulcers as longitudinal vs transverse, which are more common in Crohn's and TB, respectively, has also been used as a diagnostic criterion.[20] A recent meta-analysis found that the addition of steroids to anti-TB therapy may be more effective than antitubercular therapy alone (RR 0.18); however, this was only seen in patients with tubercular peritonitis.[21]

DISCLOSURES

Author contributions: All the authors contributed equally to this manuscript. G. Castillo is the article guarantor.

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