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CASE REPORT | COLON

Colonic Wall Thickening as the First Indicator of Relapse of Acute Lymphoblastic Leukemia

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ABSTRACT

The gastrointestinal (GI) tract is a rarely reported site of extramedullary relapse of acute lymphoblastic leukemia (ALL). We report a patient being effectively treated with immunotherapy for relapsed ALL who was incidentally noted to have colonic wall thickening on imaging that was subsequently pathologically confirmed to be the result of disease infiltration of colonic tissue. Primary ALL involvement of the GI tract should be considered in the evaluation of GI complaints in patients with ALL, particularly those with relapsed disease otherwise effectively treated with immunotherapy.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) accounts for less than 0.5% of cancers in the United States.[1] The central nervous system is a frequent site of extramedullary disease involvement. The gastrointestinal (GI) tract in contrast is not frequently identified as a site of disease involvement. We present a case of colonic relapse in a patient with ALL being treated with blinatumomab, a bispecific T-cell engager, and nivolumab, an anti-programmed cell death-1 (PD1) monoclonal antibody. Unlike traditional chemotherapy, immune therapy relies on effective stimulation of local immune effector cells, specifically cytotoxic T-cells. This may leave the GI tract and other extramedullary sites vulnerable to disease relapse and progression.

CASE REPORT

A 57-year-old man with Philadelphia chromosome-positive (Ph+) ALL presented to the emergency department with shortness of breath and chest pain. Four years earlier, he was diagnosed with Ph+ ALL. He was initially treated with rituximab, hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) chemotherapy, and the ABL tyrosine kinase inhibitor dasatinib. He entered a complete remission and proceeded to a matched related donor allogeneic stem cell transplant. Dasatinib was restarted post-transplant, and immune suppression was administered for the prevention of graft-versus-host disease. He did well until 27 months from transplant when he was diagnosed with relapsed Ph+ ALL. His relapsed disease was treated with ponatinib, a third-generation ABL kinase inhibitor, because of the presence of a T315I ABL mutation which confers resistance to dasatinib. Because of disease progression, he was transitioned to blinatumomab plus investigational administration of nivolumab (NCT02879695). He had received 3 cycles of therapy at the time of his presentation.

On the night of presentation, the patient awoke with shortness of breath and pleuritic chest pain. He denied weight loss, abdominal pain, anorexia, or alteration in bowel habits. Vital signs were notable for blood pressure of 139/79 mm Hg, heart rate of 78 beats per minute, respiratory rate of 28 breaths per minute, but oxygen saturation of 97% on room air. His physical examination was notable for clear lungs to auscultation and a benign abdomen. Electrocardiogram was normal. Blood tests of the liver were normal. There was mild leukopenia (white blood cell count of 3.16 K/μL, absolute neutrophil count of 2.39 K/μL) without blasts, anemia (hemoglobin

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of 10.4 g/dL), and thrombocytopenia (98 K/μL). Computed tomography (CT) confirmed pulmonary emboli in the left upper segmental and subsegmental branches. Also noted was segmental wall thickening of the splenic flexure with soft tissue and fat stranding and extensive mesenteric inflammation.

He was admitted to the hospital to initiate anticoagulation. Abdominal computed tomography (CT) performed the following day to further investigate abnormal radiographic findings of the large bowel revealed severe segmental colonic wall thickening with associated pericolonic and mesenteric fat stranding involving a 6-cm segment of the distal transverse colon (Figure 1). Colonoscopy demonstrated an ulcerated stricture in the distal transverse colon, which was unable to be traversed (Figure 2). Biopsies demonstrated sheets of atypical immature lymphoid cells which stained strongly positive for TdT, CD19, and CD22, and weakly positive for CD20 and CD34, and negative for CD3, consistent with relapsed ALL (Figure 3).

After confirmation of leukemic involvement of the GI tract, a positron emission tomography scan confirmed extramedullary relapse in the stomach, colon, mesenteric lymph nodes, and omentum (Figure 4). A bone marrow biopsy confirmed relapsed medullary disease (5%–10% of the cellularity composed of lymphoblasts). The patient was transitioned to alternative salvage therapy (inotuzumab ozogamicin) and achieved a complete remission with plan to proceed to a second stem cell transplant.

DISCUSSION

Involvement of the GI tract by ALL is rarely reported in the literature although may be more common in advanced disease because autopsy series have reported GI involvement in 25% of patients.[2] In the modern era, extramedullary relapses are being seen more commonly with patients treated with immune-mediated regimens.[3–5]

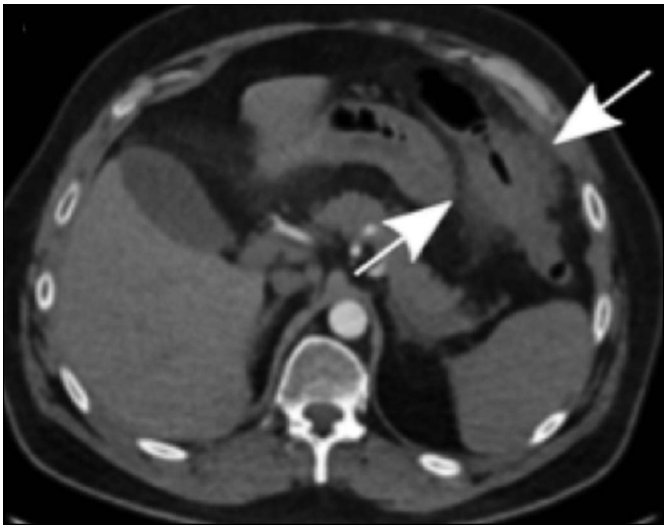

Figure 1. Contrast-enhanced abdominopelvic computed tomography revealed focal thickening of the transverse colon with adjacent fat stranding (arrows).

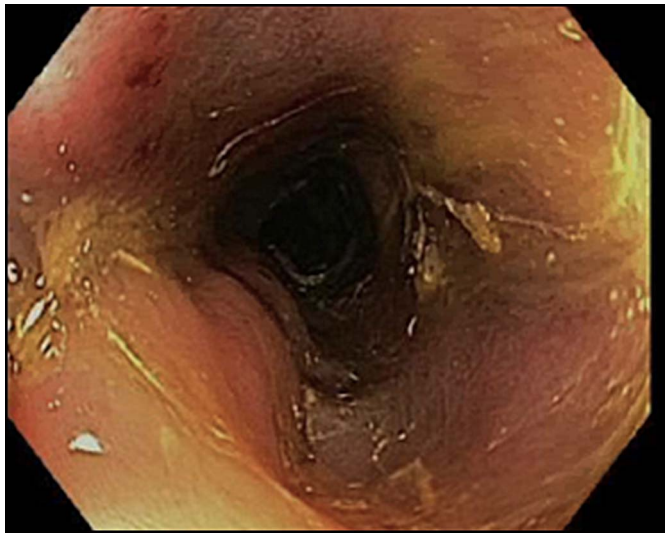

Figure 2. Colonoscopy demonstrating ulcerative stenosis at the transverse colon.

GI manifestations of leukemia can involve any aspect of the GI tract, as reported in several case reports.[2,6,7] Kletzel et al reported on a 15-year-old who presented after stem cell transplant with abdominal pain and diarrhea, diagnosed on random biopsy of the upper GI tract to have recurrent B-cell ALL.[8] Papadakis et al reported on a 13-year-old in remission for 10 years who presented with abdominal pain, fever, and hemorrhagic diarrhea and was found to have ulcerative lesions in the stomach, duodenum, and ascending colon, all consistent with relapsed ALL.[9] Weisdorf et al described a 45-year-old with nausea, cramping, and abdominal pain, who was found to have a lesion in the lesser curvature of the stomach, consistent with ALL, despite complete remission on bone marrow biopsy.[10] More recently, Issak and Agrawal reported on a 61-year-old who presented with acute diarrhea and sepsis after stem cell transplant and was found on random sigmoid biopsies to have ALL.[11]

Our patient was incidentally noted to have colonic thickening on imaging but soon developed corresponding symptoms. Notably, he was receiving immune therapy for his ALL with nivolumab and blinatumomab. Nivolumab, a PD-1 inhibitor which has been associated with colitis in previous reports, was an initial consideration.[12] Blinatumomab is a monoclonal antibody that enables CD3-positive T-cells to recognize and eliminate CD19-positive ALL blasts. Blinatumomab failure is associated with loss of CD19 expression, increased regulatory T-cell populations, and altered PD1/cytotoxic T-lymphocyte-associated protein 4 (CTLA4) expression.[13–17] In the case of extramedullary, including GI, relapses, the relative paucity of effective T-cells in the local environment likely leaves these compartments vulnerable

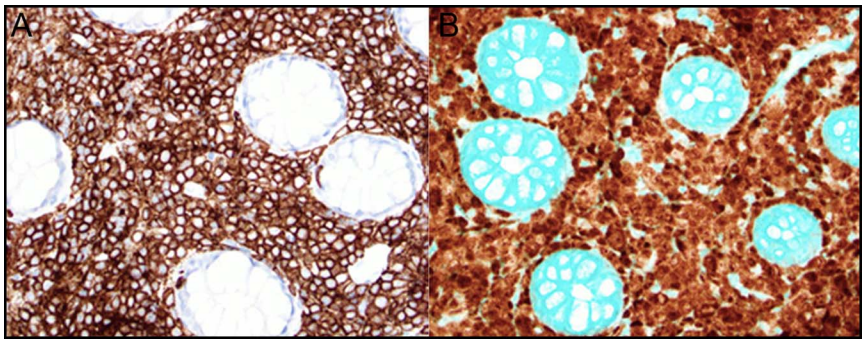

Figure 3. Colonic mucosa demonstrating lamina propria infiltrate composed of a monomorphic population of small round cells with fine nuclear chromatin and inconspicuous nucleoli. On immunohistochemical staining, these lesional cells were strongly positive for (A) CD19 and (B) terminal deoxynucleotidyl transferase (TdT) and weakly positive for CD20 and CD34 (not shown).

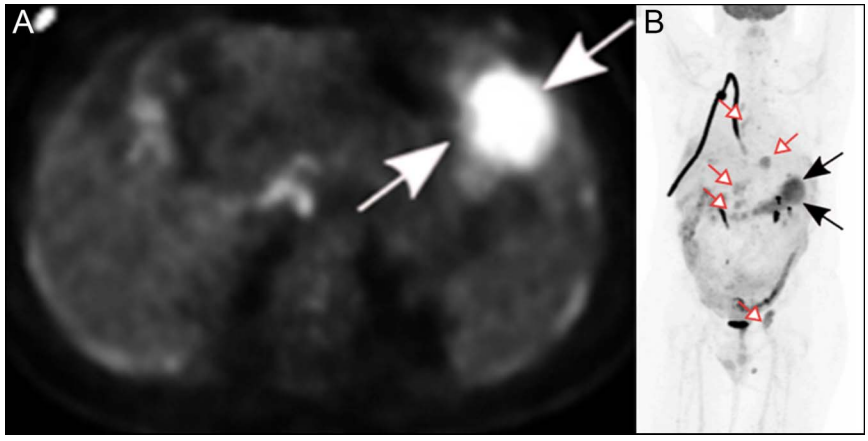

Figure 4. (A) Subsequent 18F-fluorodeoxyglucose positron emission tomography (PET) at the same axial level of the transverse colon showed intense radiotracer uptake in the affected colon (arrows), indicating elevated glucose metabolism. (B) Whole-body, 3D maximum intensity projection fluorodeoxyglucose PET highlighted the colonic lesion (black arrows) and additional multistation fluorodeoxyglucose-avid lymph nodes (red arrows).

to incomplete disease eradication, even in the setting of response in the primary medullary disease compartment.

This case highlights a rare extramedullary relapse of leukemia in the GI tract in a patient receiving blinatumomab for relapsed ALL. We found severe ulcerative stenosis of the transverse colon, which has not been described in previous reports. Imaging then demonstrated additional extramedullary disease and marrow involvement, which led to an alternative therapeutic plan of care. Because therapies evolve for ALL, patterns of disease progression are likely to change. Index of suspicion for disease involvement of the GI and other extramedullary compartments must increase. Pathologic diagnostic evaluation is imperative given the broad differential diagnoses including sequelae of both disease and treatment.

DISCLOSURES

Author contributions: KE Hathorn gathered data and wrote the manuscript. MT Caton gathered data. MR Luskin, DJ DeAngelo, and JR Saltzman critically revised the manuscript. JR Saltzman is the article guarantor.

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