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CASE REPORT | SMALL BOWEL

Indolent T-Cell Lymphoproliferative Disease: A Rare Case of a Benign Lymphoma of the Gastrointestinal Tract With Extra-Gastrointestinal Involvement

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ABSTRACT

Indolent T-cell lymphoproliferative disease of the gastrointestinal (GI) tract is an exceedingly rare benign proliferation of clonal and mature-appearing lymphoid cells originating from the GI tract. We discuss the case of a 52-year-old woman with indolent T-cell lymphoproliferative disease of the GI tract manifesting as chronic diarrhea and profound weight loss. Interestingly, the patient also had extra-GI involvement of her disease process, which has not been previously reported. Our patient was managed with steroids with improvement in symptoms and weight gain. We provide a review of the literature to highlight the importance of early recognition and intervention of this disease entity.

INTRODUCTION

Primary gastrointestinal (GI) lymphomas are rare and constitute 1%–4% of all GI malignancies.[1] Indolent T-cell lymphoproliferative disease of the GI tract (ITLPD-GI) is a benign, low-grade monoclonal proliferation that consists of small, mature-appearing lymphocytes arising in the GI tract, most commonly in the small bowel and colon.[2] The World Health Organization provisionally recognized ITLPD-GI as a distinct clinical entity in 2016.[3] It classically presents with diarrhea, weight loss, and abdominal pain. The biggest challenge remains timely identification because there is overlap with more common pathologies such as inflammatory bowel disease, aggressive gut lymphoma, or autoimmune disease. Although survival rates are high even without treatment, patients with ITLPD-GI often demonstrate a prolonged clinical course with persistent symptoms.[4] We report the first case of ITLPD-GI with pulmonary involvement presenting as a protracted course of diarrhea and weight loss.

CASE REPORT

A 52-year-old African American woman with sarcoidosis on chronic steroids presented to clinic with diarrhea, crampy abdominal pain, and weight loss. She had persistent watery diarrhea for the past 8 years and 30-pound unintentional weight loss despite a normal appetite. She denied diet changes, new medications, and recent travel. Notably, she had an identical twin without similar symptoms. Imaging at initial presentation revealed diffuse lymphadenopathy throughout the chest and abdomen, concerning for lymphoma. Bone marrow and lymph node biopsy were negative for malignancy but demonstrated a reactive process. Celiac disease was ruled out based on negative serologies. Angiotensin receptor blocker-associated enteritis was ruled out because the patient's symptoms and endoscopic findings did not improve after discontinuation of the medication. Endoscopic examination revealed a single 6 mm gastric inflammatory polyp with ulceration, and the duodenum and terminal ileum demonstrated scalloping and blunting of the villi (Figure 1). Stomach biopsies showed atrophic gastritis and focal intestinal metaplasia. Biopsies from the stomach to the colon had lymphoplasmacytic inflammation in the lamina propria and

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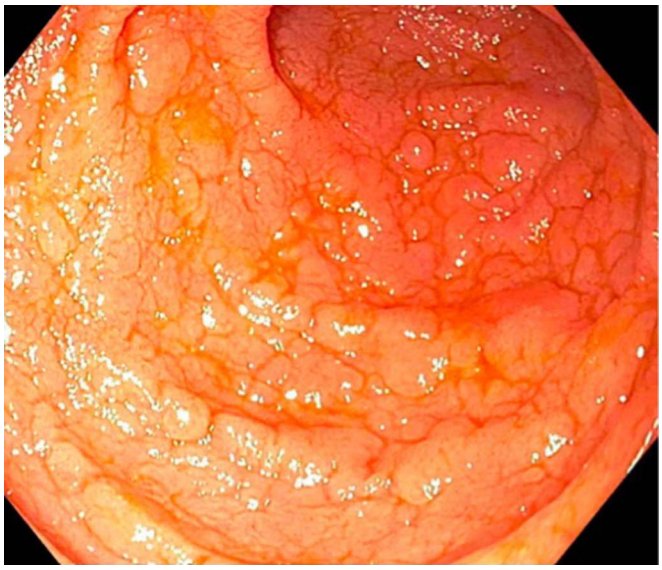

Figure 1. A 6 mm gastric inflammatory polyp with ulceration, and the duodenum and terminal ileum with scalloping and blunting of the villi.

intestinal intraepithelial lymphocytes composed of small mature T cells that were largely CD3 and CD4-positive with a partial loss of CD5 and CD7 (Figure 2). The Ki-67 proliferation index was <5%. Subsequent T-cell receptor rearrangement studies revealed a large clonal population of T cells, and *JAK2* (9p24.1) rearrangement was identified by using fluorescence in situ hybridization analysis. These T cells were densely present in the lamina propria of the stomach, duodenum, terminal ileum, and colon. A diagnosis of ITLPD-GI was performed, and the patient was started on open-capsule budesonide with gradual weight gain and improvement in her GI symptoms.[5] Repeat endoscopy showed decreased lymphocytosis in the colon but persistent proliferation in the small bowel. Months later, the patient developed dyspnea and chronic cough prompting a bronchoscopy, which revealed an increase in the percentage of lymphocytes and an elevated CD4/CD8 ratio of 7.6. Transbronchial biopsies revealed a clonal proliferation of small, mature T lymphocytes concerning for pulmonary involvement of ITLPD.

DISCUSSION

ITPLD-GI is a benign proliferation of small, clonal, and mature-appearing lymphocytes that often lead to persistent symptoms. It is a rare clinical entity with fewer than 80 cases identified in the literature to date.[6–13] Although the pathogenesis remains unclear, next-generation sequencing studies show vast heterogeneity of molecular markers with genetic alterations present in up to 80% of patients.[14] Interestingly, our patient has an identical twin raised in the same household who does not have similar symptoms. The disease is more prevalent in men than women and typically presents at a median age of 51 (range 15–77) years.[6] Associated diseases that have been reported in the literature include Crohn's disease, autoimmune enteropathy, rheumatoid arthritis, and certain viral infections such as herpes simplex virus, human herpesvirus 6, and human T-lymphotropic virus type 1.[8] Sarcoidosis and lymphoma are generally believed to be separate diseases that need to be ruled out in a patient who presents with weight loss and peripheral and mediastinal lymphadenopathy. The epidemiology and pathogenesis of both sarcoid and ITLPD are not well understood, but genetic variations in JAK2 have been described in both diseases.[11] We speculate that this alteration leads to excess production and accumulation of T lymphocytes in both the pulmonary system and the GI tract.

ITLPD-GI is often a diagnosis of exclusion, performed when more common etiologies of dense lymphocytic infiltration of the GI tract are ruled out, such as autoimmune and inflammatory diseases. It is important to distinguish ITLPD from aggressive gut lymphomas, such as enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic intestinal T-cell lymphoma because these cancers are associated with high rates of morbidity and mortality and require aggressive intervention.[15] As seen with our patient, presenting symptoms of ITLPD-GI include diarrhea (70%), weight loss (60%), and abdominal pain (50%).[14] While these symptoms may also be present in enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic intestinal T-cell lymphoma, up to 50% of patients with aggressive gut lymphomas will present with an obstruction or perforation. Pathology of aggressive lymphomas shows transmural invasion of lymphocytes while ITLPD-GI is limited to the mucosa.[16] Immunohistochemical studies of ITPLD show mainly $CD8^+$ or $CD4^+$ T cells. A multi-institutional study by Soderquist et al found that endoscopic evaluation of ITLPD-GI demonstrates mucosal nodularity (70%), scalloping (40%), erythema (40%), decreased duodenal folds (30%), and polyps (20%).[14] Although ITLPD-GI shows poor response to conventional chemotherapy and immunotherapy, it is reasonable to try conservative management or oral corticosteroids for persistent symptoms, as was attempted in our patient.[10]

ITLPD-GI is an often-overlooked diagnosis, and unfortunately, many patients will have an extensive workup and sometimes even aggressive interventions before its consideration. ITPLD-GI most commonly involves the colon and small bowel, presents with multiple polypoid lesions, has no appreciable adenopathy, and is predominantly CD8-positive. This case is unique because the patient had involvement from the stomach to the colon, imaging showing prominence of mesenteric lymph nodes and CD4-positive T-cell predominance. In addition, the patient had clonal T-cell proliferation in the lungs, which has not been reported previously. This suggests that the lymphoproliferative disease extends beyond the GI tract. Further research is required to determine whether a common disease process can lead to lymphoproliferation in multiple organ systems. This case report highlights the importance of a high index of suspicion when patients have persistent symptoms despite adequate treatment of more common enteropathies.

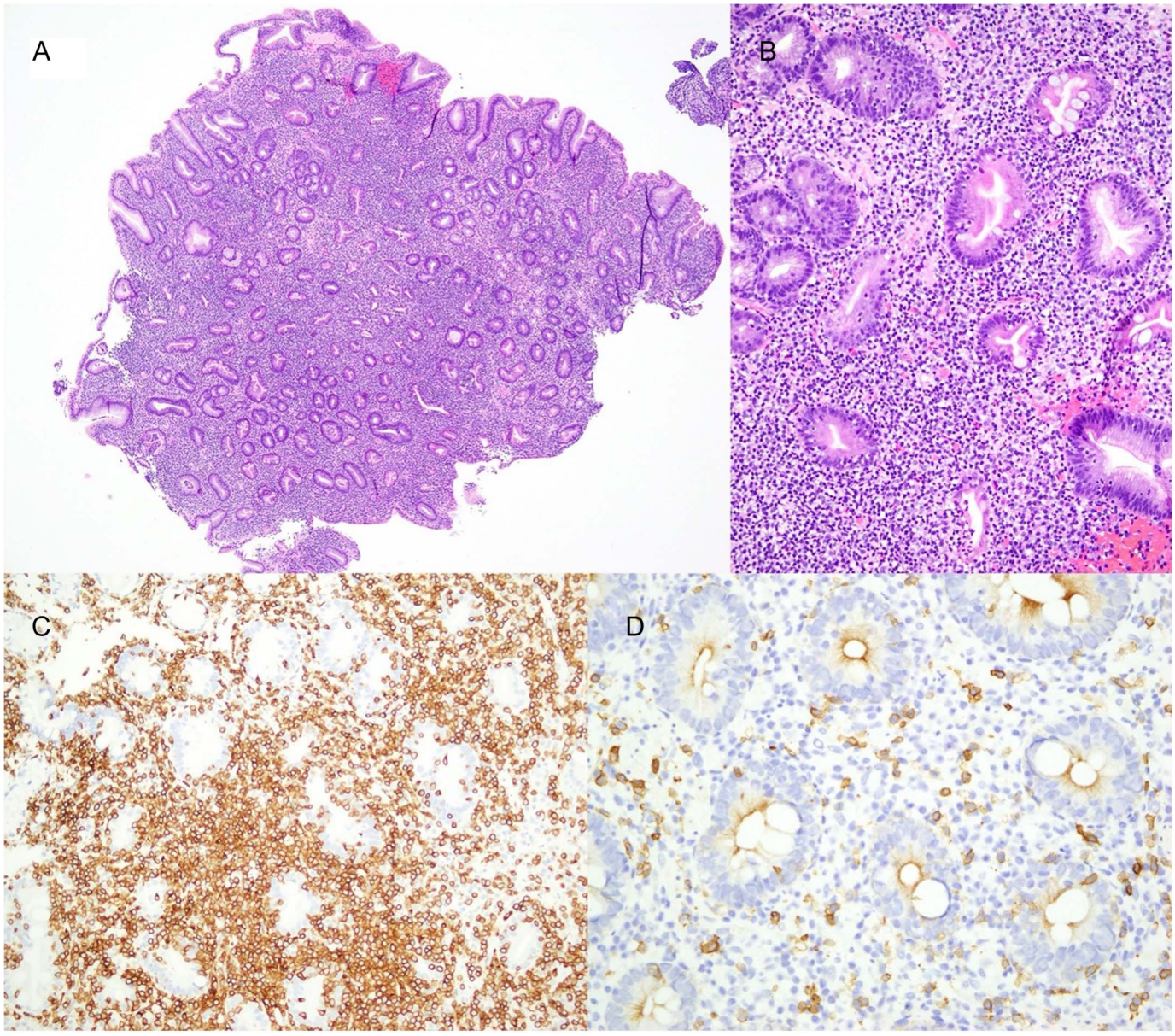

Figure 2. Biopsy showed intraepithelial lymphocytes composed of small mature T cells.

DISCLOSURES

Author contributions: R. David wrote the manuscript and is the article guarantor. K. Mishra and S. Hendler revised and edited the manuscript. K. Mirza provided the pathology slides. ER Gilbert assisted with the pulmonary findings.

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