Primary Enteropathy-Associated T-Cell Lymphoma Type 2: An Emerging Entity?

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Summary: Intestinal T-cell lymphoma is a rare hematological malignancy that can present as primary intestinal lymphoma or as a manifestation of systemic disease. Primary involvement accounts for approximately 0.1% to 0.5% of all colorectal neoplasms. It is an aggressive disease with a poor prognosis and low survival rate. Inflammatory bowel disease, celiac disease, immunosuppression, and infectious etiologies, such as Epstein–Barr and human T-lymphotropic viruses, have been reported as risk factors, but no direct causal link has been established. Herein, we examine the case of a Hispanic man 69 years of age diagnosed with positive CD3, CD7, CD8, CD43, and Bcl-2 diffuse primary colorectal T-cell lymphoma. The patient did not exhibit a concomitant autoimmune or genetic disease. Because of the patient's history of polyps, surveillance colonoscopy was performed and the diagnosis was confirmed.

Background
Gastrointestinal (GI) lymphoid tissues exist in the intestinal epithelium, lamina propria, submucosa, and lymph nodes. An accumulation of lymphocytic tumor cells can be seen in any of these tissue layers in GI lymphomas. Colorectal lymphomas manifest as either primary tumors or generalized lymphoma with associated colorectal involvement. Primary extranodal GI lymphomas are rare neoplastic processes accounting for 1% to 4% of all GI malignancies. Primary extranodal lymphomas of the GI tract are most common on the stomach (50%–60%) and small intestine (20%–30%). Cases of primary lymphomas of the colon are rare and most are of B-cell origin. Primary T-cell lymphomas of the lower GI tract are infrequent, representing approximately 0.1% to 0.5% of all colorectal neoplasms. Establishing a diagnosis of primary colorectal lymphoma requires histological confirmation that the lymphoproliferative neoplasm is isolated to the colon and the regional lymph nodes.

This hematological malignancy has a male predominance and a higher incidence in those 50 to 70 years of age. Inflammatory bowel disease, celiac disease, immunosuppressive states, and infectious etiologies, such as Epstein–Barr virus (EBV) and human T-lymphotropic virus (HTLV), have been reported to be risk factors; however, no direct causal link has been established.

Upon presentation, symptoms are typically non-specific and may include changes in bowel habits, weight loss, abdominal pain, diarrhea, and rectal bleeding. Acute abdomen secondary to intestinal obstruction and tumor perforation requiring emergent surgical intervention have also been reported on initial presentation.

Early diagnosis is crucial in obtaining local control of the disease as well as to increase the likelihood of achieving remission with surgical intervention and adjuvant chemotherapy. Although colonoscopy is a crucial diagnostic tool in the diagnosis of colorectal disease, little is known of its value in the diagnosis of primary colorectal lymphoma.

Herein we present the case of a man diagnosed with diffuse primary colorectal T-cell lymphoma while being evaluated for unexplained weight loss.

Case Report
A Hispanic man 69 years of age presented with a past medical history of hypertension, type 2 diabetes mellitus, gout, arthritis, and hyperlipidemia. He admitted to tobacco use and alcohol abuse. He was evaluated for worsening dysphagia to solids and liquids that had lasted for 5 months and was associated with a 30-pound weight loss. He denied fever, chills, nausea, vomiting, abdominal pain or distention, changes in bowel habits, pencil-like stool, early satiety, food intolerance, odynophagia, tenesmus, or GI bleeding.

Findings on the physical examination were grossly unremarkable. In particular, the abdomen was soft, nontender to palpation, and had normal bowel...
sounds. No palpable organomegaly was present, nor were masses or lymphadenopathy. Findings on the rectal examination were also unremarkable. The patient had adequate sphincter tone with no evidence of fissures, nodules, or ulcers. Routine blood work was similarly unremarkable, with no evidence of anemia or leukocytosis, and the peripheral smear confirmed a normal leukocyte distribution.

In the setting of chronic dysphagia and weight loss accompanied by alcohol and tobacco use, upper endoscopy was obtained. Findings were remarkable for diffuse, severe nonerosive gastritis and mild nonerosive duodenitis without evidence of mucosal scalloping or other duodenal pathology. No evidence suggested the presence of esophageal lesions, rings, webs, or mucosal defects. Results from the rapid urease test (also known as the *Campylobacter*-like organism test) and gastric biopsies were negative for *Helicobacter pylori*.

Colonoscopy was also scheduled due to the patient’s remote history of colon polyps of unknown histology diagnosed more than 5 years prior to his current visit. Colonoscopy revealed the presence of a sessile polyp at the cecum (0.5 × 0.3 × 0.2 cm), 2 sessile polyps at the ascending colon (0.5 × 0.3 × 0.3 cm), 1 sessile polyp at the rectum (0.5 × 0.2 × 0.2 cm), and 1 polyp 15 cm from the anal verge (2 × 1 × 0.7 cm). The findings also demonstrated evidence of an erythematous and edematous fold 60 cm from the entry site and a flat lesion 27 cm from the anal verge (Fig 1).

All polyps were excised, and the histology was consistent with tubular adenomas. Histological examination of the colonic flat lesions biopsy samples revealed abundant intraepithelial lymphocytes (Figs 2 and 3), and immunophenotyping revealed an intraepithelial T-cell population positive for CD3 and negative for CD10 and CD5. Because of these findings, immunostains were performed to rule out lymphocytic colitis or neoplastic T-cell proliferation. The specimens were sent for further evaluation to the National Cancer Institute.

Histologic examination of the biopsies also identified infiltration by monomorphic, medium-sized lymphocytes with a rim of pale cytoplasm and round dark nuclei. Florid intraepithelial infiltration of the crypts was present as well as prominent intraepithelial lymphocytosis. Minimal inflammatory background without necrosis was also documented. Immunostains of the crypt infiltrate were highlighted by CD3, CD8, CD56, TIA-1, and T-cell receptor (TCR) γ; they were focally positive for perforin; and they had weak staining for CD2. CD20, CD4, CD5, TCR-β, granzyme B, and Epstein–Barr encoding region in situ hybridization were negative. Polymerase chain reaction studies showed evidence of clonal rearrangements of the TCR gene. The histology and immunophenotype supported the diagnosis of enteropathy-associated T-cell lymphoma (EATL) type 2 with evidence of the δ phenotype.

Staging computed tomography of the chest, abdomen, and pelvis showed no evidence of lymphadenopathy or extranodal organ involvement. Positron emission tomography was obtained and revealed no avid lesions. Results from HIV by enzyme-linked immunosorbent assay (ELISA) and antibodies against HTLV types 1 and 2 were negative. EBV serology was remarkable for negative antibodies against EBV viral-capsid antigen immunoglobulin (Ig) M, Epstein–Barr nuclear antigen, and early antigen with positive IgG antibodies against viral capsid, which has been associated with primary infection in the acute phase.

Positive serology against EBV brought contention regarding the diagnosis of EATL. However, no evidence suggested the presence of pleomorphic lymphoma cells, polymorphic inflammatory

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Fig 1. — A large, flat ulcerated lesion with surrounding erythema and edema 27 cm from the anal verge.

Fig 2. — Section of colon showing neoplastic intraepithelial lymphocytes infiltrating the colonic crypts (hematoxylin and eosin, × 400).
infiltrate, angioinvasion, angiocentricity, or zonal necrosis — all of which are features of the nasal type of natural killer (NK)/T-cell lymphomas. Furthermore, the patient had TCR gene rearrangements positive for CD8, which are not seen in the nasal type of NK/T-cell lymphoma. Celiac disease was excluded based on undetectable tissue transglutaminase antibody (< 1 U/mL) in the setting of an adequate IgA level (201 mg/dL; reference range, 131–407). Viral serology for hepatitis B and C (hepatitis B core antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis C antibody by ELISA) was negative. Lactate dehydrogenase (LDH) levels were within normal limits. Bone marrow biopsy and aspirate were morphologically normal with no B or T cells. Monoclonal cells were apparent by flow cytometry.

Given the localized disease, the patient subsequently underwent total abdominal colectomy with ileorectal anastomosis (Fig 4). The pathology report identified 36 regional lymph nodes with focal areas of diffuse paracortical monotonous tumor consistent with a malignant lymphomatous tumor. Microscopic examination of the colon further demonstrated extensive lymphomatous involvement extending to the distal and radial margins.

The immediate postoperative period was complicated by multiple episodes of diarrhea that required aggressive hydration and antidiarrheal medications, including loperamide and diphenoxylate/atropine. Because of the extent of the disease, adjuvant chemotherapy was started with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP).

Response to the induction cycle was poor. Due to septic shock secondary to community-acquired pneumonia, the patient died 3 months after the diagnosis was established.

**Discussion**

Lymphomas are hematological malignancies with a wide variety of histological subtypes and a broad spectrum of clinical behaviors, aggressiveness, and prognosis. It is the eight and ninth most common cause of cancer-related death in US women and men, respectively. The incidence rate for non-Hodgkin lymphoma (NHL) slightly increased among men between 2007 and 2011. In the United States, an estimated 80,900 new cases of lymphoma will be diagnosed in 2015; of those, 71,850 will be NHL. The GI tract is the main site for the extranodal dissemination of lymphoma and constitutes 40% of all cases. However, primary colorectal lymphoma is relatively rare, making up approximately 0.1% to 0.5% of all colorectal neoplasms and representing the third most common large bowel malignancy after adenocarcinoma and neuroendocrine tumor. The most common location for colorectal lymphoma is the cecum and is suspected to be secondary to the abundance of lymphoid tissue in this anatomical region. Tumors of the descending and rectosigmoid colon account for approximately 25% of all colorectal lymphomas.

EATL is the only well-defined clinicopathological entity of primary T-cell GI lymphomas. It represents a rare NHL of T-cell origin, and it accounts for less than 1% of all NHLs. The World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue distinguishes between 2 types of EATL, with type 1 accounting for 80% to 90% of cases. The 2 subtypes, types 1 and 2, are classified based on histology, immunophenotype, and relationship to celiac disease. EATL is an infrequent type of aggressive lymphoma in most parts of the world, with an estimated annual incidence of 0.5 to 1 per 1 million people in Western countries. A higher incidence has been reported in northern Europe, where it overlaps...
with celiac disease. Type 1 is more common in Europe and type 2 is more common in Asia, whereas both EATL types are equally common in North America.\textsuperscript{12} EATL has a male predominance with a median onset during the sixth decade of life.\textsuperscript{14}

Type 1 accounts for two-thirds of all cases of EATL and is associated with celiac disease, which is a food intolerance disorder in Western populations that has a prevalence of 0.5% to 1%.\textsuperscript{13} The relationship between EATL type 1 and celiac disease is well established and is characterized by positive results on serology tests, HLA DQ2/8 expression in up to 90% of cases, and associated clinical findings such as dermatitis herpetiformis and hypoplasia.\textsuperscript{10}

**Type 1**

Microscopic findings of EATL type 1 are characterized by medium- to large-sized lymphocytes with round or angulated vesicular nuclei, prominent nucleoli, and moderate to abundant pale-staining cytoplasm.\textsuperscript{12} Neoplastic tissue tends to be infiltrated with abundant eosinophils and histiocytes, which may obscure the small numbers of tumor cells.\textsuperscript{10} Coagulative necrosis is common.\textsuperscript{12} The intestinal mucosa adjacent to the tumor frequently has enteropathic features consisting of villous atrophy, crypt hyperplasia, increased inflammatory cells in the lamina propria, and intraepithelial lymphocytosis.\textsuperscript{10,12,14}

Because EATL type 1 may present with monomorphic, small- to medium-sized cells, immunohistochemistry is generally helpful in distinguishing between the 2 subtypes. In general, type 1 tumors cells are positive for CD3, CD7, and CD103, but negative for CD5, CD4, and CD56; however, 10% of cases are positive for CD56.\textsuperscript{15} Tumor cells can also be positive or negative for CD8 and TCR-β, and a varying proportion of cells express CD30.\textsuperscript{10} Furthermore, EATL can conceal complex segmental chromosomal amplifications or deletions, and type 1 frequently displays deletions of 16q12.1 and gains of 1q, 5q, and 9q31.3.\textsuperscript{10,16}

**Type 2**

Type 2 accounts for 10% to 20% of all cases and has a broader geographical distribution.\textsuperscript{10,15,17} Typically, it occurs sporadically, but up to one-quarter of patients have a history of celiac disease and 30% to 40% express HLA DQ2/8.\textsuperscript{12} Histologically, type 2 is characterized by multiple foci of small, round uniform cells with dark nuclei and a rim of pale cytoplasm. Heavy infiltration of the intestinal crypt epithelium is present and a few admixed inflammatory cells may be seen; coagulative necrosis is absent. The adjacent intestinal mucosa shows villous atrophy and crypt hyperplasia with marked intraepithelial lymphocytosis involving both the crypt and surface epithelium.\textsuperscript{10} Immunohistochemistry of the tumor cells and intraepithelial lymphocytes on the adjacent mucosa will be negative for CD4 and positive for CD3, CD8, and CD56 in 80% to 90% of cases and TCR-β.\textsuperscript{17} This subtype is also characterized by chromosome 8q24 (MYC) amplifications and, less commonly, by gains of 1q and 5q.\textsuperscript{10,16}

Both types of EATL can be distinguished from reactive expansion by testing the clonality of the TCR genes.

**Clinical Presentation**

The clinical presentation of primary colorectal lymphomas is diverse and the duration of the presenting symptoms can widely vary.\textsuperscript{11} Patients with EATL most commonly present with abdominal pain, weight loss, diarrhea, vomiting, fatigue, and anorexia.\textsuperscript{10,11} In addition, a palpable abdominal mass, bowel perforation, bowel obstruction, B symptoms, and hemophagocytic syndrome have been reported in some cases.\textsuperscript{11,17}

A history of adult-onset celiac disease with or without a disease-free period is typically present in patients with EATL type 1; childhood onset of celiac disease has also been associated with this subtype but not as frequently.\textsuperscript{10} In some patients, EATL is simultaneously diagnosed with celiac disease.\textsuperscript{10}

Our patient presented with unintentional weight loss alone, which has been reported in 27% to 80% cases in the literature.\textsuperscript{7} Serology tests for celiac disease were negative. Patients typically ignore this relatively nonspecific symptom for an extended period of time, thus further contributing to an advanced stage of disease at the time of diagnosis. In addition, performance status is variable at the time of presentation, with most patients having a WHO performance status of 1 to 3.\textsuperscript{11}

More than 90% of EATLs arise in the small intestine; the jejunum and proximal ileum are the most frequent sites.\textsuperscript{10,12} EATL of the large intestine, as in our patient, has been reported in approximately 16% to 18% of cases.\textsuperscript{12,14} Growth patterns tend to be diverse and lesions may range from multiple, ulcerating raised mucosal masses to 1 or more ulcers, large exophytic masses, strictures, or plaques.\textsuperscript{1,12} Classical lymphoma staging systems have failed to provide adequate prognostic treatment guidance for patients with EATL. Although they have not been validated, several case series have identified other novel adverse predictors of survival in patients with this type of lymphoma, such as elevated levels of C-reactive protein and LDH, tumor size larger than 5 cm, and a nonambulatory performance status.\textsuperscript{16,18}

**Diagnosis**

An exact diagnostic algorithm for EATL remains...
undefined because of the lack of studies aimed at comparing the accuracy of the different diagnostic modalities. Colonscopy is valuable in the diagnosis of primary intestinal lymphoma, but a high index of suspicion is needed for tissue biopsy and diagnosis. In 1 series, colonoscopy accurately diagnosed primary intestinal lymphoma in 23% of cases. Explana
tion for this may involve an insufficient specimen for pathological evaluation, because random biopsies in the absence of apparent pathology are often needed to accurately identify and determine the extent of lymphoma. Colorectal lymphoma is most often imaged using computed tomography, which can provide extraluminal and anatomical information regarding tumor size, depth of invasion, and regional lymph node involvement. Positron emission tomography may be of use for diagnosis and for following-up patients, but its role has not been determined. A study published in 2012 showed that EATL type 2 is fluorodeoxyglucose (FDG) nonavid in 67% of cases, whereas type 1 is uniformly FDG avid. In this case, computed tomography and positron emission tomography imaging failed to discover any colorectal disease, thus highlighting the importance of high-quality colonoscopy in detecting rare GI pathologies that would have not been diagnosed otherwise.

**Treatment**

EATL has limited validated treatment strategies because of the lack of randomized clinical trials. Historically, treatment options have included surgical resections with or without anthracycline-based chemotherapy; however, results with these treatment modalities are limited. The National Comprehensive Cancer Network recommends an anthracycline-based combination therapy followed by autologous stem cell transplantation in eligible patients. A CHOP-like regimen, similar to what our patient received, has an overall response rate of 30% to 60%. With current treatment strategies, the median overall survival rate is approximately 10 months; the 5-year estimated survival rate is 20%. As in our patient, due to comorbidities, performance status, and his fragile state following total colectomy, only 50% of patients are eligible to undergo planned chemotherapy.

Given data regarding their use in other CD30+ T-cell lymphomas, agents such as brentuximab vedotin, an anti-CD30 conjugated antibody, can be considered in patients with evidence of disease progression after induction therapy; a median duration of remission of 13.6 months has been reported. Khalaf et al reported on a patient with EATL successfully treated with brentuximab vedotin as salvage treatment who had a good response and disease remission at 9 months of follow-up. Due to its efficacy and tolerance, this medication could be considered as first-line treatment in CD30+ EATL in addition to current strategies to improve survival and response rates in patients whose tolerance to anthracycline-based therapy is expected to be poor. Additional case reports using alemtuzumab, a monoclonal antibody against CD52, and romidepsin, a histone deacetylase inhibitor, have shown promising clinical responses.

**Conclusion**

This case satisfies the histology and immunophenotypic criteria for enteropathy-associated T-cell lymphoma type 2 and highlights the difficulties in appropriately diagnosing T-cell malignancies. The incidence and localization rates of primary gastrointestinal lymphomas are known to vary based on race and geographical location, but their incidence and prevalence in the Hispanic population have not yet been determined. A significant increase can be seen in the incidence of EATL in the United States, most likely reflecting the increasing seroprevalence of celiac disease and better recognition of the rare types of T-cell lymphomas. It will be important to monitor the incidence of both EATL and premalignant conditions as evidence accumulates among whites and ethnic minorities. Although emerging data are encouraging, a significant need still exists for improved treatment modalities in this disease.

**References**


