Rare Variant Of Intestinal T-Cell Lymphoma In An Elderly Female With Monomorphic Epitheliotropic Features

C Parsa, C Yeh, R Orlando, J Guo

Citation

C Parsa, C Yeh, R Orlando, J Guo. *Rare Variant Of Intestinal T-Cell Lymphoma In An Elderly Female With Monomorphic Epitheliotropic Features*. The Internet Journal of Pathology. 2021 Volume 22 Number 1.

DOI: 10.5580/IJPA.55555

Abstract

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a rare and aggressive extranodal T-cell lymphoma of the gastrointestinal tract with exceedingly poor prognosis. Its diagnosis and clinical management are complicated by a broad differential, frequently manifesting with non-specific clinical presentation. While recent studies have provided useful insights in regard to its molecular and genetic characteristics, its pathogenesis remains poorly understood. We present a case of an 81-year-old female with T-cell lymphoma, showing MEITL morphologic features, involving the ileum. The patient presented with repeated episodes of nausea, decreased oral tolerance and abdominal pain. Amongst the many lymphoid markers studied, CD3, TIA-1, and bcl-2 were the only ones that were positive by immunohistochemistry (IHC) and T-cell receptors beta and gamma by molecular studies. Although positive in most reported cases, CD8 and CD56 were negative in our case. Recognition of various IHC and molecular markers of this rare neoplasm may elucidate a better understanding of its pathogenesis and eventual approach to therapeutic modalities.

INTRODUCTION:

Intestinal T cell lymphomas are believed to arise from intraepithelial lymphocytes. They are categorized into two distinct types: enteropathy-associated T cell lymphomas (EATL), occurring in patients with celiac disease; and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), not associated with celiac disease [1,2]. Although strongly linked with EATL, celiac disease may also occur in some MEITL patients [11]. The challenges posed by the aggressive nature and lack of established therapy for MEITL are compounded by its resemblance to gastrointestinal inflammatory disorders [9].

While EATL has increased prevalence in populations of Northern European descent, MEITL exhibits greatest prevalence in populations of East Asian, Southeast Asian and Hispanic descent [3,6-9]. EATL typically reveals pleomorphic cytomorphologic features with eosinophils and histiocytes [4]. In contrast, as its name suggests, MEITL cells are histologically small-to-intermediate in size and monomorphic in appearance. Molecular studies have shown that MEITL exhibits a predominantly gamma-delta T-cell receptor (-TCR+) phenotype, whereas EATL displays a predominantly negative T-cell receptor (TCR-) phenotype [2]. MEITL is frequently CD56+ and CD8+ by immunohistochemistry. Genetic analysis has revealed MYC oncogene locus gain and rare gains of chromosomes 1q and 5q [5].

CASE REPORT

An 81-year-old Hispanic female presented to the emergency department on multiple occasions, over an eighteen-month period, complaining of nausea, episodes of vomiting, generalized weakness, and decreased food tolerance without abdominal pain or diarrhea. Computed tomography (CT) of the abdomen showed fat stranding suspicious for gastroenteritis. The patient showed improvement following one day of observation and was discharged with subsequent treatment for acute gastritis and urinary tract infection.

The patient did well on antiemetics for 15 months, but her symptoms returned, now notable for 15 pound weight loss, two weeks of decreased oral intake, and abdominal pain with episodes of nausea and vomiting. Abdomen remained soft and nontender. The patient was unable to tolerate oral food intake.

Pertinent laboratory findings included lymphocytopenia of 672/mm³ and anemia of chronic disease with hemoglobin of

10 g/dL.

CT of the abdomen showed severe circumferential wall thickening of a short segment of distal small intestine with dilatation of upstream (proximal) intestinal segment, favoring obstructive changes (figure 1).

An exploratory laparotomy was then performed, followed by small bowel resection. The gross specimen consisted of a tightly folded segment of small intestine, overall 24 cm long, incorporating a compact mass, 13 cm long and 7 cm wide. On section, the intestinal wall measured up to 2.5 cm in thickness (figure 2). Touch preparation of the thickened intestinal wall showed monotonous small to intermediate cells with round to variably irregular nuclei (figure 3).

Histologic sections of the intestinal wall showed full-thickness involvement by diffuse infiltrate of monomorphic small-to-intermediate cells (figure 4), similar to those seen in the touch preparation. The mucosal surface was partially ulcerated. Immunostains CD3, TIA-1, and bcl-2 were positive. The lymphoid markers CD56, CD4, CD8, CD20, CD79a, CD5, CD10, bcl-1, bcl-6, MUM-1, c-MYC, and EBER were all negative. The epithelial markers CKAE1/AE3, CK7, synaptophysin, chromogranin, CDX2, and villin were also negative. In addition, CD117 and S100 were negative. The Ki-67 (proliferative index) was 50%.

Molecular genetics, polymerase chain reaction (PCR) assays, for T-cell receptor beta and gamma gene rearrangements, performed at Neo-Genomics (Aliso Viejo, CA), were both positive.

The patient was admitted again three months later, status post-small bowel resection, with new generalized weakness and diffuse pain. She denied vomiting or diarrhea but complained of decreased appetite. Other significant findings, for which the patient continued receiving treatment, included cerebrovascular accident (CVA) and bilateral pulmonary embolism (PE) from a right-sided deep vein thrombosis (DVT). Physical exam was notable for cachectic appearance and bizarre affect.

Figure 1

Circumferential wall thickening of short segment of distal small bowel in the lower abdomen (CT scan of abdomen with contrast).

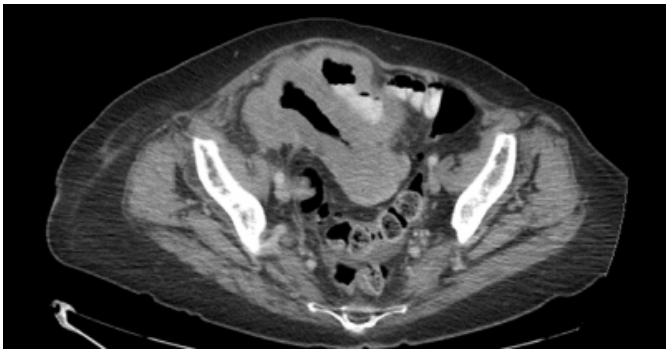


Figure 2

Gross section of the small intestine shows markedly thickened wall with homogeneous white "fish flesh" discoloration. A detached smaller intestinal segment shows the transition with normal colonic wall.

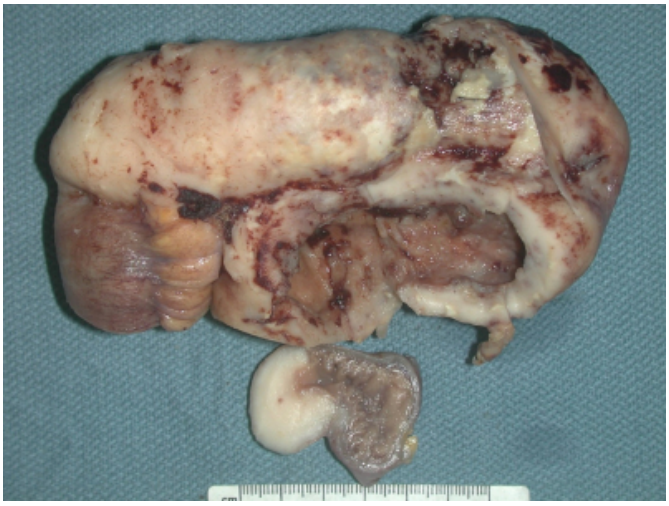


Figure 3

Touch preparation of the thickened intestinal wall shows monotonous small to intermediate cells with round to variably irregular nuclei.

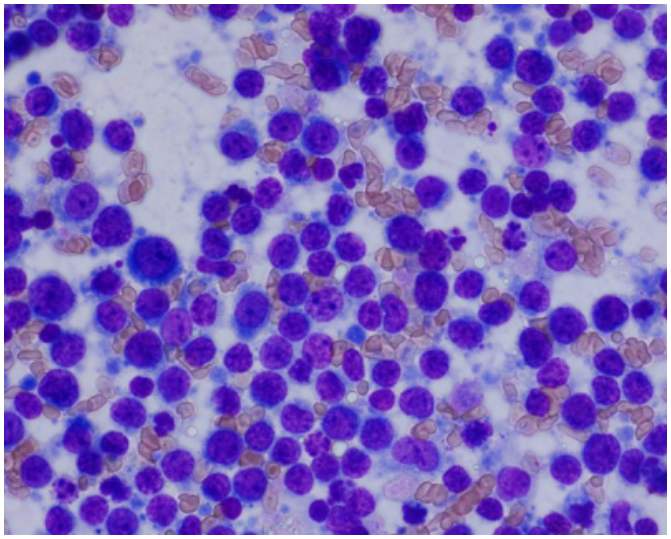


Figure 4

Low power histologic section of small intestine shows diffuse lymphocytic infiltration of the intestinal wall.

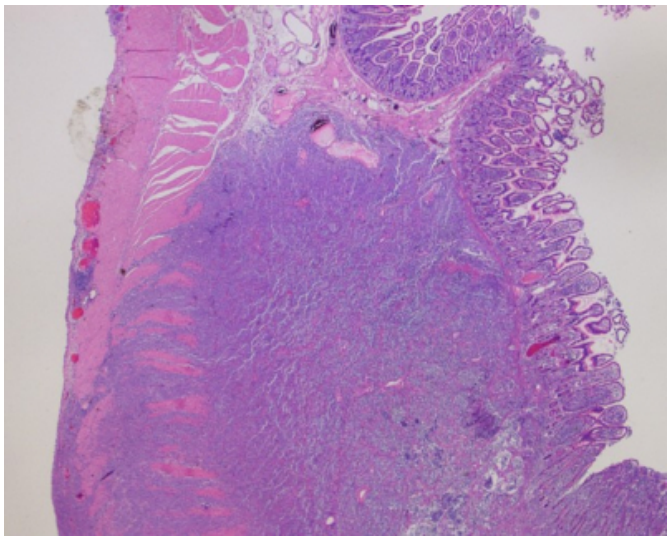
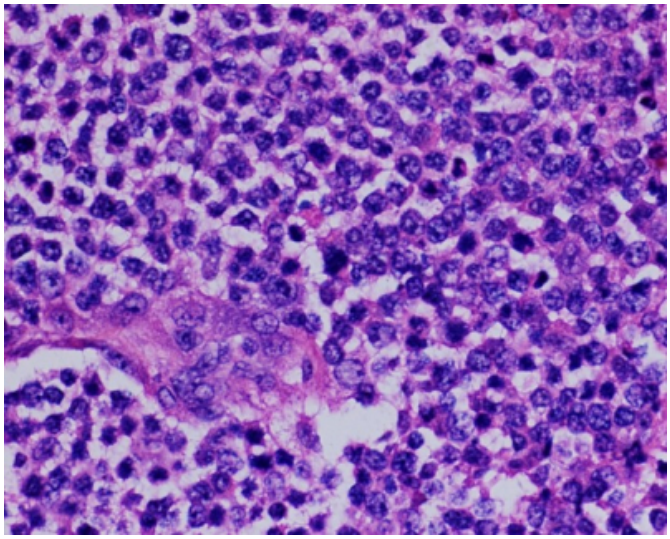


Figure 5

Higher magnification (400 X) shows essentially similar morphologic features as those seen on touch preparation of the thickened intestinal wall.



DISCUSSIONS:

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly known as type II enteropathy associated T-cell lymphoma (type II EATL), is a rare, aggressive primary intestinal T-cell lymphoma with poor prognosis and incompletely understood pathogenesis. Diagnosis and management of MEITL is complicated by its constellation of clinicopathologic features with a broad differential consideration, including nonspecific gastroenteritis, inflammatory bowel disease, microscopic colitis, EATL, intestinal NK/T-cell lymphoma, indolent T-cell lymphoproliferative disease, as well as other intestinal neoplasms. Our patient presented with nonspecific gastrointestinal symptoms of acute gastroenteritis and displayed fat stranding on computerized tomography, which is consistent with various abdominal wall abnormalities that have been documented in MEITL [15,19].

There is increased risk of MEITL in populations of either East Asian, Southeast Asian, or Hispanic descent [1,3,7] with increased prevalence in males [2,3,7]. Mortality rate due to lymphoproliferative disorders of the gastrointestinal tract may be as high as 59.3% by 1 year post-diagnosis [6]. The median overall survival calculated from a cohort of thirty-eight patients with histologically-confirmed MEITL was 7 months post-diagnosis with a progression-free survival of 1 month [3]. Distant metastases to lymph nodes (58%), thoracic structures (50%) and the brain (25%) were found in 12 cases diagnosed by imaging [14,17].

Difficulty in diagnosing MEITL is likely a contributing factor to its generally poor prognosis, as patients may not be diagnosed until the late clinical stages of the disease. MEITL often mimics other inflammatory or neoplastic disorders of the alimentary canal [3,6,9].

Molecular studies of MEITL specimens have revealed markedly increased cytoplasmic expression of the lymphocyte signal transducers spleen tyrosine kinase (SYK) and 70 kDa -associated protein kinase (ZAP-70) [2]. They also Display positive T-cell receptor (TCR+) phenotype [2,8]. While -TCR+ lymphocytes are sparse in systemic circulation, they represent a major population of migratory cells in the lamina propria of the intestinal mucosa and appear to engage in cross-talk with gut microbiota [12,16]. In murine models, T-cell knockdown subjects are more susceptible to induced mucosal injury and experience delayed tissue repair thereafter [13].

Our patient's positive immunostaining for CD3 and TIA-1 are representative of a significant portion of documented cases world-wide [3,7,18]. To our knowledge, positivity for B-cell lymphoma 2 (bcl-2) has not been reported in MEITL. The overall morphologic findings of our case were those of an intestinal T-cell lymphoma, despite the negativity for CD8 and CD56. Negativity for these markers is, however, documented in a minority of cases [3,7,18].

Tissue biopsy and molecular studies continue to be helpful in the diagnosis of MEITL due to the otherwise relatively minor and non-specific findings often seen on radiographic imaging and endoscopy. The histomorphologically characteristic MEITL features in the currently presented case with positive immunostaining for bcl-2 and negative staining for CD8 and CD56 is a rare occurrence in these intestinal lymphoproliferative disorders that may be helpful in the elucidation of their pathogenesis.

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Author Information

Cyrus Parsa, D.O., FCAP, FASCP
Western University of Health Sciences, Department of Pathology

Christopher Yeh, Medical Student
Western University of Health Sciences

Robert Orlando, MD, PhD, FCAP

Jin Guo, MD
Western University of Health Sciences, Department of Pathology