Endoscopic features and clinical outcomes of enteropathy-associated T-cell lymphoma: A tertiary center retrospective study

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Abstract

Background: Enteropathy-associated T-cell lymphoma (EATL) is a rare but aggressive primary gastrointestinal lymphoma. The initial complaints of EATL patients are usually gastrointestinal symptoms, but the diagnosis is very difficult. Endoscopy can identify abnormal mucosa in most patients. However, the endoscopic appearance of EATL is still largely unknown.

Methods: In this retrospective study, we investigated the endoscopic and clinical features of patients with EATLs at a tertiary center, from January 2008 to October 2020.

Results: From a total of 248 patients with primary intestinal lymphoma, only 11 patients were finally diagnosed with EATLs, all of which were EATL type II. Men were affected twice as commonly as women. The median patient age was 47 years. The most common initial symptom was diarrhea (63.6%). Five patients (45.4%) were at late stage (IV) at diagnosis. The endoscopic appearances were classified into four distinct types: ulcerative type (54.5%), epithelial mass type (18.2%), diffuse infiltration type (9.1%), and nodular type (18.2%). The small bowel was the most common site of involvement (72.7%). The initial endoscopic impression of lymphoma was made in only 3 patients (27.3%). Only 4 patients (36.4%) were histologically confirmed as having EATLs based on the initial biopsy specimen. Five patients (45.5%) received emergency surgery. The median overall survival (OS) was 8 months. The use of chemotherapy and the absence of emergency surgery were associated with a significantly better median OS (P < 0.05).

Conclusions: EATL may show various endoscopic appearances, and its prognosis is poor. Endoscopists should obtain more knowledge of EATL in order to make an early diagnosis.

Keywords: Endoscopy, enteropathy-associated T-cell lymphoma, clinical feature, survival
INTRODUCTION

Enteropathy-associated T-cell lymphoma (EATL), which is derived from intraepithelial intestinal cytotoxic T-lymphocytes, is a rare primary gastrointestinal (GI) lymphoma. It represents 10%–16% of all primary lymphomas of the GI tract and 5.4% of peripheral T-cell/natural killer (NK) cell lymphomas. According to the revised World Health Organization (WHO) classification published in 2016, two subtypes of EATLs have been designated due to their distinct nature. EATL type I, now simply designated EATL, is closely related to celiac disease and common in Europe. EATL type II, due to its distinctive nature and lack of association with celiac disease, was segregated from EATL type I and given the new name of monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). MEITL is usually positive for CD8 and CD56 and appears to be increased in incidence in Asians and Hispanic populations. EATL Type II, less common than type I, comprises 34% of all EATL cases. Both subtypes are highly aggressive disorders with 5-year survival rates below 20% and few treatment options available. The most common involvement site of EATLs is the small bowel, accounting for 90% of all EATL patients. The clinical presentation of EATL can vary from diarrhea, malabsorption, and abdominal pain to acute abdominal emergency. Common emergency complications include GI bleeding, bowel perforation, obstruction, and enterocolic fistulae. EATL has a poor prognosis due to treatment resistance and severe complications (for example, sepsis, perforation, obstruction, bleeding) at diagnosis or during treatment. A previous study showed a median overall survival (OS) of only 10 months and a median progression-free survival (PFS) of only 6 months. With regard to EATL Type II alone, a poorer prognosis was found, with a median OS of 7 months and PFS of 1 month.

Although the prognosis of EATLs is poor, the majority of patients with EATLs are diagnosed at a late stage. In fact, endoscopy can identify abnormal mucosa in most patients at a relatively early stage. However, the endoscopic features of EATLs are nonspecific, and many endoscopists are unfamiliar with this rare disease, which makes early diagnosis difficult. Although there have been some multicenter studies focusing on this disease, these usually studied the clinical characteristics of EATLs alone. To date, only a few case reports have detailed the endoscopic morphologic features of EATLs. In addition, due to a lack of specific endoscopic features, it is difficult to distinguish EATLs and other GI diseases, such as inflammatory bowel disease (IBD) and GI solid tumors, at the time of presentation. To advance knowledge of this disease, we retrospectively reviewed the cases of EATLs diagnosed within a 13-year period in a single tertiary center and summarized the clinical characteristics and endoscopic features of the EATLs.

METHODS

Patients

We retrospectively reviewed patients with EATLs diagnosed at Xijing Hospital of Digestive Diseases from January 2008 to October 2020. Clinical characteristics, endoscopic features and treatment outcomes were collected for analysis. In general, B symptoms refer to unexplained weight loss greater than 10% within 6 months, night sweats, or fever of unknown reason greater than 38°C for 3 days. The clinical stage was defined by the Lugano staging system for GI lymphomas. The International Prognostic Index (IPI) score was computed, and patients with EATLs were defined as low risk (score ≤2) or high risk (score >2) according to the IPI score. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the local Ethics Committee of Xijing Hospital affiliated with Air Force Medical University (number: KY20203290-1).

Pathologic diagnosis

EATL, based on the definition by the WHO, was diagnosed by a consensus panel of two experienced lymphoma histopathologists. The tissue specimens were obtained from endoscopic biopsy sampling and/or surgical resection. Immunohistochemical analysis was performed in all patients, and the following markers were included: CD3, CD5, CD4, CD8, CD30, CD56, and T-cell intracellular antigen-1 (TIA-1). Other additional markers were investigated according to the discretion of the reported histopathologists. Epstein-Barr virus (EBV)-encoded RNA (EBER) was detected by in situ hybridization (ISH), and T-cell receptor (TCR) gene clonal rearrangement was detected by polymerase chain reaction (PCR). The Ki-67 labeling index was also recorded.

Evaluation of endoscopic features

Two GI endoscopists (C. M. and Z. Y.) retrospectively reviewed the endoscopic images of all the patients. Based on the endoscopic features, EATLs were classified into four endoscopic types: ulcerative type, epithelial mass type, diffuse infiltration type, and nodular type. Ulcerative type was defined as multiple, large, and deep ulcers in the gastrointestinal tract with/without bleeding or perforation. Epithelial mass type was defined as a single or multiple large mass with/without obstruction. Diffuse
infiltration type was defined as extensive infiltration of the lesions with no obvious mass on the surface. Nodular type was defined as multiple small nodules, usually with scattered erythematous inflammation. The endoscopic concomitant features, numbers, locations of lesions, and initial endoscopic impressions were also investigated.

Statistical analysis
Continuous statistics are reported as medians (interquartile range), and categorical variables are presented as numbers (%). Correlations between endoscopic features and clinical stage and IPI score were assessed using the Chi-square test. All statistical tests were 2-sided and conducted at the alpha = 0.05 level. OS was measured from the time of diagnosis to death or last follow-up. PFS was measured from the time of diagnosis to disease progression, death, or last follow-up. Survival analysis was performed by the Kaplan-Meier method, and comparisons of survival between treatment groups were analyzed using the log rank test. The statistical analysis was performed using SPSS software 26.0 (Chicago, IL, USA).

RESULTS
Clinical features at diagnosis
Among a total of 248 patients with primary intestinal lymphoma, only 11 patients (4.4%), all of whom had EATL type II, were histologically diagnosed with EATL within the last 13 years. There was a predominance of male patients (8/11, 72.7%), and the median age was 47 (23–69) years. The most common initial symptom was diarrhea (63.6%), followed by abdominal pain (45.5%) and GI bleeding (18.2%), with a median disease duration of 7 (1–120) months. None of the patients; however, had a history of celiac disease or malabsorption before the lymphoma diagnosis. Notably, 5 of 11 (45.5%) patients underwent emergency surgery due to uncontrolled GI bleeding, acute intestinal perforation, or obstruction. B symptoms were present in 10 patients (90.9%). Bone marrow involvement was infrequent and was confirmed absent in 9 patients; the other two patients did not undergo bone marrow puncture because of serious illness. Five of 11 (45.4%) patients were at late stage IV at diagnosis according to the Lugano staging system. Most patients (9/11, 81.8%) were low risk according to the IPI score. Regarding laboratory tests, lactate dehydrogenase (LDH) levels were elevated in 1 of 11 (9.1%) patients, β2-microglobulin levels were elevated in 10 of 11 (90.9%) patients, C-reactive protein (CRP) levels were elevated in 9 of 11 (81.8%) patients, and albumin levels were decreased in 10 of 11 (90.9%) patients. The demographic and clinical features of the 11 patients with EATLs are summarized in Table 1.

Endoscopic type and diagnostic yield
All 11 patients underwent endoscopy, of whom 3 patients underwent double-balloon enteroscopy, 6 patients underwent colonoscopy, and 2 patients underwent gastroscopy. With regard to the four endoscopic types, the ulcerative type was the most common (6 patients, 54.5%). Other types, including epithelial mass type, diffuse infiltration type and nodular type, accounted for 18.2%, 9.1%, and 18.2%, respectively. With regard to endoscopic concomitant performance, stricture was the most common (6 patients, 54.5%), followed by villous atrophy (3 patients, 27.3%) and mucosal edema (3 patients, 27.3%). The small bowel was the most common site of involvement (8 patients, 72.7%); 4 patients (36.4%) had isolated small bowel involvement and 1 patient (9.1%) had small bowel and pancreas involvement. Large bowel involvement was found in 5 patients (45.5%). Interestingly, isolated stomach involvement was found in 1 patient (9.1%), and this patient had the longest disease duration (10 years) and a good prognosis. An initial endoscopic impression of lymphoma was made in only three patients (27.3%). Crohn’s disease was the most common initial endoscopic impression for EATLs (36.3%). Endoscopic features are summarized in Table 2. There was no relationship between endoscopic type and clinical stage ($P = 0.334$) [Table 3]. There was also no relationship between endoscopic type and IPI score ($P = 0.555$) [Table 4].

With regard to the initial tissue acquisition and histologic diagnostic method, forceps biopsy sampling was performed in all 11 patients (100%). However, only four patients (36.4%) were histologically confirmed as having EATLs with the initial biopsy specimen. Five of the
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7 patients who were not diagnosed with EATL through the initial biopsy specimen received a confirmed diagnosis of EATL based on the second or third biopsy specimen. However, in the other 2 of the 7 patients, EATLs were confirmed by surgery specimens. Figure 2 summarizes and schematizes the diagnostic yields of endoscopic biopsy sampling and surgery in the histologic confirmation of EATL.

**Immunophenotyping**

The expression of CD3, CD5, CD4, CD8, CD30, and TIA-1 was detected in all 11 patients. The positive percentages of immunohistochemical staining were 100%, 18.2%, 18.2%, 63.6%, 9.1%, 63.6%, and 81.8%, respectively. TCR gene clonal rearrangement was performed in two cases, all showing clonal TCR gene rearrangement. Epstein–Barr virus–encoded RNA in situ hybridization stain (EBER-ISH) was positive in 1/11 (9.1%) of the cases, which showed clonal TCR gene rearrangement, implying bona fide T-cell lineage. With regard to the Ki-67 index, 5/11 (45.5%) of the patients showed hyperproliferative activity with a Ki-67 index >80%, 3/11 (27.3%) of the patients had a Ki-67 index of 50%–60%, 3/11 (27.3%) of the patients had a Ki-67 index of 10%–30%. The immunophenotypes of the patients with EATLs are summarized in Table 5.

**Treatment and clinical outcomes**

Due to acute emergency presentations, including GI hemorrhage, perforation and obstruction, surgical resection of the tumor was performed in 5/11 (45.5%) of the patients. The three patients who underwent surgery only died within 1.5 months (0.5–1.5 months) after diagnosis. Five patients (45.5%) received chemotherapy only. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or anthracycline-based chemotherapy was the most common regimen (n = 4), followed by etoposide, prednisone, VinCRISTine, cyclophosphamide, DOXOrubicin (EPOCH) therapy (n = 1). Complete response (CR) was achieved in two patients (40%), and the other three patients had disease progression. Two patients received combination treatment, one of whom underwent autologous hematopoietic stem cell transplantation (AHSC) and survived for 18 months and the other survived for 2 months. One patient received no treatment because of a poor general condition and died within 15 days. The treatment modalities and clinical outcomes are depicted in Table 6.
Table 2: Endoscopic findings of the patients with enteropathy-associated T-cell lymphoma

| Finding                                | No. of patients (%) |
|----------------------------------------|---------------------|
| Endoscopic type                        |                     |
| Ulcerative type                        | 6 (54.5)            |
| Epithelial mass type                   | 2 (18.2)            |
| Diffuse infiltration type              | 1 (9.1)             |
| Nodular type                           | 2 (18.2)            |
| Endoscopic concomitant performance     |                     |
| Villous atrophy                        | 3 (27.3)            |
| Stricture                              | 6 (54.5)            |
| Mucosal edema                          | 3 (27.3)            |
| Endoscope for diagnosis                |                     |
| Double balloon enteroscopy             | 3 (27.3)            |
| Colonoscopy                            | 6 (54.5)            |
| Gastroscope                            | 2 (18.2)            |
| Multiplicity of lesions                |                     |
| Single                                 | 3 (27.3)            |
| Multiple                               | 8 (72.7)            |
| Location                               |                     |
| Small bowel alone                      | 4 (36.4)            |
| Large bowel alone                      | 1 (9.1)             |
| Small and large bowels                 | 3 (27.3)            |
| Large bowel and stomach                | 1 (9.1)             |
| Small bowel and pancreas              | 1 (9.1)             |
| Stomach alone                          | 1 (9.1)             |
| The initial endoscopic impression      |                     |
| Lymphoma                               | 3 (27.3)            |
| Lesions other than lymphoma            | 8 (72.7)            |
| Cancer                                 | 2 (18.2)            |
| Crohn’s disease                        | 4 (36.3)            |
| Ulcerative colitis                     | 1 (9.1)             |
| Lymphatic follicular hyperplasia       | 1 (9.1)             |

Table 3: Endoscopic types and clinical stages of enteropathy-associated T-cell lymphoma

| Endoscopic types     | Clinical stage at presentation | P   |
|----------------------|-------------------------------|-----|
|                      | I    | II and II₆ | IV  |
| Ulcerative type      | 1    | 2           | 3   | 0.334 |
| Epithelial mass type | 0    | 1           | 1   |      |
| Diffuse infiltration type | 1 | 0 | 0   |      |
| Nodular type         | 1    | 0           | 1   |      |

Table 4: Endoscopic types and IPI score of enteropathy-associated T-cell lymphoma

| Endoscopic types     | IPI score | P   |
|----------------------|-----------|-----|
|                      | 0/1 | 2 | 3 | 4/5 |
| Ulcerative type      | 2    | 3 | 1 | 0   | 0.555 |
| Epithelial mass type | 1    | 0 | 1 | 0   |      |
| Diffuse infiltration type | 1 | 0 | 0 | 0   |      |
| Nodular type         | 1    | 1 | 0 | 0   |      |

The median OS of all the patients was 8 months (0.5–77), and the median PFS was 1.5 months (0–56) [Figures 3a and 4a]. The use of chemotherapy was associated with a significantly better OS [P = 0.001; Figure 3b] and PFS [P = 0.003; Figure 4b]. Low risk of the disease, according to IPI score, was associated with a significantly better OS [P = 0.015; Figure 3c] and PFS [P < 0.05; Figure 4c]. Surgery, with no emergency, was associated with a better OS [P = 0.024; Figure 3d] but was not associated with PFS. An age less than 60 years was associated with a better PFS [P < 0.05; Figure 4d] but was not associated with OS. The presence of B symptoms, stage at diagnosis, and endoscopic type did not significantly impact OS or PFS.

DISCUSSION

EATL is a rare but aggressive non-Hodgkin lymphoma arising from the intestinal tract, documented to affect only 62 patients from 22 centers worldwide over a 13-year period.[11] Our study identified only 11 patients in a single tertiary center within a 13-year period, comprising 4.4% of all primary intestinal lymphomas in our center. Although the incidence is very low, EATLs have a poor prognosis. The initial complaints of EATL patients are usually GI symptoms and they often come to the gastroenterology department first. Endoscopy can identify abnormal mucosa in most patients; however, it is nonspecific. To date, only a few case reports[7‑16] have detailed the endoscopic features of EATLs. The endoscopic appearances of EATL are still largely unknown. Our study is the largest series of endoscopic features of EATL to date and systematically classifies them into several distinct types. Substantially, our findings increase our knowledge of this high-mortality disease, which is meaningful to help us pay more attention to this lymphoma and make an early diagnosis.

In our study, we found that the endoscopic appearances of EATL varied widely and could be classified into four distinct types. The type of endoscopic finding had no relation to the clinical stage or to IPI score. The ulcerative type was the most common type, accounting for more than half of all EATL patients, followed by the epithelial mass and nodular and diffuse infiltration types. The ulceration of EATLs usually appears large and deep, with sharp edges, along with strictures in the majority of patients of this type (4/6, 66.7%), which could be seen in some previous case reports.[13,15,16] However, this finding is different from those of a previous case series, which found that the small intestine exhibited multiple circular or semicircular shallow ulcerations.[10] A correct real-time endoscopic impression is important to make an early diagnosis of EATL. It is also important to perform repeat biopsy sampling in patients whose first forceps biopsy sampling fails to obtain a confirmative histologic diagnosis. However, the initial endoscopic impression of lymphoma could be made in less than 30% (only 27.3%) of our EATL patients. Crohn’s disease was the most common incorrect diagnosis on initial endoscopic impression, particularly in ulcerative type patients. The epithelial mass type is most often mistaken as a GI cancer. In addition, the initial histological confirmation percentage of EATLs from endoscopic biopsy specimens...
was very low, at only 36.4%. Due to the low rates of correct initial endoscopic impression and initial histological confirmation, we emphasize the importance of educating endoscopists about the endoscopic features of EATLs, a rare disease entity. Endoscopists should obtain large and deep biopsies when suspecting this disease in clinical practice. The most common site of involvement was the small bowel, especially the jejunum, which is in agreement with previous studies. Notably, isolated stomach involvement was found in one patient in our study, who had the longest disease duration (10 years) and a good prognosis. However, another patient with both large bowel and stomach involvement had a relatively poor prognosis. This patient underwent emergency surgery due to bowel obstruction initially and received combination treatment after surgery, but still died 18 months later because of disease progression. As seen in previous case reports, stomach involvement was rare, and documented in only one case. Another previous study showed that stomach involvement occurred in only 5% of patients with EATL type II.

Our study reported a significant predominance of men among those affected by EATLs. Remarkably, all cases were histologically EATL type II, and none had a history of celiac disease. This observation is consistent with a previous study of EATLs in Asian populations. The median age at diagnosis was 47 years, and the median disease duration was 7 months. The most common initial symptom was diarrhea, followed by abdominal pain and GI bleeding. Approximately half of the patients had advanced disease (stage IV) at presentation. B symptoms and elevated levels of β2-microglobulin and CRP were common in EATL patients; however, LDH levels were usually normal. Bone marrow involvement was infrequent.

Our study showed that patients with EATL had a dismal prognosis with a median OS of 8 months and PFS of only 1.5 months, which is consistent with previous studies. Currently, there are no standard treatment guidelines for EATLs. We found that chemotherapy and low risk of the disease, according to IPI score were significantly associated with better OS and PFS in EATLs. In addition, emergency surgery, which occurred in 45.5% of our EATL patients, was associated with a worse OS. These findings emphasized the importance of early diagnosis of EATL because patients may have the opportunity to receive chemotherapy and avoid emergency surgery at an early stage. In fact, there are already abnormal endoscopic manifestations in the majority of EATL patients. Therefore, clinicians and endoscopists should become more aware of this disease in order to make an early diagnosis.

Our study has limitations. First, the sample size was small to allow us to draw definite conclusions. Meanwhile, we could not investigate risk factors for disease progression that are important for physicians in daily clinical practice. Second, owing to the retrospective nature of this study, we could not suggest the best treatment strategy based on scientifically
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In conclusion, EATLs show various endoscopic appearances, and the diagnosis of EATL is challenging. Certain types of endoscopic features may provide clues for both endoscopists and clinicians in diagnosing EATLs, especially for patients with endoscopic suspicion or patients with idiopathic diarrhea, abdominal pain, GI bleeding or bowel obstruction. There is still no standard therapy for EATLs, and the optimal choice of chemotherapy remains to be defined. Further prospective, multicenter studies with large sample sizes are needed to establish the proper diagnosis and treatment strategy.

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Figure 3: Overall survivals of enteropathy-associated T cell lymphoma. (a) Overall survival. (b) Chemotherapy significantly improved OS. (c) Low IPI score significantly improved OS. (d) No emergency surgery significantly improved OS

Figure 4: Progression free survivals of enteropathy-associated T cell lymphoma. (a) Progression free survival. (b) Chemotherapy significantly improved PFS. (c) Low IPI score significantly improved PFS. (d) Age less than 60 years significantly improved PFS
Conflicts of interest
There are no conflicts of interest.

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