

Endoscopic Findings of Enteropathy-Associated T-Cell Lymphoma Type II: A Case Series

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Enteropathy-associated T-cell lymphoma (EATL) is a rare extranodal T-cell lymphoma arising from the intestine. Two types of EATL have been reported. In contrast to the classic EATL type I, EATL type II occurs sporadically, is unrelated to celiac disease, and comprises 10% to 20% of all EATL cases. A total of five cases of EATL type II were diagnosed at our clinic from January 2009 to September 2012. Four of the five patients were diagnosed with the help of endoscopy. Among the four patients, two of the cases involved both the small and large intestines, whereas in the other two patients, EATL was limited to the small intestine. Common endoscopic findings included innumerable fine granularities (also called mosaic mucosal patterns) and diffuse thickening of the mucosa with a semicircular shallow ulceration in the lesions of the small bowel. In contrast, the endoscopic findings of the colon were nonspecific and could not distinguish EATL type II from other diseases. There are only few published reports regarding the representative endoscopic findings of EATL. Here, we present the clinical and endoscopic findings of four cases of EATL type II diagnosed by endoscopy. (**Gut Liver 2016;10:147-151**)

Key Words: Enteropathy-associated T-cell lymphoma type II; Gastrointestinal lymphoma; Endoscopy; Double-balloon enteroscopy

INTRODUCTION

Enteropathy-associated T-cell lymphoma (EATL) is a rare intestinal tumor, accounting for less than 5% of gastrointestinal lymphoma. It is known to arise from T lymphocytes that reside

in the intraepithelial space of the intestines and is classified into two types.¹ The classic EATL, also known as EATL type I, is predominantly found in Western countries and is strongly associated with refractory celiac disease. In this type, tumor cells are large and pleomorphic and positive for CD3 and CD7 in immunohistochemistry staining, but negative for CD4, CD8, or CD56. The other type, namely EATL type II, comprises 10% to 20% of all EATL cases. EATL type II is mainly composed of small to medium-sized cells, which show positivity for CD3, CD7, CD8, and CD56. It develops sporadically and is independent of celiac disease.² EATL is most frequently found in the small intestine, especially the proximal jejunum, followed by stomach, colon, and rectum. It is clinically associated with symptoms of malabsorption and is typically diagnosed upon laparotomy, as the first presenting signs are usually spontaneous intestinal perforation and/or obstruction.³ Currently, only few published reports are available regarding the endoscopic findings of EATL type II distinct from classic EATL. Here, we present four cases of EATL type II diagnosed preoperatively with the endoscopy.

CASE REPORTS

Five cases of EATL type II were diagnosed from January 2009 to September 2012 at Samsung Medical Center. Of the five cases, four were diagnosed endoscopically and the other one surgically. None of the patients had a history of celiac disease or malabsorption. The patients (three men and one woman) ranged in age from 48 to 67 years (median, 52.5 years). Two patients presented with chronic diarrhea and the other two with abdominal pain. Both the small and large intestines were involved in two patients while the disease was limited to the small intestine

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Table 1. Clinicopathologic and Endoscopic Characteristics of Four Cases of Enteropathy-Associated T-cell Lymphoma Type II

Case no.	Age/sex	Initial presentation	Location	Endoscopic finding	Immunophenotyping	Stage/IPI	BM*	No. of procedures [†]	Treatment	Time interval [‡]	Follow-up [§]
1	67/M	Abdominal pain	Terminal ileum, cecum, D-colon	Hyperemic, thickened mucosa with central ulceration	CD4-CD8+, CD56+ EBV-	IIE/2	No	1	CTx	6 mo	4 mo (D)
2	50/M	Abdominal pain, fever	Ileum, A-colon	An ulcerative lesion with hyperemic, edematous mucosa	CD4-CD8+, CD56+ TIA-1+, EBV-	IIE/2	No	1	Resection CTx APSCT [¶]	20 day	60 mo (A)
3	48/M	Chronic diarrhea	Jejunum	Diffuse mucosal thickening and nodularity with multiple shallow ulcerations	CD4-CD8+, CD56+ EBV-	NA/NA	NA	3	Refused	2 yr	14 mo (D)
4	55/F	Chronic diarrhea, bowel obstruction	Duodenum, jejunum	Edematous mucosa with innumerable fine granular elevations and shallow ulcerations	CD4-CD8+, CD56+ TIA-1+, EBV-	III/3	No	2	CTx APSCT	1 yr	13 mo (D)

IPI, international prognosis index; M, male; CTx, chemotherapy; (D), dead; TIA-1, T-cell intracellular antigen 1; APSCT, autologous peripheral stem cell transplantation; (A), alive; NA, not available; F, female.

[†]The presence of bone marrow involvement; [‡]The number of endoscopic procedures for final diagnosis; [§]The time interval between the symptom onset and diagnosis; [¶]The follow-up period since diagnosis; ^{||}Autologous peripheral stem cell transplantation after the first recurrence.

in the other two patients (Table 1).

1. Case 1

A 67-year-old man was admitted for evaluation of abdominal mass, night sweating and weight loss over the period of 6 months. computed tomography (CT) scanning and positron emission tomography (PET) showed a 6-cm-sized homogeneous mass on the terminal ileum and ascending colon. Colonoscopy revealed hyperemic, thickened mucosa with central ulceration on the cecum (Fig. 1A) and a 1.5-cm-sized pinkish flesh-like, flat thickened lesion on the proximal descending colon (Fig. 1B). Biopsy specimens from each lesion showed diffuse infiltration of small- to medium-sized atypical lymphoid cells with CD4-, CD8+ and CD56+ immunophenotypes. Despite conventional chemotherapy, leptomenigeal seeding was confirmed after the fourth cycle of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). He died of disease progression and septic shock due to pneumonia.

2. Case 2

A 50-year-old man was admitted with complaints of abdominal pain and low grade fever for 20 days. Colonoscopy revealed about 3-cm-sized discrete ulcerative lesion with hyperemic edematous mucosa on the proximal ascending colon (Fig. 1C). Biopsy specimens from the lesion showed diffuse infiltration of small- to medium-sized atypical lymphoid cells with CD4-, CD8+, CD56+, and T-cell intracellular antigen 1 (TIA-1)+ immunophenotypes (Fig. 2). As abdominal pain progressively worsened, he underwent urgent exploratory laparotomy. During laparotomy, bowel wall thickening on the distal ileum extended 15 cm in length, its severe adhesion to surrounding structures forming a mass. The involved segment including the mass was resected. The surgical specimen also was pathologically consistent with EATL type II. Successful complete remission was achieved after six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). After 3 years, abdominal pain developed. Double-balloon-enteroscopy (DBE) revealed diffuse fine granularity with circumferential shallow ulceration in the mid-ileum (Fig. 3A) and pathological examination confirmed the recurrence of EATL. He underwent autologous peripheral blood stem cell transplantation (APBSCT) and has been free of disease for 11 months.

3. Case 3

A 48-year-old male was admitted with complaints of chronic diarrhea and weight loss of 14 kg over the course of 1 year. Although the initial esophagogastroduodenoscopy (EGD) and colonoscopy were unremarkable, CT scan revealed the focal enhancing lesion in small bowel. DBE via antegrade approaches revealed diffuse mucosal thickening and nodularity with multiple shallow semicircular ulcerations from mid to distal jejunum (Fig. 3B). Pathologic specimens from the lesions demonstrated

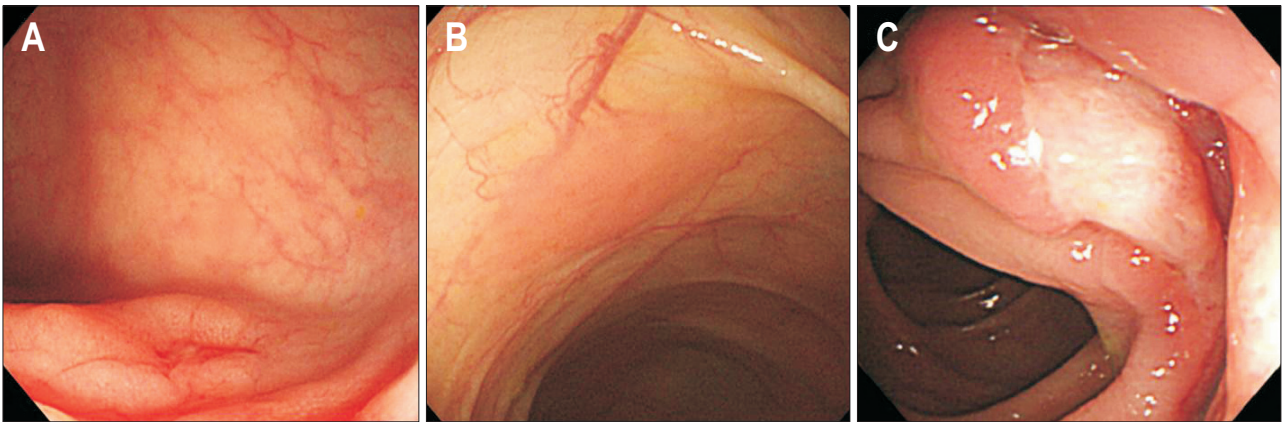


Fig. 1. Representative features of endoscopic findings of colonic enteropathy-associated T-cell lymphoma. (A) Colonoscopy revealed hyperemic, thickened mucosa with central ulceration on the cecum and (B) flesh-like flat thickened lesions on the proximal descending colon. (C) There was a discrete ulcerative lesion with diffuse mucosal thickening and edematous mucosa on the ascending colon.

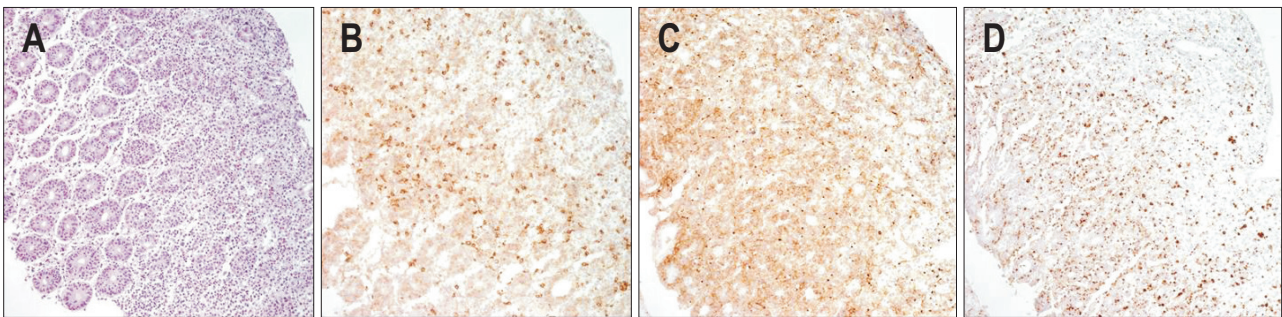


Fig. 2. Representative features of typical pathologic findings of colonic enteropathy-associated T-cell lymphoma. (A) The colon biopsy showed heavy intraepithelial lymphocytosis involving the surface epithelium (H&E stain, $\times 200$). Many CD8-positive (B), CD56-positive (C), and T-cell intracellular antigen 1-positive (D) intraepithelial lymphocytes were scattered ($\times 200$).

diffuse infiltration of small- to medium-sized atypical lymphoid cells. Immunohistochemistry was negative for CD4 but positive for CD8 and CD56. After the diagnosis, the patient refused further treatment and died at 14 months after diagnosis.

4. Case 4

A 55-year-old woman was referred to Gastroenterology Department because of chronic diarrhea, abdominal pain, and weight loss, which persisted for 1 year. Although the initial EGD was unremarkable, abdomen and pelvic CT revealed luminal narrowing in the 3rd portion of duodenum. She was admitted for evaluation and during admission, obstructive symptoms, such as vomiting, developed. Re-evaluation with EGD showed luminal obstruction due to an encircling mass at the proximal jejunum. However, only necrotic debris was found on the pathology. Moreover, without definite 2-deoxy-2-[fluorine-18]fluoro-D-glucose uptake, PET suggested inflammatory condition of the lesion rather than malignancy. During the surgery, there was diffuse swelling and luminal narrowing from the ligament of Treitz to proximal jejunum and the involved segment was 15 cm in length. Because surgeon judged to have no resectability, gas-

trojejunostomy without duodenectomy was performed to relieve obstructive symptoms after the biopsy of enlarged lymph node. Biopsy specimens from enlarged lymph node revealed only reactive change with no evidence of malignancy. Only 2 weeks after discharge, she was re-admitted for abdominal pain, nausea, and poor oral intake. A subsequent EGD through the gastrojejunostomy site revealed shallow ulcerations which encircled the diffusely swollen lumen of the afferent loop of the jejunum (Fig. 3C). Edematous mucosa with innumerable fine granular elevations, described as velvety or sand-like mucosa, caused obstruction of the, mid to distal jejunum (Fig. 3D). Biopsy specimens from these lesions revealed diffuse infiltration of small- to medium-sized atypical lymphoid cells with CD4-, CD8+, CD56+, and TIA-1 positivity (Fig. 4). Tissue DNA analysis demonstrated monoclonal T-cell receptor γ rearrangement. Based on these findings, the diagnosis of EATL type II was made. She was unresponsive to CHOP and chemotherapy regimen was changed. After ten months of therapy, she underwent APBSCT because of disease progression but during the course, she died of sepsis.

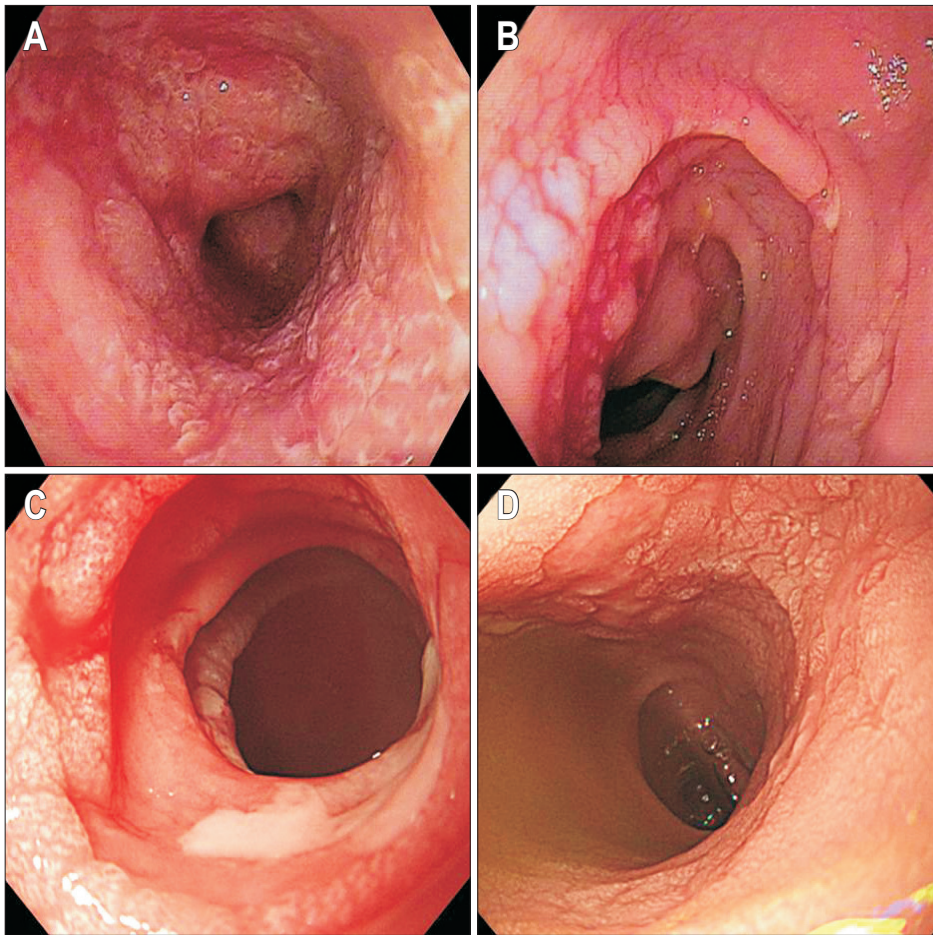


Fig. 3. Representative features of endoscopic findings of the small-bowel enteropathy-associated T-cell lymphoma. (A) Double-balloon-enteroscopy (DBE) showed diffuse fine granularity and edematous mucosa with circumferential shallow ulcerations on the ileum. (B) DBE revealed diffuse mucosal thickening and nodularity with multiple shallow semicircular ulcerations from the mid to distal jejunum. In another cases, shallow ulcerations encircled the diffusely swollen mucosa of the jejunum (C), and innumerable fine granular elevations (velvety or sand-like mucosa) were observed on the mid to distal jejunum (D).

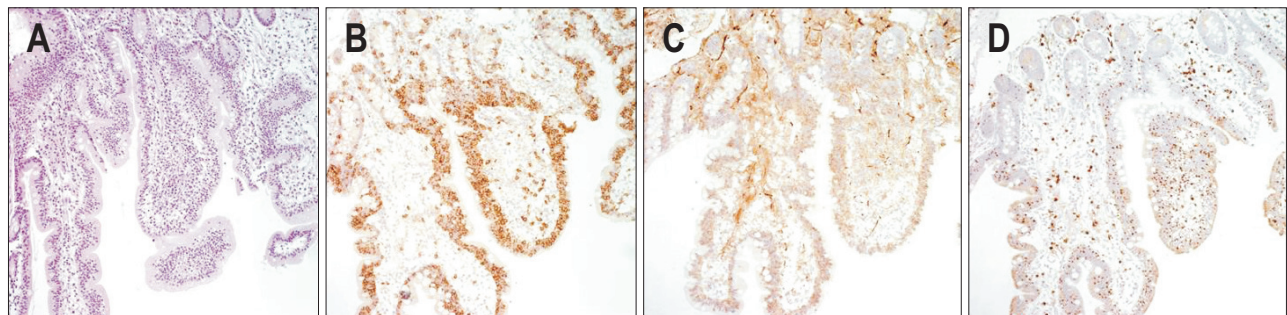


Fig. 4. Representative features of typical pathologic findings of small-bowel enteropathy-associated T-cell lymphoma. (A) The small intestine biopsy showed heavy intraepithelial lymphocytosis involving the surface epithelium (H&E stain, $\times 200$). Many CD8-positive (B), CD56-positive (C), and T-cell intracellular antigen 1-positive (D) intraepithelial lymphocytes were scattered ($\times 200$).

DISCUSSION

EATL is a rare disease in Asia and only a few case series have been reported.^{2,4,5} The classic EATL is known to be strongly associated with celiac disease. Tumor cells are large and pleomorphic, which are positive for CD3 and CD7, but negative for CD4, CD8, or CD56. EATL type II is mainly composed of small- to medium-sized monomorphic cells, showing immunophenotypic positivity for CD3, CD7, CD8, and CD56. It develops sporadically

and is independent of celiac disease.⁶ In our cases, CD3, CD8, and CD56 were positive in all patients, while none of them had a history of celiac disease. These results are consistent with another study conducted in Taiwan.⁷

The typical endoscopic features of EATL have scarcely been reported. Recently, there have been a few literatures of EATL type II findings based on double-balloon endoscopy and capsule endoscopy. They reported that diffuse mucosal thickening and edema with multiple shallow ulcerations, and a nodular or

mosaic mucosal pattern were characteristics of the disease.⁸⁻¹⁰ In our cases, small bowel was almost always involved and colonic involvement was found in half the patients. Endoscopy of the small intestine revealed multiple circular or semicircular shallow ulcerations covered with whitish mucus-like exudate. When the ulcers were encircling the lumen of the small bowel, it was often associated with obstruction. The surrounding mucosa was edematous and thickened by countless fine granularities, showing so-called mosaic mucosal pattern or velvety mucosa. These endoscopic features of small bowel may be specific to the disease and thus could be useful for the detection of EATL type II. On the contrary, endoscopy of the colon revealed discrete ulcer with edematous margin or mucosal thickening, sometimes combined with central ulcer. These endoscopic findings of colon are nonspecific to distinguish EATL type II from other disease. Therefore, it may be difficult to diagnose EATL type II only by endoscopic findings of the colon without clinical suspicion.

Patients treated with anthracycline-based chemotherapy regimens had better survival rates than those treated with other forms of therapy (including surgery) or no therapy at all. However, long-term survival is known to be poor even with treatment. According to a retrospective study of 31 patients, the 1- and 5-year survival rates were 38.7% and 19.7%, respectively.³ Another recent study showed that patients treated with high-dose chemotherapy followed by APBSCT had a significantly improved survival. It has been estimated that approximately 70% of all EATL patients may benefit from this therapy.¹¹

In summary, we report four cases of EATL type II diagnosed by endoscopy. The endoscopic findings are the mosaic mucosal pattern and diffuse thickening of the mucosa with circumferential shallow ulcerations causing luminal narrowing or obstruction in the small bowel and a discrete ulcer with diffuse mucosal thickening in the colon. EATL mainly involves the small bowel causing diagnostic delay due to the difficulty of access, especially if the symptoms were mild. However, modalities for evaluating the small bowel, such as enteroscopy and capsule endoscopy, have become more developed. Hence, certain typical endoscopic features may give a clue to both clinicians and pathologists in diagnosing EATL in patients with unknown causes for abdominal pain, diarrhea, or bowel obstruction. Currently, there is no treatment guideline for EATL. High-dose chemotherapy followed by autologous stem cell transplantation may be a better treatment option for EATL compared to conventional chemotherapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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