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■ BRIEF CASE REPORT ■

A Case of Type II Enteropathy-Associated T-Cell Lymphoma with Epstein-Barr Virus Positivity

Min Jeong Song · Chan Sik Park · Hee Sang Hwang · Cheol Won Suh[1] · Dok Hyun Yoon[1] · Jooryung Huh

Departments of Pathology and [1]Oncology, Asan Medical Center, University of Ulsan Collage of Medicine, Seoul, Korea

Enteropathy-associated T-cell lymphoma (EATL) is defined as an intestinal lymphoma of intraepithelial T lymphocytes. EATL is further classified into two distinct types: type I (classical) EATL, which comprises 80%–90% of all cases; and type II EATL, a monomorphic variant of the disease. Type I EATL occurs at a higher frequency in northern Europe, where celiac disease is more common, and is characterized by the presence of large tumor cells with a $CD3^+CD4^-CD8^-CD56^-$ immunophonotype.[1] Conversely, type II EATL, originally described as $CD56^+$ intestinal lymphoma, consists of monomorphic small- to medium-sized tumor cells, typically with a $CD3^+CD4^-CD8^+CD56^+$ immunophenotype, with weak or no association with celiac disease.[1,2] Recently, a number of reports have defined type II EATL as a distinct T-cell neoplasm predominant in patients of Asian ethnicity with no history of enteropathy or Epstein-Barr virus (EBV) association. In addition, type II EATL is characterized by frequent expression of gamma-delta T-cell receptors (γδ TCR). EBV-positive cases were suggested to represent extranodal natural killer (NK)/T-cell lymphoma rather than type II EATL. Whether EBV-positive cases with similar morphology and phenotype should be included in the definition of EATL and whether a proportion of these cases are γδ T-cell lymphomas remain debatable. Herein, we report a case of T-cell lymphoma of the jejunum with a $CD3^+$ $CD4^-CD8^+CD56^-$betaF1$^+$ phenotype, rearranged γ TCR genes, and diffuse EBV-encoded RNA (EBER) positivity.

Corresponding Author
Jooryung Huh, M.D.
Department of Pathology, Asan Medical Center, University of Ulsan Collage of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
Tel: +82-2-3010-4553, Fax: +82-2-472-7898, E-mail: jrhuh@amc.seoul.kr

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CASE REPORT

A 54-year-old Korean man was referred to our institute for evaluation of recurrent hematochezia. In the previous three years, the patient had experienced five episodes of hematochezia, the last occurring three days prior to presentation, and all occasions required embolization of the superior mesenteric artery. He appeared chronically ill but was mentally alert. Initial vital signs were within normal limits: blood pressure, 112/75 mm Hg; heart rate, 82/min; respiration, 16/min; and body temperature, 36.4°C. Complete blood counts were as follows: white blood cell count, 6,100/μL; hemoglobin, 10.4 g/dL; and platelet count, 187×10^3/μL with normocytic normochromic peripheral blood morphology. Abdominopelvic computed tomography showed diffuse thickening of the proximal jejunal wall without obstruction and multiple enlarged mesenteric lymph nodes (Fig. 1A). Endoscopy showed multiple discrete geographic ulcers oozing fresh blood in the proximal jejunum (Fig. 1B). The patient underwent a segmental resection of the small intestine. On macroscopic examination, multiple ill-demarcated geographic ulcers covered with hemorrhagic exudate were identified in the jejunum. Obstruction or perforation was not observed. The intestinal mucosa was diffusely edematous (Fig. 1C). Microscopically, the central zone of the ulcer showed dense lymphocytic infiltration in the lamina propria and submucosa. The infiltrate was composed of monotonous, small- to medium-sized lymphocytes with scanty cytoplasm and round, hyperchromatic nuclei (Fig. 2A, B). Angiocentricity, angioinvasion, or coagulative necrosis was not observed. On immunophenotyping, the tumor cells were $CD3^+$ $CD5^+CD8^+$TIA-1$^+$TCR-βF1$^+$$CD20^-CD56^-$ and $CD4^-$ (Fig. 3). *In situ* hybridization for EBER showed strong signals in the majority of tumor cells, which were $CD3^+$ T-cells.

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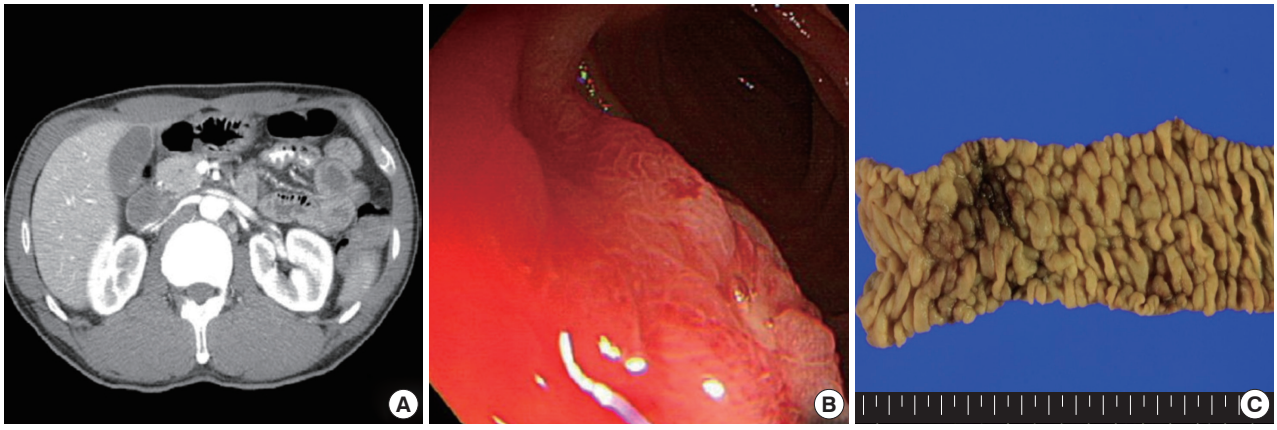

Fig. 1. Abdominopelvic computed tomography reveals diffuse thickening of the proximal jejunum with no discrete mass lesions or obstruction and multiple enlarged mesenteric nodes (A). (B) On endoscopy, multiple discrete ulcers oozing fresh blood are observed. (C) The jejunum shows multiple geographic ulcers covered with hemorrhagic exudates without obstruction or perforation. The adjacent mucosa is diffusely edematous.

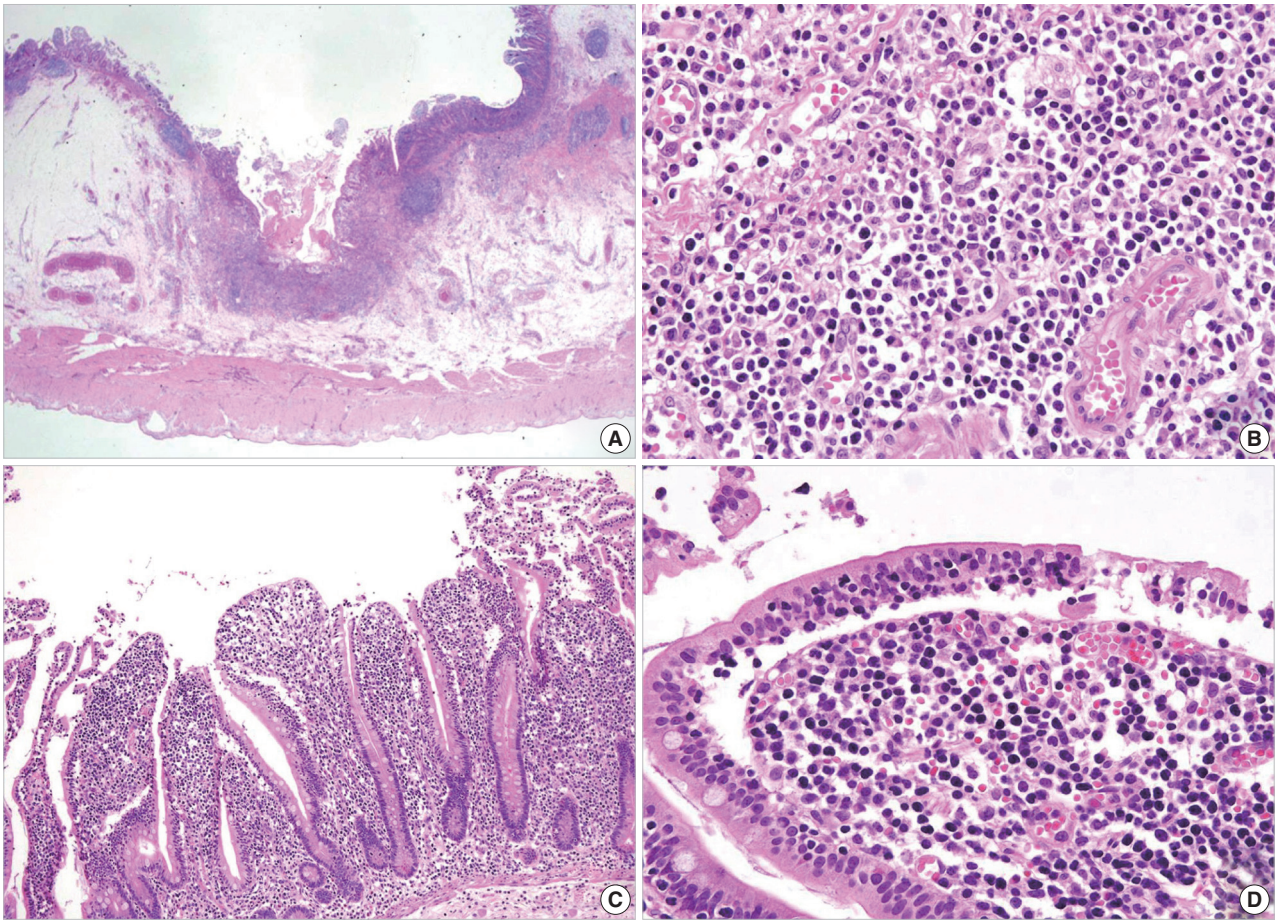

Fig. 2. Microscopic examination. (A, B) The central zone of the tumor is ulcerated with monotonous small- to medium-sized lymphocytic infiltration in the mucosa and submucosa. The adjacent mucosa shows mild villous atrophy and crypt hyperplasia (C) and extensive intraepithelial lymphocytosis (D).

The adjacent jejunal mucosa showed extensive intraepithelial lymphocytosis in the epithelium, mild villous atrophy, and crypt hyperplasia (Fig. 2C, D). These lymphocytes revealed cytological and immunologic features identical to those of the central

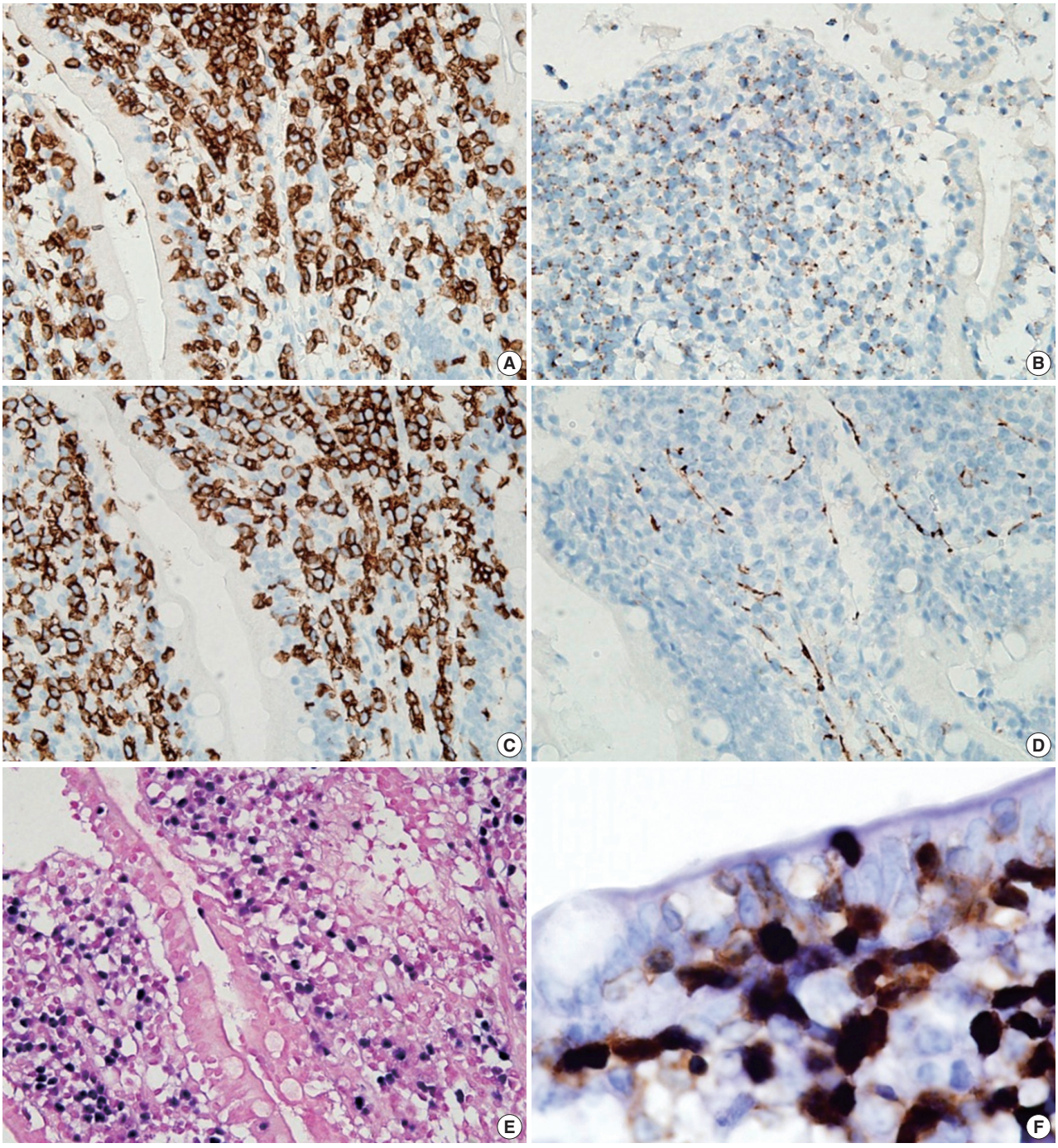

Fig. 3. Immunohistochemical stains. Tumor cells are positive for CD3 (A), TIA-1 (B), and CD8 (C), but negative for CD56 (D). (E) *In situ* hybridization for Epstein-Barr virus (EBV)–encoded RNA (EBER) shows diffuse nuclear positivity in tumor cells. (F) Dual staining for EBER (black) and CD3 (brown) reveals that the EBV-positive cells are CD3-positive T-cells.

zone. Polymerase chain reaction analysis using Biomed primers showed clonally rearranged TCR γ genes. Based on these findings, the lesion was diagnosed as type II EATL with EBV positivity. Chemotherapy with cyclophosphamide, doxorubicin, and vincristine was started, and the patient was alive with no evidence of recurrence at 23 months after the surgery.

DISCUSSION

Type II EATL is a newly recognized entity that requires fur-

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Table 1. Summary of previously published reports including a patient with EBV-positive EATL

Reference	Country	No. of cases	No. of EBV-positive cases	EBV-positive cell population
Tse *et al.* (2012)[6]	Multinational (Asia)	34	3	Cytotoxic T cells
Ng (2012)[7]	Singapore	1	1	$CD3^+$, $CD4^-$, $CD8^-$, $CD56^-$ tumor cells
Delabie *et al.* (2011)[1]	Multinational (North America, Europe, and Asia)	58	4	Subpopulation of likely reactive cells
Takeshita *et al.* (2011)[8]	Japan	24	2 1	$CD56^-$, $CD8^-$ T cells $CD56^+$, $CD8^+$ T cells
Quintanilla-Martinez *et al.* (1997)[9]	Multinational (Mexico, Austria, and Germany)	6	1	Pleomorphic medium and large cells
Pan *et al.* (1993)[10]	UK	11	3	Large $CD3^+$ tumor cells

EBV, Epstein-Barr virus; EATL, enteropathy-associated T-cell lymphoma.

ther characterization and exhibits distinctive clinicopathological features. This lymphoma is the predominant type of EATL in Asian populations and is not associated with celiac disease. Histologically, type II EATL reveals monotonous small- to medium-sized tumor cells and lack of EBV infection of the tumor cells. The immunophenotype of this tumor is typically $CD3^+$ $CD8^+CD56^+CD4^-$ and frequently γδ TCR^+.[2]

On histological and immunohistochemical analyses, the present case is compatible with type II EATL as shown by enteropathic features (villous atrophy, crypt hyperplasia, and diffuse intraepithelial lymphocytosis) and a $CD3^+CD8^+$TIA-1^+TCR-$\beta F1^+CD4^-$ immunophenotype. Although type II EATL typically expresses CD56, approximately 9% of cases are CD56- as in the present case.[3] However, EBV positivity is not a typical feature of type II EATL,[1,2,4,5] and most authors report a complete absence of EBV in type II EATL.[2,4,5] Several authors have suggested that diffuse positivity of EBER is an indication that the tumor in question should be diagnosed as extranodal NK/T-cell lymphoma.[4] However, Tse *et al.*[6] reported three cases with extensive EBER expression but without histological features of NK/T-cell lymphoma in a study of 34 type II EATLs in an Asian population. Furthermore, two of the EBER-positive cases in that study had clonal TCR gene rearrangement, implying T-cell lineage. In addition, other authors have also reported EBV-positive EATL (Table 1). Although the CD56 status was not specified in that study, except for one case positive for CD56, our case resembles those of Tse *et al.*,[6] suggesting that a small minority of type II EATL cases may be EBV-positive. These observations suggest that type II EATL is a heterogeneous disease with distinct phenotypic and genotypic characteristics.

Conflicts of Interest

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

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