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Fulminant Epstein-Barr Virus-associated T-cell Lymphoproliferative Disorder in an Immunocompetent Middle-aged Man Presenting with Chronic Diarrhea and Gastrointestinal Bleeding

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The World Health Organization (WHO) recently defined systemic Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disorders (LPD) of childhood as a life-threatening illness. However, this rare disease has not been extensively studied. Here we report a case of systemic EBV-positive T-cell LPD in a previously healthy middle-aged man with a chief complaint of chronic diarrhea. The initial colon biopsy showed focal infiltration of EBV-positive small lymphocytes without any atypia. However, the disease rapidly progressed and the patient required a total colectomy due to severe gastrointestinal bleeding. Three and half months after admission, the patient died from a complication of disseminated intravascular coagulation. The resected colon showed diffuse infiltration of EBV-positive atypical lymphocytes with ischemic change. Most atypical lymphocytes were CD3+ or CD5+. The monoclonality of EBV was demonstrated by sequence variation analysis of the latent membrane protein 1 (LMP1) gene in the colectomy specimen as well as in the initial biopsy.

Key Words: Epstein-Bar Virus Infections; Lymphoproliferatife Disorders; Atypical T-cell Proliferation

INTRODUCTION

Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (LPDs) are common in immunocompromised patients, particularly in a post-transplantation setting. More than 90% of these disorders are EBV-associated lesions of B-cell origin in the setting of pharmacologic immunosuppression (1) or after an organ transplantation (2). Resting memory B cells are thought to be the site of EBV persistence within the body (3), but it has become increasingly apparent that EBV can also infect T-lymphocytes (4). This conclusion is supported by the frequent detection of EBV in T-cell non-Hodgkin's lymphoma and cultures of peripheral blood lymphocytes from patients with chronic active EBV infection (CAEBV) (4). EBV infection is also associated with natural killer (NK)/T-cell lymphomas and aggressive NK cell leukemia (5).

Two major types of EBV-positive T-cell LPDs of childhood have recently been defined by the World Health Organization (WHO) (6). One is systemic EBV-positive T-cell LPD of childhood with a fulminant clinical course, and the other type is hyroa vacciniforme-like lymphoma with an indolent clinical course. Systemic EBV-positive T-cell LPDs develop shortly after primary, acute EBV infection in previously healthy children and young adults.

Although it is a systemic disease, it mostly involves the liver and spleen, and rare cases have illustrated the involvement of the lymph nodes, bone marrow, skin, and lungs (4, 7). All patients present with acute viral respiratory disease, jaundice or slight lymphadenopathy (4) and die within days up to a year after diagnosis (7). Most reported cases show a monoclonal pattern of T-cell proliferation, either with wild-type or a 30 bp deleted product of latent membrane protein 1 (LMP1) gene (4, 7).

Here, we report a fatal case of systemic EBV-positive T-cell LPD with unique clinical presentation that mimicked inflammatory bowel disease, and with a monoclonal pattern of EBV LMP1 gene.

CASE DESCRIPTION

A 45-yr-old male presented with diarrhea lasting for 45 days and weight loss (7 kg/month). He was healthy prior to experiencing these symptoms. The laboratory findings showed elevated C-reactive protein (CRP; 6.8 mg/dL), erythrocyte sedimentation rate (ESR; 80 mm/hr), white blood cell count (WBC; 12.28×10^9/L), and platelet count (453×10^9/L). The patient had decreasing numbers of red blood cells (RBC; 4.19×10^{12}/L), and hemoglobin (12.5 g/dL), but his liver function test was normal with ala-
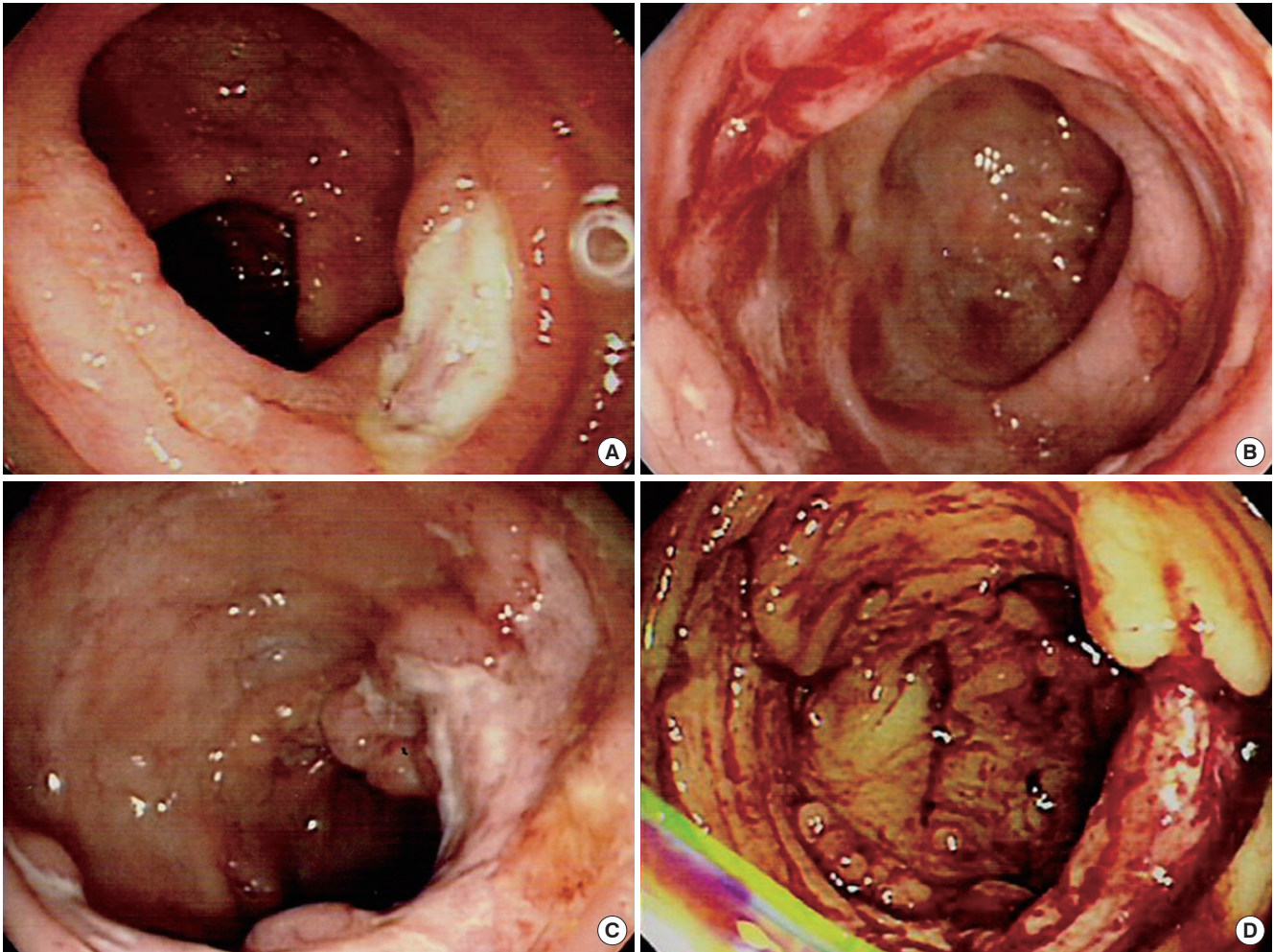
Fig. 1. Endoscopic findings. (**A**) The first endoscopy revealed multiple ulcerations scattered along the whole colon and ileocecal valve. (**B**, **C**) Endoscopy performed after antibiotic therapy showed that the ulcers had increased in size and depth. (**D**) After steroid therapy, the ulcers continued to progress and were covered with fresh blood.

nine aminotransferase (ALT) at 20 IU/L and aspartate aminotransferase (AST) at 13 IU/L. A peripheral blood smear (PBS) showed normocytic normochromic anemia with no immature cells. There was no ova nor parasite in stool examination. The patient did not have a fever or symptoms of an upper gastrointestinal disorder. The first colonoscopy revealed multiple, variable sized, irregular shallow ulcerations from the rectum to the ileocecal valve (Fig. 1A). The microscopic findings showed minimal crypt distortion with focal aggregation of normal looking lymphocytes (Fig. 2A). Empirical oral metronidazole for the treatment of infectious colitis was prescribed. Three weeks after treatment, the patient's diarrhea progressed. However, the follow-up colonoscopy and microscopic evaluation of the biopsies did not show any interval change (Fig. 2B). The treatment of infectious colitis continued with intra-venous (IV) antibiotics. A follow-up colonoscopy, performed a week after the initiation of IV antibiotic therapy, showed the ulcers were progressively getting worse (Fig. 1B, C). A combination of a high dose of steroid (budenofalk) and antibiotics (salazopyrin) were prescribed un-

der the presumptive diagnosis of ulcerative colitis. Unfortunately, three weeks after beginning steroid therapy, the patient developed a fever (38.2℃) and hematochezia, and liver function tests were abnormal (ALT 85 IU/L and AST 339 IU/L). The laboratory findings showed severe pancytopenia (WBC, 0.18×10^9/L; RBC, 1.72×10^{12}/L; platelet count, 7×10^9/L; and hemoglobin, 12.5 g/dL) with few atypical lymphocytes in the peripheral blood smear (PBS). The last colonoscopy showed extensive ulcerations along the whole colon with fresh blood (Fig. 1D). The pathologic findings of the last colonoscopy showed severe infiltration of small to medium sized lymphocytes with slight atypia (Fig. 2C, D). We confirmed the diagnosis of EBV-associated fulminant T-cell LPD from the last biopsy by immunohistochemistry and in situ hybridization for EBV early RNA (EBER). The immunohistochemical stains were positive for CD3 and CD5. In addition, we were able to rule out the possibility of both B-cell LPD by negative staining of CD20, and NK/T-cell lymphoma by negative staining of CD56. The patient underwent a total colectomy due to uncontrolled hematochezia, with an excisional liver bi-
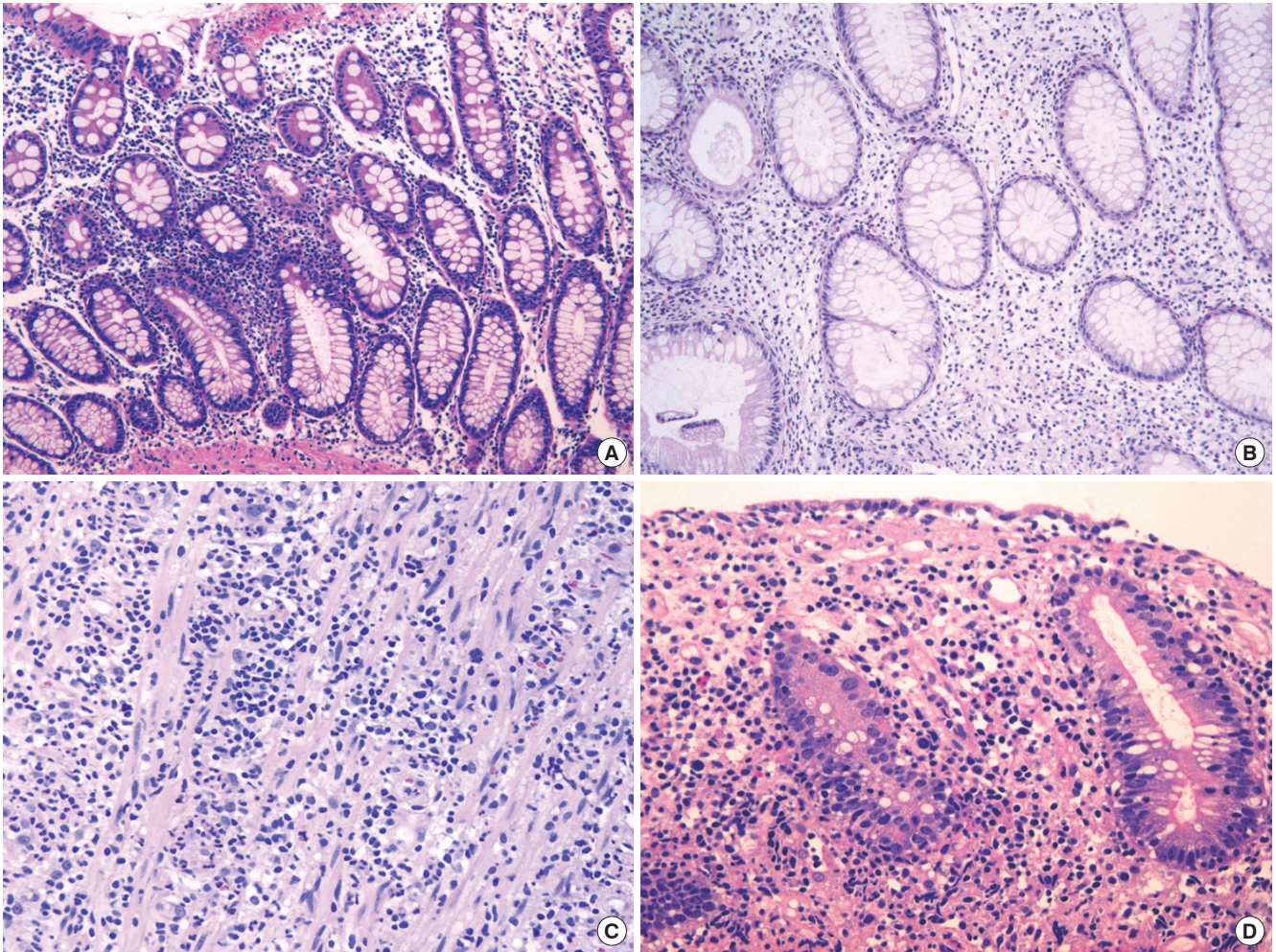
Fig. 2. Pathologic findings of the biopsies. (**A**) The first biopsy showed normal colon mucosa with a slight increase in lymphocytic infiltration. No cytological atypia of the lymphocytes are found (hematoxylin-eosin [H&E] stain, × 200). (**B**) The biopsies from the follow-up colonoscopy showed edematous stroma with vessel proliferation and irregularly shaped, dispersed crypts with minimal lymphocytic infiltration (H&E stain, × 200). (**C**, **D**) The biopsies taken after the patient developed hematochezia showed severe small to medium sized lymphocytic infiltrations in the mucosa, splitting muscle fibers, and cuffing blood vessels (H&E stain, × 400).

opsy for pathological evaluation. The resected colon showed diffusely scattered multiple geographic ulcers of variable size involving the whole colon from the ileocecal valve to the rectum. The ulcers extended to muscle layers (Fig. 3A, B), but no significant wall thickening or mass-like lesions were present. There were several lymph nodes of variable size in the pericolic fat tissue. Microscopically, the slides from the resected colon showed loss of glands and diffuse infiltration of medium- to large-sized pleomorphic atypical lymphocytes with an ischemic change of the colon (Fig. 3C). The cytological lymphocyte atypia was slightly increased compared with previous biopsies. All lymph nodes from the pericolic fat showed infiltration of atypical lymphocytes in the sinusoids (Fig. 3D, E). The liver biopsy showed mild infiltration of lymphocytes in the portal tract and sinusoid (Fig. 3F). The atypical lymphocytes in both the colon and liver were CD3 positive (CD3+) mixed with several CD5+ lymphocytes. There were no CD20+ or CD56+ cells (Fig. 4A, B, D). In situ hybridization for (EBER) was positive in almost all of the lympho-

cytes (Fig. 4C, E). Analysis for gamma T-cell receptor (TCR) gene rearrangement revealed a polyclonal pattern. However, agarose gel electrophoretic analysis of polymerase chain reaction (PCR) products of LMP1 gene in the resected colon and lymph nodes demonstrated a monoclonal pattern (Fig. 4F). Three days after surgery, the patient died with accompanying disseminated intravascular coagulation (DIC) and massive gastrointestinal bleeding. Monoclonality of the EBV genome was shown by retrospective sequence variation analysis of the initial and follow-up biopsies (Fig. 4F).

DISCUSSION

Systemic EBV-positive T-cell LPD is a life-threatening disease that has recently been categorized in the spectrum of EBV-related T-cell LPDs by the WHO (6). This disease mostly occurs with an apparent primary EBV infection, or more rarely, is associated with severe CAEBV in children or young adults. The survival rate
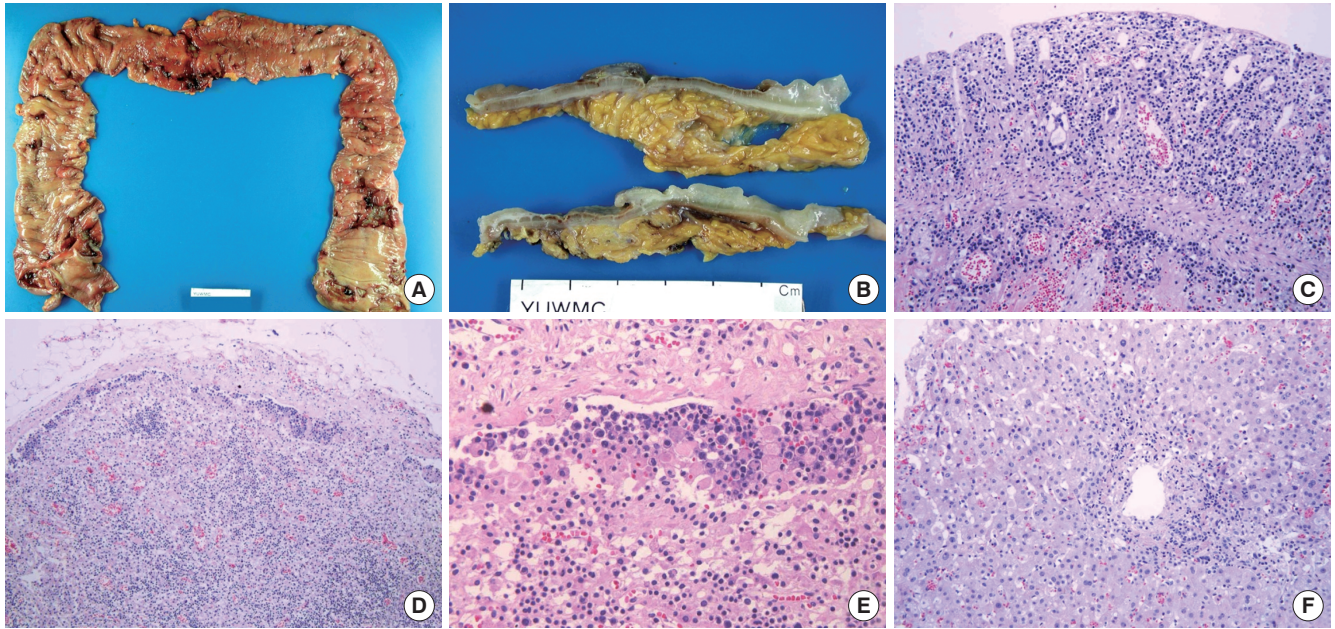
Fig. 3. Pathologic findings of the resected colon and liver. (**A**) The resected specimen showed diffusely scattered multiple geographic ulcers of variable size involving the whole colon from the ileocecal valve to the rectum. (**B**) On cut sections, the ulcers were shallow without any mass formation. (**C**) The microscopic findings showed a loss of glands and diffuse infiltration of atypical lymphocytes with an ischemic change of the colon wall (H&E stain, × 200). (**D**) The pericolic lymph node showed severe sinusoidal involvement of lymphocytic infiltration (H&E stain, × 200). (**E**) The lymphocytes were large and pleomorphic (H&E stain, × 400). (**F**) The liver biopsy showed mild infiltration of lymphocytes in the portal tract and sinusoid (H&E stain, × 200).
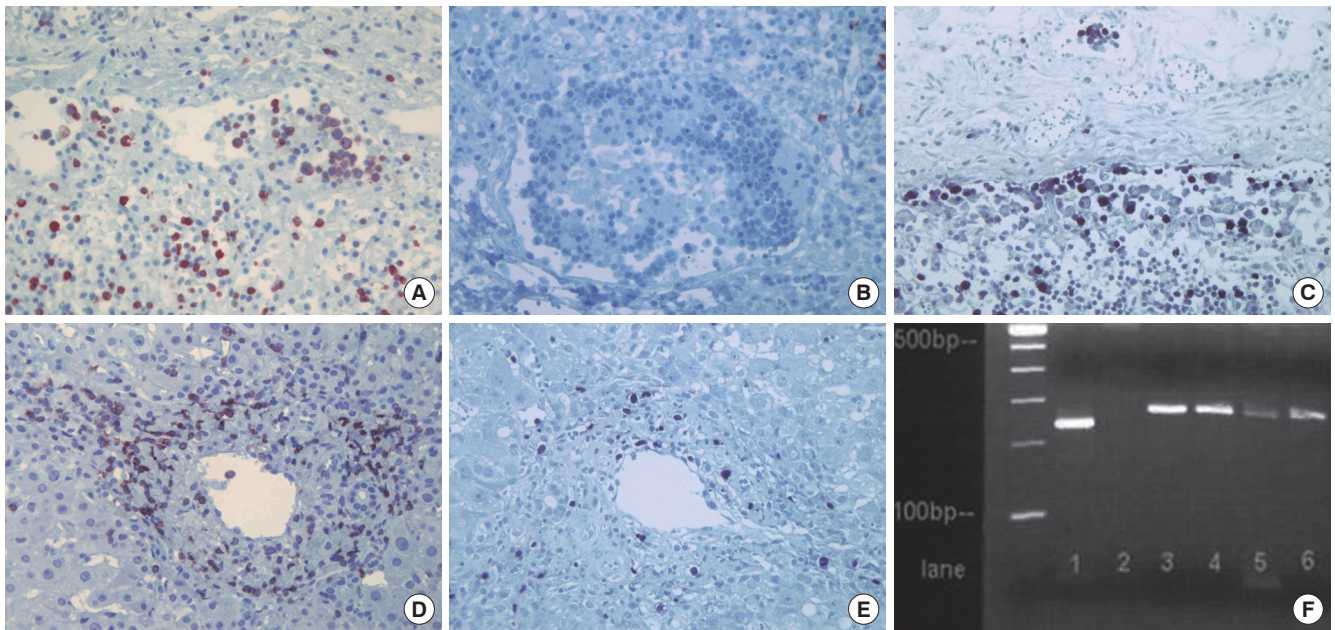

Fig. 4. Immunohistochemical stain, in situ hybridization and PCR findings. Immunohistochemical stains and in situ hybridization showed that most of the atypical lymphocytes in colon and liver were EBER+, CD3+ or CD56- (colon: **A**, CD3; **B**, CD56; **C**, EBER ISH; and liver: **D**, CD3; **E**, EBER ISH; × 400 H&E counterstained). Agarose gel electrophoresis analysis of the PCR products corresponding to the LMP1 gene showed a monoclonal pattern. (**F**; lane 1: positive control [243 bp] "B cell lymphoma cell line BJAB", lane 2: negative control, lane 3: initial biopsy [273 bp], lane 4: second biopsy [273 bp], lane 5 & 6: colectomy [273 bp]).

is extremely low due to hemophagocytosis and multiple organ failure occurring over the course of days to weeks. Awareness of this disease category and accumulation of patient data will be necessary to reach an understanding of this fatal disease and to develop new modalities for early diagnosis and treatment.

In patients with a normal immune system, sustained T-cell infection by EBV occurs rarely, raising the possibility that the infection of T lymphocytes and their subsequent unregulated growth is due, at least in part, to a defect in immune surveillance (7). The clinical course of EBV-induced T-cell LPD reported by Quinta-

nilla-Martinez et al. (7) is similar to the time course of cases that have been described in EBV-induced LPDs in immunocompromised patients that developed B-cell proliferation, mainly in the post-transplantation setting (8). The CAEBV infection and T-cell involvement of EBV show shorter survival times than those with B-cell infections (9).

In a review of the literature, we found that most cases of T-cell LPD following primary infection with EBV were reported in East Asian patients (6, 7), mostly in children and young adults. The clinicopathologic descriptions were similar to our current case, with the exception of the patient's age and presenting symptoms. All cases were monoclonal, as demonstrated either by TCR gene rearrangement or clonality of the EBV genome (10-12). The clinical course for all reported patients was fulminant with patients dying within days and up to a few months after their diagnoses. The organs most commonly involved in EBV-associated LPD were the liver, spleen (7) and heart (4). Although some cases of intestinal involvement in EBV-associated B-cell LPDs have been reported (2, 13, 14), to our knowledge, the case described here is the first case of EBV-positive T-cell LPD in a previously healthy patient presenting with intestinal involvement.

The clinicopathological findings of this case showed that adult T-cell leukemia/lymphoma, extranodal NK/T cell lymphoma, enteropathy associated T-cell lymphoma and aggressive NK cell leukemia could be considered as a differential diagnosis. Adult T-cell leukemia/lymphoma is associated with human T-cell leukemia virus type 1 (HTLV-1) rather than EBV. Several cases of intestinal NK/T-cell lymphomas have been reported, most of which involved the small intestine (5). Immunohistochemically, the atypical lymphocytes of this case were CD56- and CD3+. The patient showed features of hemophagocytosis and multiple organs were involved without upper respiratory system infection or gross occurrence of mass-like lesions. Neither a previous history, nor histologic evidence of enteropathy was found. The clinicopathologic features of aggressive NK cell leukemia show some overlap with systemic T-cell LPD. The cells showing CD56 negativity with strong membranous staining of CD3 as well as the PBS test for this case were compatible with systemic T-cell LPD. The remarkable clinical features of this case were: (i) the presence of EBV-associated T-cell proliferation in a middle-aged, healthy patient without detectable immunodeficiency; and (ii) the patient's presentation with intestinal involvement.

The correct diagnosis of this patient was delayed because of minimal cytologic atypia of the lymphocytes. However, EBER+ and monoclonality of the EBV genome were detected in the initial biopsies despite the unremarkable histologic atypia. We therefore conclude that in situ hybridization for EBER and sequence variation analysis of the EBV LMP1 gene, together with awareness of this rare and fatal disease are helpful for its early diagnosis.

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