Epstein-Barr Virus-associated Enteropathy as a Complication of Infectious Mononucleosis Mimicking Peripheral T-cell Lymphoma

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Abstract

A 32-year-old man presented with a fever. A laboratory examination detected atypical lymphocytes and liver enzyme elevation. The serological tests for Epstein-Barr virus (EBV) were consistent with an acute infection pattern. Computed tomography showed bowel wall thickening, and colonoscopy revealed numerous ulcerations. The histological findings from the biopsy specimens from the colon were consistent with peripheral T-cell lymphoma (PTCL), and in situ hybridization detected EBER-1 in the atypical lymphocytes. Because his clinical and endoscopic abnormalities improved without medication, we diagnosed the patient with EBV-associated enteropathy. We herein report a rare case of EBV-associated enteropathy that required careful differentiation from PTCL.

Key words: Epstein-Barr virus, peripheral T-cell lymphoma, enteropathy, infectious mononucleosis


Introduction

Although a primary infection with Epstein-Barr virus (EBV) is usually asymptomatic, it sometimes presents as infectious mononucleosis (IM) in young adults. IM is a well-known clinical syndrome caused by a primary EBV infection. It is characterized by fever, tonsillopharyngitis, lymphadenopathy, enanthema, skin rashes and hepatosplenomegaly (1, 2). Nearly all patients with this disease recover uneventfully without any complications within one to two months. The majority of B cells in patients with IM are latently infected with EBV (1, 2). Although a variety of clinical complications of IM have been reported, gastrointestinal complications are very rare (1-3). Two recent reports have revealed that gastritis and colitis are complications of IM (4, 5).

EBV is frequently detected in patients who are also afflicted with a wide range of human malignancies, including those of B-cell origin, peripheral T-cell lymphoma (PTCL) and natural killer (NK) cell lymphoma (2, 6-8). In these lymphomas, T-cells and NK cells are the infectious targets of EBV, suggesting that EBV functions as a viral oncogene (2). Since EBV can be detected in some T-cell lymphoma cells, these cases should be considered as EBV-positive T-cell lymphoma (9, 10). We herein report a case of EBV-associated enteropathy as a complication of IM that was mimicking PTCL in an immunocompetent patient.

Case Report

A 32-year-old man was admitted to a community hospital with a fever of 38 degrees Celsius. He did not have abdominal pain, diarrhea, or any other symptoms. Laboratory examinations revealed the following significantly abnormal findings: a white blood cell count of 15,300/µL (with 36%...
lymphocytes including 19% atypical lymphocytes), an aspartate aminotransferase (AST) level of 236 IU/L, an alanine aminotransferase (ALT) level of 380 IU/L, a lactate dehydrogenase level of 1,024 IU/L, an alkaline phosphatase level of 393 IU/L and a C-reactive protein level of 10.1 mg/dL. The patient tested negative for antibodies to hepatitis A virus and hepatitis C virus. In addition, tests for antibodies to both human immunodeficiency virus-1 and Entamoeba histolytica were negative. Computed tomography revealed wall thickening throughout the entire colon and lymphadenopathy (less than 1.5 cm in diameter) of the pelvis, without hepatosplenomegaly or swelling of the tonsils and the superficial lymph nodes. Colonoscopy detected multiple erosions and ulcerations throughout the entire colon and terminal ileum (Fig. 1a-c). A histological examination of the biopsy specimens of the colonic mucosa revealed that atypical lymphocytes had infiltrated into the lamina propria of the colon. An immunohistochemical examination found that these cells were positive for CD3 and CD8, but negative for CD4, CD30, and CD56. Therefore, PTCL, and intestinal T-cell lymphoma in particular, was suspected. Therefore, the patient was referred to our institution for treatment of the suspected lymphoma. He was asymptomatic. His white blood count and blood chemistry results, including his hepatic enzyme levels (AST: 30 IU/L, ALT: 53 IU/L), did not display any apparent abnormalities. Tests for hepatitis B surface antigen, antibodies to hepatitis B core antigen and hepatitis B surface antigen and human T-cell leukemia virus type 1 were also negative at our hospital. Four weeks after the initial colonoscopy had been performed at the community hospital, a second colonoscopy was performed at our hospital. The testing revealed multiple lymphoid follicles in the terminal ileum. However, the erosions and ulcerations in the patient’s colon had markedly improved (Fig. 2a), and there was no histopathological evidence of lymphoma. Capsule endoscopy revealed multiple lymphoid follicles throughout the entire small intestine (Fig. 2b). Four weeks later, enteroscopy was performed using the double-balloon system to evaluate the small intestinal lesions. Most of the lesions had disappeared, and residual lesions were only present in the terminal ileum (Fig. 2c). A histological examination of the biopsy specimens of the terminal ileum showed scattered lymphocytes with normal morphology. As the patient’s clinical course was strongly suggestive of an EBV infection in the intestine, serum samples that had been obtained when the patient was first hospitalized at the community hospital were examined to assess the EBV serological status. The levels of IgM for viral capsid antigen (VCA), VCA-IgG and Epstein-Barr nuclear antigen (EBNA) were measured by enzyme immunoassay. As a result, we detected an elevated level of VCA-IgM value (2.4 index), while the findings for VCA-IgG and EBNA were negative. The serum samples ob-

Figure 1. A colonoscopic examination performed at a local hospital revealed numerous ulcerations throughout the entire colon and terminal ileum: (a) rectum, (b) sigmoid colon, (c) terminal ileum.

Figure 2. A colonoscopic examination performed upon admission to our hospital revealed that the ulcerations had improved (a). The capsule endoscopic (b) and double-balloon enteroscopic (c) examinations only detected a few lymphoid follicles in the terminal ileum.
Figure 3. Microscopic findings of the biopsy tissue specimens obtained by Hematoxylin and Eosin staining (a, ×100; b, ×400). Immunohistochemical examinations of the tissue showed positivity for CD3 (c, ×400), CD8 (e, ×400), and TIA-1 (g, ×400), and negativity for CD4 (d, ×400) and CD20 (f, ×400). In EBER-1 in situ hybridization, the nuclei of numerous atypical lymphocytes produced positive results (h, ×400).


tained at our hospital exhibited positivity for VCA-IgG (1.4 index), whereas the patient’s VCA-IgM value had decreased to within the normal range. These findings therefore indicate that the patient had been suffering from IM at the time of admission to the community hospital.

We reviewed the clinicopathological features of the biopsy specimens of the colonic mucosa that had been obtained at the community hospital. Using hematoxylin and eosin staining, it was revealed that the ulcerative lesions contained diffuse cellular infiltrates composed of moderately-sized atypical lymphocytes that extended into the lamina propria (Fig. 3a, b). The majority of these lymphocytes were positive for both CD3 and CD8, and there were a few scattered CD4- and CD20-positive cells (Fig. 3c-f). Numerous cells were also positive for the cytotoxic marker TIA-1 (Fig. 3g). In situ hybridization revealed that the majority of the atypical lymphocytes expressed EBV-encoded small RNA-1 (EBER-1) (Fig. 3h). A polymerase chain reaction (PCR) for the T-cell receptor (TCR) γ gene, which was performed according to the method of McCarthy et al. (11), did not detect any clonal populations in the biopsy specimen. Colonoscopy and biopsy examinations were performed at one and two years after the patient first visited our institution, and they each showed no evidence of inflammatory changes or lymphoma. These findings supported the diagnosis of EBV-associated enteropathy, but not PTCL, in an immunocompetent individual.

Discussion

The case described herein involved EBER-positive cells that expressed CD8 and TIA-1, and were identified as EBV-infected cytotoxic T-cells. During IM, the rapid proliferation of CD8-positive T cells occurs in the peripheral blood and tonsils; however, EBER and T-cell antigens including CD3 and CD45RO are not always detected in such patients (1, 2, 12). Thus, the EBV-infected lymphocytes that were observed in the present case displayed a phenotype that is not usually observed in IM (12). Some cases with a chronic active EBV infection (CAEBV) that is characterized by chronic or recurrent IM-like symptoms are related to EBV-infected CD8-positive T-cells (13). An atypical T-cell proliferation during IM is occasionally difficult to use in conjunction with morphologic and immunophenotypic findings in differentiating EBV-associated lymphoproliferative disorders including CAEBV. A careful clinical follow-up is
required to prevent misdiagnosis. The EBV infection in our case was resolved without medication without recurrence. Therefore, we considered that our patient had EBV-associated enteropathy.

Patients with inflammatory bowel disease (IBD), such as Crohn’s disease and ulcerative colitis (UC), display increased numbers of EBV-infected lymphocytes in their inflammatory mucosae (14, 15). Immunosuppressive therapy in IBD patients can reactivate latent EBV infections, which can lead to enteropathy (16). In particular, EBV-associated enteropathy frequently occurs during intensive immunosuppressive therapy in UC patients (16, 17). In addition, enteropathy that is associated with the reactivation of latent EBV infections has also been reported to occur following both allogeneic stem cell transplantation and intestinal transplantation (18, 19). Therefore, immunosuppressive conditions can contribute to the development of enteropathies that are mainly associated with EBV-infected B cells. However, in our patient, the enteropathy seemed to be associated with EBV-infected cytotoxic T-cells, even though he was not immunosuppressed. Although the mechanism of an ectopic EBV infection of the T-cells remains unclear, mature T-cells that are normally found in human peripheral blood express low levels of CD21 (20). In addition, NK cells activated by EBV-infected B-cells acquire CD21 by synaptic transfer, and these ectopic receptors were shown to allow EBV binding to the novel NK cell hosts (21, 22). Considering these findings, EBV might infect T-cells primarily and latently, suggesting that these cells participate in the inflammation in the intestinal mucosa. A recent case report demonstrated that a primary EBV infection that mainly targeted T-cells was involved in the development of enteropathy in an immunocompetent patient (5). Our results also indicate that the cytotoxic T-cells that are primarily infected by EBV play a role in the pathogenesis of enteropathy.

PTCL in the gastrointestinal tract is rare. Enteropathy-associated T-cell lymphoma (EATL), a form of PTCL, is a rare disease with a poor prognosis that predominantly affects the small intestine (23). Histologically, two unique types of EATL have been documented. Eighty percent of the cases fall under EATL type I, which mainly affects patients with celiac disease and involves large cells with a CD3+/CD4-/CD8+/CD56- phenotype. The other variant is EATL type II, which affects patients with no history of celiac disease and is composed of small to medium-sized cells with the CD3+/CD4+/CD8+/CD56- phenotype. In our case, the majority of atypical lymphocytes in the lamina propria exhibited the CD3+/CD4+/CD8+/CD56 phenotype, which is different from the two phenotypes seen in EATL. However, in a recent study that was conducted in a non-endemic area for celiac disease in Japan, two patients with EATL type II exhibited CD8-positive and CD56-negative lymphocytes (24). About 10-20% of patients with EATL type II had EBER-1-positive lymphoma cells (23, 24). In addition, it was also necessary to rule out extranodal NK/T-cell lymphoma of the intestine due to the positivity for TIA-1 and EBER-1 in our case (25). The pathological findings of this previous case were similar to those of our case, although the clinical features were inconsistent. Therefore, cases of EBV-associated enteropathy require careful differentiation from PTCL. TCRγ gene rearrangement was not detected in our specimen, suggesting that the patient did not have a gastrointestinal T-cell lymphoma such as EATL.

In conclusion, we herein reported a rare case of EBV-associated enteropathy mimicking PTCL as a complication of IM in an immunocompetent patient. We should take EBV-associated enteropathy into consideration when diagnosing suspected cases of PTCL. In addition, a careful assessment of the patient’s clinical appearance and course are critical for achieving a definitive diagnosis in order to avoid needless chemotherapy.

The authors state that they have no Conflict of Interest (COI).

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