SHORT REPORT

EBV-associated lymphoproliferative disorders misdiagnosed as Crohn's disease

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Abstract

Epstein–Barr virus (EBV) plays an etiological role in various diseases. EBV-associated lymphoproliferative disorder (LPD) is usually observed in individuals with congenital or acquired immune deficiencies but was also recently reported in non-immunocompromised individuals. Two cases of immunocompetent patients with EBV-associated T-cell LPD of the small bowel and colon who were initially misdiagnosed as Crohn's disease (CD) are reported here. EBV-associated T-cell LPD with primary gastrointestinal tract involvement can manifest as multiple discrete ulcers of the small and/or large bowel that are similar to the lesions found in CD or intestinal tuberculosis. However, when patients have multiple intestinal ulcers that are not typical of CD or intestinal tuberculosis and the clinical course is unusual, clinicians should consider the

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1. Introduction

Epstein-Barr virus (EBV) plays an etiological role in various diseases, including infectious mononucleosis, chronic active EBV infection, malignancies such as nasopharyngeal cancer and Burkitt’s lymphoma.\(^1\,^2\) EBV-associated lymphoproliferative disorder (LPD) is usually observed in individuals with congenital or acquired immune deficiencies, particularly patients who have undergone solid organ or hematopoietic transplantation.\(^3\,^4\) Recently, however, EBV-associated LPD has been reported in non-immunocompromised individuals.\(^5\) It is very rare to encounter immunocompetent patients with EBV-associated LPD involving gastrointestinal tract primarily. The cases of two immunocompetent patients with EBV-associated T-cell LPD of the small bowel and colon who were initially misdiagnosed as Crohn’s disease (CD) are described here.

2. Case report

2.1. Case 1

A previously healthy 50-year-old man with no personal or family history of immunodeficiency presented with an 8-year history of loose stools (1–3 times per day) and intermittent febrile sensation. He had been diagnosed with intestinal tuberculosis (TB) 5 years earlier when multiple ulcerations in the colon were detected. When standard first-line anti-tuberculous medication was administered for 9 months, he showed some clinical improvement. Four years ago, he visited the department of oncology at our hospital because of recurrent symptoms. Various examinations, including colonoscopy, abdominal computed tomography (CT) and positron emission tomography (PET)-CT, were performed. Multiple active ulcers were observed on colonoscopy but a definite diagnosis could not be made. Although it was recommended that he should be evaluated further to rule out the possibility of colonic LPD, he refused and was lost to follow-up. After that, at another hospital, he was treated with second and third courses of first-line anti-tuberculous medication for 9 and 18 months, respectively. Since colonic ulcers persisted during the third course, the diagnosis was revised to CD. Prednisolone and mesalamine were prescribed but he did not take these medications and visited our hospital for a second opinion.

At presentation, he complained of general weakness, anorexia, weight loss (12 kg over 2 months), loose stools, and fever. The physical examination revealed mild tenderness on both lower abdomen quadrants. Laboratory tests showed mild leukocytosis (11,600/mm\(^3\)), anemia (11.8 g/dL), increased C-reactive protein (CRP) levels (4.46 mg/dL), hypoalbuminemia (1.8 g/dL), and elevations of the liver enzymes aspartate aminotransferase (58 IU/L) and alanine aminotransferase (56 IU/L). The stool assays were all negative.

Figure 1. Endoscopic and histologic findings of case 1. (A) Colonoscopic finding. It shows multiple well-demarcated deep ulcers with clean bases. (B) Histopathology of a colon biopsy. It shows infiltration of atypical, hyperchromatic lymphoid cells (H&E stain, ×200). (C) EBV in situ hybridization. It shows marked infiltration of EBV-positive cells into the mucosa and submucosa (×40).
CT indicated diffuse dilatation of the small bowel, thickening of the walls of the sigmoid colon and rectum, and multiple enlarged lymph nodes along the mesenteric vessels. Colonoscopy revealed an ulcer at the terminal ileum and multiple discrete ulcers with a clean base that were scattered from the distal ascending colon to the rectum (Fig. 1A). The size and shape of the ulcers varied and their direction was not evident. Double-balloon enteroscopy revealed scattered ulcers in the jejenum whose characteristics were identical to those found in the colon. Histological examination of biopsy samples from the terminal ileum and colon revealed ulcerated mucosa with diffuse lymphoid cell infiltration that extended to the submucosal layer; this was accompanied by atypical hyperchromatic lymphoid cells (Fig. 1B). Immunohistochemical staining showed that these cells were diffusely positive for T-cell markers, including CD3 and CD5. EBV in situ hybridization showed marked infiltration of EBV-positive cells into the mucosa and submucosa (Fig. 1C). The histological diagnosis was EBV-associated T-cell LPD. His peripheral blood EBV titer was 3,750 copies/mL. A review of the histological slides of the colonic ulcers that were taken 4 years earlier when he visited our hospital for the first time confirmed this pathological diagnosis. Moreover, a review of the medical records of the hospitals where he had been treated for intestinal TB revealed that the histology, AFB stain, and Mycobacterium tuberculosis culture assays performed then were not diagnostic for intestinal TB. Treatment with daily prednisolone 40 mg was initiated, after which was tapered off slowly. However, 3 weeks after discontinuing prednisolone, he complained of aggravated lower abdominal pain. His peripheral blood EBV titer was high (34,500 copies/mL). He underwent an emergency small bowel resection due to jejunal perforation on hospital day 2 and jeuno-ileostomy due to anastomotic leakage on hospital day 10. After recovering from surgery, he was started on the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy regimen. During the third chemotherapy cycle, 8 months after the diagnosis of EBV-associated T-cell LPD and 3 months after the small bowel resection, he died of septic shock caused by small bowel perforation.

**2.2. Case 2**

A 49-year-old woman presented with recurrent hematochezia. Nineteen months earlier, at another hospital, she had undergone angiographic embolization of the ileum due to massive hematochezia without a definite diagnosis. Ten months later, she visited another hospital due to hematochezia and was presumptively diagnosed with CD on the basis of multiple ulcers observed on colonoscopy. She was treated with prednisolone 20 mg daily (tapered to 10 mg daily after 3 months) with azathioprine 100 mg/day for 4 months. Due to recurrent hematochezia, she underwent three courses of infliximab (5 mg/kg) infusion (weeks 0, 2 and 6). However, intermittent hematochezia persisted.

On presentation to the emergency department, her vital signs were stable. She was admitted for further evaluation. The physical examination was unremarkable. Laboratory tests showed anemia (10.4 g/dL) and increased CRP (2.71 mg/dL). Her serum albumin and protein concentrations were 2.6 g/dL and 5.0 g/dL, respectively. Colonoscopy revealed inflammatory polyps in the terminal ileum and multiple ulcer scars in the cecum and ascending colon. Other segments of the colon appeared normal. CT and small bowel series revealed circumferential ulcerative lesions involving the mid to terminal ileum; these findings are not characteristic of CD. A double-balloon enteroscopy revealed multiple well-demarcated circumferential or geographic deep ulcers with fresh blood in the small bowel (Fig. 2). Multiple biopsies led to a pathological diagnosis of peripheral T-cell lymphoma. EBV in situ hybridization revealed positive cells that had a diffuse distribution. Her peripheral blood EBV titer was 1,750 copies/mL. A review of the medical records, including colonoscopic images from other hospitals, showed no evidence of CD. On hospital day 5, she underwent embolization due to aggravation of active bleeding. Staging work-ups showed the involvement of the ileum, colon, mesenteric nodes and bone marrow. These findings are compatible with stage IV_Cx. She was discharged and was supposed to visit the department of oncology for chemotherapy.

One month later, before starting chemotherapy, she underwent an ileocecal resection due to small bowel perforation. The histopathological findings were consistent with a diagnosis of EBV-associated T-cell LPD. During the next 8 months, she underwent three additional embolizations and an additional operation (near-total small bowel resection) for small bowel bleeding. To date, she has received third cycles of DHAP (cytarabine, dexamethasone and cisplatin) chemotherapy and is preparing to start her fourth cycle.

**3. Discussion**

EBV is a ubiquitous virus that infects over 90% of humans and persists for life. EBV usually infects B cells but may also infect T cells and NK cells. EBV-associated LPD is a heterogeneous group of disorders in which excessive lymphoid proliferation is common. Although it is usually observed in patients with iatrogenic, congenital or acquired immunodeficiency, it has also been reported in immunocompetent individuals.

Similarly, the patients described here were previously healthy and had no personal or family history of immunodeficiency. Moreover, none of the initial medical examinations and
laboratory analyses in the past medical records from the other hospitals was suggestive of an immunodeficient state. Although they were erroneously treated with anti-tuberculous medications or immunomodulators at other hospitals, it is reasonable to assume that they were initially immunocompetent.

The organs that are most frequently involved in EBV-associated LPD are the liver, spleen, bone marrow, lymph nodes and skin.\(^5\) Gastrointestinal involvement is very rare: to our knowledge, only three prior cases in immunocompetent hosts have been reported.\(^10\)–\(^12\) In two of these cases, the lymphoid cells that were involved were of the B-cell lineage. The cell type that was involved in the other patient was not reported. Since immunochemical assays of both patients described here showed proliferation of T-lymphoid cells, we believe that this is the first time that immunocompetent individuals have been diagnosed with EBV-associated T-cell LPD with primary GI involvement.

EBV-associated T-cell LPD is a category that was newly adopted by the WHO in 2008.\(^9\),\(^13\) One of its features is excessive lymphoid proliferation of T cells, and it usually occurs in children and young adults.\(^13\) Many features of this disease overlap with those of chronic active EBV infection (CAEBV) and infantile fulminant EBV-associated T-LPD (IFEBV).\(^5\),\(^13\) EBV-associated T-cell LPD is most prevalent in East Asian countries and it usually shows a fulminant clinical course that results in high mortality rates.\(^5\) The pathogenetic mechanism of the disease has not been established.\(^5\),\(^9\) However, given that it is associated with primary EBV infection and there is a racial predisposition, it may be associated with a genetic defect in T-cell responses to EBV.\(^9\)

In both of our patients, endoscopy showed multiple ulcers of variable sizes that were scattered throughout the small and large bowel. Although the discrete ulcers mimicked lesions found in CD, their endoscopic features differed from those of CD ulcers in that longitudinal ulcers, a cobblestone appearance or longitudinally arranged aphthous ulcers were not observed.\(^14\) Features that were suggestive of intestinal TB, such as transverse ulcers, scars with pseudopolyps or patulous ileocecal valves, were not observed either.\(^14\)

Since the treatment strategy and prognosis of patients with EBV-associated LPD differ markedly from those of patients with CD or intestinal TB, it is essential to provide a proper differential diagnosis. Clinicians should be aware that the presence of multiple gastrointestinal ulcers that are not consistent with other common conditions, such as CD or intestinal TB, together with an atypical clinical course may indicate EBV-associated LPD.

**Conflict of interest statement**

No author has any financial conflict of interest to declare. There is no funding source for this manuscript.

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Na HK and Ye BD conceived the study; Na HK, Yang DH, Jung KW, Kim KJ, Byeon JS, and Myung SJ collected and interpreted the data; Na HK drafted the manuscript; Yang SK and Kim JH critically reviewed the manuscript; Ye BD revised and approved the final manuscript. All authors read and approved the final manuscript. None of the authors have any competing interests to declare.

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