Int J Clin Exp Pathol 2017;10(6):7116-7120
www.ijcep.com /ISSN:1936-2625/IJCEP0048595

Case Report

Solitary Epstein-Barr virus-positive cytotoxic T cell lymphoproliferative disease in stomach mimicking extranodal NK/T cell lymphoma

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Received January 10, 2017; Accepted January 26, 2017; Epub June 1, 2017; Published June 15, 2017

Abstract: Epstein-Barr virus (EBV)-associated lymphoid tissue diseases are complex disorders, presenting EBV-related immunodeficiency and non-immunodeficiency symptoms and signs; the latter includes benign lymphoid tissue hyperplastic disorders, EBV-related lymphoma, and EBV-positive lymphoproliferative diseases (LPDs). Herein, we report a case of a 52-year-old female who had an epigastric pain, with occasional acid regurgitation and nausea, and was diagnosed with gastric solitary EBV-positive cytotoxic T cell lymphoproliferative disease. The patient was treated with radical gastrectomy, without aggressive chemotherapy, and had disease-free survival of 14 months (based on the last follow-up). To our best knowledge, this was the first report of solitary EBV-positive cytotoxic T cell LPD in stomach. Our findings suggest that EBV+ T cell LPD could be present as focal or solitary disease.

Keywords: Lymphoproliferative disease, EBV, solitary gastric mass, extranodal NK/T cell lymphoma

Introduction

Epstein-Barr virus (EBV)-associated lymphoid diseases may present as EBV-related immunodeficiency [1] and non-immunodeficiency diseases [2]. The latter also includes the following diseases: (1) benign lymphoid tissue hyperplastic disorders, such as infectious mononucleosis; (2) EBV-related lymphoma, such as Hodgkin's lymphoma, NK/T cell lymphoma, and Burkitt lymphoma [2]; and (3) EBV-positive lymphoproliferative diseases (LPDs) [3, 4], such as Epstein-Barr virus-associated T/NK-cell LPDs, which are prevalent in Asians and characterized by high EBV viral load and symptoms such as fever, organomegaly and skin lesions [3, 4]. EBV-associated lymphoid diseases often show systemic manifestations, such as systemic EBV-positive T-cell LPD of childhood (CSEBV+ T-LPD).

Diagnosis of EBV+ T-LPD relies on the confirmation of chronic or persistent EBV infection of T cells, as defined as a severe illness of greater than 3- or 6-months in duration with the following clinical and laboratory evidences: (i) primary EBV infection or markedly abnormal EBV antibody titers (e.g. anti-EBV viral capsid antigen IgG ≥ 5120, anti-EBV early-antigen IgG ≥ 640, or anti-EBNA < 2); (ii) major organ involvement such as interstitial pneumonia, hypoplasia of the bone marrow, uveitis, lymphadenitis, persistent hepatitis, and splenomegaly; and (iii) increased EBV RNA or protein levels in affected tissues [4].

Systemic EBV-positive T-cell LPD is a life-threatening condition that occurs with an apparent primary EBV infection. Its survival rate is extremely low due to hemophagocytosis and multiple organ failure occurring over the course of days to weeks [2]. Historical therapeutic approaches, before the use of bone marrow or stem-cell transplantation, include the use of high-dose immunoglobulin, IL-2, antiviral agents, IFN-α or IFN-γ, corticosteroids, and rituximab. In addition, antiviral therapy may have some clinical benefits [4-6]. However, solitary

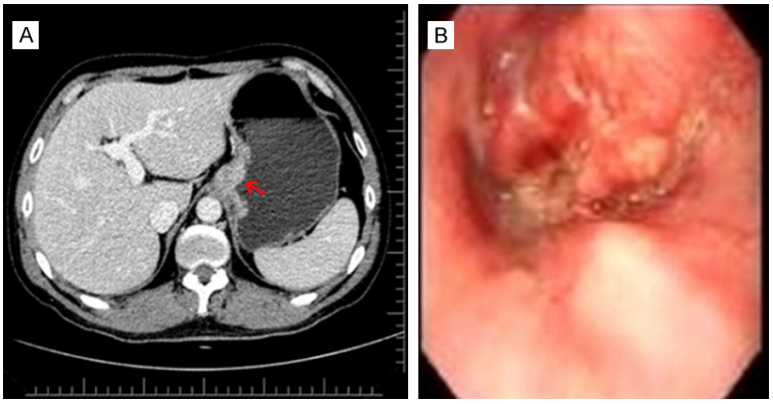

Figure 1. Mucosal destruction and stomach wall rigidity as indicated by the red arrow in the CT scan (A) and the gastroscope image (B), showing a large irregular mass at gastric cardia and gastric body.

EBV+ T-LPD did not appear in the literature. Herein, we describe an interesting case of gastric solitary EBV positive cytotoxic T cell LPD, mimicking extranodal NK/T cell lymphoma that did not require aggressive chemotherapy. The patient had a relatively long-term disease-free survival.

Case report

A 52-year-old female presentedwith intermittent epigastric pain on August 3, 2014, with occasional acid regurgitation and nausea. The pain lasted about 10 minutes each time, without fever, abdominal distention, or diarrhea, and could be alleviated after rest or adopting a supine position. Clinical blood tests (on August 21, 2014) showed a positive EB-VCA-IgG titer (1:1600). However, she did not receive antiviral treatment. The patient continued to have gastritis-like symptoms for more than three months, and the duration of symptoms became longer, and was not relieved by drug treatments such as omeprazole. The patient developed weight loss (approximately 6 kg/month) and became significantly emaciated. Her physical exam revealed no major abnormal findings.

On November 3, 2014, her blood tests revealed the following findings: normal white blood cell count (WBC 8.41 × 10^9/L), red blood cell count (RBC 3.90 × 10^{12}/L, platelet count (PLT 218 × 10^9/L), neutrophil percentage (NEUT% 65.5%), lymphocyte percentage (LYMPH% 25.7%), and NEUT# 5.51 × 10^9/L. The patient had decreased a hemoglobin level (HGB 106 g/L). Her liver function test results were within normal ranges: alanine aminotransferase (ALT), 13 IU/L and aspartate aminotransferase (AST), 23 IU/L. Ultrasound showed no abnormal findings on liver and spleen. A remarkable irregular filling defect displayed at the gastric cardia and gastric body on X-ray imaging and CT scan (**Figure 1A**), showing mucosal destruction and stomach wall rigidity. Gastroscopy showed a lesion with an unclear boundary and no peristalsis (**Figure 1B**); endoscopic findings in dicateda suspected diagnosis of gastric cancer. During the operation of a radical gastrectomy, the size of lesion was found to be 5 × 4 × 3 cm, locating at gastric cardia and gastric body with diffuse thickening of the stomach wall; several enlarged lymph nodes next to the left gastric artery were found.

Histological analysis of the tissue samples obtained from radical gastrectomy indicated that the lesion was predominantly located in stomach mucosa and submucosa, showing a diffuse pattern with a large lymphocyte infiltration (**Figure 2A**). The cells were round with mildly irregular, inconspicuous or small nucleoli and dispersed chromatin (**Figure 2B**). The majority of lymphocytes expressed CD3 (**Figure 3A**), CD5, TIA-1, and Granzyme B (**Figure 3B**), but not CD56. There were only few scattered lymphocytes with CD20 expression (**Figure 3C**). EBV-encoded RNA (EBER) was detected in many lymphocytes (**Figure 3D**). T cell clonality analysis revealed a monoclonal rearrangement. Based on these findings, the patient was diagnosed with Grade 2 gastric solitary EBV-positive cytotoxic T cell lymphoproliferative disease.

After the surgery, the patient has no symptoms for 12 months and received no aggressive chemotherapy. Atthe sixth-month follow-up (April 27, 2015), blood test showed normal levels of WBC (7.09 × 10^9/L), HGB (126 g/L), PLT (171 × 10^9/L), NEUT% (55.4%), and LYMPH% (41.5%), and her liver function test was within normal range. There were signs of incision infection at the twelve-month follow-up (November 15,

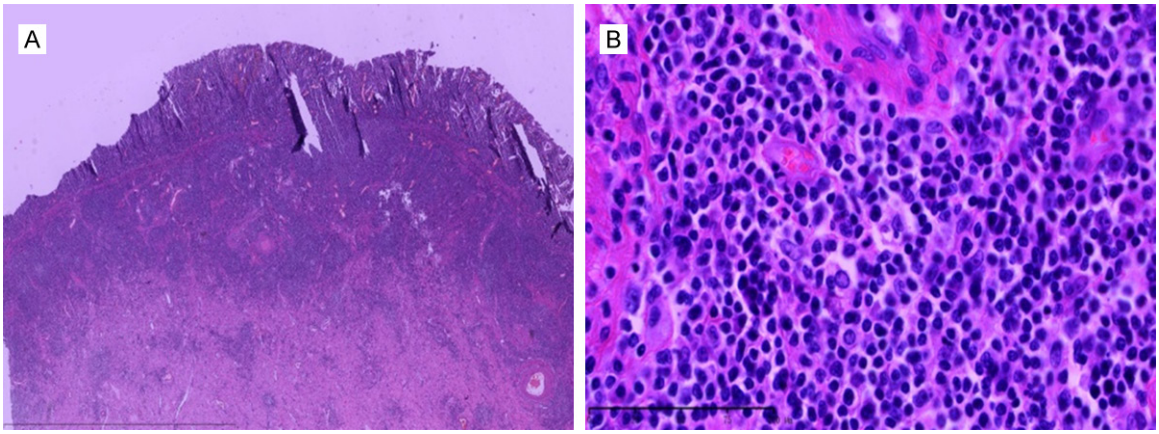

Figure 2. Morphology of Solitary Epstein-Barr Virus-positive Cytotoxic T Cell Lymphoproliferative Disease in Stomach. A. The lesions were diffuse with a large number of lymphocytes (H&E × 40). B. In the lesion, there were numerous infiltrating lymphocytes with medium size, round and mild irregular nuclei, inconspicuous or small nucleoli and dispersed chromatin (H&E × 400).

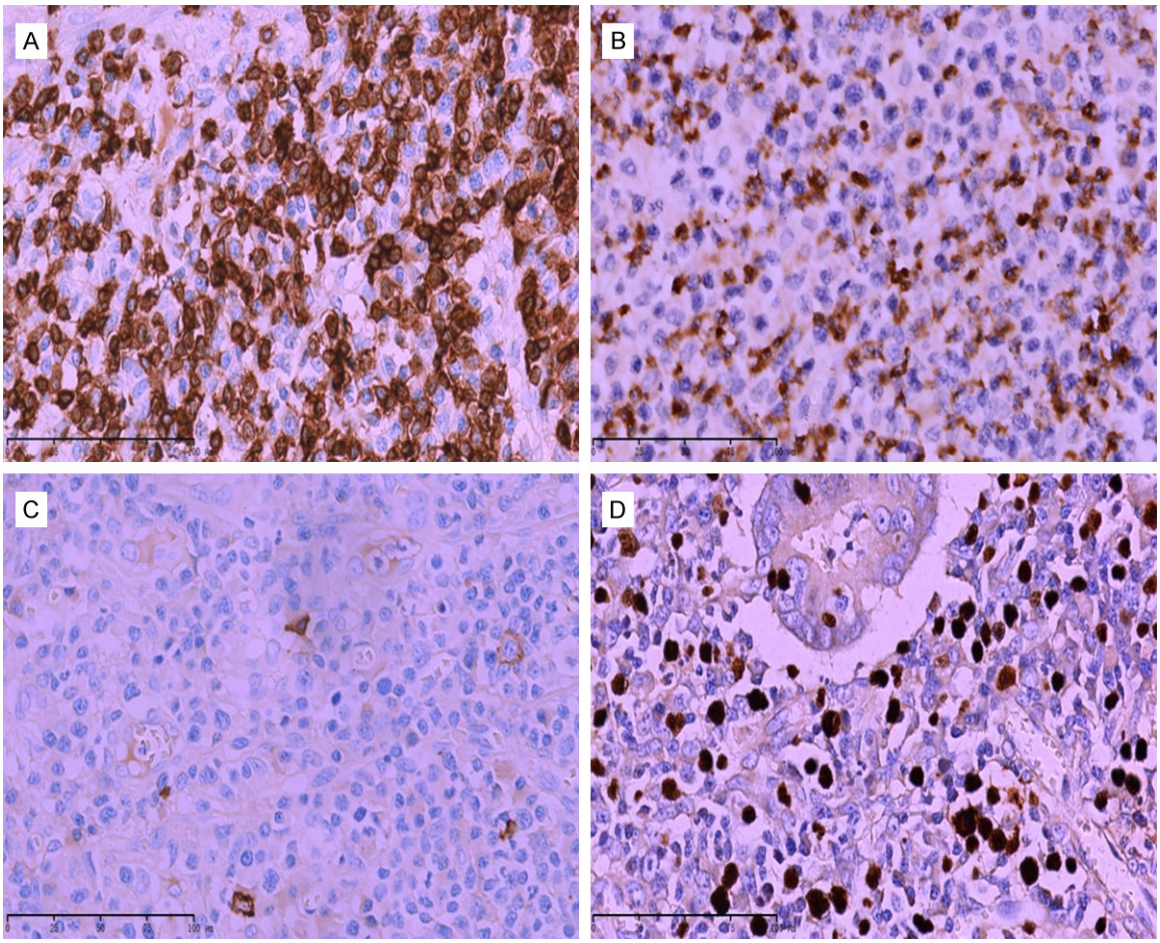

Figure 3. A. Immunophenotype of morphology of Solitary Epstein-Barr Virus-positive Cytotoxic T Cell Lymphoproliferative Disease in Stomach. The majority of lymphocytes in the lesion expressed CD3 (A), and Granzyme B (B); only a few scattered lymphocytes expressed CD20 (C); EBER was detected in around 30% of all cells (D). × 400.

2015); blood test showed elevated WBC (14.04 × 10^9/L) and NEUT% 83.1%, decreased HGB (102 g/L) and LYMPH% (10.0%), but normal PLT (216 × 10^9/L). The CT scan showed no mass or

enlarged lymph nodes in abdomen, or other abnormal findings. At the fourteenth month, the patient had no symptoms of infection after antibiotic therapy for two months, and the blood tests and CT scan showed no abnormalities (January 21, 2016).

Discussion

To our best knowledge, our case is the first report of solitary EBV-positive cytotoxic T cell LPD in stomach. The patient was diagnosed with EBV-positive T-LPD, based on a large number of EBER+ T-cell infiltrates in the gastric tissue, elevated EBV-antibodies in blood, and expansion of monoclonal EBV-infected T cells in the stomach. The patient received no aggressive chemotherapy or radiotherapy aftera radical gastrectomy buthad a disease-free survival of 14 months at the latest follow-up.

The clinical and laboratory findings showed that an extranodal NK/T cell lymphoma, EBV positive T cell lymphoproliferative disease. Lymphomatoid gastropathy could be considered as a differential diagnosis. NK/T cell lymphoma often exhibits aggressive progression with short survival rates and poor response to therapy. Such lymphomas are characterized by angiocentric or angiodestructive atypical lymphoid proliferation associated with necrosis [2]. These lesions are almost always associated with EBV and show CD56 expression. According to the lesion sites, they are classified into nodal and extranodal NK/T cell lymphoma (ENTCL). The stomach may be one of the sites of primary ENTCL [7, 8]. Despite the present case having some features mimicking ENTCL in morphologic and immunohistochemical findings, the differentiation diagnosis was made based onthe clinical course which was non-aggressive and did not necessitate chemotherapy or radiotherapy.

Most cases of T-cell LPD following primary infection with EBV have been reported in East Asian [2-4], mostly in children and young adult patients. The organs most commonly involved in EBV-associated LPD are the liver, spleen, and bone marrow. The pathological manifestations are similar to that of our presented case, with the exception of the patient's age and symptoms. Most of the reported cases exhibit monoclonality, although some possess oligo- or polyclonal populations of EBV. As a life-threatening disease, the poor response to therapy is linked to the high mortality rate [9]. In the present case, as the solitary lesions were located in the stomach which was surgically removed, no chemotherapy or radiotherapy was needed. The patient survived surgery indicating thatthis type of EBV infection has a significantly different presentation and prognosis from systemic EBV-associated LPD.

Lymphomatoid gastropathy, a new evolving pathological entity that has been characterized recently, is regarded as a distinct clinicopathological entity and should be observed clinically without treatment [10]. It is designated to describe CD56-positive atypical gastric lymphoid proliferation, mimicking NK/T cell lymphomas, which shows an indolent clinical course with spontaneous regression [11, 12]. For most cases reported thus far, the lesions are commonly located in the stomach; gastroscopy demonstrates ulcerative or elevated lesion(s)-1 cm in diameter in the stomach. Some cases present with superficial erythematous mucosa and physical examination are often unremarkable, as are blood cell counts and chemistry, including lactic dehydrogenase levels that are within normal ranges. Additionally, EBER *in situ* hybridization is consistently negative [13, 14]. In the presented case, the differentiation points were a large lesion mass locatedin the stomach and numerous EBER positive lymphoid cells in the lymphoid tissue. Our findings indicated that EBV+ T cell LPD could present not only as a systemic disease, but also as focal or solitary disease, which underpinsthe clinical importance of solitary EBV positive atypical cytotoxic T cell LPD. At present, specific therapies for this condition havenot been developed. Therefore, a correct and early diagnosis of this rare disorder is essential for improving current knowledge and developing an effective therapeutic approach.

Acknowledgements

This work was supported by a grant from National Natural Science Foundation of China (81272633).

Disclosure of conflict of interest

None.

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