

# Systemic EBV T-Cell Lymphoproliferative Disease of Young Adults

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**Abstract-** T/NK cell proliferative EBV associated disease is a rare one which is more common in eastern Asian countries. EBV is originally associated with B cells, and EBV associated T cell lymphoma is so rare. Hence we decided to describe a patient treated with misleading diagnoses such as TB and sarcoidosis for almost two years. The liver was biopsied after admission in this center, and gastric and colonic biopsy was also performed due to gastrointestinal bleeding. Diffuse infiltration of chronic inflammatory cells was seen, especially lymphocytes some of which were atypical. T lymphocyte markers were seen in these cells by immunohistochemical staining. Further studies demonstrated T lymphocytes associated with EBV to be positive which is very rare event. Although going under chemotherapy, there were no response and the patient died.

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**Keywords:** Lymphoma; T-Cell; Lymphoma; B-cell; Burkitt's lymphoma; Epstein - Barr virus

## Introduction

EBV (Epstein-Barr Virus) is a member of human herpes viruses with double-strand DNA discovered by isolation from linear cells of Burkitt's lymphoma by Epstein in 1964 (1). Generally, EBV infects B-cells using CD21 and major-histocompatibility-complex (MHC) class II on B-cell surface as a receptor and a cofactor, respectively. In most cases, EBV infected B-cells are mainly eliminated by cytotoxic T-lymphocytes (CTLs), and natural killer (NK) cells, while remaining infected B-cells persist in the resting stage (2,3). EBV might infect T-cell, NK-cell, or epithelial cells, so that it has a significant role in several cancer metastases, particularly nasopharyngeal as well as lymphoproliferative disorders (LPDS) such as Burkett's Lymphoma, Hodgkin's lymphoma, and NK-cell lymphoma (4).

NK/T-cell associated EBV in adult patients can be divided into two categories: 1) newly developed (de novo) lymphoma, and 2) chronic active EBV (CAEBV) associated lymphoma. It has two peak ages as well: 1) 18-25 years-old, and 2) 56-65 years-old which are more common among Korean and Japanese patients (5).

The disease is strongly associated with race; most diseases take place in Korea, Japan, some parts of

America, and western hemisphere including Mexico, Peru, and Mid-America. It is rare in African-Americans and Caucasians.

The medical term T/NK-cell lymphoma includes a wide range of diseases including the systemic form which might be polyclonal-spontaneous (6).

## Case Report

The patient is a 32 years-old man under study from 2 years ago because of fever and chill. A liver biopsy is performed by a physician due to his abnormal liver enzymes, and the patient is treated as sarcoidosis. However, after a year of no response to treatment, the patient starts coughing and is treated with a diagnosis of TB. There is no response to anti-TB medications as well, and the patient is referred to this center for further studies.

He was weak at the time of referral to this center. His body temperature was 38°C. No lymphadenopathy was detected in physical examination. The lungs were clear in auscultation. He was aware and answered questions properly. He had soft abdomen without any organomegaly. There was a scar of appendectomy in right lower quadrant (Table 1). Laboratory data were as

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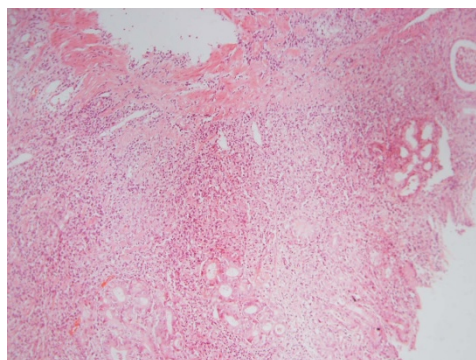
**Table 1. Patient's Laboratory data**

Parameter	Value	Parameter	Value
AST	158	Bilirubin D	0.6
ALT	206	WBC	3900
ALP	800	Hemoglobin	12.2
Bilirubin T	2.1	Platelets	141000

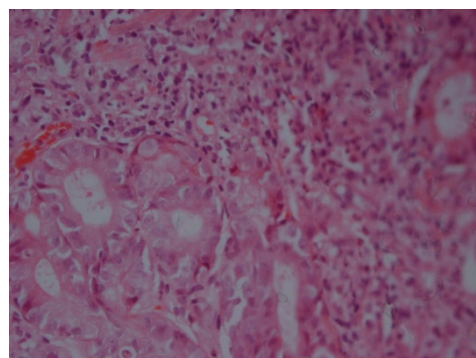
In this center, he underwent another liver biopsy. During the admission, he had two upper and lower GI-bleedings. Several lesions were seen in the body of the stomach during upper endoscopy, and several linear lesions were detected in cecal area of the colon during colonoscopy.

Although going under one course of chemotherapy including cisplatin, gemcitabine, and dexamethasone, the patient died due to septic complications of neutropenia.

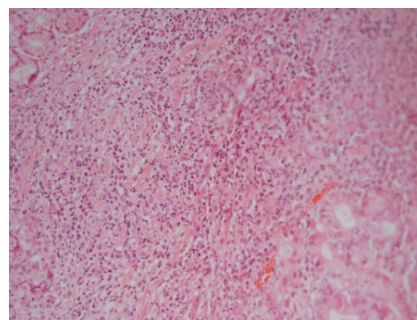
Light microscopic evaluations from gastric mucosa shows mucosal ulcer with active inflammatory component. Severe inflammation mostly composed of lymphocytes some with atypical changes, few eosinophils, histiocytes and plasma cells are noted. No epithelial atypia or granulomatous reactions are seen (Figures 1-3).



**Figure 1.** Gastric mucosa with ulcerated surface epithelium and severe inflammation

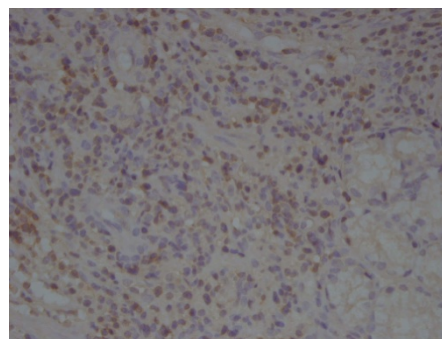


**Figure 2.** Gastric glands infiltrated by lymphocytes and eosinophils

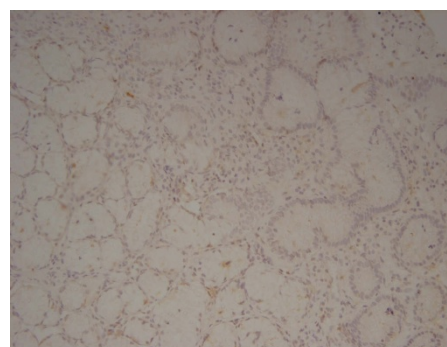


**Figure 3.** Severe inflammation of gastric mucosa mostly composed of lymphocytes, few eosinophils and histiocytes

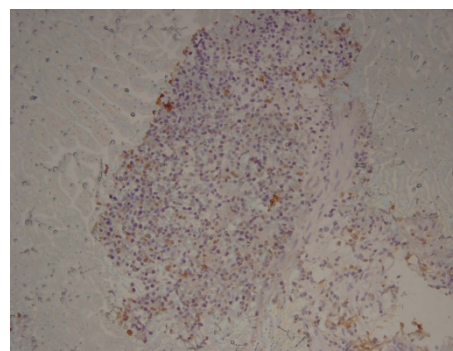
Immunohistochemistry studies show positive staining for CD3 and negative staining for CD10, CD15 and CD20 in lymphoid cells (Figures 4-7).



**Figure 4.** CD3



**Figure 5.** CD10



**Figure 6.** CD15

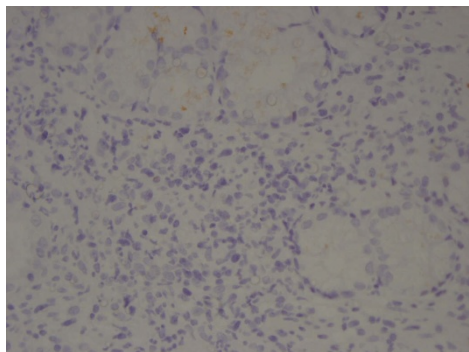


Figure 7. CD20

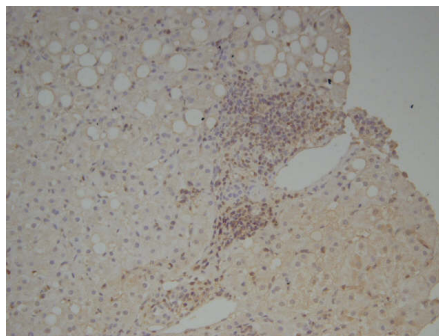


Figure 10. CD3

Microscopic examination of liver biopsy shows patchy infiltration of lymphoid cells some with atypical features within the lobules as well as portal tracts. No granulomatous reaction or specifications of viral or autoimmune hepatitis are noted (Figures 8,9).

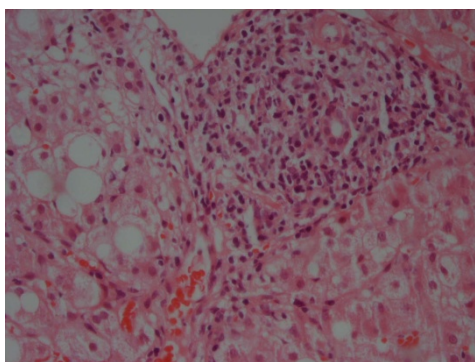


Figure 8. Liver portal tract with patchy infiltration by lymphocytes

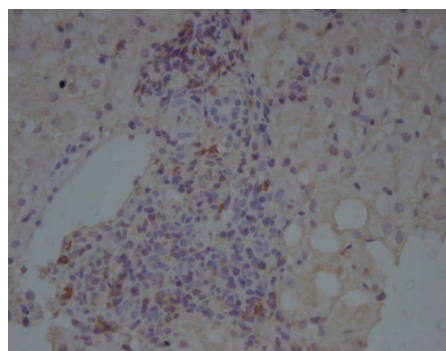


Figure 11. CD20

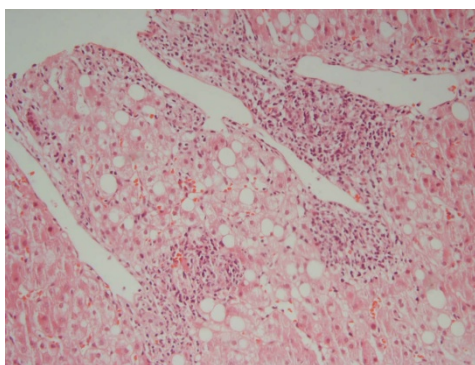


Figure 9. Liver biopsy with marked macro and mediovesicular steatosis and chronic inflammatory infiltration

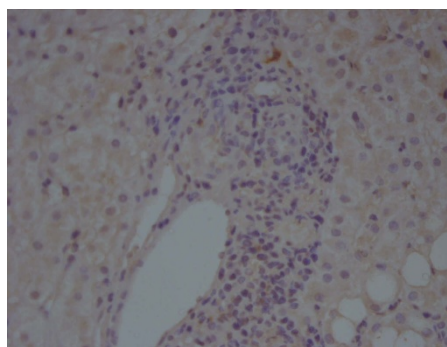


Figure 12. CD30

Fluorescence double stains clearly demonstrate that EBV-positivity (as evidenced by EBER in situ hybridization) is present in T-cells rather than in B-cells. Molecular analysis revealed an oligoclonal expansion of T cells (TCR-GAMMA, MIX I), while monoclonality could not be established. So the diagnosis is best classified as chronic active EBV infection of the T/NK cell lineage.

### Discussion

Immunohistochemistry studies show positive staining for CD2, CD3, CD5, CD7,  $\beta$ -F1 and negative staining for CD20, CD15 and CD30. Further subtyping shows a slight predominance of CD8-positive T-cells, some of which may express the cytotoxic marker Perforin. The B-cell component is unremarkable (figures 10-12). The proliferative activity (Ki67) is slightly increased.

Immunocompromised individuals are more prone to EBV associated lymphoma, especially in post-transplant recipients of solid organ and bone marrow. According to the WHO classification, PTLN, may be classified to early lesions, by EBV derived polyclonal

lymphoproliferation and true monoclonal disease.

Despite the ability of EBV to infect B cells but it can also infect other cells. The mechanism underlying EBV infection of T and NK cell, which do not express CD21, remain unresolved. It has been shown that NK cells, activated by EBV infected B cell acquire CD21 by synaptic transfer, which allow EBV binding to hosts (7, 8).

For the first time, Ithumjeu *et al.*, described EBV associated peripheral T cell lymphoma of activated CD8 in children (7).

T cell lymphoproliferative EBV associated include subset of peripheral T cell lymphoma, angioimmunoblastic T cell lymphoma, extra nodal nasal type NK, T cell lymphoma and other types.

Systemic chronic active EBV disease is rare lymphoproliferative disorder and predominantly occurs in Asia and South America, presenting with multisystem failure, rapid progression, high mortality and morbidity (9).

Isobey *et al.*, reported 7 cases of EBV associated lymphoma, documented by EBV viral load in blood and evidence of EBV infection in T cell or NK cells (10).

Tabanei *et al.*, reports a 23 year old boy with fever and hepatosplenomegaly and pancytopenia arouse in EBV active syndrome.

In this regard, fulminant EBV affected CD8 positive T cell s is classified as systemic EBV active syndrome, in reviewing the literature (11).

There are various factors associated with prognosis among EBV T/NK-LPDS patients. The age of disease onset being upper than 8 and liver dysfunction are dependent mortality risk factors. Patients receiving liver transplantation have the better prognosis (ebv6).

The disease course of clinical symptoms severely aggressive; with a survival time less than one year, large spleen and liver, and liver dysfunction during weeks, patients proceed to progressive failure of different body organs, coagulopathy, sepsis, and final death. Usually, there is advanced pancytopenia and liver enzyme abnormalities in laboratory results. In rare cases, there are patients with the sub-acute disease which will survive for some years (ebv2).

Because of its infrequency while to some extent being treatable, in patients with long term fever and liver enzyme dysfunction, lymphoma should be considered after taking history and performing routine studies and its histology should be revised by a pathologist.

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