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Activated Epstein-Barr Virus Causes the Post-Transplant Lymphoproliferative Disorder in the Central Nervous System

Akira Tempaku, MD

Department of Neurosurgery, Hokuto Hospital. 7-5 Inada-cho-kisen, Obihiro, Hokkaido, Japan.

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Corresponding Author:** ***Akira Tempaku, *Department of Neurosurgery, Hokuto Hospital, 7-5, Inada-cho-kisen, Obihiro, Hokkaido, 080-0833, Japan.*

Abstract

Introduction: *Post-transplant lymphoproliferative disorders (PTLD) generally result in high mortality complications because the organ recipient must remain on long-term oral immunosuppressant. It is well known that the Epstein-Barr virus (EBV) undergoes reactivation during immunosuppressive drug administration, resulting in the formation of various neoplasms.*

Case: *A 56-year-old woman was diagnosed with primary central nervous system lymphoma (PCNSL) as PTLD. The patient had previously undergone renal transplantation 17 years earlier. The brain lesion was found to contain EBV-positive lymphocytes. Further serologic testing demonstrated elevated antibodies in the EBV lytic cycle pattern, which contained viral capsid and early antigens.*

Discussion: *Typically, the presence of PLTD due to EBV is identified by elevated levels of EBVDNA in serum or by the detection of EBV-encoded RNA in lesions via histopathological analysis. In contradistinction to systemic lymphoproliferative diseases, PCNSL is isolated by the blood-brain barrier and resides in the central nervous system. PCNSL does not have systemic lymphoid neoplasms, which makes it difficult to detect EBV-containing PCNSL-specific lymphocytes. Serum antibody tests against to the EBV lytic cycle for EBV-associated PCNSL would be a useful diagnostic tool. Further clinical studies and observation are required to establish standard criteria for the diagnosis.*

Keywords: *Primary Central Nervous System Lymphoma, Post-Transplant Lymphoproliferative Disorder. Epstein-Barr Virus*

1. Introduction

Epstein-Barr virus (EBV) is frequently characterized as a subclinical infection [1-3], yet it has the capacity to be reactivated by immunosuppression. [4,5] EBV was traditionally regarded as a causative agent for infectious mononucleosis (IM) and some neoplasms, including Burkitt's lymphoma and nasopharyngeal carcinoma. [6-10] Recent reports have indicated its involvement in various types of cancer, including gastric cancer [10], leiomyosarcoma [11], salivary gland cancer [13], and breast cancer. [14-16]

Activation of EBV by suppression of immune function is hypothesized to be implicated in carcinogenesis. Post-transplant lymphoproliferative disorder (PTLD) complications have been observed in 1-10% of patients following organ transplantation, necessitating long-term immunosuppressive therapy. [17,18] The incidence of this condition after kidney transplantation is low, ranging from 0.8 to 2.5% [19-21], but when limited to PCNSL-PTLD, 68-85% of cases occur after kidney transplantation. [22-24] it is noteworthy that cases of EBV infection have also been reported in PTLD. [25-29]

2. Case Presentation

A 56-year-old female patient was admitted to the hospital with symptoms of elevated brain dysfunction and Gerstman's syndrome. The patient had a medical history which included diabetic nephropathy and a renal transplantation which had been performed 17 years earlier.

Her current medication regimen comprised tacrolimus (Prograf) 1 mg and mycophenolate

mofetil (CellCept) 1000 mg on a daily basis. In addition, she was prescribed hypoglycemic medication and insulin in order to treat her impaired glucose tolerance. No disturbance of consciousness, motor paralysis, sensory disturbance, or ataxia was observed. Head imaging revealed a mass lesion in the left inferior parietal lobule, as indicated by hypo intensity on magnetic resonance imaging (MRI) T2-weighted, fluid attenuated inversion recovery (FLAIR). In contrast, the lesion indicated hyper intensity on diffusion-weighted image (DWI), and positive ring enhancement on gadolinium contrast T1-weighted (figure 1). Positron emission tomography (PET) scanning revealed a weak accumulation of 5-fluorodeoxyglucose (FDG) and methionine (figure 1). Following a 20-day period, an escalation in perifocal edema was observed, accompanied by the onset of right-sided paralysis and sensory impairment.

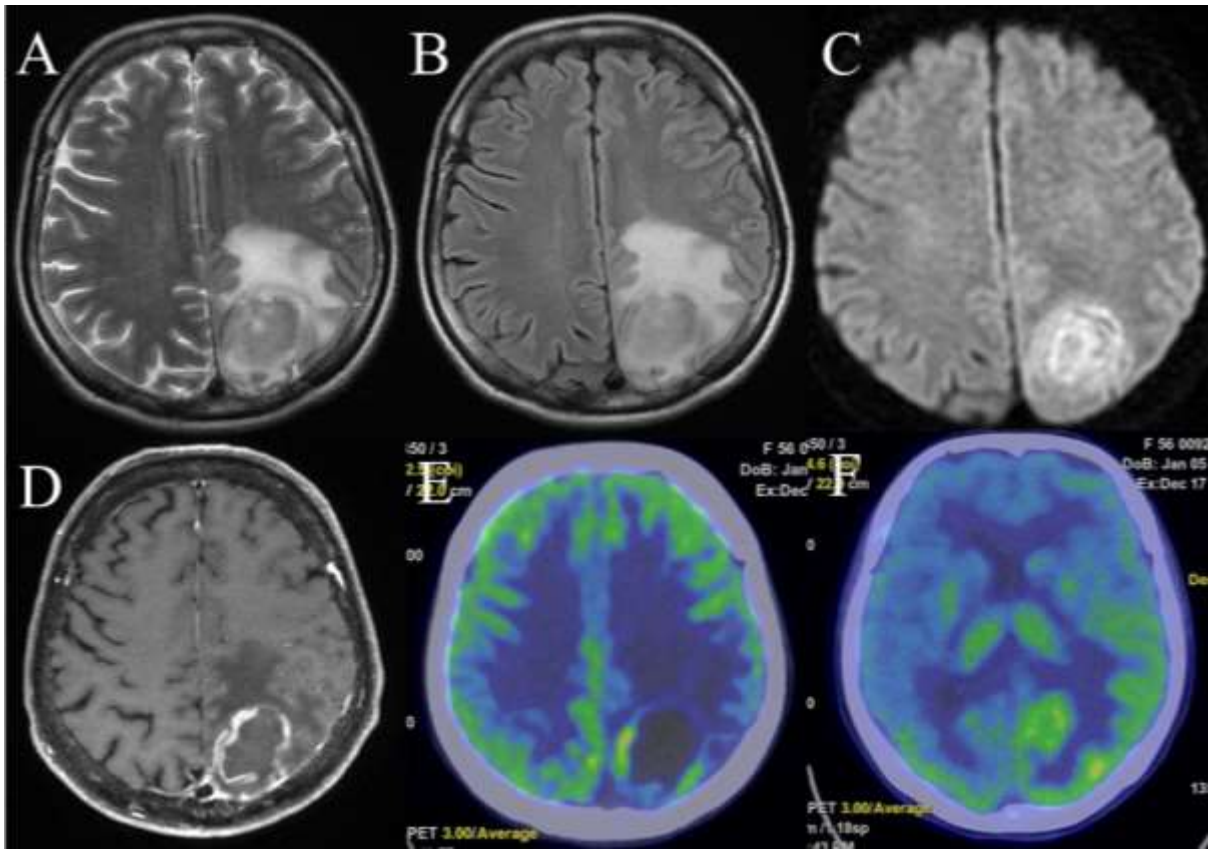

Figure 1. *The radiographic image of the head is presented below. The magnetic resonance imaging are shown below. T2-weighted (A), fluid-attenuated inversion recovery (B), diffusion-weighted image (C), and gadolinium-contrasted T1-weighted (D). The positron emission tomography (PET) scans of the head with 5-fluorodeoxyglucose (E) and methionine (F) are displayed below.*

Consequently, the patient underwent a craniotomy under general anesthesia with optical navigation. Histological analysis revealed an accumulation of atypical lymphocytes. A comprehensive pathological examination revealed the presence of cluster domain (CD) 20-positive (figure 2), CD3-negative (data not shown), Epstein-Barr virus-encoded RNA (EBER)-positive (figure 2), and B cell lymphoma (BCL)-2-negative features (data not shown), thereby establishing a diagnosis of EB-associated B cell lymphoma, central primary malignant lymphoma, and post-transplant lymphoproliferative disorder. The patient's condition was further characterized by the presence of elevated early antigen (EA) and viral capsid antigen (VCA) antibodies, which are indicative of an EBV lytic cycle status.

The serum antibody amounts were as follows: EB-EA IgG-enzyme immunoassay (EIA), 6.8 (normal range below 0.5); EB-VCA IgG-enzyme-linked immunosorbent assay (EL), 2.3 (normal range below 0.5); and EB-EBNA IgG, 3.4 (normal range below 0.5).

The patient developed PCNSL while undergoing immunosuppressive therapy. She was treated with chemotherapy at the same hospital where she had previously undergone renal transplantation.

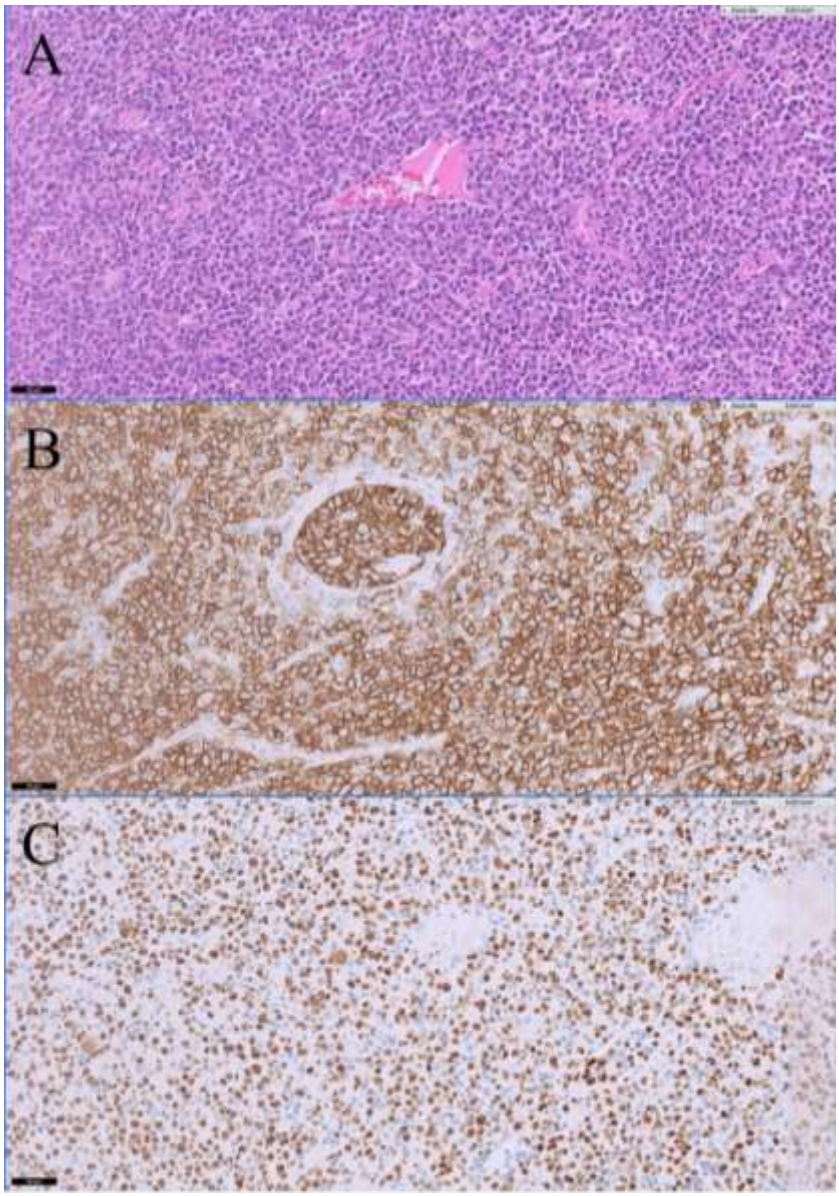

Figure 2. *A pathological analysis was performed on tumor tissue obtained by surgical resection. (A) illustrates features from hematoxylin-eosin staining at high magnification. As illustrated in (B), the features are demonstrated through the use of CD-20 staining, with an emphasis on high-magnification imaging. (C) illustrates the features observed through the utilization of EBER staining at a high magnification level. The indicator bar situated in the lower left quadrant of the figure indicates a measurement of 50 μm.*

3. Discussion

It has been documented that PCNSL manifests in 7 percent of PTLD cases. [30] EBV positivity in PTLD has been documented in 82% of cases. [30] In addition, in cases of PCNSL, EBV positivity has been documented to account for 48% of cases. [31] Reports indicating EBV involvement in PCNSL have cited the detection of EBER and EBV DNA as evidence. [32-35] Conversely, the detection of anti-EA and anti-VCA antibodies has received less attention. [36]

There are also reports of changes in EBV-specific antibodies focusing on the EBV nuclear antigen (EBNA) and the latent membrane protein 1 (LMP1). [37-40] However, only a few reports have focused on antibodies specific to the lytic cycle. [36,41]

It has been suggested that EBV-specific antibodies could be used to monitor the development of EBV-associated lymphoma in long-term immunosuppressed patients, such as those who have received immunosuppressive drugs after organ transplantation. In addition to radiographical imaging tests, serological checks including the EBV related antibodies may be useful.

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