# Brain Tumor as an Unusual Presentation of Posttransplant Lymphoproliferative Disorder

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## Abstract

***Objectives:*** **Posttransplant lymphoproliferative disorder following solid organ transplant is a life-threatening form of posttransplant malignancy. Its occurrence is typically associated with Epstein-Barr virus and profound immunosuppressive therapy. We describe a case of posttransplant lymphoproliferative disorder in the brain parenchyma, 4 years after renal transplant.**

***Case Report:*** **A 23-year-old man was evaluated for generalized headache 4 years after receiving a deceased donor renal transplant. After initial immunosuppression with tacrolimus and prednisolone, mycophenolate mofetil was added for maintenance immunosuppression. A tumor in the right occipitoparietal lobe was detected by magnetic resonance imaging and excised. Immunohistochemical testing of the tumor revealed B-cell marker and Epstein-Barr virus. After surgery, the dosage of immunosuppressive drugs was reduced, and the patient was treated with chemotherapy and radiotherapy. Our patient is well after treatment.**

***Conclusions:*** **Reduction in immunosuppressive therapy is an important component of treatment for Epstein-Barr virus-positive posttransplant lymphoproliferative disorder and may lead to remission in early disease. If reduced immunosuppression fails to control early disease, cytotoxic chemotherapy, surgery and radiotherapy, antiviral therapies, and cell-based therapies are other options for treatment.**

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**Key words:** *Epstein-Barr virus, Renal transplant, Immunosuppressive therapy, Viral load monitoring, B-cell.*

Posttransplant lymphoproliferative disorder following solid organ transplant is a life-threatening form of posttransplant malignancy. Its occurrence is typically associated with Epstein-Barr virus and profound immunosuppressive therapy. It has a variable presentation. Type of transplant, intensity of immunosuppression, negative pretransplant Epstein-Barr viral serostatus of the recipient, and age are well-known risk factors. Epstein-Barr viral infection is frequently acquired in adolescence; therefore, seronegative pediatric transplant recipients are at particular risk for posttransplant lymphoproliferative disorders. The prevalence of posttransplant lymphoproliferative disorder in the Iranian kidney transplant population is approximately 0.47%, and occurrence in the brain is associated with the worst outcome.

### Case Report

A 23-year-old man was admitted because of generalized headache to Chamran Hospital affiliated with the Shiraz University of Medical Sciences. He had received a deceased donor renal transplant 4 years earlier. After transplant, the patient's renal allograft functioned well, and his serum creatinine level declined from 10.0 mg/dL to 1.2 mg/dL. The patient was prescribed tacrolimus and prednisolone for initial immunosuppression. The initial dosage of tacrolimus was 0.15 mg/kg per day. The daily dosage was adjusted according to the target blood trough tacrolimus concentration of 10 ng/mL. After 3 months, the target trough tacrolimus concentration was decreased to 5 ng/mL for long-term maintenance. In addition to tacrolimus and prednisolone, mycophenolate mofetil (15 mg/d) was

given as 2 equally divided doses for maintenance immunosuppression. During follow-up, the patient developed urinary tract infections and pneumonia that resolved after appropriate management.

On physical examination at hospital admission, no diplopia or dysphagia was noted. The examination of the peripheral nervous system was normal, and no meningeal signs were detected. There was no palpable lymphadenopathy. Protein level and cell counts of the cerebrospinal fluid were within normal limits with no bacterial or viral isolations. The level of blood urea nitrogen was 30 mg/dL, and the level of serum creatinine was 1.6 mg/dL. Results of tests for complete blood count, liver function, and electrolytes were normal. Results of the patient's electrocardiogram and chest radiograph showed no abnormality. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a mass with ringed enhancement in the right occipitoparietal lobe (Figure 1). The patient underwent total tumor excision via a right occipitoparietal craniotomy.

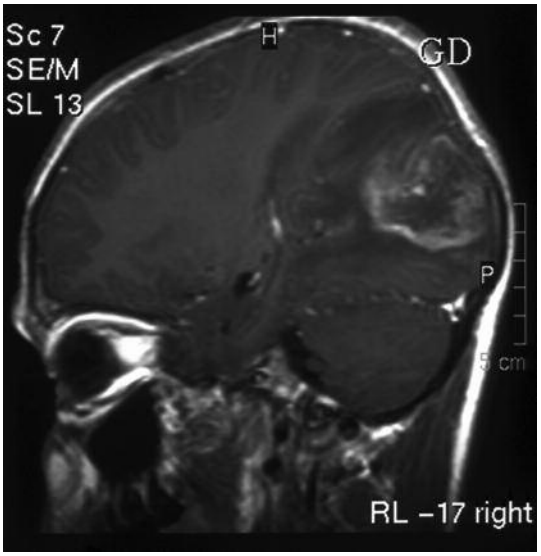


**Figure 1.** An enhanced lesion in the right occipitoparietal lobe by magnetic resonance imaging (MRI).

Pathological examination of the tumor revealed dense perivascular and parenchymal infiltration of atypical mononuclear cells with extensive areas of necrosis (Figure 2). On immunohistochemical study, the tumor cells tested positive for B-cell marker (membrane-spanning 4-domains, subfamily A, member 1 [MS4A1], also known as CD20) (Figure 3), but tested negative for T-cell marker (CD247 antigen [CD247], also known as CD3) and natural killer cell marker (neural cell adhesion molecule 1 [NCAM1], also known as CD56). Epstein-Barr virus was detected on paraffin-embedded sections by immunohistochemistry using a monoclonal anti-LMP1 antibody (Figure 4). The Epstein-Barr viral serologic status before transplant was not known; however, testing for the viral capsid antigen IgG was

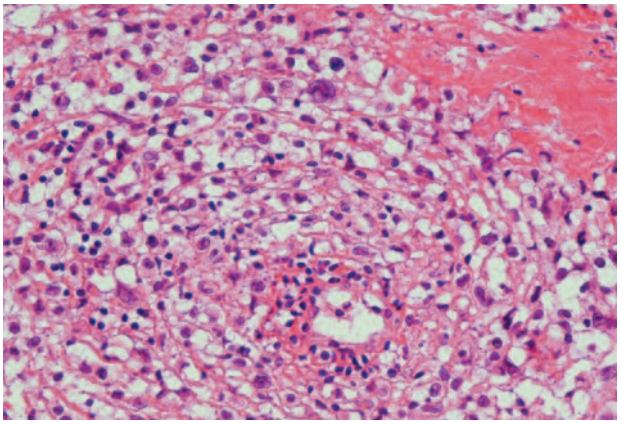

**Figure 2.** The angiocentric atypical lymphoid aggregation in brain parenchyma (hematoxylin-eosin, original magnification ×400).

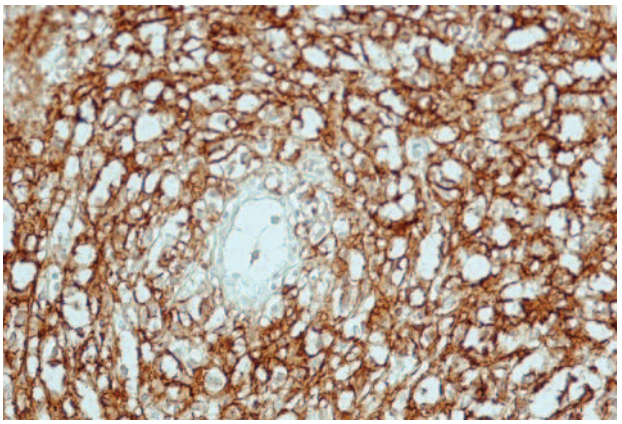

**Figure 3.** Immunohistochemical labeling of atypical lymphocytes for MS4A1 (CD20). (original magnification ×400).

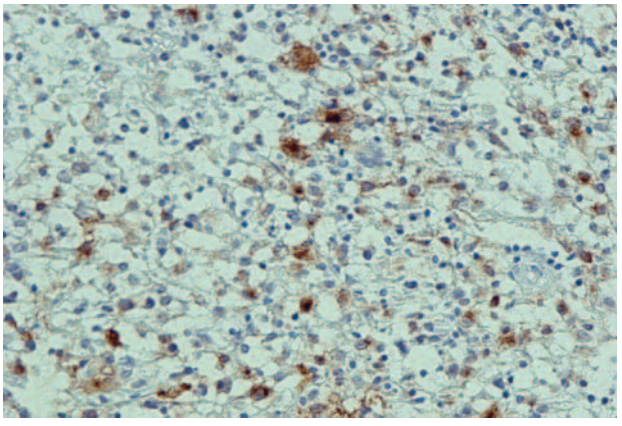

**Figure 4.** Identification of Epstein-Barr virus in lymphoma cells (original magnification ×400).

positive. Complete postoperative systemic evaluation, comprising thoracoabdominal CT and bone marrow biopsy, did not identify other organ involvement. The final diagnosis was primary central nervous system posttransplant lymphoproliferative disorder, B-cell type.

The dosage of immunosuppressive drugs was decreased, and the patient received chemotherapy and radiotherapy. The patient is currently in good condition (January 2009) with no recurrence, as examined by brain MRI.

## Discussion

Epstein-Barr virus-related posttransplant lymphoproliferative disorder occurs in up to 15% of solid organ transplant recipients. Its prevalence depends on several factors such as the type of organ transplanted, the Epstein-Barr virus immunological status of the donor and recipient, and the type and intensity of immunosuppressive drugs (1). The overall risk of posttransplant lymphoproliferative disorder in recipients is between 1% and 2%, but the type of transplanted organ is an important risk factor. The prevalence is highest at 31% in multivisceral transplants and intestinal transplants, mid-range in lung (3.8%-11.7%) and liver (6.8%-13.1%) transplants, and lowest in kidney transplant recipients (1.2%-9%) (2-4). Recipients without previous infection with Epstein-Barr virus (ie, IgG negative) are at greatest risk for posttransplant lymphoproliferative disorder (1).

The type and intensity of immunosuppressive regimen are independent risk factors for the development of posttransplant lymphoproliferative disorder. Patients who are treated with T-cell depleting therapies, such as monoclonal antibody (eg, anti-CD247 antibody: OKT3) or polyclonal antibodies (eg, antithymocyte globulin) in combination with other potent oral immunosuppressive drugs (eg, tacrolimus), are at higher risk of developing posttransplant lymphoproliferative disorder (5). Patients treated with mycophenolate mofetil or azathioprine-based regimens have a relatively lower risk of posttransplant lymphoproliferative disorder (6). The pathological diagnosis of posttransplant lymphoproliferative disorder is based on morphological and immunophenotypical analysis and classified according to the World Health Organization guidelines. Three major categories of posttransplant lymphoproliferative disorder have been identified: hyperplastic, polymorphic, and monomorphic. Monomorphic or lymphomatous posttransplant lymphoproliferative disorder resembles non-Hodgkin lymphoma; it is more aggressive, occurs later after transplant, and is rarely responsive to a reduction in immunosuppression (7,8).

It is well known that primary central nervous system posttransplant lymphoproliferative disorders behave more aggressively than those involving other organ systems (9). Differentiating T-cell from B-cell posttransplant lymphoproliferative disorder is essential. The T-cell posttransplant lymphoproliferative disorder develops much later after transplant than the B-cell type, and its prognosis is poorer (9). In this case report, the perivascular monomorphic mononuclear cells expressed MS4A1 (CD20) but not CD247 (CD3) or NCAM1 (CD56); therefore, monomorphic B-cell lymphoma was confirmed by pathologic and immunohistochemical studies. Our patient was seropositive for Epstein-Barr virus at the time of lymphoma diagnosis, and tacrolimus had been used as an immunosuppressive drug, which may have increased the risk of posttransplant lymphoproliferative disorder. Although there are several reports of posttransplant lymphoproliferative disorder in the literature (10-12), we report this case because the brain is a rare site for posttransplant lymphoproliferative disorder. Quantitative monitoring of Epstein-Barr virus viral load is recommended for early detection of posttransplant lymphoproliferative disorder in high-risk recipients; if detected in its early phase, this may be a curable disease.

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