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CASE REPORT

Epstein–Barr virus-positive post-transplant lymphoproliferative disorder of the central nervous system, after renal transplantation with a discrepancy in viral load between peripheral blood and cerebrospinal fluid

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Summary

A 43-year-old female developed an Epstein–Barr virus (EBV)-positive post-transplant lymphoproliferative disorder (PTLD) in the central nervous system (CNS), 14 years after renal transplantation. One year prior to presentation, the patients' treatment regimen was altered from cyclosporine, azathioprine, and prednisone to mycophenolate mofetil and prednisone. Magnetic resonance imaging of the brain revealed lesions suspect for malignant lymphoma. The EBV real-time polymerase chain reaction (PCR) on peripheral blood was negative, but highly positive on cerebrospinal fluid. EBV-positive PTLD was confirmed using histological analysis of cerebral biopsies. Despite tapering of immune suppressive medication and treatment with rituximab and chemotherapy, the patient deceased 50 days after presentation. This case illustrates that vigilance is required when presented with a negative EBV PCR result on peripheral blood when PTLD of the CNS is suspected. This late presentation suggests a relation to the switch in immunosuppressive regimen 1 year earlier.

Introduction

Post-transplantation lymphoproliferative disorder (PTLD) is known for extreme heterogeneity in presentation ranging from a self-limiting infectious mononucleosis like illness to an aggressive widely disseminated lymphoma. The incidence of PTLD is highest first year post-transplantation, especially in Epstein–Barr virus (EBV) seronegative patients [1]. The overall incidence after renal transplantation is 1–2.3% [1].

PTLD originates from B-lymphocytes in the vast majority of cases (approximately 85–90%) and is usually positive for EBV (60–80%) [1]. Early detection of PTLD is of great importance to prevent the development of aggressive lymphoma. As EBV-related PTLD is often accompanied by an increase in EBV load in the blood, measurement of EBV DNA using polymerase chain reaction (PCR) in the peripheral blood provides a screening test for PTLD [1]. The case report presented herein, however, illustrates that the diagnosis of PTLD may not always be straightforward.

Case report

A 43-year-old patient suffering from fatigue and low grade fever, presented to our hospital. She had undergone kidney transplantation from a deceased donor 14 years prior because of glomerulosclerosis secondary to urinary reflux. Both the recipient and donor had positive serology for EBV infection. The post surgery period was complicated by a Banff borderline interstitial rejection with good

response to corticosteroids. She had been discharged with an immunosuppressive regimen consisting of prednisone, azathioprine (AZA), and ciclosporine (CSA). Her physical condition and creatinine clearance has been excellent ever since. One year before the current presentation, i.e., 13 years after transplantation, CSA was tapered because of gingival hyperplasia, whereas AZA was replaced with mycophenolate mofetil (MMF) 1000 mg b.i.d.

At presentation, she complained about progressive fatigue and anorexia over the past several months. She appeared dehydrated, her blood pressure was 110/80 mmHg, heart rate 104/min, and temperature 38.1 °C. On general neurologic examination, there were no abnormalities; a maximum Glasgow coma score (GCS), no meningismus, motor or sensibility problems. Additional physical examination proved unremarkable with no lymphadenopathy noted. Peripheral blood studies disclosed a leukocyte count of 7.8×10^9/l [normal (N) 4.0–10.0×10^9/l], C-reactive peptide 0.1 mg/dl (*N* <1 mg/dl), stable serum creatinine 1.04 mg/dl (*N* 0.5–1.0 mg/dl). A plethora of routine laboratory analyses, radiologic procedures, cultures, and serologic tests revealed no abnormalities. However, a PCR analysis of a throat specimen proved positive for herpes simplex, and treatment was started with acyclovir 600 mg t.i.d. PCR on additional specimens, including an EBV real-time PCR of the peripheral blood were negative.

On the fourth day postadmission, she developed progressive amnesia and bradyphrenia. The MMF, of which the dose had been reduced during admission, was stopped, and prednisone increased to 20 mg q.d.

Magnetic resonance imaging (MRI) of the brain showed several pathologic lesions of the periventricular space with rim enhancement, which was highly suspicious for lymphoma (Fig. 1a–c). Cerebrospinal fluid (CSF) appeared clear, glucose was 32.4 mg/dl (*N* 39.5–70.2 mg/dl), proteins were 211×10^6 mg/dl (*N* 20–50 mg/dl), and leukocytes were 52×10^6/l (*N* $<5 \times 10^6$/l). Multiple serologic tests and PCR on the CSF, in particular, for herpes simplex virus, were negative. Therefore, other than the herpes simplex infection of the throat, no other opportunistic peripheral or cerebral infection was diagnosed. However, EBV real-time PCR of the CSF was positive with a high number of 1.66×10^6 copies/ml at day 7 after admission. A repeated EBV real-time PCR of the peripheral blood on the same day remained negative. Microscopy of the brain biopsy revealed lymphoid infiltrates with blast cells, which stained positive for CD20 and CD79a using immunohistochemistry. EBV encoded RNA staining was positive too.

An EBV-positive PTLD of the CNS was diagnosed and treatment was started with rituximab, methylprednisone, methotrexate, tenoposide, and carmustine. Despite intensive treatment for 30 days, there was no clinical improvement or evidence of lesion resolution (via MRI observation) was noted. The patient deceased 50 days after admission.

Discussion

EBV infection is a risk factor for developing PTLD and 60–80% of PTLD is positive for EBV infection. The pro-

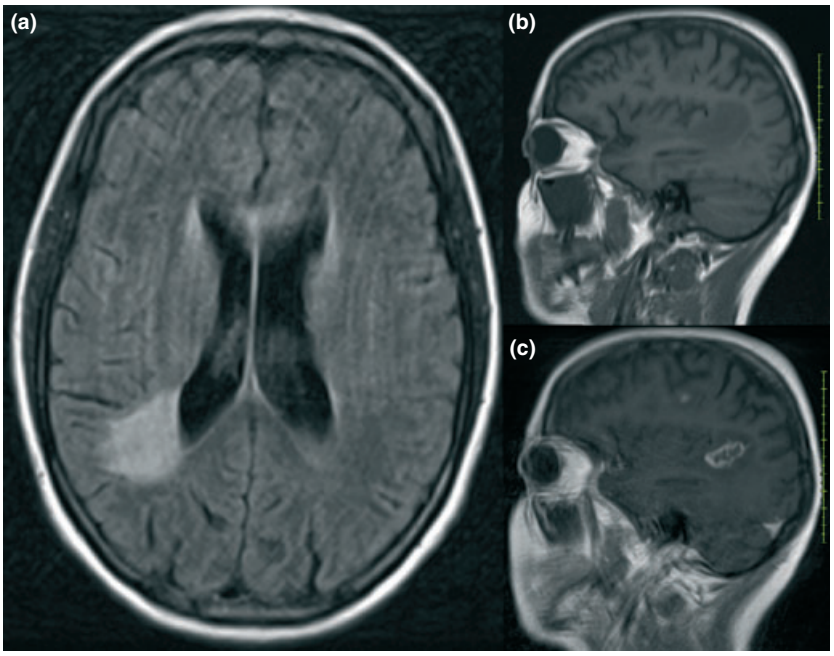

Figure 1 Magnetic resonance imaging of the brain. (a) T2 weighed images without contrast, axial view, showing periventricular lesions. (b) T1 weighed images without contrast, coronal view, showing edema. (c) T2 weighed images with gadolinium contrast, coronal view, showing rim enhancement.

Table 1. Characteristics of patients with isolated EBV-positive PTLD located solely in CNS with negative PCR of peripheral blood.

					PCR EBV	
Case report	Age at Tx (years)	Transplanted organ	Time from Tx	Medication	PB	CSF
This patient	29	Kidney	14 years	MMF, prednisone	–	+
[10]	27	Kidney	13 years	CsA	–	?
[11]	38	HSCT	6.5 months	Tacrolimus, prednisone	–	+
[12]	49	HSCT	6 months	MMF, prednisone	–	+
[13]	29	HSCT	6 months	MMF, prednisone	–	+
[14]	3	Cord blood	12 months	??	–	+
Two patients	4	HSCT	6 weeks	Alemtuzumab	–	+

Tx, transplantation; PB, peripheral blood; MMF, mycophenolate; HSCT, haematopoietic stem cell transplantation; CSF, cerebrospinal fluid.

vision of immunosuppressive therapy prevents cytotoxic T-lymphocytes to control proliferation of EBV-infected B-lymphocytes ultimately leading to transformation into PTLD [2]. Hence, in addition to EBV infection, the burden of immunosuppressive therapy is the second most important risk factor for PTLD [1]. The mainstay of treatment is therefore reduction of immune suppression, in conjunction with rituximab (a CD20 monoclonal antibody) as monotherapy or in combination with chemotherapy, surgery or radiation therapy [2].

Several studies have shown that EBV load is elevated in patients with EBV-positive PTLD compared with post-transplant patients without PTLD [3–8]. The sensitivity to diagnose PTLD with elevated EBV load is estimated at 92–100% for different solid organ transplantations and haematopoietic stem cell transplantation (HSCT) [3–8]. It is generally advised to use EBV load in plasma to assess the risk of EBV-positive PTLD after transplantation, especially in the first year and in EBV-seronegative patients [9].

In the presented patient with a cerebral EBV-positive PTLD, an EBV infection was suspected on initial presentation. However, the viral load tested using real-time PCR on plasma was repeatedly below the detection threshold of 50 copies/ml, whereas the EBV real-time PCR on the CSF was highly positive. This case report underscores that EBV-positive PTLD limited to the CNS is not necessarily detectable using PCR for EBV on peripheral blood.

Five previous case reports have described a negative EBV PCR of the peripheral blood in the presence of an EBV-positive PTLD isolated to the CNS [10–14]. See Table 1. In all cases, the EBV PCR was negative on samples from the peripheral blood. In case 2, liquor puncture was not performed because of thrombocytopenia. All other cases had a positive EBV PCR of the CSF, similar as in our case. It remains unclear whether this phenomenon is common in PTLD that is limited to the CNS. In the presence of an isolated EBV-positive PTLD of the CNS, both positive EBV PCR and both negative EBV PCR of the peripheral blood and CSF are reported as well [15,16].

Furthermore, patients with human immunodeficiency virus (HIV) and primary central nervous system lymphoma (PCNSL) often have a discrepancy between EBV load in the peripheral blood and CSF [17]. The cause of this discrepancy in patients with HIV and PCNSL and patients with PTLD of the CNS remains unknown. However, EBV testing in the peripheral blood might not be adequate when PCNSL in HIV or PTLD of the CNS is suspected and therefore EBV PCR on CSF should be performed early in the disease course.

The average time to develop PTLD isolated to the CNS differed in retrospective studies ranging from 12.6 months to 4.4 years [18,19]. The patient in this case developed a PTLD as late as 14 years after transplantation. Therefore, the alteration of the drug regimen is of particular interest considering the presentation of a PTLD soon thereafter, providing some basis that the alteration may have been a trigger event precipitating genesis of a PTLD.

In a retrospective study examining patients who developed a cerebral PTLD that developed more than 3 years after kidney transplantation, it was revealed 6 out of 10 patients had experienced a regimen change from AZA to MMF shortly before PTLD appeared [20]. Another case report presents four patients developing lymphoproliferative disorder of the CNS after the use of MMF alone for another indication than transplantation [21]. In summary, although the sample size of the aforementioned studies are obviously too small to draw conclusions, it can be speculated that a switch from CSA and AZA to MMF might have been the trigger for developing a PTLD so late after transplantation.

Conclusion

This case report demonstrates that the diagnosis of PTLD cannot solely be excluded by negative EBV-PCR on peripheral blood. Therefore, when a transplantation patient has persisting nonspecific or neurological symptoms, especially after switching immune suppressive medication, one should rule out a cerebral manifestation of a

PTLD by examination of CSF. Finally, PTLD should be suspected even 14 years after renal transplantation.

Authorship

MNB: wrote the paper. AZ: revised the paper, performed additional serologic tests. GDL: revised the paper. JSS: gathered additional information about the case in clinical file in University Medical Center Groningen, revised the paper. PAMV: treated the patient, organized the writing of the paper, revised the paper.

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