

Late Primary B Cell Cerebral Lymphoma After Kidney Transplant: A Case Report and Literature Review

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Abstract: Background: Primary central nervous system post-transplant lymphoproliferative disorder (PCNS-PTLD) is a serious and uncommon complication which can be developed months or years after a Kidney transplant. Immunosuppressive agents administered before and after transplantation to minimize the chances of allograft rejection has proved to be a double-edged sword that puts the host at risk of infectious, neoplastic and vascular diseases, including PCNS-PTLD. The immunosuppressive therapy leads to decreased innate malignant and viral immune surveillance and this has been shown to play a role in lymphoproliferative diseases after transplantation. In most cases, PCNS-PTLD is Epstein-Barr virus related. Case Description: A 60-year-old female with history of kidney transplant presented to the emergency room with history of low fever, dizziness nausea and vomiting for 1 month. MRI and CT scans showed a mass cerebellar lesion and a biopsy revealed Primary central nervous system post-transplant lymphoproliferative disorder (PCNS-PTLD). Conclusion: This case highlights the need for a careful long-term follow up of patients with kidney transplant. PCNS-PTLD represents a continuing long-term risk after transplantation, although less common. This case report supports observational data that suggests that peripheral blood screening for EBV DNA does not seem helpful for identification of PCNS-PTLD. Suspicion of PCNS PTLTLD should be considered when patients with long-term history of kidney transplant present neurological complaints.

Keywords: Central Nervous System, Primary B Cell Lymphoma, Transplantation, Kidney

1. Introduction

Primary central nervous system post-transplant lymphoproliferative disorder (PCNS-PTLD) is a serious and uncommon complication which can be developed months or years after Kidney transplant [3, 13, 15, 18]. Immunosuppressive agents are administered before and after transplantation to minimize the chances of allograft rejection. Nevertheless, immunosuppressive therapy is a double-edged sword that puts the host at risk of infectious, neoplastic and vascular diseases, including (post-transplant lymphoproliferative disorder) PTLTLD [2]. Immunosuppressive therapy leads to

decreased innate malignant and viral immune surveillance which has been shown to play a role in lymphoproliferative diseases after transplantation [1, 6, 11]. In renal transplant recipients, a regimen containing calcineurin inhibitors (CNI), such as tacrolimus or mycophenolic acid (MPA) such as mycophenolate mofetil and corticosteroids are considered the standard of care. Mycophenolic acid (MPA) irrespective of duration of use has high toxicity profile and have been associated with a higher incidence of lymphoproliferative disorder of the CNS. Neurological symptoms improvement after withdrawal after a relatively short period of 8 months of use has been reported [20, 27]. Calcineurin inhibitors increase production of growth factor TGFβ-1 and its involvement in

carcinogenesis is evidenced in biologically aggressive tumors which have shown to contain significant TGF β -1 than more highly differentiated tumors. TGF β -1 acts on the host to suppress antitumor immune responses, enhance extracellular matrix production and augment angiogenesis. Recent data have demonstrated anti-apoptotic and proliferation-promoting effects of corticosteroids in carcinoma cells from a wide variety of tumors in addition corticosteroids enhance tumor cell resistance to apoptosis in solid tumors [11].

In most cases, PTLD is Epstein–Barr virus (EBV) related, with immunosuppression-induced deficient EBV-specific cellular immune response being the underlying pathogenic mechanism leading to uncontrolled growth and proliferation of EBV-infected B cells. In early-onset of PCNS PTLD two distinct stages are recognized in EBV infection. The lytic phase being the first is characterized by active viral replication and the expression of all EBV proteins, which may lead to cell death and release of virions. The second is the latency phase during which B cells are infected via their CD21 receptor and persist in the cell without lysis. The underlying molecular pathogenesis is based on an uncontrolled proliferation of EBV-infected B cells after immunosuppressive therapy. Pathogenesis of the remaining EBV negative, posttransplant lymphoproliferative disorder which arise in most cases more than 1 year following transplant is less clear. Possible explanations include the involvement of other infectious agents or loss of EBV during evolution lymphoproliferative disease ('hit and run' hypothesis). Early PTLD is usually EBV positive, late PTLD is more often EBV negative [6, 15, 16, 24, 30].

A study showed that EBV DNA in both blood and CSF was not detected during the time when CNS PTLD was diagnosed in a renal transplanted Patients who was previously treated for EBV positive diffuse large B-cell lymphoma of the mediastinum, neck, right and inguinal regions [30].

A few case reports have strongly linked the development of isolated CNS PTLD to the use of Mycophenolate Mofetil immunosuppressor because of its toxicity profile [13, 20, 30]. This study seeks to highlight the need for close follow of patients who have been previously treated with Immunosuppressive drugs especially Mycophenolate Mofetil.

Besides the EBV status of the host, human cytomegalovirus (HCMV) and hepatitis C infection has been reported to increase the risk of PTLD through specific cytokines. Emerging evidence show that the progression of some tumors may be enhanced by oncomodulatory signals produced by regulatory proteins encoded by human CMV and hepatitis C [17, 23].

Radiological features of PCNS-PTLD are frequently multicentric lesions. Other lesions of the immunosuppressed brain are single thin capsule (abscess), incomplete and diffuse lesions (demyelination). CNS PTLD in the cerebellum is very rare. An estimated 81% of CNS PTLD affect cerebral hemisphere (cortex/white matter, basal ganglia, corpus callosum), 15% brainstem, 4% cerebellum [2, 8, 18].

Only isolated cases and very small series of PCNS-PTLD have been reported. Till today evidence-based treatment protocols are lacking and there is still no consensus regarding

therapeutic regimens. Several modalities, including surgery, radiation and chemotherapy are being used. The prevailing and most effective reported therapy is high-dose intravenous methotrexate when kidney function permits. Therapy with high doses of methotrexate given intravenously improves penetration into the CNS, leading to sustained and durable tumor responses and improved neurologic outcomes [19, 25].

2. Case Description

A 60-year-old female was presented from the emergency of a local hospital with history of low fever (36.8 - 37.7), dizziness nausea and vomiting for 1 month. She was treated with an antibiotic (Sulperazone) and experienced improvements in the vomiting and nausea but the dizziness persisted. On physical examination, she was Glasgow 15 with the presence of vertical bilateral nystagmus. Dysmetria was observed with the right-hand whiles Kernig and Babinski were negative. Over the period of 29 years, she had a medical history of membranous nephropathy and in the year 2000 she had a right kidney transplant. Although she started with tacrolimus, she later switched to Mycophenolate Mofetil (Cellcept) 500mg bid 12/12h as the monotherapy for maintenance of immunosuppression at time of diagnosis. Computed tomography scan of the thorax and abdomen showed no evidence of lymphadenopathy or other organ involvement by lymphoma. Serum EBV-DNA was negative (< 500/ml).

Brain gadolinium-enhanced magnetic resonance imaging (MRI; T1-weighted image). [Figure 1] shows an Abnormal circular hyperintense signal in the right cerebellum. Repeated MRI 11 days later [Figure 2] revealed a fast-growing tumor accompanied by perilesional edema. Patient underwent total tumor resection via right occipital craniotomy with intra operatory biopsy.

2.1. Radiographic Features

MRI [Figure 1] shows an Abnormal circular hyperintense signal measuring 2.72 x 1.73cm in the right cerebellum.

Repeated MRI 11 days later [Figure 2] revealed a fast-growing tumor measuring 3.38 x 2.13 cm, depicting a vast difference between the size of tumor after 11 days accompanied by perilesional edema.

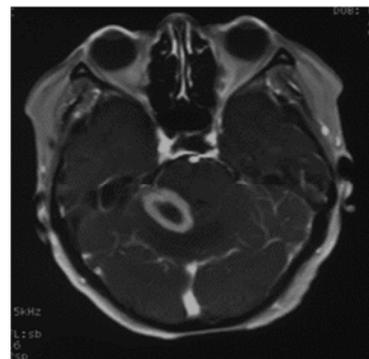


Figure 1. Abnormal circular hyperintense tumor in MRI.

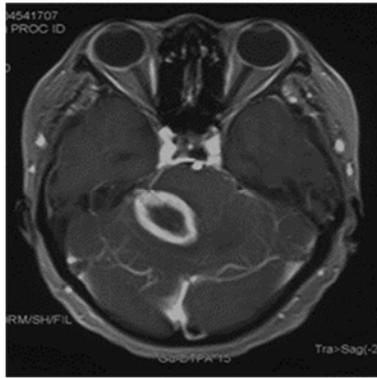


Figure 2. Repeated MRI 11 days later revealed a fast-growing tumor.

2.2. Histopathological Examination of Tissue

The histopathological examination revealed lymphoproliferative Atypical B-cell lesion characterized by large and medium size cells with irregular and hyperchromatic nuclei, with evident nucleoli and mitotic figures observed in Hematoxylin and eosin. Necrosis was observed. Immunohistochemical reaction for Epstein–Barr virus demonstrates diffuse involvement of the atypical B-cell infiltrate with the virus. The neoplastic cells are diffusely and strongly positive for CD79a and P53 (wild type). The Ki-67 proliferation index was high (75%). Nuclear fragmentation and neutrophil diffuse infiltration, supported by immunohistochemical studies, were consistent with a primary diffuse large B-cell lymphoma of the CNS.

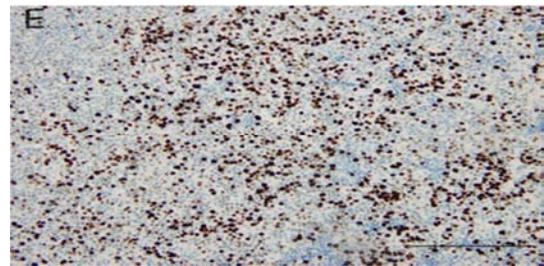
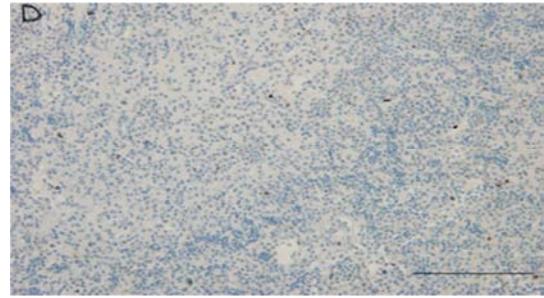
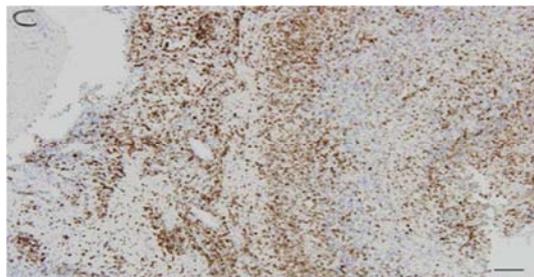
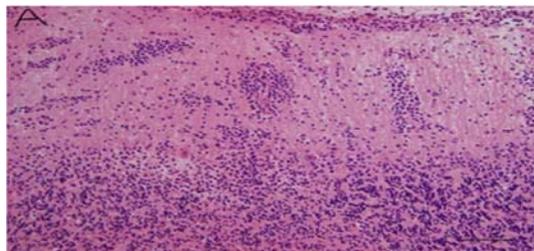


Figure 3. A High-power microscope examination shows A. an atypical B-cell infiltrate with considerable nuclei pleomorphism hyperchromatic nuclei with evident Nucleoli and mitotic figures observed in Hematoxylin and eosin. B. Immunohistochemical reaction for Epstein–Barr virus demonstrates diffuse involvement of the atypical B-cell infiltrate with virus. C. The neoplastic cells are diffusely and strongly positive for CD79a. D. The neoplastic cells are strongly positive for P53 (wild type). E. A large proportion of the neoplastic cells are also positive for Ki-67.

3. Treatment

Patient underwent post operative chemotherapy treatment in the ICU with Rituximab 500mg IV once on 17/05/2019 and a second chemotherapy on 31/05/2019 with Intrathecal injection with Rituximab 25mg, Methotrexate 10mg, Cytarabine 5mg and dexamethasone 5mg. The option of intrathecal administration was opted because of patient's infection condition at the time of the second chemotherapy and a low dosage of Methotrexate was administered due to rise in patient serum creatinine concentration during treatment (1.6-3.6mg/dL). Patient died on admission from pneumonia.

4. Discussion

Mycophenolate mofetil has been reported to be a major contributing factor to isolated PCNS PTLD and PTLD like diseases. In support of this data we present the case of this patient who received a long-term immunosuppressive regimen with mycophenolate mofetil associated with a higher risk of developing PTLD. EBV infection is a persistent contributing factor although not all PCNS PTLD are EBV serum positive. The blood serum test for this patient was negative for EBV but a neoplastic cells test was positive for EBV. In this case an isolated primary diffused large B cell CNS PTLD developed 19 years after transplantation although series of studies have shown that majority of primary diffuse large B cell CNS PTLD develops frequently within 5 years post transplantation (Table 1).

This fact is also supported by a study conducted with 21

patients, out of which only 6 patients were diagnosed after 5 years [25].

Table 1. Summary of Reported Cases of B-Cell Lymphoma Post Kidney Transplantation.

Author	Number of Patients Diagnosed with CNS large B-cell lymphoma	Time between transplantation and Diagnosis (years)	EBV Positive (DNA/RNA or PCR)	Location of lesions	Outcome
Chou AP. et al [3]	1 patient	1.25 years	CNS Tissue: positive	Supratentorial	Alive
Degen D. et al [5]	1 patient	8 years	CNS Tissue: Positive CSF: Positive	Supratentorial	Alive
Gavrilina OA. et al. [7]	1 patient	3 years	CNS Tissue: positive	Infratentorial	Remission of lesion and alive
González F. et al [9]	1 patient	8 years	Not available	Not available	Alive and asymptomatic
Guglielmo N. et al. [10]	1 patient	2 years	CNS Tissue: Negative Blood: Negative	Supratentorial	Alive and asymptomatic
Hansen PB. et al. [12]	1 patient	3 years	CNS Tissue: positive	Supratentorial	Regression of lesion and alive
Haoliang X. et al. [13]	1 patient	0.5 years	CNS Tissue: positive CSF: positive	Supratentorial	Alive and in good condition
Higuchi M. et al. [14]	1 patient	1.2 years	CNS Tissue: Positive	Supratentorial	Alive and in good condition
Snanoudj R. et al. [25]	21 patients	0.3 – 22 years	CNS Tissue: 20 Positive	Supratentorial	Overall Median survival time was 26 months.
Oyama H. et al. [21]	1 patient	Not available	Blood: Positive	Supratentorial	Patient died
Sola-Valls N. et al. [26]	4 patients	2.6	CNS Tissue: positive in 3 patients and data unavailable in 1 patient CSF: positive	Supratentorial 1	3 out of 4 patients died
		7		Supra and	
		2.6 years respectively		infratentorial 3	
Vaglio A. et al. [28]	1 patient	2 years	CNS Tissue: positive CSF: positive	Supratentorial	Alive and asymptomatic
Valavoor SH et al. [29]	1 patient	6 years	CNS Tissue: positive Blood: positive	Supratentorial	Regression of brain lesion
		20		3 patients had	
		13		Supratentorial	
Velvet AJJ. et al [30]	4 patients	6	CNS Tissue: positive in 2 patients and unknown for 1 patient. CSF: negative for 2 patients and undone in 2 patients	1 patient had	All died
		2		Supra and	
		years respectively		infratentorial.	
Yaginuma T. et al. [31]	1 patient	5 years	Blood: positive CSF: Positive	Supratentorial	Alive and asymptomatic

5. Conclusion

This case highlights the need for a careful long-term follow up of patients with kidney transplant, although risk associated with PCNS PTLD is less common a favorable toxicity profile of Mycophenolate mofetil can be associated with a higher incidence of PTLD. This case report also supports observational data that suggest that peripheral blood screening for EBV DNA does not seem helpful for identification of PCNS PTLD. Suspicion of PCNS PTLD should be considered when patients with history of kidney transplant present neurological complaints as early diagnosis and treatment is necessary for a better outcome. Despite the fact that PCNS PTLD is recognized as a complication of kidney transplantation, no standard protocols exist for its treatment but high-dose of methotrexate given intravenously can be beneficial when nephrotoxicity does not develop.

Conflict of Interest

Authors do not have any conflict of interest.

Declaration of Patient Consent

Consent was sought for and obtained. Identity of patient is preserved.

Abbreviations

- Primary central nervous system post-transplant lymphoproliferative disorder: PCNS-PTLD
- Epstein–Barr virus: EBV
- Cerebrospinal fluid: CSF
- Central Nervous System: CNS
- Mycophenolate mofetil: MM
- Mycophenolic acid: MPA
- Transforming growth factor beta 1: TGFβ-1
- Human Cytomegalovirus: HCMV
- Calcineurin Inhibitors: CNI
- Deoxyribonucleic acid: DNA
- Ribonucleic acid: RNA
- Polymerase chain reaction: PCR
- Magnetic resonance imaging: MRI
- Computerized Tomography: CT

Hematoxylin and eosin: H&E

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