

# Atypical Primary Central Nervous System Post-Transplant Lymphoproliferative Disorder

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## Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication following kidney transplantation, with Epstein-Barr virus (EBV) infection being a major risk factor. Central nervous system (CNS) involvement occurs in 5%-30% of cases, but primary CNS-PTLD is rare and has a poor prognosis. We report two cases of primary CNS-PTLD in kidney transplant recipients with atypical presentation. The first case involved a 42-year-old female who presented with vertigo 22 years post-transplant. The second case was a 70-year-old male who exhibited abnormal gait 2 years after transplantation. They were initially misdiagnosed, respectively, as vestibular neuritis and stroke. Imaging studies revealed an isolated cerebellar lesion in both cases; diffuse large B-cell lymphoma was unveiled on the biopsies. The first case was EBV-related and its management included immunosuppression reduction, surgical resection, and radiotherapy. Both patients ultimately died from infectious complications. These cases highlight the diagnostic challenges and poor outcomes associated with primary CNS-PTLD, even with treatment. The variable latency periods, atypical focal cerebellar involvement, and differing EBV status underscore the heterogeneity of this rare entity. Further research is needed to establish optimal diagnostic and treatment protocols for primary CNS-PTLD in kidney transplant recipients.

**Keywords:** Epstein-Barr Virus Infections; Kidney Transplantation/adverse effects; Lymphoproliferative Disorders; Post-operative Complications

## INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a well-recognized complication following kidney transplantation (KT).<sup>1,2</sup> Compared to the general population, KT recipients (KTR) have an eightfold higher lifetime risk of developing a lymphoproliferative disorder.<sup>2</sup> The cumulative incidence in the first 10 years post-transplantation reaches 1%-2% in adults and 3% in children.<sup>1</sup> Incidence appears to be decreasing in recent years, exhibiting a bimodal distribution, with a peak in the first year and another after five years post-KT.<sup>1,2</sup> Risk factors include the recipient's age, immunosuppressive state, and Epstein-Barr virus (EBV) primary infection/reactivation.<sup>1,2</sup> Most PTLD is EBV-related, particularly in the early post-KT period, and a donor/recipient mismatch (i.e. EBV-positive donors with EBV-negative recipients) is a major risk factor.<sup>1,2</sup>

Extranodal involvement is common and central nervous system (CNS) disease occurs in 5%-30% of cases.<sup>3,4</sup> However, primary CNS-PTLD is a rare entity, with a poorer prognosis than systemic PTLD.<sup>3,4</sup> Nonspecific symptoms

render the definitive diagnosis challenging, with a wide range of potential hypotheses.<sup>4,5</sup> Due to its low incidence, treatment recommendations in this setting remain poorly defined.<sup>4</sup>

Herein, we report two cases of primary CNS-PTLD in KTR with atypical presentation, and include a literature review on risk factors and management, emphasizing the high clinical suspicion needed for diagnosis.

## CASE REPORTS

### Case 1

A 42-year-old female with end-stage kidney disease (ESKD) due to primary focal segmental glomerulosclerosis (FSGS) underwent deceased-donor KT at the age of 20. Prior to KT, the patient had not received immunosuppressive therapy for FSGS. Induction therapy included basiliximab, followed by triple therapy with cyclosporine, mycophenolate mofetil (MMF), and prednisolone. The patient was EBV-seropositive before KT. During the 22-year

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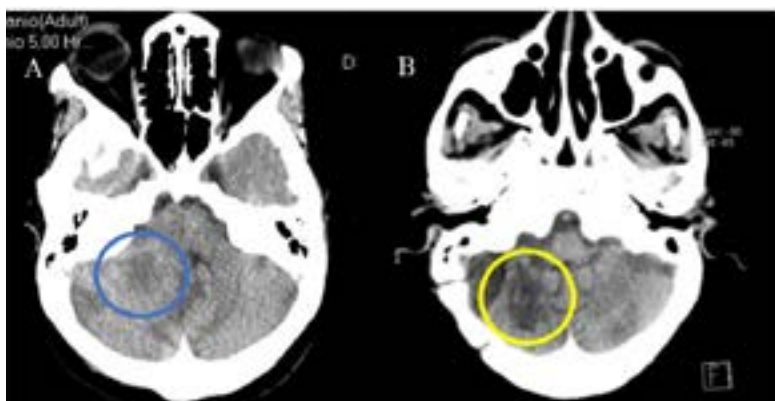
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post-KT follow-up, no acute rejection or FSGS relapse occurred. Cyclosporine was replaced with everolimus 12 years after KT due to biopsy-proven calcineurin inhibitor nephrotoxicity.

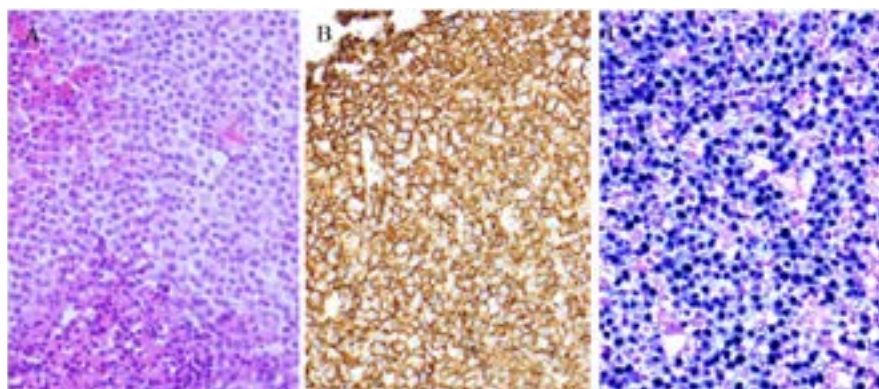
Twenty-two years after KT, the patient presented with a seven-day history of vertigo. Chronic allograft dysfunction was present (serum creatinine of 3 mg/dL), and immunosuppressive therapy consisted of everolimus (with adequate plasma trough levels, i.e. 5-7 ng/mL), MMF (250 mg twice daily), and prednisolone (5 mg/day). Initial evaluation by the Otolaryngology team revealed a positive left "head impulse test", suggesting left vestibular neuritis. Thrice-daily betahistine and 1 mg/kg/day prednisolone were prescribed, followed by a three-week steroid tapering protocol. Symptom relief was achieved until the last week of steroid tapering. Relapse of vertigo prompted imaging investigation. Cranial computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed an isolated lesion in the right cerebellar hemisphere, with perilesional edema, suggestive of a neoplasm (Fig. 1). Full-body CT scan and breast imaging were negative

for neoplastic disease. Dexamethasone was initiated for perilesional edema control, and everolimus was switched to cyclosporine to prevent wound healing impairment. Surgical resection was performed one month after initial presentation. Histopathological analysis (Fig. 2) was consistent with diffuse large B-cell lymphoma (DLBCL), expressing EBV-encoded RNA (EBER). The patient was positive for IgG anti-EBV, negative for IgM anti-EBV, and plasma EBV DNA was absent. Postoperative complications included *Pseudomonas aeruginosa*- and *Staphylococcus epidermidis*-related meningitis treated with meropenem-vancomycin for three weeks. Everolimus was resumed, MMF was discontinued, and adjuvant radiotherapy was administered for two months. Given the patient's frailty and high risk of subsequent infectious complications, neither rituximab nor chemotherapy were administered. Despite clinical improvement, localized relapse was identified four months post-surgery (Fig. 1). Five months after surgery, the patient was admitted to the hospital due to acute pancreatitis complicated by fatal septic shock.



**Figure 1.** Right cerebellar lesion from Case 1, in cranial CT scan.

A) Cranial CT scan (axial view) showing a hypodense lesion in the right cerebellar hemisphere (blue circle); B) Cranial CT scan (axial view) showing the relapsed lesion in the right cerebellar hemisphere four months after surgery (yellow circle).



**Figure 2.** Post-resection histopathology analysis of cerebellar lesion from Case 1.

A) Cerebellar tissue infiltration by diffuse large B-cell lymphoma (H&E; X 400); B) Immunohistochemistry analysis with CD20-positive tumor cells (X 400); C) Immunohistochemistry analysis with EBER-positive tumor cells (X 400).

## Case 2

A 70-year-old male with ESKD due to autosomal dominant polycystic kidney disease was submitted to deceased-donor KT at the age of 68. Polyclonal rabbit anti-thymocyte globulin (rATG) was used as induction immunosuppressive therapy (cumulative dose of 5 mg/kg), followed by a tacrolimus-MMF-prednisolone regimen. The patient was EBV-seropositive before KT. During the two-year post-KT period, diabetes mellitus and BK polyomavirus viremia were identified. No acute rejection was reported. MMF was replaced with everolimus one year after KT, due to persistent BK polyomavirus viremia.

Two years after KT, the patient presented with a five-day history of abnormal gait. Immunosuppressive therapy included tacrolimus (with adequate plasma trough levels, i.e. 2-5 ng/mL), everolimus (with adequate plasma trough levels, i.e. 5-7 ng/mL), and prednisolone (5 mg/day). Physical examination revealed nystagmus and left hemiataxia. Cranial CT scan demonstrated left cerebellar edema, but angiography was unremarkable for occlusive or malformative lesions.

Vertebrobasilar stroke was presumed, prompting hospitalization and antiplatelet therapy initiation. Cardiovascular studies, including 24-hour Holter, transthoracic echocardiography, and carotid and vertebral arteries Doppler ultrasound, were unremarkable. MRI showed a minor left cerebellar lesion, posing difficulties in its characterization and warranting subsequent reassessment. Two months post-discharge, the patient showed no clinical improvement and MRI revealed a growing lesion at the same site, suggestive of a neoplasm (Fig. 3). Cerebrospinal fluid (CSF) analysis, following lumbar puncture, was negative for malignancy or infection. Transcranial biopsy was performed four months after the initial presentation, complicated by a mild left cerebellar hematoma (Fig. 3). Histopathological analysis was consistent with EBER-negative DLBCL (Fig. 4). The patient was positive for IgG anti-EBV, negative for IgM anti-EBV, and no plasma EBV DNA was detected. Full-body CT scan was negative for extracranial involvement. Hospitalization was complicated by a *Klebsiella pneumoniae*-related pyelonephritis associated with septic shock and death 15 days after the procedure.

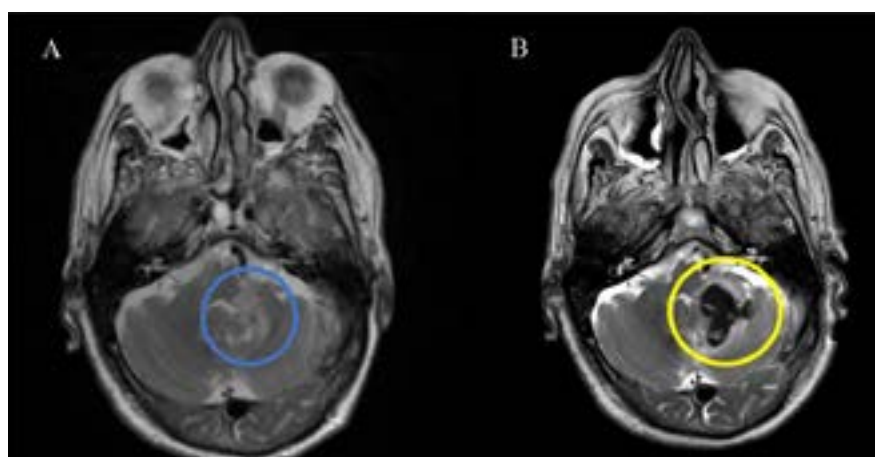


Figure 3. Left cerebellar lesion from Case 2, pre- and post-biopsy.

A) Cranial MRI (axial view) showing a lesion in the left cerebellar hemisphere with T2 hyperintense signal (blue circle); B) Cranial MRI (axial view) showing a post-biopsy left cerebellar hematoma with T2 hypointense signal (yellow circle).

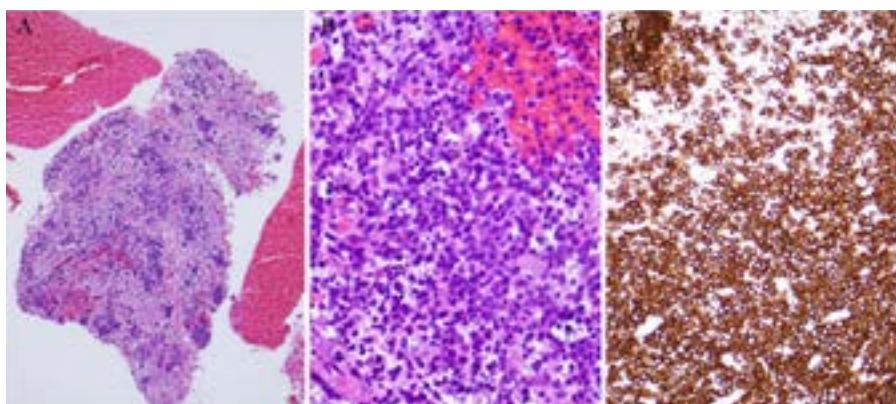


Figure 4. Post-biopsy histopathology analysis of cerebellar lesion from Case 2.

A) Cerebellar tissue infiltration by diffuse large B-cell lymphoma (H&E; X 100); B) Cerebellar tissue infiltration by diffuse large B-cell lymphoma (H&E; X 400); C) Immunohistochemistry analysis with CD20-positive tumor cells (X 400).

## DISCUSSION

Primary CNS-PTLD is a rare subset of PTLD and usually consists of monomorphic DLBCL, as seen in the aforementioned cases.<sup>3,4,6</sup> However, the atypical features observed and the significant differences in diagnostic techniques and management warrant discussion. Firstly, we report a middle-aged female and an elderly male KTR. While systemic PTLD incidence is higher in young and old KTR (aged  $\leq 17$  and  $\geq 65$  years, respectively), primary CNS-PTLD shows no significant age-related incidence variations.<sup>3</sup> Unlike systemic PTLD, primary CNS-PTLD does not follow a bimodal peak distribution in the time elapsed between KT and diagnosis. It is generally identified four to five years after transplantation, with the greatest incidence in the first 1.5 years.<sup>3,4</sup> In a large case series of 84 patients with primary CNS-PTLD, one-third were diagnosed  $>10$  years post-transplantation.<sup>7</sup> Case 2 followed the expected pattern, whereas the latency period was exceptionally long in Case 1 (22 years).

EBV primary infection/reactivation is a major risk factor, particularly for early-onset PTLD.<sup>1,2</sup> Similar to systemic PTLD, pre-transplant EBV-seronegative patients are at increased risk, which was not observed in any of our cases.<sup>3</sup> EBV-positive tumor cells are present in  $>90\%$  of primary CNS-PTLD.<sup>3</sup> Only the patient from Case 1 presented with EBV-related DLBCL, despite the extended latency period and the absence of an active or recent EBV infection. The cumulative immunosuppressive burden during the 22-year post-transplant period may have been an important risk factor. Drug-specific risk remains debatable as previous studies have yielded conflicting results.<sup>2,3</sup> Induction therapy might play a role in early-onset PTLD, whereas late-onset disease is likely associated with cumulative immunosuppression.<sup>8</sup> Studies from the early 2000s reported a higher incidence of PTLD with rATG-based induction therapy.<sup>2,9</sup> Nonetheless, rATG dosing has decreased over time and data regarding current protocols are scarce.<sup>2</sup> A recent study including 6620 KTR with EBV donor/recipient mismatch found a twofold higher risk of PTLD with rATG compared to basiliximab.<sup>10</sup> In primary CNS-PTLD, one study also showed a twofold greater incidence with rATG than with basiliximab as induction therapy.<sup>3</sup> In Case 2, induction therapy with rATG might have contributed to the early onset of PTLD. Moreover, maintenance immunosuppressive therapy in both patients included everolimus, an inhibitor of the mammalian target of rapamycin (mTOR). This class of drugs has previously been thought to have antineoplastic properties, with a decreased risk of PTLD.<sup>2,8</sup> Despite the promising results, other trials showed a higher risk of PTLD with mTOR inhibition in maintenance therapy.<sup>2,8</sup> Of note, neither patient was treated with belatacept, which is a known risk factor, particularly in EBV-seronegative KTR.<sup>2</sup>

Clinical presentation of primary CNS-PTLD is highly variable.<sup>6</sup> Most patients report nonspecific symptoms, such as

headache, dizziness, or nausea.<sup>6</sup> Focal neurologic deficits have also been described.<sup>6</sup> Considering this broad spectrum of manifestations, misdiagnosis is not uncommon. In Case 1, signs of cerebellar dysfunction were initially associated with vestibular neuritis. Despite advancements in neuroimaging, its interpretation is complex in this setting, with a challenging differential diagnosis.<sup>6</sup> CT-scan and MRI are commonly used techniques, but the latter shows higher sensitivity and remains the recommended modality in CNS-PTLD.<sup>6,11</sup> Lesions are most frequently multifocal and supratentorial.<sup>6</sup> Imafuku *et al* reported a focal cerebello-pontine lesion presenting with facial nerve palsy.<sup>12</sup> To our knowledge, these are the first reported KTR with a focal cerebellar primary CNS-PTLD.

Differential diagnosis includes metastases, glial tumors, and abscesses.<sup>6</sup> Metastases tend to be multifocal, whereas glial tumors and abscesses are typically focal.<sup>6</sup> Infectious diseases are particularly relevant in KTR given their susceptibility to opportunistic agents, such as *Toxoplasma gondii*, *Aspergillus*, and *Mycobacterium tuberculosis*.<sup>6</sup> CSF analysis, including microbiological and cytological studies, may be valuable in differentiating these entities. A positive polymerase chain reaction for EBV DNA is highly suggestive of CNS-PTLD, and it may be present even when undetected in peripheral blood.<sup>11</sup> In Case 1, technical limitations precluded the feasibility of a lumbar puncture. CSF analysis in this patient could reveal EBV DNA, especially as the lesion expressed EBV.

Definitive diagnosis relies on histological examination of biopsied tissue.<sup>6</sup> After confirmation, proper staging is mandatory and includes a full-body CT scan or positron emission tomography (PET).<sup>2,8</sup> <sup>18</sup>F-fluorodeoxyglucose PET/CT is a combination of both techniques, with higher sensitivity and discriminatory capability, particularly for extracranial disease.<sup>2,6,11,13</sup> Several guidelines recommend PET/CT for PTLD staging, although larger prospective validation is still needed.<sup>13</sup>

The cornerstone of PTLD treatment is a reduction of immunosuppressive therapy (RIS).<sup>2,8</sup> The initial strategy generally includes reducing calcineurin inhibition (targeting a 50% decrease in serum trough levels) and discontinuing the antimetabolite, although the latter does not seem to increase PTLD risk.<sup>2,8</sup> All nonsteroid agents should be discontinued in critically ill patients with extensive disease.<sup>8</sup> Decisions on the timing and duration of RIS are complex, and several factors must be considered, namely time from KT, history of rejection, and center-specific practices.<sup>14</sup> Graft function monitoring is of utmost importance following RIS.<sup>8</sup> Polymorphic and EBV-related PTLD tend to respond better to RIS.<sup>8,14</sup> Nevertheless, RIS is rarely sufficient and poor results have been observed when used alone in primary CNS-PTLD.<sup>4,8,14</sup> After the PTLD-1 trial, rituximab emerged as the standard of care for CD20-positive PTLD.<sup>2,14</sup> RIS combined with a four-week rituximab regimen is a common first-line approach, followed



by chemoimmunotherapy based on response.<sup>14</sup> Poor CNS penetration has raised concerns about the efficacy of intravenous or subcutaneous rituximab in CNS disease.<sup>3,4</sup> Few studies reported the efficacy and safety of intrathecal rituximab in PTLD with CNS involvement, but it was mostly used in combination with systemic rituximab or chemotherapy.<sup>15</sup> Standard treatment protocols have yet to be established in primary CNS-PTLD. Common regimens also include high-dose steroids or chemotherapy with whole-brain radiotherapy.<sup>5-6</sup> Surgical resection has shown limited efficacy.<sup>6</sup> In Case 1, dexamethasone was initiated, MMF was discontinued, and surgical resection was performed, followed by two-month adjuvant radiotherapy. Despite this effort, the disease relapsed at the same site four months post-surgery.

New opportunities for intervention are under development. Tabelecleucel, an allogeneic EBV-specific T-cell immunotherapy, received approval in Europe in 2022 for relapsed/refractory EBV-related PTLD.<sup>14</sup> Phase 3 ALLELE study reported an overall response rate of 51%, including 70% in CNS-PTLD.<sup>16</sup> Chimeric antigen receptor T-cell also documented promising results in several case reports, although immune-related adverse events remain a concern.<sup>14</sup>

Primary CNS-PTLD has a worse prognosis than systemic PTLD.<sup>3</sup> Median survival varies between 13 and 47 months, with a five-year survival rate of 30% compared to 50%-60% in systemic PTLD.<sup>3,6</sup> Mortality may be attributed to CNS involvement or treatment-related toxicity.<sup>3</sup> Perioperative complications, namely infectious diseases, can have a significant impact on morbidity and mortality.<sup>6</sup> In both

cases, infectious complications followed CNS biopsy: a meningitis and a pyelonephritis. A delay in diagnosis was also reported, potentially affecting survival.

## CONCLUSION

Primary CNS-PTLD is a serious complication in KTR with high mortality rates. Due to its rarity and nonspecific presentation, a high level of suspicion is required for diagnosis. Physicians managing KTR should be aware of this risk, particularly in EBV-seronegative patients, as a delayed diagnosis can lead to worse outcomes.

## Learning points

1. Primary CNS-PTLD is a rare subset of PTLD, typically presenting as diffuse large B-cell lymphoma.
2. Unlike systemic PTLD, primary CNS-PTLD does not show a bimodal peak distribution, and is generally diagnosed four to five years after transplantation.
3. Clinical presentation of primary CNS-PTLD is highly variable and nonspecific, making diagnosis challenging. Definitive diagnosis relies on histopathological examination.
4. EBV-positive tumor cells are present in >90% of primary CNS-PTLD cases, but EBV DNA may not always be detectable in peripheral blood or CSF samples.
5. Treatment of primary CNS-PTLD typically involves reduction of immunosuppressive therapy combined with other modalities such as rituximab, chemotherapy, and radiotherapy. However, standard treatment protocols are not well-established, and prognosis remains poor compared to systemic PTLD.

## Awards and Previous Presentations

Poster presentation of one case in “XX Congresso Luso-Brasileiro de Transplantação” (2022).

## Ethical Disclosures

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## Contributorship Statement

**GP:** Designed, acquired the data and drafted the work.

**MC:** Interpreted the biopsies and reviewed the work.

**ACM, LLS, TJC and AW:** Drafted and reviewed the work.

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