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Case Report

Isolated Primary Central Nervous System Lymphoma Renal Transplant Treated with Surgical and Pharmacologic Intervention: A Case Report and Review of Literature

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Abstract

We present a rare variant of Post–Transplant Lymphoproliferative Disorder (PTLD); Primary Central Nervous System (PCNS) lymphoma, in a demographic not consistent with previous reports. A 51-year-old non-Hispanic white female with a history of adult polycystic kidney disease, status-post two renal transplants presented five years after her 2nd transplant with new onset neurological symptoms. Radiography confirmed a single 11 x 10 mm left posterior parietal lobe ring-enhancing mass with surrounding edema and abnormal spectroscopy highly suggestive of malignancy. Histomorphology and immunohistochemical findings were consistent with WHO 2008 classification for Diffuse Large B-Cell Lymphoma (DLBCL). Treatment included surgical resection and high dose methotrexate instead of the recommended initial therapy. Primary central nervous system lymphoma is a rare presentation of post-transplant lymphoproliferative disorder whose clinical attributes are not well known to many clinicians. As the number of successful transplants increases, the likelihood of encountering Primary Central Nervous System Post-Transplant Lymphoproliferative Disorder (PCNS-PTLD) increases. It is important for clinicians to be aware of the current literature, risk factors, variance in presentation, and options for management of this rare disease.

Introduction

Post–Transplant Lymphoproliferative Disorder (PTLD) is a lymphoid proliferation in the setting of immunosuppression, especially in solid organ or allogenic hematopoietic cell transplantation [1]. It is the most common malignancy complicating solid organ transplantation after non-melanoma skin cancer and in situ cervical cancer [2,3]. PTLD usually (>80%) presents in the first year post-transplant with lymphoid proliferation in the allograft tissue, in blood or in adjacent organs [4-6]. However, approximately 5-15% of PTLD present as Primary Central Nervous System Post-Transplant Lymphoproliferative Disorders (PCNS-PTLD) [6,7](Table 1).

Risk Factor	Systemic PTLD, early presentation <1 year	Systemic PTLD, Late presentation, >1 years	PCNS-PTLD	Study Reference
Age at transplantation	<25 yrs, mostly children.	Bimodal <20 years old and >50 years old	Median age of 60 years	Systemic [8-10] PCNS
Ethnicity	Non-hispanic white	Non-hispanic white	Asian/pacific islander = 2x incidence than non-hispanic white	Systemic [4-6] PCNS [11]
Time from transplant	60-80% within 1.5 yrs	30% within 1-5 years. (EBV negative median is 4.5 yrs)	Median= 54 months Typically 4-5 years	Systemic [4-6] PCNS [4,11-13]
EBV status on histology at diagnosis	70-95% positive	38% of late were EBV negative.	>90% positive	Systemic [5] PCNS [14]
Note: PTLD= Post-Transplant Lymphoproliferative Disorder, PCNS= Primary Central Nervous System, EBV= Ebstein-Barr Virus				

Table 1: Epidemiology and Risk PTLD VS PCNS-PTLD.

This rare presentation portends a poorer prognosis, with an estimated three-year survival rate of 32–38% [4,6]. The World Health Organization (WHO) divided PTLD into three general types (Figure 1). PCNS-PTLD histology is most often monomorphic with large B-cell morphology [4,15,16]. Monomorphic PTLD is a monoclonal lymphoid proliferation that meets criteria for one of the B-cell or T/NK cell lymphomas [17]. A combination of Magnetic Resonance Imaging (MRI) and histopathology are the gold standard in diagnosis [18,19].
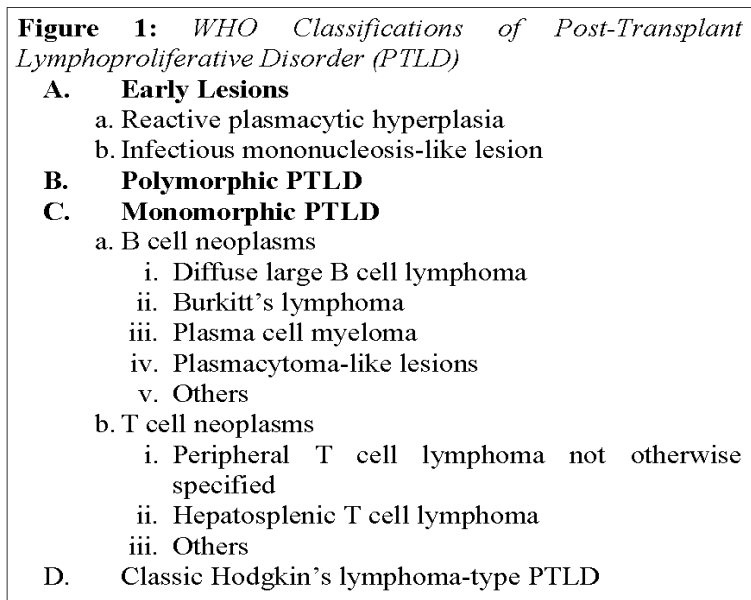
Figure 1: *WHO Classifications of Post-Transplant Lymphoproliferative Disorder (PTLD)*
A. **Early Lesions**
    a. Reactive plasmacytic hyperplasia
    b. Infectious mononucleosis-like lesion
B. **Polymorphic PTLD**
C. **Monomorphic PTLD**
    a. B cell neoplasms
        i. Diffuse large B cell lymphoma
        ii. Burkitt's lymphoma
        iii. Plasma cell myeloma
        iv. Plasmacytoma-like lesions
        v. Others
    b. T cell neoplasms
        i. Peripheral T cell lymphoma not otherwise specified
        ii. Hepatosplenic T cell lymphoma
        iii. Others
D. **Classic Hodgkin's lymphoma-type PTLD**

Figure 1: WHO Classification of Post-Transplant Lymphoproliferative Disorder (PTLD).

As transplantation and immunosuppression advance, the number of successful transplants exponentially increases, and with it the incidence of PCNS-PTLD. However, there are no current standards for screening or treatment of patients with PCNS-PTLD. Therefore, we present here a case report and review of literature to distinguish the differences between systemic and PCNS PTLD, and distill the growing evidence for management.

Case Report

Our patient is a 51-year-old non-Hispanic white female with a history of adult polycystic kidney disease, status-post two renal transplants. She underwent a deceased donor renal transplant in 2005, at which time she was EBV and CMV positive. Immunosuppressive therapy included mycophenolate mofetil 1000

mg bid, cyclosporine (ranging from 200 mg bid to 150 mg bid over 3 years), prednisone tapering (30 mg to 10 mg over 1 year), and antiviral therapy included valgancyclovir (3 months). The transplant failed within a year due to medication non-adherence, and she resumed dialysis until her second transplant in 2014. The recipient and second donor were both CMV and EBV positive. Her initial immunosuppressive therapy included alemtuzumab (monoclonal antibody) induction, tacrolimus 1.5 to 2 mg bid., mycophenolate 720 mg bid., in addition to antiviral valgancyclovir 450 mg. Due to rejection, seven doses of thymoglobin, pulse steroids and eventually daily prednisone 10 mg were prescribed.

Intermittent numbness in the right arm was reported in November 2018. She could not tolerate an MRI due to anxiety. CT brain without contrast revealed a subtle hypo-attenuating focus within the left parietal lobe designated "most likely a small remote infarct" (Figure 2). When neurological symptoms progressed further, sedation assisted brain MRI with contrast revealed a left parietal mass demonstrating extensive enhancement. Radiography confirmed an 11 x 10 mm left posterior parietal lobe ring-enhancing mass with surrounding edema and spectroscopy was highly suggestive of malignancy (Figure 2). Neurosurgery biopsied and resected the tumor.
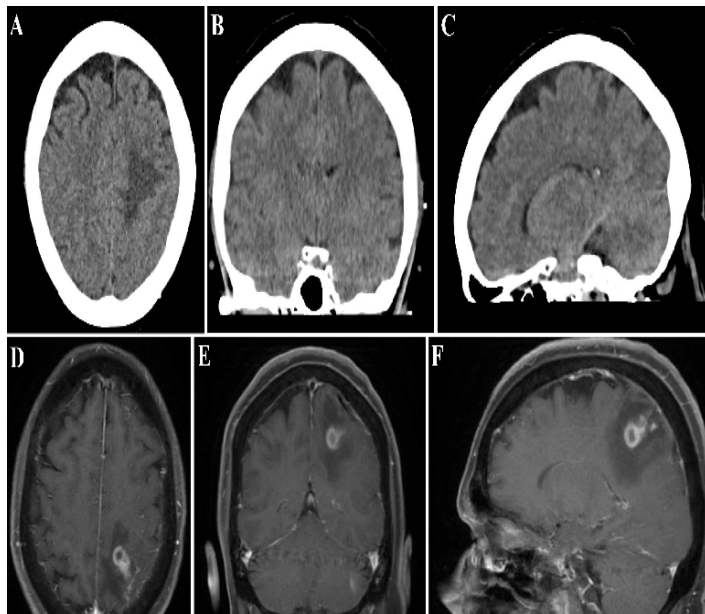

Figure 2: CT without contrast and MRI. A: CT axial **B:** CT coronal **C:** CT sagittal **D:** MRI T1 axial **E:** MR T1 coronal **F:** MRI T1 sagittal. **A-C:** CT without contrast exhibited a subtle hypo-attenuating focus within the left parietal lobe, designated "small remote infarct" (red arrow). This is most visible on the sagittal view C. **D-F:** MRI confirmed a left posterior parietal lobe ring-enhancing mass, measuring 11 x 10 mm, with surrounding edema.

The mass was described as a spherical homogenous lesion measuring 40 x 20 x 10 mm. Histopathological examination of multiple representative sections revealed sheets of large atypical cells and normal appearing lymphocytes (Figure 3). Ancillary immune histochemical staining was performed to profile the tumor (Figure 4). The atypical cells were negative for GFAP. Strong positivity for both CD20 and CD30 confirmed B-cell origin. Immunostains were consistent with large B-cell lymphoma of non-germinal center type; CD10 was negative, while both BCL6 and Mum1 were positive. Scattered T-cells in the background stained positively for CD3. Immunohistochemical analysis revealed a lack of Myc and p53 expression. EBV in situ hybridization was strongly positive in the lymphocytes. B-cell clonality determination by PCR was performed at an outside facility and demonstrated positivity for IgH and IgK gene rearrangement. The final pathologic diagnosis was large B cell CNS lymphoma according to WHO 2008 classifications.
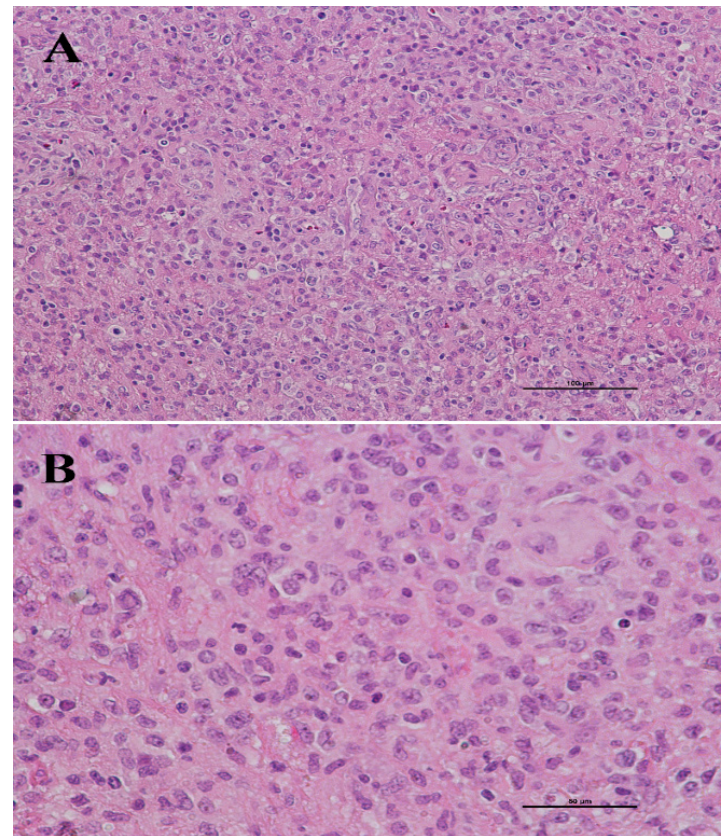

Figure 3: Brain Biopsy A: Tissue section; low power view displaying infiltration of the brain tissue by atypical lymphoid cells (Hematoxylin-eosin stain, original magnification X 200). **B:** Tissue section; higher power view displaying large atypical lymphoid cells to small normal appearing lymphocytes (Hematoxylin-eosin stain, original magnification X 400).
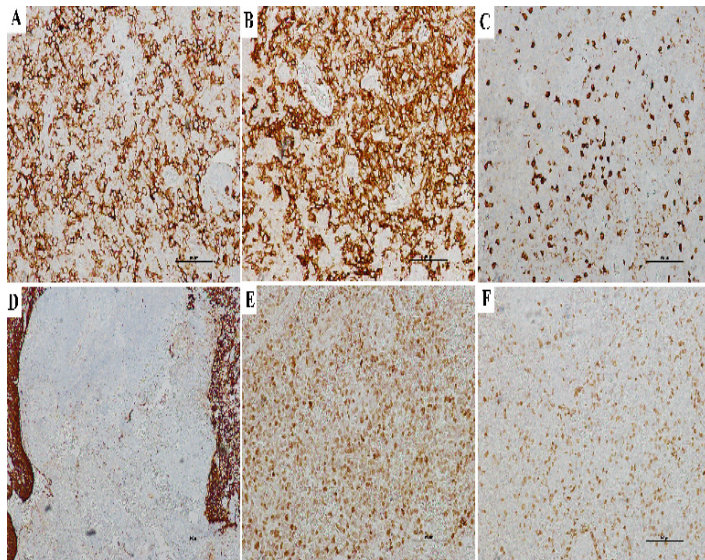
Figure 4: Immunohistochemistry A: CD20 stain of brain tissue biopsy reveals CD20+ B-cell infiltrates. **B:** many of the large cells were also strongly positive for CD30. **C:** CD3 stain suggests increased presence of scattered T-cells in the background. **D:** The atypical cells were negative for GFAP. E, BCL6 staining was positive. F, Mum1 staining was positive. Many cells also stain positive for EBV-encoded RNA (not depicted).

The post-surgical treatment consists of high-dose methotrexate infusion and leucovorin treatments. As anticipated, increased creatinine was reported after methotrexate administration. Her immunosuppressive therapy was switched to an mTOR based regimen.

Discussion

Epidemiology

The incidence of PCNS-PTLD varies with age, organ type transplanted, ethnicity, and type of immunosuppression. This non-Hispanic white woman in her 6th decade of life presented with neurologic symptoms approximately 13 years following her first renal transplant and approximately 4 years after her second renal transplant. The median age of PCNS-PTLD diagnosis is between 48-60 years [2,8] and disease typically presents 4-5 years post-transplant [4,5,12,13]. Both systemic and PCNS PTLD are more common in non-Hispanic white individuals, while PCNS-PTLD has a 2 times higher incidence in Asian/pacific islanders than non-Hispanic white patients [11] (Table 1). Unlike systemic PTLD [9,13,20], PCNS-PTLD is commonly associated with renal transplants [4,15,11] (Table 2).

EBV and CMV

EBV, CMV, and other viruses have an association with the development of PTLD [4-6,21,22]. However, there are inconsistent screening guidelines for early PTLD based on these viruses and there are no guidelines for PCNS-PTLD or late-presenting PTLD. Viral screening was positive for EBV and CMV at her first transplantation. Only the donor of her second renal transplant was positive for EBV and CMV. EBV is able to induce uncontrolled proliferation of B cells, and is theorized to induce PTLD [8,23]. Evens et al. reported 97% of PCNS-PTLD tumors positive for EBV virus [4]. Most cases of systemic PTLD and PCNS-PTLD are related to the presence of EBV in either the recipient or the transplanted organ [4,8,11] (Table 2).

Risk Factor	Systemic PTLD	PCNS-PTLD	Study Reference
De novo CMV infection			
CMV status of recipient at transplant	Seronegativity 2-4x avg risk	No recent data	[4-6]
CMV status of donor	CMV-negative receiving CMV positive organ 4-6x more likely	No recent data	[4-6]
EBV status			
EBV status of recipient at transplant	Seronegativity 10-75x incidence over that of EBV seropositive	Seronegative 2x incidence	[11,21,22]
EBV status of donor	No recent data	No recent data	
Type of transplant treatment			

Calcineurin inhibitors	2x-5x increased risk with prolonged high doses of tacrolimus vs cyclosporine. Cyclosporine increases in higher doses (>6.6mg/kg/day)	Does not significantly increase risk. If added to MMF, reduces the risk association to only 18x fold increased risk.	[10,15,24,25]
MMF without calcineurin inhibitor	Lower risk of PTLD	118x higher odds of PCNS.	[15,24,26,27]
mTOR inhibitors	Sirolimus, 1-2x increased risk	Conflicting data	[24,28]
Polyclonal antibodies: ATG (Antithymocyte globulin)	3-4x increased risk in the 1st year post transplant	2.03x incidence	[11,24,10]
Monoclonal antibodies: OKT3(Anti-CD3 monoclonal antibody)	3-4x increased risk in the 1st year post transplant with high cumulative doses (contested in more recent studies)	1.83x incidence	[11,24,10,29]
IL-2 receptor antibodies	No increased risk	No recent data	[10,24]
Anti-CD52 antibody	No increased risk with alemtuzumab	3.12x aiRR	[8,11,28]
Type of Organ Transplant			
Small bowel	6-18x incidence of kidney	No recent data	[9]
Lung	2-3x incidence of kidney	0.5x incidence of kidney	[9,11]
Multiple organ transplant	1-2x incidence of kidney	2.45x incidence of just 1 kidney transplant	[9-11]
Liver	Same incidence as kidney	0.5x incidence ofkidney	[9,11]
Kidney	1%-3% of all transplants, lowest of all solid organ transplants	58-79% of All PCNS-PTLD	[4,9,11]
Organ involved	More commonly arise in graft itself, GI or extranodal sites.	5%-25% of all PTLD cases are primary CNS, 11.77 % of PTLD following kidney transplant are PCNS	[3,11,15]
Type of lymphoma most associated	Monomorphic PTLD, B-cell	83% monomorphic PTLD, B-cell	[6]
Note: Airr = Adjusted Incidence Ratio, MMF= Mycophenolate Mofetil, PTLD= Post-Transplant Lymphoproliferative Disorder, PCNS= Primary Central Nervous System, EBV= Ebstein-Barr Virus, CMV= Cytomegalovirus, Avg= Average			

Table 2: Risk factors PTLD VS PCNS-PTLD.

However, Mahale, et al. reports a higher incidence of PCNS-PTLD in transplant recipients who are seronegative for EBV and at risk for primary infection following transplant [11]. Some have suggested monitoring for EBV DNA in the peripheral blood in the early transplant period in high risk seronegative patients [30]. Unfortunately, these guidelines fail to account for individuals presenting with late onset PTLD, which is often EBV negative, and miss approximately half of EBV-positive cases with no detectable EBV in the peripheral blood [8,31]. Our PCR results demonstrated positive serum EBV followed by negative serum EBV within two months of each other, further supporting the notion that serum EBV is not a reliable screening method. Screening Cerebrospinal Fluid (CSF) for EBV to monitor for PCNS-PTLD also proved futile by Evens et al, as only 10% of PCNS-PTLD were detectable in CSF [4]. In fact, the presence of EBV DNA in CSF due to PCNS-PTLD was lower than EBV DNA levels in encephalitis or brain abscess [32]. Ancillary testing was positive for EBV on in-situ hybridization and negative for CSF involvement despite having isolated, aggressive PCNS-PTLD. Other viruses, such as human T-cell lymphotropic virus, human herpesvirus 8, CMV, simian virus 40 and hepatitis C have been proposed to increase the incidence of PTLD although they were not observed in this case [6,33].

Clinical Presentation

The clinical presentation of PCNS-PTLD can be remarkably variable, corresponding to the specific region (s) of the brain involved [6,19,34]. Certain lab findings such as anemia, leukopenia, thrombocytopenia, elevated LDH, elevated calcium ion in blood, or hyperuricemia may be useful in narrowing the diagnosis and prognostication [8]. Significant lab values in this case included elevated serum creatinine, worsening thrombocytopenia, low haptoglobin, and elevated LDH.

Diagnostic imaging

In post-transplant patients who fit the epidemiologic profile for development of PCNS-PTLD and have supportive clinical or laboratory findings, prompt imaging with CT and early follow-up MRI should be conducted as these lesions are often aggressive [11]. PCNS-PTLD most frequently presents as multiple ring-enhancing lesions that are typically supratentorial, lobar or paraventricular, and involve subcortical white matter or basal ganglia [4,19]. However, radiography exhibited a larger, single supratentorial ring-enhancing lesion of the peripheral sub cortex inconsistent with the literature.

Histology

Ultimately, a definitive diagnosis of PCNS-PTLD can only be accomplished by histologic assessment to profile the lesion and rule out opportunistic infections that often present with similar imaging findings [19]. Immunohistochemical examination will typically demonstrate EBV positivity, lack of p53 expression, lack of Myc expression, and numerous background T lymphocytes [14] which is consistent with our pathologic findings (Figure 4). Isolated PCNS-PTLD is most frequently a monomorphic B cell lesion (2008 WHO classification) which is typically more aggressive [4,11,15,16].

Immunosuppression

Certain drug therapies may be risk modifying for PCNS-PTLD development based on their mechanism of action and degree of immunosuppression [3]. After her first renal transplant, she received Mycophenolate Mofetil (MMF), cyclosporine, and prednisone as part of her standard immunosuppressive therapy to prevent allograft rejection. MMF has been associated with increased risk of PCNS-PTLD [15], particularly when administered without calcineurin inhibitors (cyclosporine, tacrolimus) [8,15]. Calcineurin inhibitors are protective against PCNS-PTLD, despite an association with increased risk for systemic PTLD [5,9,10,25], (Table 2). These calcineurin inhibitors protect against the increased risk of PCNS-PTLD conferred by mycophenolate mofetil [5].

Following the second renal transplant, she received alemtuzumab induction, mycophenolate mofetil, tacrolimus and several doses of thymoglobulin for rejection. According to Oliver et al. 2017, Alemtuzumab induction is not associated with increased risk of systemic PTLD in kidney transplantation [35]. However, it is associated with increased incidence of PCNS-PTLD [8,11]. The use of thymoglobulin has also been associated with increased incidence of PCNS-PTLD [11]. After surgery the immunosuppressive regimen was switched to mTOR based regimen. While there are conflicting data regarding whether or not mTOR inhibitors impart an increased risk of PCNS-PTLD, sirolimus increases risk of PTLD twofold [24,28].

Management

Owing to the rarity of PCNS-PTLD and its aggressive clinical course, there is little published data regarding treatment. Options commonly proposed include reduction or withdrawal of immunosuppression, whole brain radiotherapy, rituximab and high dose methotrexate [4,8,36-38]. Unlike monomorphic PTLD [39], the recommended initial step in treatment of PCNS-PTLD is reduction of immunotherapy [4]. This must be supplemented by radiation or another pharmaceutical first line therapy [4]. Withdrawal of immunosuppression should be balanced against the risk of transplant rejection. There is one case report by Yaginuma et al. of successful treatment of isolated PCNS-PTLD by whole brain radiotherapy alone [38]. However, other sources suggest radiotherapy may not be as effective on late onset PCNS-PTLD as early systemic PTLD [8]. Some case reports demonstrate complete resolution of PCNS-PTLD after treatment with rituximab, an anti-CD20 antibody [1,13]. Although anti-CD20 antibody has been proven effective against systemic PTLD, it is known to have difficulty passing through the blood-brain barrier [38], making it unlikely to be effective as the sole treatment of PCNS-PTLD. High dose methotrexate has been effective as an isolated therapy for PCNS-PTLD in several cases [23,37,40]. Due to the isolated nature of the brain lesion, surgical excision was considered the best course of action and was followed by administration of high dose methotrexate. Leucovorin was also incorporated into her treatment regimen.

Other treatments described in the literature have demonstrated mixed results, including laboratory treated cytotoxic T-cell lymphocyte infusion with craniotomy, temozolomide, surgical resection and antiviral medication [8,41,42]. Factors such as age, timing of disease onset, laboratory findings and histology may be useful in prognostication. As reported by Caillard, et al. CNS localization is an independent prognostic indicator of poor survival [43]. Age >55 years at diagnosis, late onset PTLD, high LDH and creatinine levels, widespread PTLD, T cell lymphoma and monomorphic histology are also associated with poor prognosis [43]. The most dominant prognostic factor reported by Evens et al. was the lack of response to first line therapy [4]. The clinician should start with reduction of immunotherapy as an initial step in treatment and supplement with radiotherapy and rituximab. When

the response is limited or isolated lesion is excised, one should discontinue that regimen and treat with high dose methotrexate.

Conclusion

PCNS-PTLD is a rare complication of solid organ transplantation after receiving immunosuppressive therapy for several years [1]. Historically this diagnosis has portended a dismal prognosis with an estimated three-year survival rate of 32–38% [4,6]. Therefore, aggressive diagnosis and low threshold for imaging is important, especially in those who fit the epidemiologic and clinical profile. The rarity of this disease has impeded development of guidelines for prevention, screening, or management. Scattered case reports in the literature were enhanced by a large (84 patients) series reported in 2013 by Evens et al. and [1,4]. Over the past decade the number of successful transplants performed has grown, and so has the incidence of PCNS-PTLD, enabling more actionable analysis. This case report contributes case-based evidence to a limited, albeit growing body of literature on PCNS-PTLD and highlights a novel approach in successful treatment incorporating both surgical and pharmacologic intervention. It is important that, as the literature grows, the medical communities update guidelines, identify outliers and pursue trials to better understand the many factors that determine disease progression and prognosis.

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