Review Article

Post-transplantation primary central nervous system lymphoma: A case report and review of the literature

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Abstract

Background: Post-transplantation primary central nervous system lymphoma (PT-PCNSL) is a rare neoplasm that can develop within months to years after transplantation, and imaging often reveals multiple lesions with homogeneous or ring enhancement. The clinical and imaging presentation of PT-PCNSL can often be nonspecific and present a diagnostic challenge.

Case Description: A 56-year-old woman presented to a tertiary university emergency room with altered mental status 15 months after undergoing renal transplantation. On brain MRI, she was found to have three rim-enhancing mass lesions, and biopsy revealed PT-PCNSL.

Conclusion: There has been a steady increase in the number of patients living following organ transplantation in the United States and an increasing likelihood that PT-PCNSL will increasingly be encountered in neurosurgical practice. We present here a case of PT-PCNSL and a brief review of the relevant clinical characteristics, treatment options, and prognosis of PT-PCNSL.

Key Words: Primary central nervous system lymphoma, transplantation

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a type of non-Hodgkin’s lymphoma confined to the brain and spinal cord which represents approximately 3% of all primary intracranial neoplasms.1 The most common form of PCNSL is diffuse large B-cell lymphoma; PCNSL has been associated with immunodeficiencies such as AIDS and iatrogenic immunosuppression. The median age of disease onset for PCNSL is in the fifth decade for immunocompetent patients and the third decade for immunocompromised patients.2,6,18 Post-transplantation primary CNS lymphoma (PT-PCNSL) is a rare primary brain or spinal neoplasm that develops in post-transplantation patients with the tumor confined to the CNS. Given the improved survival following organ transplantation in the United States and the consequent increased likelihood that PT-PCNSL will be encountered in neurosurgical practice, we present here a case report of PT-PCNSL and a review of the relevant literature.

HISTORY

An otherwise healthy female patient initially presented
with hypertension at the age of 53 and was found to have bilaterally atrophic kidneys. She was later diagnosed with end-stage renal disease of unknown etiology and considered a good candidate for renal transplantation. She subsequently underwent living-related renal transplantation in April 2009 at the age of 56. She underwent induction immunosuppression with alemtuzumab, methylprednisolone, and intravenous immunoglobulin. She tolerated the transplantation without complications and postoperatively was placed on mycophenolate 500 mg twice a day, tacrolimus 2 mg every morning and 1 mg every night, and prednisone for the maintenance of immunosuppression.

She was well until she presented to the emergency room in July 2010 with 5 days of headaches, 2 days of lethargy, and 1 day of nausea and vomiting. On physical examination, she was found to be slightly somnolent but otherwise neurologically intact. A noncontrast head CT demonstrated left frontal hypodensities with 10 mm of a left-to-right shift. An MRI with contrast demonstrated three rim-enhancing lesions in the left frontal and parietal lobes with significant perilesional edema [Figure 1]. Diffusion-weighted imaging (DWI) did not show significant diffusion restriction in the three lesions. A lumbar puncture was not performed due to the significant mass effect, and she was started on dexamethasone, levetiracetam, and empiric antibiotics for possible cerebral abscess. She was continued on tacrolimus but mycophenolate was discontinued. Her overall clinical picture was concerning for cerebral abscess, and she was taken to the operating room on an urgent basis.

**OPERATION**

Intraoperatively, stereotactic needle biopsies of the left parietal-occipital and posterior frontal lesions were attempted but were nondiagnostic, consisting of necrotic tissue on frozen sections. There was no frank evidence of infection. In order to secure a diagnosis, a gross total excision of the left frontal lesion (the largest lesion and associated with the most perilesional edema) was carried out. The patient tolerated the procedure well with no new neurological deficits postoperatively.

**PATHOLOGICAL FINDINGS**

Pathologic examination revealed a predominantly angiocentric lymphoproliferative lesion characterized by large atypical lymphocytes with prominent nucleoli and moderate amounts of cytoplasm. Numerous mitotic figures and apoptotic bodies were seen. Zones of necrosis were present in multiple areas [Figure 2]. The neoplastic cells were strongly immunoreactive with CD20 and Mum-1 antibodies. In addition, the tumor cells were positive for Epstein–Barr-encoded RNAs (EBER). The Ki-67 proliferation index was very high (estimated at 70–80%). The morphologic findings, supported by

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**Figure 1:** Pre-operative (a) T2, and (b,c) contrast-enhanced T1-weighted MRI demonstrating three ring-enhancing lesions with significant perilesional edema. (d) Postoperative contrast-enhanced T1-weighted MRI demonstrating postoperative changes from biopsy of the left parietal-occipital and left frontal lesions.

**Figure 2:** (a) Angiocentric pattern of tumor cells (arrow) and necrosis (×400, hematoxylin and eosin stain). (b) High Ki-67, estimated at 70–80% (×200). (c) Neoplastic cells are immunoreactive with CD20 (×400). (d) Virtually all of the cells are Epstein–Barr virus EBER positive (×200).
immunohistochemical studies, were consistent with a primary diffuse large B-cell lymphoma of the CNS, nongerminal center, or activated B-cell type, with extensive necrosis.

Postoperative course
Further workup showed that the patient had isolated CNS disease. CT of the chest, abdomen, and pelvis was negative for malignancy. A bone-marrow biopsy was performed which showed no evidence of lymphoproliferative disease. Serology was negative for human immunodeficiency virus (HIV), Epstein–Barr virus (EBV), and cryptococcus. Cytomegalovirus (CMV) IgG and IgM were positive, but CMV PCR was negative. Intraoperative cultures were negative for infection.

Postoperatively, the patient was continued on dexamethasone and her antibiotics were discontinued. She was treated with a single cycle of high-dose methotrexate (4 g/m²) with leucovorin rescue. She tolerated the treatment well and was discharged on postoperative day 10. Her tacrolimus was subsequently transitioned to sirolimus. She is currently doing well 5 months after surgery and is on her seventh cycle of high-dose methotrexate (6 g/m²) and rituximab (375 mg/m²). Her brain MRI 2 months and PET-CT 4 months after surgery showed stable disease.

DISCUSSION
The increased incidence of solid organ transplantation in the United States has led to an increased need for neurosurgical intervention for post-transplantation lesions of the CNS. Systemic post-transplantation lymphoproliferative disorders (PTLD) occur in approximately 1% of renal transplant patients to as high as 20% of small bowel transplant recipients. Up to 90% of PTLD cases are associated with EBV and studies have shown that two risk factors for PTLD are high levels of immunosuppression and negative EBV serology in the recipient. The first cases of PTLD confined to the CNS, or PT-PCNSL, occurred after renal transplantation and were reported in 1970. A subsequent study showed that in 1332 patients who developed post-transplantation non-Hodgkin’s lymphoma, approximately 22% (289 patients) had CNS involvement and 12% (159 patients) had lesions confined to the CNS.

Demographics
The exact incidence of PT-PCNSL is unknown although it is likely to be rising in recent years from the increased number of transplant recipients. In the past decade, there has been an increase in the overall 1-year and 5-year survival for almost every type of organ transplantation. PT-PCNSL is a relatively rare disease, and to date, only case reports and a few case series have specifically examined PT-PCNSL in the literature. In one large series of PT-PCNSL, the median age at onset was 43 years (range 6–75 years) with a sex ratio of 1:1.83 (12 women, 22 men). The median time from transplantation to the development of PT-PCNSL ranges from 9 months to 4.4 years.

Multiple case series show renal transplantation to be the most frequent type of organ transplantation among PT-PCNSL patients, followed by liver and other solid organ transplantation types. Possible risk factors for developing PT-PCNSL include high-level immunosuppression and EBV seronegativity in the transplant recipient. Negative EBV serology combined with transplant-related immunosuppression may predispose the transplant recipient to a novel EBV infection and the development of PT-PCNSL. Other risk factors include infections with CMV, hepatitis C, or induction therapy with antilymphocyte agents.

In this case report, our patient was on chronic immunosuppression post-transplantation and had a

Table 1: Published case series of Post-transplantation primary central nervous system lymphoma

| Author and year | No. of patients | Median time of onset from transplantation | Patient survival | Enhancement on MRI (%) | Multiple lesions on MRI (%) |
|-----------------|-----------------|------------------------------------------|------------------|------------------------|---------------------------|
| Schneck and Penn, 1970 | 2 | Approximately 4 and 7 months after transplant in 2 patients | 1 patient died the day after presentation. 1 patient was alive at 2-year follow-up | NA | NA |
| Phan et al., 2000 | 8 | 9 months | Median survival of 13 weeks | 7/8 (88), 2/8 (25) ring | NA |
| Snanoudj et al., 2003 | 25 | 18 months | Median survival of 26 months | 100, 87 ring | 72 |
| Castellano- Sanchez et al., 2004 | 12 | 20 months | 4 died of disease within 3 months; 4 patients were in remission at 12, 14, 23, and 62 months | 10/12 (83) showed multiple enhancing lesions. No data for 2 with solitary lesions | 83 |
| Cavaliere et al., 2010 | 34 | 4.4 years, range 0.2–17.2 years | Median survival of 47 months | 97, 29 ring enhancing | 61 |
negative EBV serology. She subsequently developed diffuse large B-cell lymphoma that was strongly immunoreactive for EBV on histology.

Clinical presentation
The most common symptoms seen in PT-PCNSL are headache, hemiparesis, mental status changes, and gait disturbances.\(^4\) Focal neurological deficits such as aphasia, seizures, and/or increased intracranial pressure have also been reported.\(^4,21\) However, these symptoms are relatively non-specific when distinguishing among other CNS mass lesions. As PT-PCNSL is localized to the CNS, a minority of patients may exhibit systemic signs such as elevated levels of the C-reactive protein, lactate dehydrogenase, or increased erythrocyte sedimentation rate.\(^21\) Supplementary diagnostic tests such as CSF analysis are often nonspecific and only diagnostic in a minority of patients.\(^4\)

Radiographic features
The presentation of PT-PCNSL on imaging can vary and a case series has suggested that MRI is more sensitive than CT for detecting lesions.\(^15\) In a series of 33 PT-PCNSL patients imaged by contrast-enhanced MRI, 41% of patients had homogeneous enhancement, 29% had ring enhancement, and 61% had multiple lesions.\(^4\) A review of available case series shows that most PT-PCNSL lesions are contrast enhancing, while 25–87% showed a ring-enhancing pattern [Table 1]. The majority of PT-PCNSL lesions were supratentorial with a preference for lobar, basal ganglia, and periventricular locations.\(^4,21\) PCNSL has also been noted to present as a subdural mass lesion in an immunosuppressed patient requiring urgent surgery in one case.\(^17\) Ring-enhancing lesions seen on MRI can have a broad differential. In a review of 221 patients with ring-enhancing lesions on MRI, the most common pathologies were glioma (40%), metastatic malignant lesions (30%), bacterial and non-bacterial abscesses (12%), multiple sclerosis plaques (6%), and lymphoma (2%).\(^20\) The patients in this study were selected from a radiology database and it is unclear what percentage of them were immunosuppressed. The study also found that gliomas were likely to occur as single lesions while most abscesses presented as multiple ring-enhancing lesions on MRI.\(^30\) Abscesses often had a T2-hypointense rim and were positive on DWI.\(^20\) Common diagnoses for immunocompromised patients with cerebral mass lesions include lymphoma, fungal infections, and toxoplasmosis,\(^5\) although the incidence of toxoplasmosis may be decreasing with the use of prophylactic antibiotics to prevent opportunistic infections.

Therapy
The first step in the treatment of PT-PCNSL is to establish a definitive diagnosis, most commonly via a needle or excisional biopsy. PT-PCNSL lesions often have significant necrosis and a needle biopsy might not be diagnostic. In our case, our initial attempts at needle biopsy of both the parietal and frontal lesions were nondiagnostic. Although there has been one case series of PT-PCNSL suggesting a high risk of hemorrhage with four cases of hemorrhage in six patients who underwent stereotactic biopsy,\(^15\) other case series have not shown such a high rate of hemorrhage.\(^3,4,21\)

Since PT-PCNSL is a rare disease that can vary in morphology, location, and subtype, a defined treatment protocol has not been established. Treatment of PT-PCNSL generally includes reducing immunosuppressive therapy, radiotherapy, and chemotherapy with the best 1-year survival resulting from the reduction of immunosuppression combined with either radiotherapy (80%) or radiotherapy plus chemotherapy (88%).\(^21\) Other options such as surgical resection alone or chemotherapy alone had poor 1-year survival rates of 50% and 45%, respectively.\(^4,21\) Chemotherapeutic agents such as methotrexate have been shown to be an effective treatment in two case series;\(^4,10\) however, its use is concerning in renal transplantation recipients given that the main toxicity of methotrexate is nephrotoxicity.\(^10\) Rituximab, an anti-CD20 monoclonal antibody, has been used effectively in patients with systemic PTLD. Unfortunately, rituximab does not cross the blood–brain barrier efficiently although high-dose rituximab was shown to be an effective treatment in a recent case report.\(^13\) Gamma knife radiosurgery combined with fractionated whole-brain radiotherapy has also been tried as a potential therapy for PT-PCNSL.\(^8\) Antiviral therapy with acyclovir or ganciclovir has been studied in EBV-induced PT-PCNSL; however, no definitive evidence for its efficacy in improving survival is available in the literature. It is postulated that antiviral therapy has low efficacy against PT-PCNSL because it only affects actively replicating viruses and has no effect on latently infected B cells that do not contain thymidine kinase.\(^4\)

Prognosis
A consensus on the best treatment of PT-PCNSL has not been established and further studies are ongoing. Surgery and reduction of immunosuppression, radiotherapy, and chemotherapy with agents such as methotrexate and rituximab seem to be the most promising. Despite treatment, the prognosis for PT-PCNSL remains poor. In the case series by Phan and co-workers, partly because of high perioperative mortality, median survival was only 13 weeks after diagnosis of PT-PCNSL.\(^15\) Better median survivals of 26 and 47 months were reported in two subsequent series utilizing a variety of treatment modalities.\(^3,21\)

CONCLUSION
PT-PCNSL is a rare disease occurring in post-transplantation patients maintained on immunosuppression. It can develop within months to years after transplantation and most often presents with...
symptoms of mass effect or focal neurological deficits. PT-PCNSL can closely resemble brain abscesses in its clinical presentation and radiographic features. Unfortunately, no single diagnostic test has been shown to reliably distinguish between the various possible pathologies that might be encountered in a post-transplantation patient. Therefore, PT-PCNSL should be included in the differential diagnosis when contrast-enhancing lesions are observed in a post-transplant patient. Treatment options for PT-PCNSL include surgery, reduction of immunosuppression, radiotherapy, and chemotherapy when tolerated. Despite therapy, prognosis remains poor for PT-PCNSL and further studies are necessary to improve the management of this disease.

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