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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

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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.[7] 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.

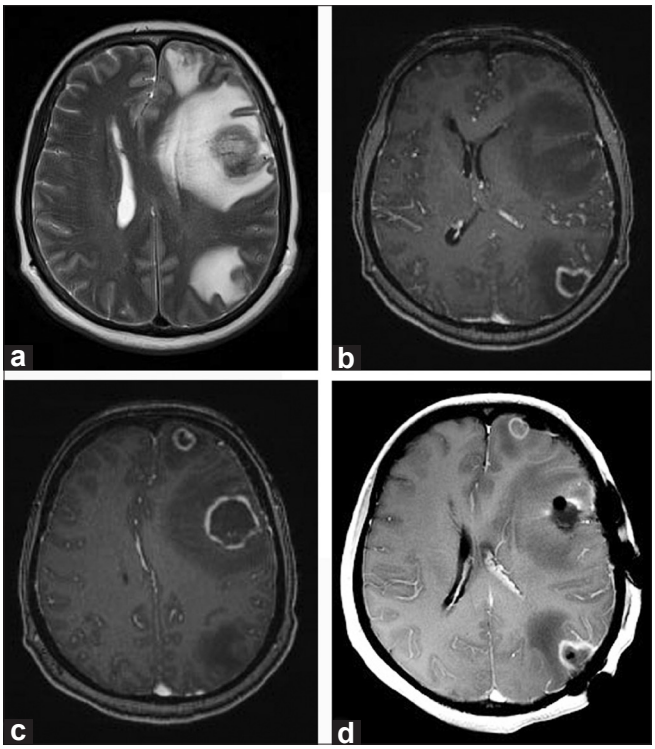

Figure 1: Pre-operative (a) T2, and (b,c) contrast-enhanced T1-weighted MRI demonstrating three ring-enhancing lesions with significant perilesional edema. (d) Postoperative contrast-enhanced T1-weighted MRI demonstrating postoperative changes from biopsy of the left parietal-occipital and left frontal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

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

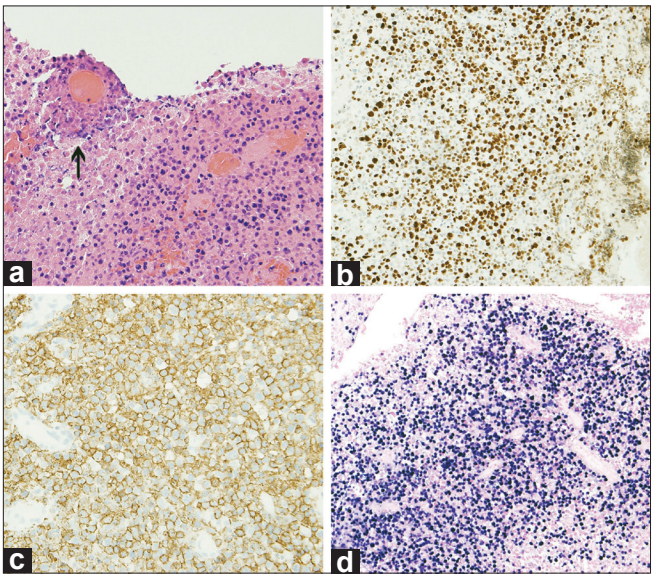

Figure 2: (a) Angiocentric pattern of tumor cells (arrow) and necrosis (×400, hematoxylin and eosin stain). (b) High Ki-67, estimated at 70–80% (×200). (c) Neoplastic cells are immunoreactive with CD20 (×400). (d) Virtually all of the cells are Epstein–Barr virus EBER positive (×200)

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/m^2) 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/m^2) and rituximab (375 mg/m^2). 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.[22] Up to 90% of PTLD cases are associated with EBV,[14] and studies have shown that two risk factors for PTLD are high levels of immunosuppression and negative EBV serology in the recipient.[9] The first cases of PTLD confined to the CNS, or PT-PCNSL, occurred after renal transplantation and were reported in 1970.[19] 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.[13]

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.[16,24] In the United States, the total number of patients living with functioning transplanted organs has increased from 163,631 in 2005 to 183,222 patients in 2007.[16,23,24] PT-PCNSL is a relatively rare disease, and to date, only case reports[15] and a few case series[3,4,15,19,21] have specifically examined PT-PCNSL in the literature [Table 1]. 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).[4] The median time from transplantation to the development of PT-PCNSL ranges from 9 months to 4.4 years [Table 1].

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.[3,4,15] Possible risk factors for developing PT-PCNSL include high-level immunosuppression and EBV seronegativity in the transplant recipient.[1,11] 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.[25] 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.[20] 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 43%, respectively.[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.[12] 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.[4,21]

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.

REFERENCES

1. Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005;80:1233-43.
2. Camilleri-Broet S, Martin A, Moreau A, Angonin R, Henin D, Gontier MF, *et al*. Primary central nervous system lymphomas in 72 immunocompetent patients: Pathologic findings and clinical correlations. Groupe Ouest Est d'etude des Leucenies et Autres Maladies du Sang (GOELAMS). Am J Clin Pathol 1998;110:607-12.
3. Castellano-Sanchez AA, Li S, Qian J, Lagoo A, Weir E, Brat DJ. Primary central nervous system posttransplant lymphoproliferative disorders. Am J Clin Pathol 2004;121:246-53.
4. Cavaliere R, Petroni G, Lopes MB, Schiff D. Primary central nervous system post-transplantation lymphoproliferative disorder: An International Primary Central Nervous System Lymphoma Collaborative Group Report. Cancer 2010;116:863-70.
5. Cortese I, Nath A. Case 11: A young woman with ring-enhancing brain lesions. MedGenMed 2006;8:3.
6. Fine HA, Mayer RJ. Primary central nervous system lymphoma. Ann Intern Med 1993;119:1093-104.
7. Gerstner ER, Batchelor TT. Primary central nervous system lymphoma. Arch Neurol 2010;67:291-7.
8. Kim M, Lee J, Kim W, Ko Y. Primary central nervous system lymphoma after liver transplantation treated by radiosurgery combined with fractionated radiotherapy. J Clin Neurosci 2009;16:583-5.
9. Knight J, Tsodikov A, Cibrik D, Ross C, Kaminski M, Blayney D. Lymphoma after solid organ transplantation: Risk, response to therapy, and survival at a transplantation center. J Clin Oncol 2009;27:3354-62.
10. Nabors LB, Palmer CA, Julian BA, Przekwas AM, Kew CE. Isolated central nervous system posttransplant lymphoproliferative disorder treated with high-dose intravenous methotrexate. Am J Transplant 2009;9:1243-8.
11. Opelz G, Daniel V, Naujokat C, Döhler B. Epidemiology of pretransplant EBV and CMV serostatus in relation to posttransplant Non-Hodkin lymphoma. Transplantation 2009;88:962-7.
12. Patrick A, Wee A, Hedderman A, Wilson D, Weiss J, Govani M. High-dose intravenous rituximab for multifocal, monomorphic primary central nervous system posttransplant lymphoproliferative disorder. J Neurooncol 2011;103:739-43.
13. Penn I, Porat G. Central nervous system lymphomas in organ allograft recipients. Transplantation 1995;59:240-4.
14. Peres E, Savasan S, Klein J, Abidi M, Dansey R, Abella E. High fatality rate of Epstein-Barr virus-associated lymphoproliferative disorder occurring after bone marrow transplantation with rabbit antithymocyte globulin conditioning regimens. J Clin Microbiol 2005;43:3540-3.
15. Phan TG, O'Neill BP, Kurtin PJ. Posttransplant primary CNS lymphoma. Neuro Oncol 2000;2:229-38.
16. Port FK, Merion RM, Roys EC, Wolfe RA. Trends in organ donation and transplantation in the United States, 1997-2006. Am J Transplant 2008;8:911-21.
17. Sacho RH, Kogels M, Plessis D, Jowitt S, Josan VA. Primary diffuse large B-cell central nervous system lymphoma presenting as an acute space-occupying subdural mass. J Neurosurg 2010;113:384-7.
18. Schabet M. Epidemiology of primary CNS lymphoma. J Neurooncol 1999;43:199-201.
19. Schneck SA, Penn I. Cerebral neoplasms associated with renal transplantation. Arch Neurol 1970;22:226-33.
20. Schwartz KM, Erickson BJ, Lucchinetti C. Pattern of T2 hypointensity associated with ring-enhancing brain lesions can help to differentiate pathology. Neuroradiology 2006;48:143-9.
21. Snanoudj R, Durrbach A, Leblond V, Caillard S, Hurault De Ligny B, Noel C, *et al*. Primary brain lymphomas after kidney transplantation: presentation and outcome. Transplantation 2003;76:930-7.
22. Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 2005;56:155-67.
23. Wolfe RA, Merion RM, Roys EC, Port FK. Trends in organ donation and transplantation in the United States, 1998-2007. Am J Transplant 2009;9:869-78.
24. Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. Am J Transplant 2010;10:961-72.
25. Xu QS, Ye S, Zhou YQ, Sheng JF, Ye K, Zheng SS. Posttransplantation lymphoproliferative disorder involving the central nervous system in liver transplant recipients. Hepatobiliary Pancreat Dis Int 2008;7:551-4.