THE ASEAN JOURNAL OF RADIOLOGY 2012: 18(1): 57-71 57

Case Report

Post-Transplant Lymphoproliferative Disorder of the Brain Mimics Brain Abscess: Case Report and Review Literature.

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Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a spectrum of hematological diseases arising in context of immunosuppression after organ transplantation. PTLD can involve any organ. We have studied two cases of polymorphic PTLD of the brain that developed in patient with relapsed acute lymphoblastic leukemia (ALL) following two times of bone marrow transplantation ongoing immunosuppressive therapy and end stage renal disease with renal transplantation. Additionally, case of PTLD in the brain was reviewed in 2004. The neoplasm showed large cell morphology and B-cell phenotype. In situ hybridization for Epstein-Barr virus (EBV) was positive. Complete remission was obtained after decreasing immunosuppressive therapy. The patient remained in remission at almost 2-years' follow up. This rare case increased our awareness of PTLD in the brain of patients following organ transplantation and immunosuppressive therapy.

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is well-recognized complication after solid organ or bone marrow transplantation. As currently defined by the World Health Organization (WHO), post-transplant lymphoproliferative disorders (PTLDs) are lymphoid proliferations or lymphomas that develop in immunosuppressed recipients of solid organ or bone marrow allograft. They are best considered as a spectrum of pathologic patterns ranging from reactive Epstein-Barr virus (EBV)-driven lymphocytic/ plasmacytic hyperplasia to high-grade malignant lymphomas that can be EBV+ or EBV-. The vast majority is of the B-cell phenotype; rare T-cell PTLDs have been described. Patient outcome generally depends on the histological grading, organ sites involved, tumor burden, and response to therapy. PTLD may involve the lymph nodes or extranodal tissue at any site, including organ allograft.

The incidence of PTLDs in the transplantation population has been estimated at less than 2%, with slightly higher rates in the pediatric population. Patients undergoing heart-lung or liver-bowel transplantation are at highest risk (5%). Risk is lower following liver, cardiac, and bone marrow allograft (1%-2%) and is lowest after kidney transplantation (<1%).

The anatomic distribution of PTLDs varies with patient age and the type of immunosuppressive therapy. Childhood PTLDs often involve lymphoid tissues including lymph nodes and adenoids and arise in the abdomen (64%), thoracic cavity (50%), and head and neck (25%). PTLDs in adults tend to localize to the liver, lung, lymph nodes, and gastrointestinal tract. In most cases, the transplanted organ is involved. PTLDs that arise following azathioprine-based immunosuppressive therapies are more common in the allograft and also might involve the central nervous system (CNS); those that follow FK-506- or cyclosporine-based regimens most frequently involve lymph nodes and the gastrointestinal tract.

A series of 90 PTLD cases occurring in 4283 solid organ transplantations over a nine-year period revealed that two thirds of the patients presented with disease in a single site, and uncommon of the cases presented in the brain. Dr Frank Gaillard[1] on September 4, 2009 contributed Post transplant lymphoproliferative disorder (PTLD) that the time between transplant and development of PTLD is variable, ranging from one month to seven years, with most occurring within a year. As a general rule, patients who present late (more than one year) have more aggressive tumors with poorer prognosis. This report showed that radiographic features are similar to lymphoma in the setting of HIV infection. Necrosis and hemorrhage were more common than in run-of-the-mill primary CNS lymphoma.

Among CNS disorders after transplantation, PTLDs follow cerebrovascular disease and infection in frequency. CNS PTLDs were seen in 2% to 7% of brains in the largest autopsy series of posttransplant patients (which most likely overestimates the incidence of clinical disease). Partly owing to their rarity, the spectrum of pathologic features of CNS PTLDs has not been characterized fully, nor has their range of biologic behavior. Case reports and small series seem to indicate that CNS PTLDs are more aggressive as a group than PTLDs involving other organ systems. Recognizing CNS PTLDs and distinguishing them from other nontransplant primary CNS lymphomas is critical because therapeutic options and clinical outcomes can vary sub-

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stantially. The report was described the features of 12 primary CNS PTLDs with the aim of better characterizing their clinical, radiographic, and pathologic features and distinguishing them from other primary CNS lymphomas.

Here we report rare cases of polymorphic PTLD of the brain in patient after second bone marrow and renal transplantation with immunosuppressive therapy, which was improved by reduction of the immunosuppression. This review summarizes the current knowledge of EBV-PTLD and, as a result of international meetings on this topic, differential diagnostic point by imaging findings and provides recommendations for future area of study.

Case presentation

Case number one

A 13-year-old Thai female (Body weight = 27 kg, height = 144 cm) with history of second relapsed acute lymphoblastic leukemia (ALL) S/P second time for bone marrow transplantation, the last one performed on February 6, 2009. She also had chemotherapy, systemic fungal infection (hepatosplenic candidiasis and invasive pulmonary aspergillosis. At admission (from June 18, 2009 to August 5, 2009) she presented with fever, diarrhea, nausea, neutropenia and CMV reactivation for one day before admission. Vital signs showed low fever (38.3°C), respiratory rate was about 24/minute and pulse rate was 120 beats/minute. Skin showed hypopigmented and erythematous patch at face. On Neurological examination; she was no significant finding. CBC showed WBC=8,400 cells with PMN=41 (neutropenia), Hb=10.9, Hct=32.1, Platelet= 23,000. Stool examination showed WBC 5-10 cells per high field and RBC 10 cells per high field (infectious diarrhea, stool cultures & sensitivity showed *Salmonella*). Electrolyte showed Na=135, K=3.32, Cl=99, CO_2=25.7 (hypokalemia). 6 days after admission, she developed alteration of her consciousness level and complex-partial seizure. EEG showed normal study. Lumbar puncture performed on June 24, 2009 showed high protein and low glucose, cannot be excluded encephalitis. MRI of her brain performed on June 25, 2009 showed small ring enhancing lesion with associated mild perilesional edema at medial left temporal lobe. (Figure 1-5). She undergone operation on June 26, 2009, place-

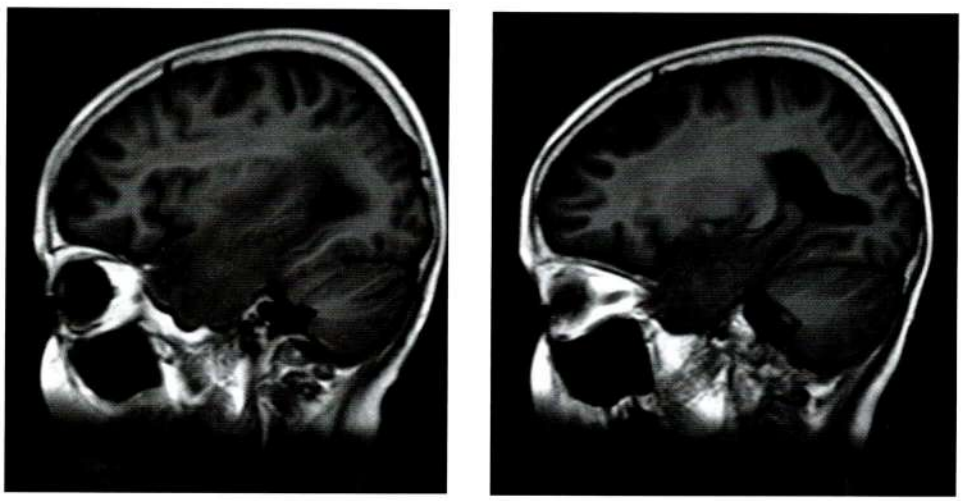

Fig.1 Sagittal T1W showed small well-defined mass with near uniform isointense-T1W wall and hypointense-T1W at central portion. Hypointensity in T1W signal surrounding this lesion could be associated perilesional edema.

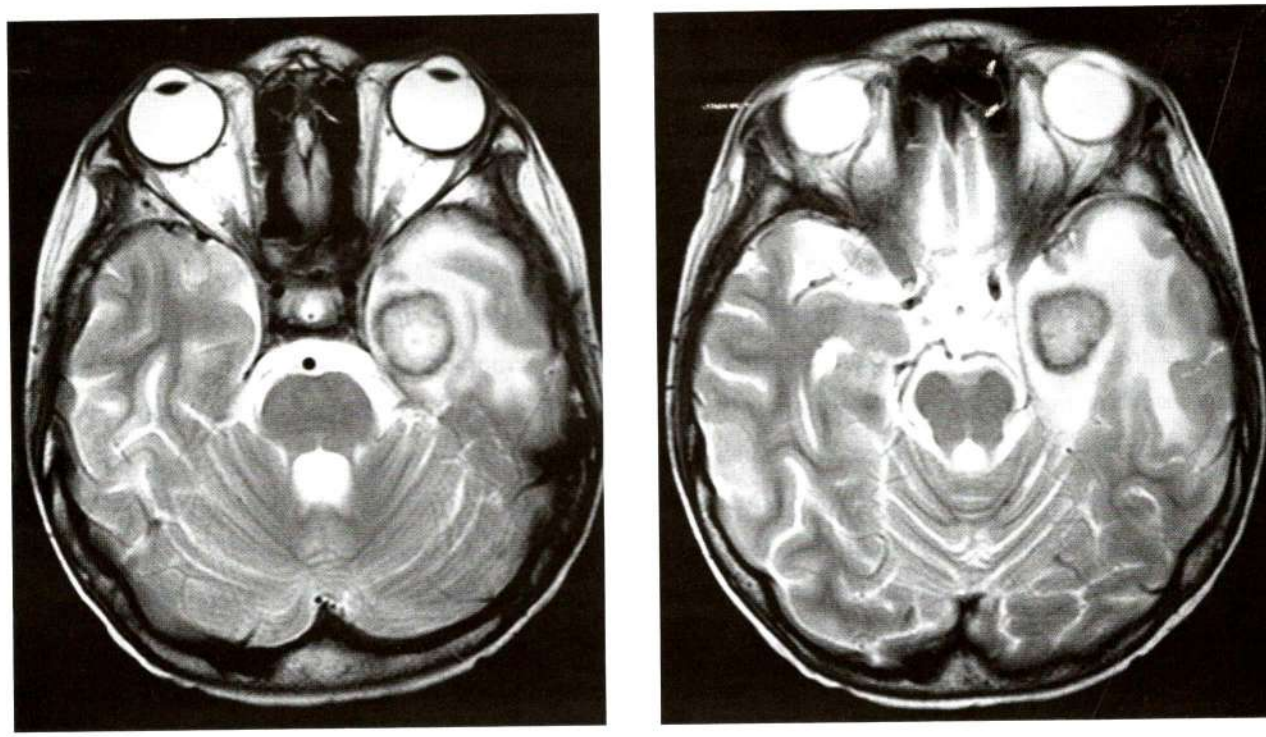

Fig.2 Axial T2W showed dark T2W signal wall with mild-hyperintense-T2W signal change in central portion. The lesion and an associated perilesional edema produce mass effect to the cortical sulci, sylvian fissure and obliteration of temporal horn of the left lateral ventricle.

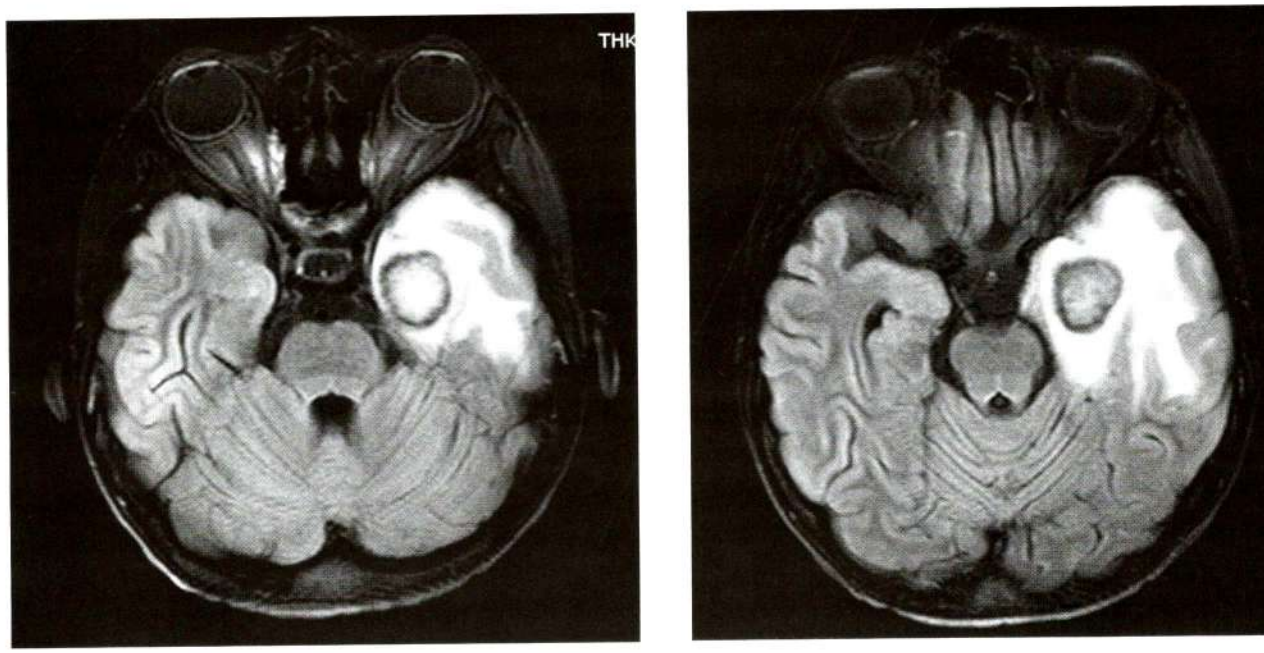

Fig.3 Axial FLAIR showed better demonstration of the signal intensity change as described in Figure 2

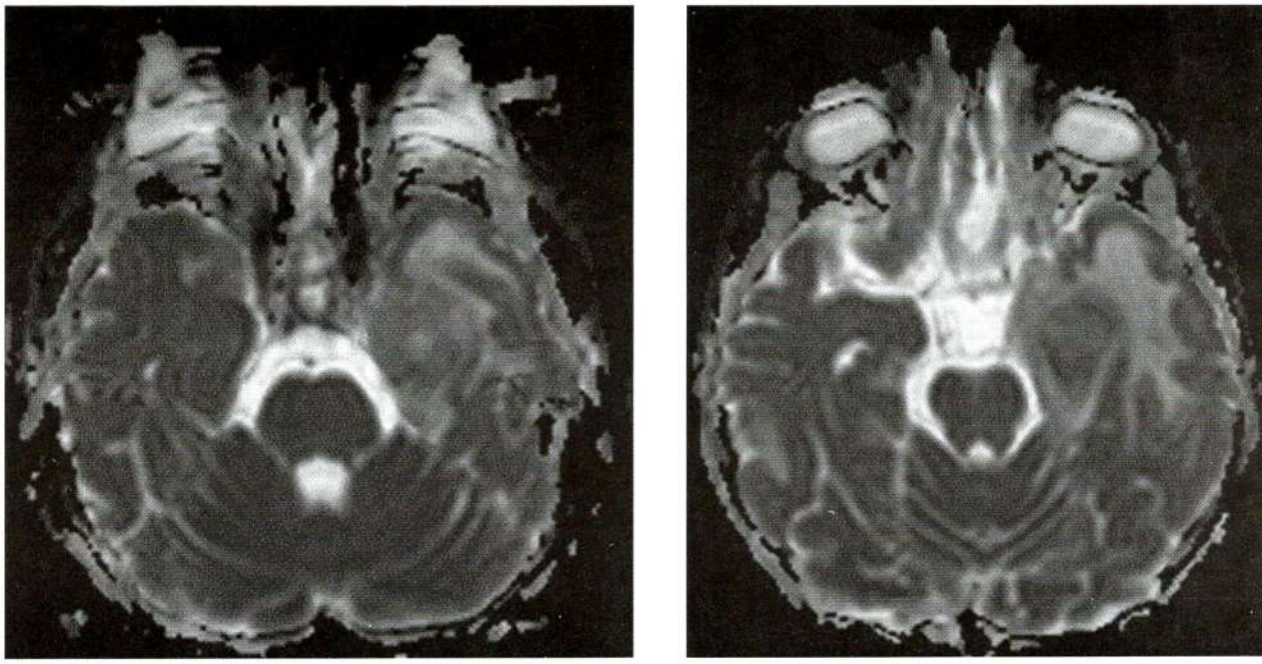

Fig.4 ADC mapping from DWI showed partial restricted diffusion at posterior wall and partly left anterolateral wall as well as some area in central portion.

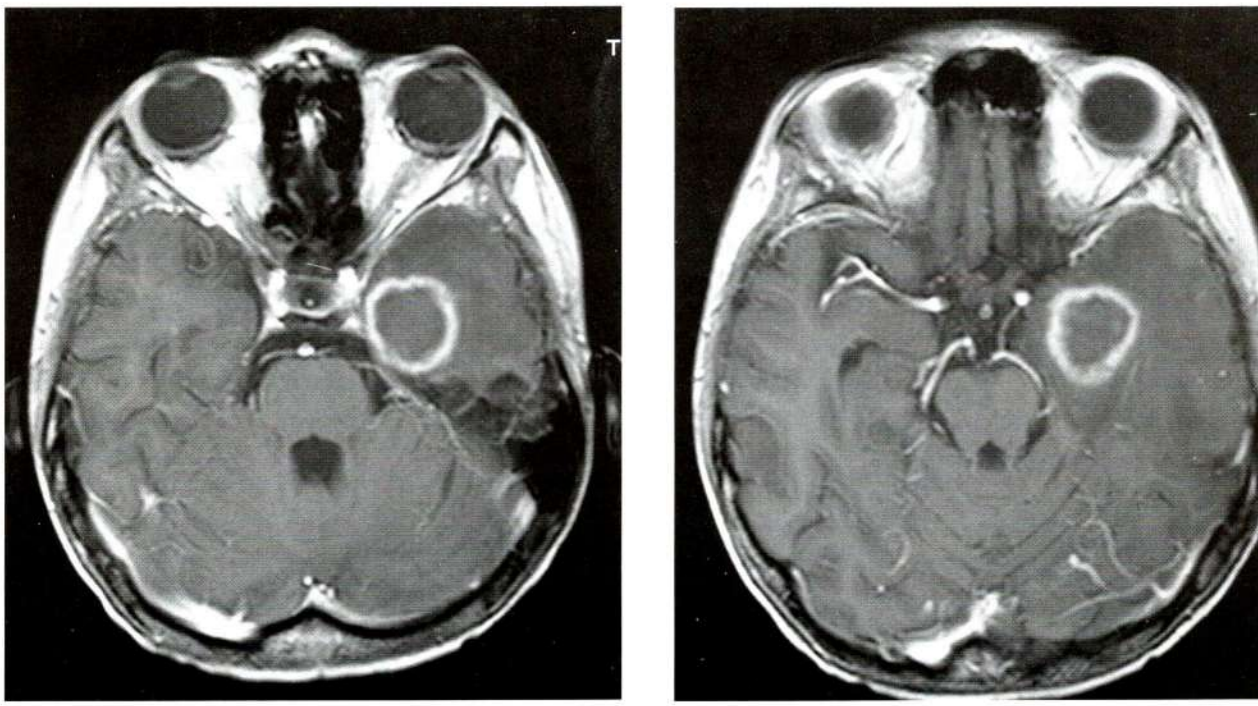

Fig.5 Axial T1W post-contrast showed complete, smooth near-uniform enhanced wall. The suspicious associated perilesional edema was not enhanced.

ment of the intracranial catheter via burr hole craniotomy with lesion biopsy under navigator. Pathologic report showed focal necrosis with focal polymorphous lymphoid cell infiltration including small lymphoid cells, immunoblasts and plasma cells, suggestive of polymorphic post-transplant lymphoproliferative disorder (PTLD). Echocardiography was performed on June 29, 2009 appeared normal. Bone marrow biopsy performed on June 19, 2009 showed marked hypo cellular marrow showing severely decreased trainer hematopoiesis. There is no residual lymphoblast.

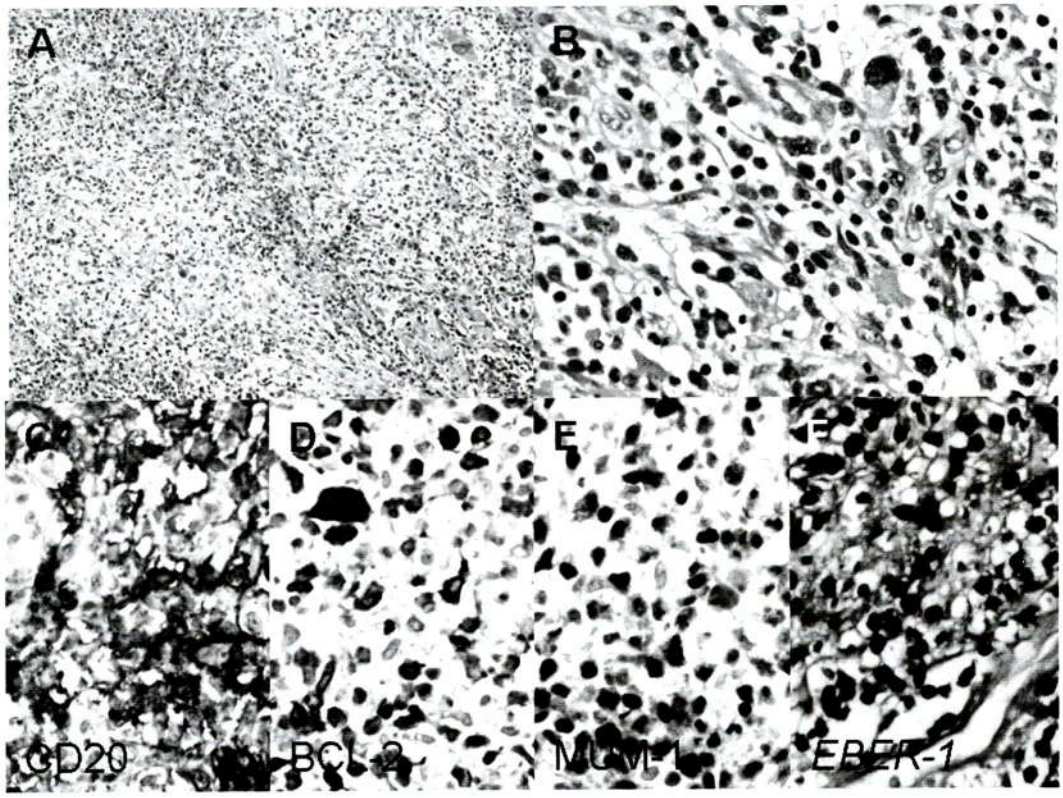

Fig.6 Histologic features of polymorphic post-transplant lymphoproliferative disorder. (A) Brain biopsy showing dense infiltration of polymorphic cells (H&E, x 100). (B) Mixed proliferation of immunoblasts, plasma cells and medium-sized lymphoid cells and large atypical lymphoid cell (H&E, x 400). Immunohistochemistry showing tumor cells are strongly positive for CD20 (C), BCL-2 (D), and MUM-1 (E) (x 400). (F) EBV in situ hybridization showing all the tumor cells are positive for EBER-1 (x 400).

The results of the immunohistochemical stains are

CD3 : negative in large lymphoid cells
CD 10 : negative in large lymphoid cells
CD 20 : Positive in large lymphoid cells
CD 30 : Positive in large lymphoid cells
CD138 : positive in large lymphoid cells
MUM-1 : positive for large lymphoid cells
Bcl-2 : positive in large lymphoid cells
Bcl-6 : positive 30% in large lymphoid cells

The EBV in situ hybridization (EBER) is positive in large lymphoid cells.

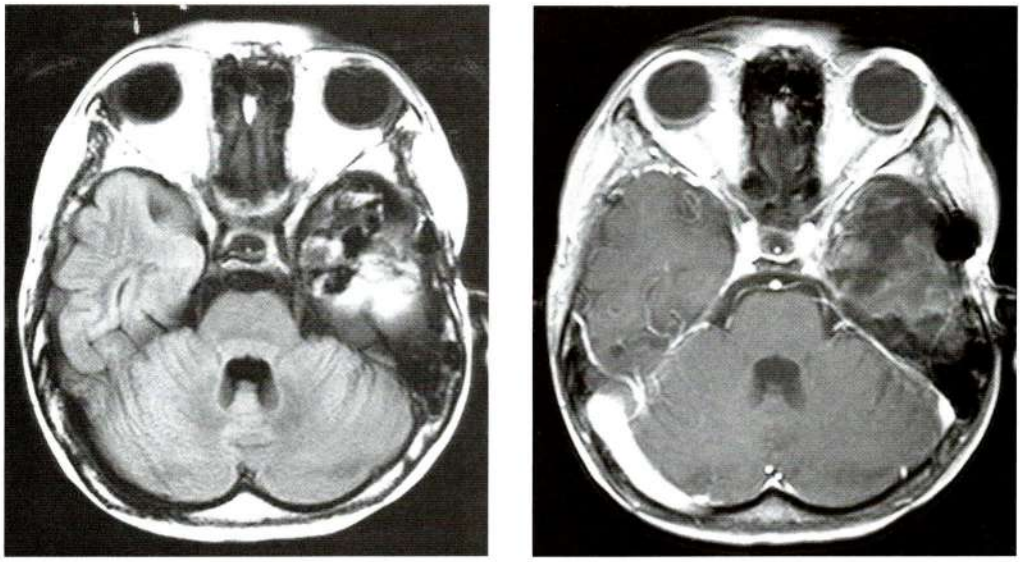

Fig.7 Follow up MRI 5 months post treatment. Axial FLAIR and Post contrast T1W. Complete resolution of the prior seen rim-enhancing lesion.

Case number two

A 51-year-old Thai male, who is a case with history of end stage renal disease (ESRD) post-renal transplantation and chemotherapy, presented with numbness of the right hand. MRI of his brain performed on April 24, 2009 showed small ring enhancing lesion with associated mild perilesional edema at left fronto-parietal lobe.

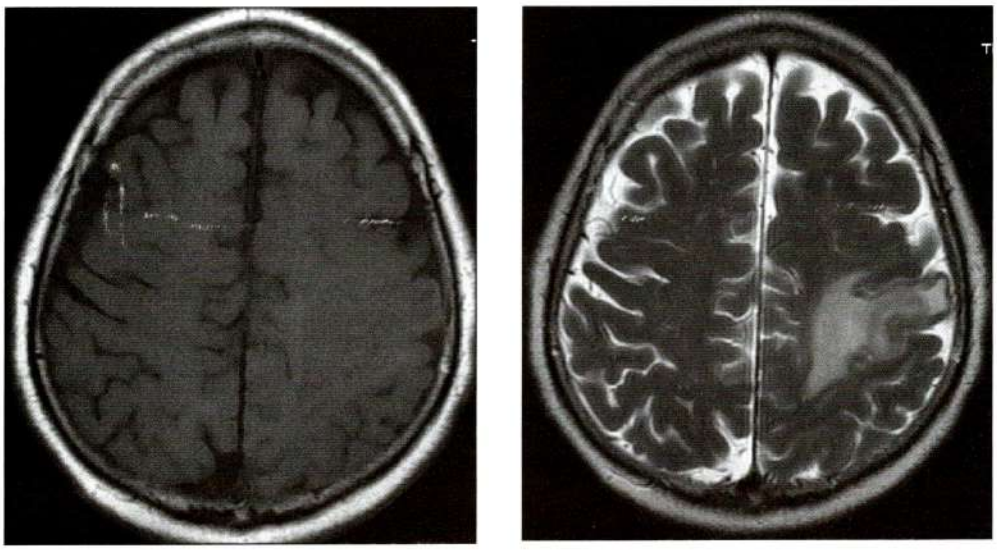

Fig.8 Axial T1W and T2W showed iso-intense-T1W/ dark T2W signal wall lesion with mild-hyperintense-T2W signal change in central portion. The lesion and an associated perilesional edema produce mass effect to the cortical sulci of the left post-central gyrus.

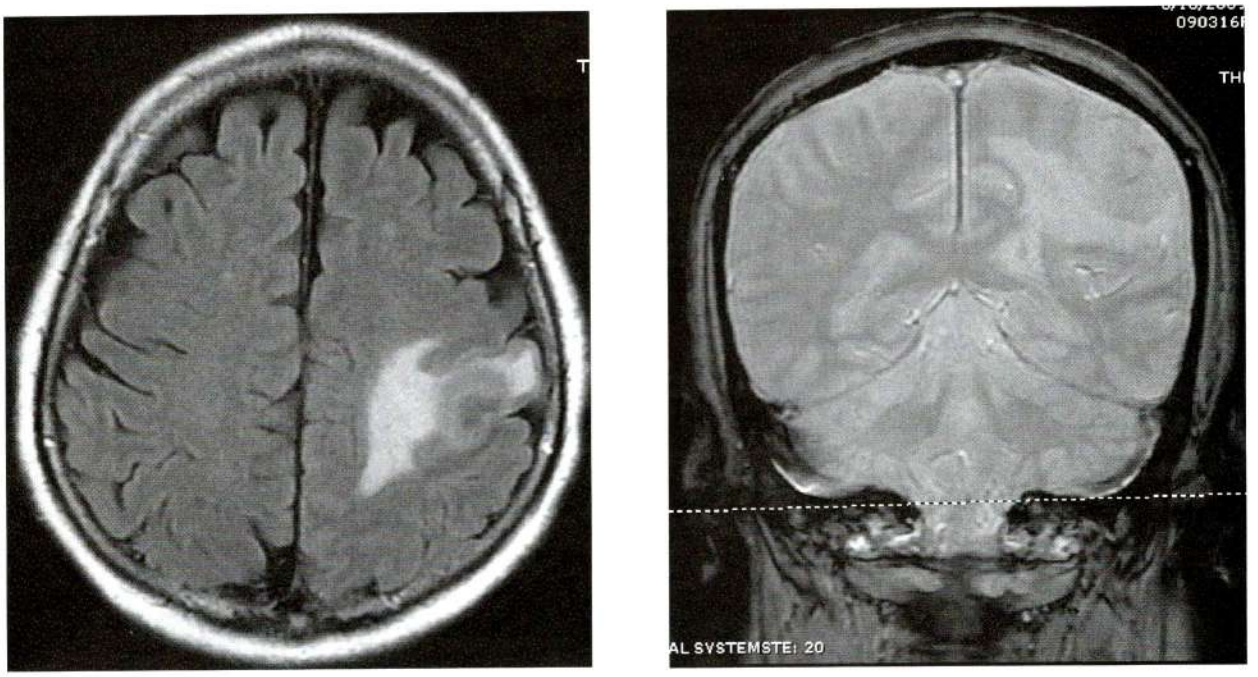

Fig.9 Axial FLAIR and coronal GRE-T2W better demonstrated dark T2W signal wall lesion with mild-hyperintense-T2W signal change in central portion.

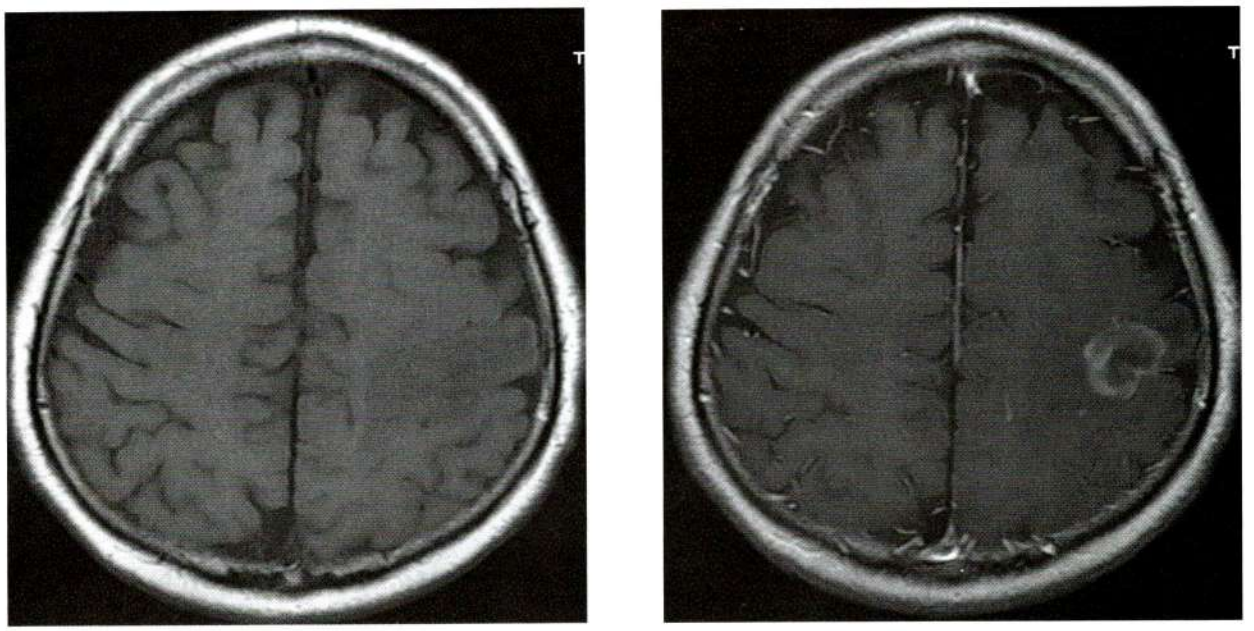

Fig.10 Axial T1W post-contrast showed complete, smooth near-uniform enhanced wall. The suspicious associated perilesional edema was not enhanced.

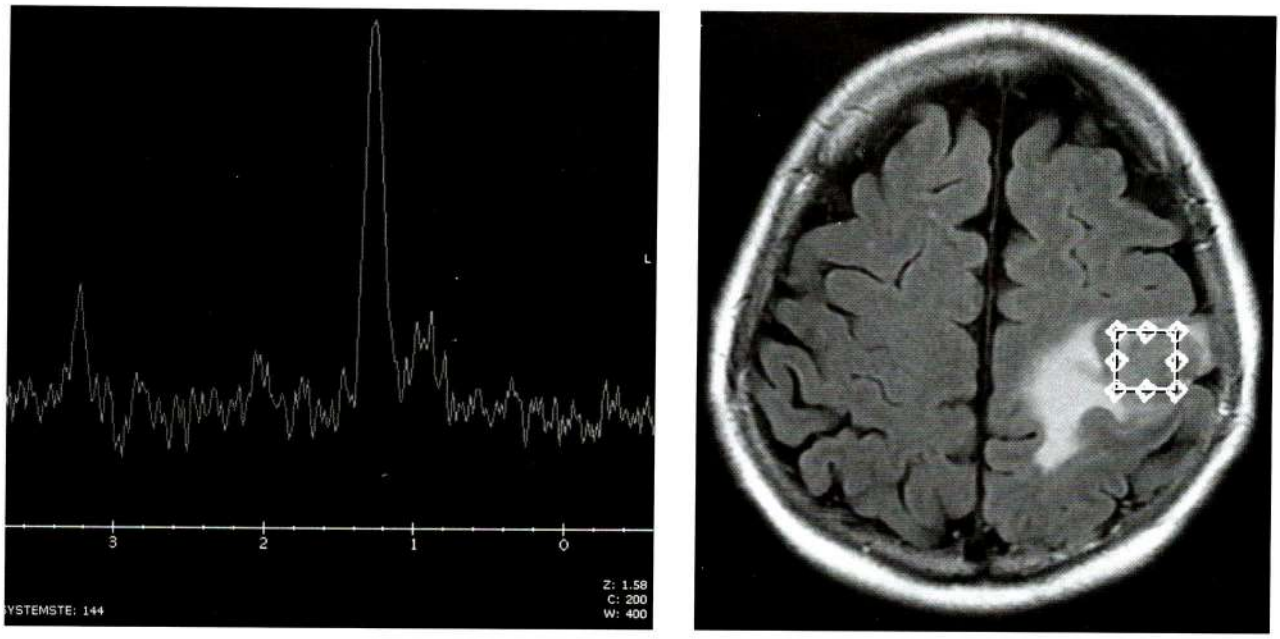

Fig.11 Single voxel MR spectroscopy in long TE showed high lactate peak at the rim-enhanced lesion.

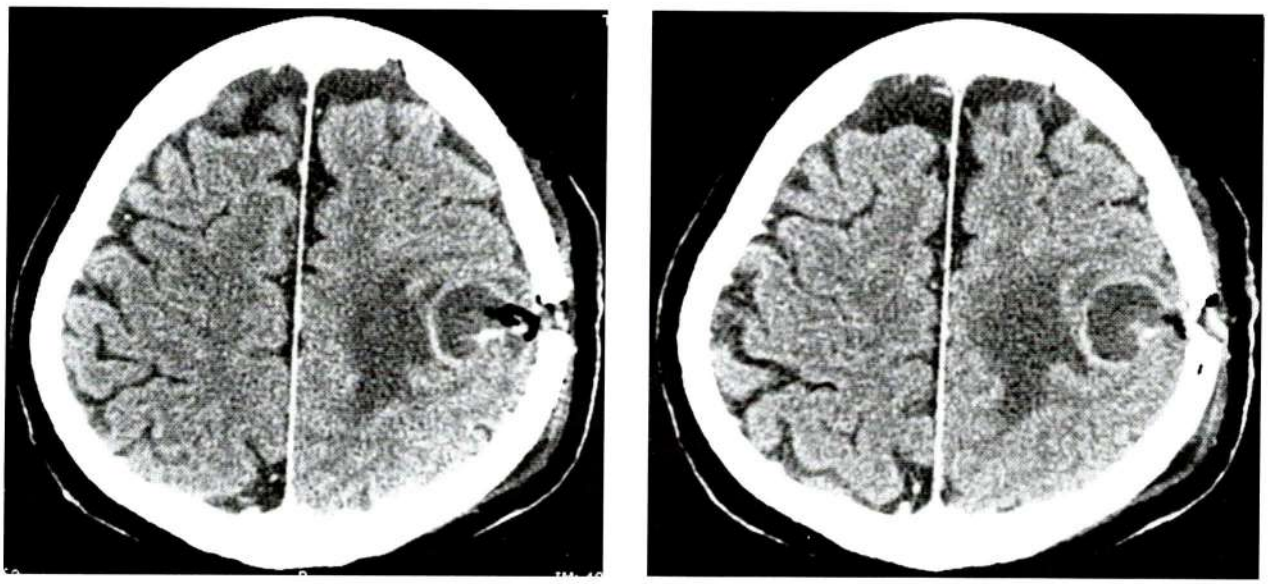

Fig.12 Follow up axial enhanced CT of the brain showed rim-enhanced lesion with persisted perilesional edema.

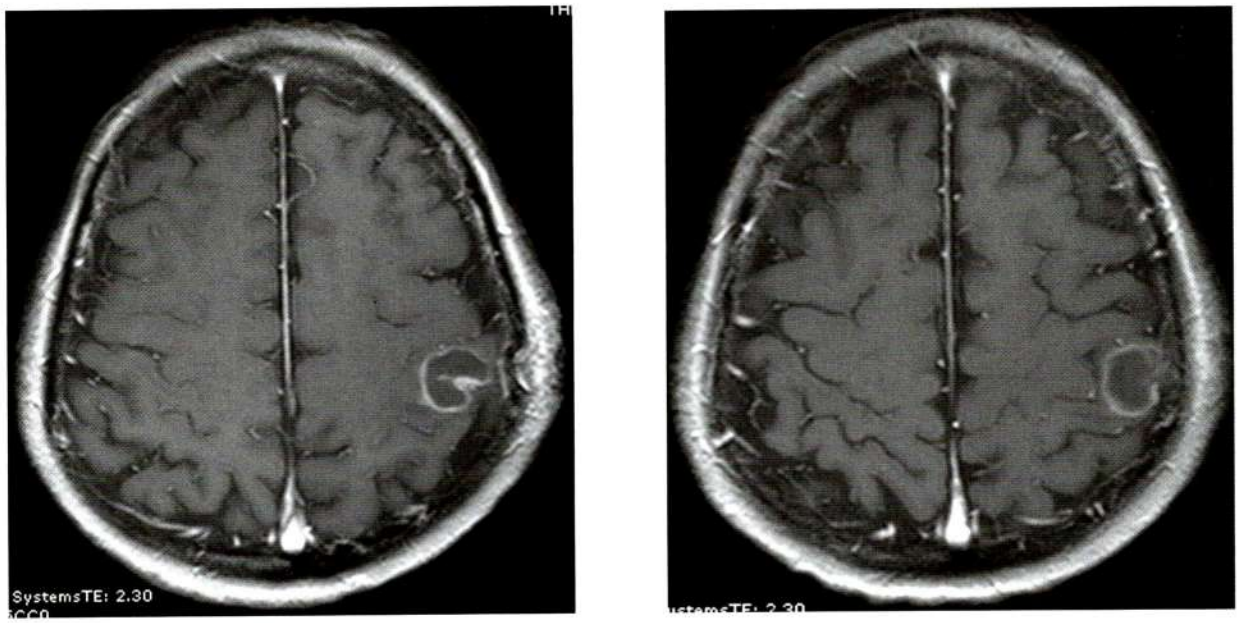

Fig.13 6-months follow up axial enhanced T1W MRI of the brain showed decreased size of the rim-enhanced lesion without perilesional edema.

Treatment: reduction of immunosuppressive therapy, the patients have complete resolution of the brain lesion.

Literature review of Primary Central Nervous System Posttransplant lymphoproliferative disorders (PTLD) by Amilcar A. Castellano-Sanchez, MD; Shiyong Li, MD, PhD; Jiang Qian, MD, PhD; Anand Lagoo, MD, PhD; Edward Weir, MD; Daniel J. Brat, MD, PhD Authors and Disclosures Posted: 02/27/2004; American Journal of Clinical Pathology. 2004; 121(2) © 2004 American Society for Clinical Pathology[2]. Posttransplant lymphoproliferative disorders (PTLDs) represent a spectrum ranging from Epstein-Barr virus (EBV)-driven polyclonal lymphoid prolife-rations to EBV+ or EBV- malignant lymphomas. Central nervous system (CNS) PTLDs have not been characterized fully. They reviewed the clinical, radiologic, and pathologic features of 12 primary CNS PTLDs to define them more precisely. Patients included 10 males and 2 females (median age, 43.4 years) who were recipients of kidney (n=5), liver (n=2), heart (n=2), peripheral blood stem cells (n=2), or bone marrow (n=1). All received immunosuppressive therapy. CNS symptoms developed 3 to 131 months (mean, 31 months) after transplantation. By neuroimaging, most showed multiple (3 to 9) intra-axial, contrast-enhancing lesions. Histologic sections showed marked expansion of perivascular spaces by large, cytologically malignant lymphoid cells that were CD45+, CD20+, EBV+ and showed light chain restriction or immunoglobulin gene rearrangement. In distinction to PTLDs in other organ systems, CNS PTLDs were uniformly high-grade lymphomas that fulfilled the World Health Organization criteria for monomorphic PTLDs. Extremely short survival periods were noted for each CNS PTLD that followed peripheral blood stem cell transplantation. Survival of others with CNS PTLD varied; some lived more than 2 years.

Radiologic and Pathologic Features

By neuroimaging that included magnetic resonance imaging (MRI) or computed tomography (CT) scan, CNS PTLDs were seen as multiple, contrast-enhancing, intra-axial lesions in 10 of 12 cases and as solitary lesions in the remaining 2 cases. In all cases, the lesions were associated with extensive peritumoral edema. CNS parenchymal lesions were distributed in highest frequency in the cerebral hemispheres (44/54 [81%]), brainstem (8/54 [15%]), and cerebellum (2/54 [4%]). In the cerebral hemispheres, lesions were most common in the cortex and white matter (18/54 [33%] each), basal ganglia (7/54 [13%]), and corpus callosum (1/54 [2%]). No spinal cord involvement was noted in the 12 cases.

By immunophenotype, all tumors were CD20+. Three tumors so tested showed expression of additional B-cell markers (CD19, CD22, or CD79a). The T-cell marker CD3 demonstrated admixed lymphocytes in the background. Results from immunohistochemical analysis for light chains were available for 7 cases. Among these, all 7 were light chain-restricted, 3 for k and 4 for l. Of 12 tumors, 11 showed evidence of EBV infection within tumor cells.

Discussion

PTLDs are clinically and morphologically heterogeneous lymphoid tumors, their common elements being a history of organ transplantation and immunosuppression. These lesions arise most often in the allograft, but also frequently affect other organs, including the gastrointestinal tract, lung, lymph nodes, and bone marrow. Although their occurrence in the brain is relatively rare, it is critical for the pathologist to distinguish them from other CNS lymphomas and lymphoid proliferations. This is especially true for CNS PTLDs: the brain was the first and only manifestation of PTLD in all patients in this study. Since immunosuppressive therapy is highly relevant to the pathogenesis of PTLDs, treatment of these disorders nearly always involves its reduction.

We have presented two rare cases of polymorphic PTLD at medial left temporal lobe and left fronto-parietal lobe of the brain with successful treatment by reduction in immunosuppression. Both two cases showed rim-enhanced lesions by CT and MRI, which were similar imaging findings to brain abscess. MR spectroscopy did not differentiate between abscess and tumor. Clinical information includes history of organ transplantation with immunosuppressive agents and chronic onset should be warning us to diagnose PTLD. As review literature by Amilcar A. et al who reviews 12 cases of Primary Central Nervous System Posttransplant lymphoproliferative disorders (PTLD) suggests that CNS PTLDs are monomorphic by WHO criteria and have histopathologic features similar to the diffuse large cell lymphomas that occur in the HIV-infected population and elderly people--so-called primary CNS lymphoma (PCNSL). CNS PTLD and PCNSL are aggressive, large cell lymphomas, nearly always with a B-cell phenotype. Both have a marked predisposition to grow within perivascular spaces, to invade vascular walls, and to display a concentric, laminar pattern around central vessels that can be highlighted by stains for reticulin or collagen IV. PCNSLs and CNS PTLDs also are similar in their ability to infiltrate CNS parenchyma, and both typically demonstrate extensive necrosis. Similar to CNS PTLDs, the PCNSLs that arise in the HIV-infected population are EBV+. PCNSLs that arise in elderly people usually do not show evidence of EBV expression. The distinction between PCNSLs and

monomorphic CNS PTLDs lies in the clinical history, response to therapy, and clinical outcomes. The requirement for transplantation--solid organ or bone marrow allograft--together with post-transplant immunosuppression is absolute for the diagnosis of PTLDs. The majority of PTLDs in other organ sites occur within 1 to 4 years after transplantation, with slightly shorter latency periods after azathioprine therapy. Similar latency periods (3-131 months) were seen for PTLDs that arose in the CNS.

The majority of CNS PTLDs were multifocal on neuroimaging studies, often with large numbers of discrete, contrast-enhancing masses. When the lesions of CNS PTLDs were multiple, the number varied from 3 to 9, and most were confined to the supratentorial compartment. In 4 cases, both infratentorial and supratentorial lesions were seen. The solitary lesions (cases 6 and 7) involved the pons and the parietal lobe, respectively. In contrast, PCNSLs can be solitary or multifocal, depending mostly on the immunologic status of the patient. Up to 80% of PCNSLs that arise in immunocompromised patients are multifocal. In contrast, the majority of PCNSLs that arise in non-immunocompromised patients are solitary. Thus, neuroimaging features of CNS PTLDs overlap most with those of PCNSLs that arise in immunocompromised patients. It has been suggested that PCNSL is a "whole brain" disease, with diffuse involvement of CNS structures manifesting as solitary or multiple masses on neuroimaging, and the same may be true of CNS PTLDs. 32 Most neuroimaging studies of PCNSLs, as well as the clinical review of PTLDs by Phan et al, have stressed the intimacy of these lymphomas with the ependymal lining and distribution in the periventricular region. Distinguishing the contrast-enhancing lesions of CNS PTLDs or PCNSLs from infection by neuroimaging is not always possible, and a tissue-based diagnosis usually is required.

The term Epstein-Barr virus (EBV) induced post-transplant lymphoproliferative disorders (PTLD) describes a heterogeneous group of lymphoproliferative disease associated with EBV infection in solid organ and bone marrow transplant recipients. Lymphoid tumors were first described in transplant patients in 1968 and were called "reticulum cell sarcoma"; or as a subgroup of termed "pseudolymphomas" in light of their ability to undergo regression. *Frizzera et al*[3] first recognized the variable histologic appearances of these tumors and in 1981 introduced a pathologic classification to accommodate this histological heterogeneity. Clinically, these disorders may differ markedly in growth rates, and patients may manifest a spectrum of presentation varying from localized to disseminated involvement, and nodal to extranodal, including the allograft organ itself. Reported incidence of PTPD ranges from 0.8 to 20% and varies with the type of solid organ transplant, the age of patients transplanted, individual transplant centers and type of immunosuppression. The diagnosis of PTLD may convey mortality rates that range up to 50-80%.

In 1969 *Penn et al*[4] reported a case of a renal transplant patient on azathioprine and prednisolone who developed a rapidly progressive left hemiparesis. Brain biopsy revealed a tumor of lymphoid origin. The patient was given radiotherapy with synchronous dosage reduction of the immunosuppressive therapy. He demonstrated marked neurologic improvement with shrinkage of the mass. Two decades later Stariz et al[8] first used the term post-transplant lymphoproliferative disorder (PTLD) and suggested that reduction and/or discontinuation of immunocompressive medications could lead to

regression of the post-transplant malignancies.

Defining the clinical course, risk factors, and therapeutic results of PTLD have been severely limited due to the lack of: 1) a standard definition of PTLD; 2) an understanding of the pathogenesis of EBV-induced lymphocyte transformation and proliferation in transplant recipients; 3) standardized diagnostic techniques, and 4) randomized multicenter trails that examine effective prophylactic and therapeutically strategies. Two separate meetings have been organized of discussion and define future direction in the management of EBV-PTLD. The following document is a summary of the current knowledge of PTLD and of recommended areas that needs further development under the suspicious effects.

In addition, there are several practical aspects regarding the diagnosis of PTLD. Tissue biopsy is necessary to establish the diagnosis of PTLD. Excisional biopsy is preferred to provide adequate tissue for evaluation of cell type, clonality, virological studies, and architectural background. Needle biopsy should only be employed when larger biopsies are not practical. Cytology has a limited role in the diagnosis of PTLD, and should not be used to subclassify PTLD. The histological sample should be interpreted by a hematopathologist or a pathologist familiar with the histopathological features of PTLD. Communication between clinicians and pathologists is essential in directing the diagnostic work-up and ensuring that appropriate tissue for evaluation as expeditiously as possible. Ancillary diagnostic tests are primarily DNA-based and it is not necessary to preserve RNA except for research purposes. The single RNA-based diagnostic test currently in use employs in situ hybridization for EBV early RNA. Because this RNA species has extensive secondary structure, it is capable of surviving routine tissue handling and processing.

Although no specific staging system exists for PTLD, the ANN Arbor Staging Classification with Cotswold Modifications, which is currently used to stage non-Hodgkin's lymphomas, has been used for PTLD. It should be noted that although most EBV-PTLDs are of B cell origin, a small proportion arise from T cells. Finally, lymphomatous PTLD can be indistinguishable from the typical lymphoma or myeloma in which EBV is not present. Thus, these diseases should be recorded but not categorized as EBV negative PTLD, as it is currently unknown whether their incidence is higher in transplant patients versus the general population.

Quantitative EBV polymerase chain reaction technology is a promising innovation that may allow for an earlier diagnosis of PTLD and identification of those patients likely to develop PTLD. However, additional study is required before recommending it for routine clinical use. Important consideration includes the standardization of specimen type and the methodology of quantitation. Efforts should be directed at correlating quantitative PCR values in relation to: 1) outcome as related to level of EBV copies in peripheral blood at the time of PTLD diagnosis; 2) genome levels and response to therapy; 3) predicting development of PTLD for different types of organ allograft. Other areas for further study include EBV protein expression in PTLD and the role of lytic virus in PTLD.

Prospective multi-institutional studies are necessary to accrue sufficient case material to assess the usefulness of present reporting systems, and examine the applicability of systems such as the international Prognostic Index for non-Hodgkin's lymphoma in PTLD. Such studies could also uncover

other features of clinical significance, which should be incorporated into the diagnostic evaluation of PTLD. Although current definition of PTLD are solely focused on histological classification, nonhistological classification such as those that address clinical features of PTLD, could be of additional value in the prognosis of PTLD and therapeutically interventions.

Ho and colleagues[6] reported on a series of pediatric kidney transplant recipients. Patients who were EBV seronegative at time of transplantation had a 10% frequency of PTLD compared with patients who were EBV positive at the time of transplantation, who had a 0% frequency of PTLD. At the same institution, PTLD frequencies in adults who were EBV seronegative and EBV seropositive were 4.9% and 1.6%, respectively. Despite these figures, Harwood and colleagues[21] were unable to document any increase in PTLD in a series of EBV-seronegative pediatric thoracic transplant patients who received organs from seropositive donors. They concluded that EBV matching was not justified in this population.

Most patients with PTLD present with at least 1 tumor. About two thirds of these tumors are extranodal, and about one third are nodal. There is a tendency to involve specific sites. The gastrointestinal tract is involved in about 26% of cases and CNS in about 27% of cases. The allograft can also be involved. In this case, the frequency of involvement varies according to the specific type of allograft. PTLDs that arise in lung or intestinal transplant recipients involve those allografts in up to 80% of cases. The reason for this is not known. However, it is interesting that the lung and bowel are transplanted with a large indigenous lymphoid population. PTLDs that occur in patients receiving other types of allografts, such as liver and kidney, involve the allograft in about one third of cases. In contrast, the transplanted heart is only rarely involved with these tumors.

Imaging findings by MRI showed ring-enhancing lesion, which its wall appeared smooth, uniform, with dark T2W signal, favored brain abscess. However, on diffusion weight imaging (DWI), typical pyogenic brain abscess commonly showed restricted diffusion, due to presentation of inflammatory cells in its central core. Contrast to neoplasm, it appeared irregular thickened hyperintense-T2W signal change at its wall, may re restricted diffusion but at its central core which are contained tumor necrotic fluid collection must be not restricted diffusion. The reported cases showed incomplete restricted diffusion in its wall and partly in central core, caused equivocal differentiation between brain abscess to brain tumor. So biopsy of the lesion was performed for the definite diagnosis.

Initial treatment for PTLD is to reduce immunosuppression. A response is usually seen within 2-4 weeks of withdrawal of immunosuppression, and reduction in immunosuppression alone leads to long-term disease-free remission in 25-73% of adults. The chances of complete remission seem to be directly related to the degree of differentiation of neoplasm. Early and infectious mononuleosis-like lesions tend to regress more often with reduction in immunosuppression alone, compared to monomorphic PTLD. A proportion of cases of both types, however, require chemotherapy. The benefit of withdrawing immunosuppression and the risk of transplant rejection need to be carefully reconciled. The institution of chemotherapy also brings inherent risks of infections and *de novo* malignancies. Antiviral agents seem to have some effects on the early hyperplastic lesions. However, these agents do not

have significant effects on the lesion once monoclonality has emerged.

Another common dilemma is differentiation opportunistic infections and PTLD. Patients with immunosuppression after organ transplantation are at increased risk of infections and sepsis. However, it should be noted that opportunistic infections with positive tissue and/or blood cultures might mask an underlying hematological malignancy. Since immunosuppressed patient are at increased risk of developing opportunistic infections and hematological malignancies, both possibilities need to be considered on the differential diagnosis. This cases report stress the importance of biopsies of brain lesion in immunosuppressed patient following bone marrow and renal transplantation to direct appropriate treatment in an expedition fashion.

Conclusion

In conclusion, we have learned much about PTLD, but much cooperative work remains to be done before this disease can be conquered. EBV positive PTLD has served as a model of virus-associated lymphomagenesis, and the lessons learned here may have applicability in other tumor systems as well. As EBV-positive lymphomas are prevented or successfully treated, our attention will turn to EBV-negative tumors and other forms of neoplasia that continue to plague transplant recipients. For the present, however, awareness of PTLD and an aggressive stance toward the diagnosis of this disease, together with graded therapy using the best means available for the individual disease, remain our best form of defense against this theoretically fascinating yet deadly enemy.

References

1. Dr Frank Gaillard. Post transplant lymphoproliferative disorder (PTLD): September 4, 2009.
2. 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 Feb;121(2):246-53.
3. Penn I. The changing pattern of post-transplant malignancies. Transplant Proc 1991 Feb;23(2):1101-3.
4. Starzl TE, Poster KA, Iwatsuki S, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine-steroid therapy. Lancet 1984;1:583(8)
5. Ho M, Breinig MK, Dummer JS, et al. Epstein-Barr virus infections and DNA hybridization studies in post-transplantation lymphoma and lymphoproliferative lesions: the role of primary infection. J Infect Dis 1985 Nov;152(5): 876-86.
6. Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders (PTLD): Summary of Society Hematopathology Workshop. Semin Diagn Pathol 1997 Feb;14(1):8-14.
7. Michael Nalesnik, MD, Anthony J. Demetris, MD, John J. Fung, MD, PhD, Posttransplantation Lymphoproliferative Disorders.
8. Parmjeet Randhawa, MD, Adriana Zeevi, PhD. Authors and Disclosures Published: 03/31/2000