**CLINICAL VIGNETTE**

# Post-Transplant Lymphoproliferative Disorder: EBV Viremia Leading to Detection of Diffuse Large B Cell Lymphoma in a Liver Transplant Patient

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The patient is a 63-year-old male with history of orthotopic liver transplant five years prior due to end stage liver disease due to alcoholic cirrhosis.

His past medical history also includes CKD and CAD, complicated by ischemic cardiomyopathy. His liver transplant was complicated by acute cellular rejection requiring increase in immunosuppression with tacrolimus and azathioprine.

He presented to the ED with abdominal pain, ocular pressure, headache, and diplopia. He was afebrile with stable vital signs. Basic laboratory data was significant for creatinine 1.4mg/dL near his baseline, mild chronic anemia with hemoglobin 12.8gm/dL, and serum LDH 823units/L.

CT abdomen/pelvis revealed a 6.5 x 5.9 x 5.4 cm retroperitoneal mass. MRI abdomen confirmed the 7.9 x 7.1 cm retroperitoneal abnormality which encased the inferior vena cava and most of the abdominal aorta. MRI brain showed abnormal soft tissue in right side of cavernous sinus and right side of sella turcica. MRI sella (pitiutary) showed a 1.0 x 1.7 x 1.2 cm mass involving the right cavernous sinus and the right sella turcica.

Interventional Radiology performed CT guided biopsy of the retroperitoneal mass. Pathology revealed CD10 positive high-grade/diffuse large B-cell lymphoma with Ki67 close to 100%. Flow cytometry was consistent with B-cell NHL (CD20+). Serum Epstein Barr viral DNA was positive at 15,700. Oncology was consulted and started Rituximab.

Review of prior outpatient labs revealed elevated EBV quantitative viral DNA as high as 96,776 copies per ML one year prior.

Following a 28-day hospitalization, he was discharged with close follow-up with oncology, transplant ID, hepatology, and neurology.

Post-transplant lymphoproliferative disorders (PTLD) are lymphoid and/or plasmacytic proliferations that occur as a result of immunosuppression in the setting of solid organ or allogeneic hematopoietic cell transplantation. These conditions lie along a continuum of disease categorized by the World Health organization PTLD classification system[1] and are among the most serious complications of transplantation.

Lymphoproliferative disorders are potentially fatal complications of chronic immunosuppression in solid organ and hematopoietic cell transplant recipients. While the overall incidence of lymphoproliferative disease is approximately 1 percent in the transplant population, the incidence varies with type of allograft, being lowest among hematopoietic cell, renal, and liver transplants, higher in heart and lung transplants, and highest in intestinal and multiorgan transplants.[2]

The pathogenesis of PTLD in most patients relates to the outgrowth of Epstein-Barr virus (EBV)-positive B cell proliferations in the setting of chronic T cell immunosuppression. However, EBV-negative tumors and T cell tumors have also been reported.[3]

EBV infection is common in most parts of the world, with up to 90 to 95 percent of adults showing serologic evidence of infection.[3] Acute EBV infection leads to a polyclonal expansion of B cells harboring the virus. In immunocompetent individuals, viral antigens expression by these B cells elicit a cytotoxic T cell response that eliminates the vast majority of the infected B cells. Such a host response is often associated with the clinical syndrome of acute mononucleosis. However, a small subpopulation of the infected B cells downregulates viral antigen expression and escapes immune surveillance. These latently infected B cells persist throughout life and, if T cell immunity wanes, can give rise to lymphoproliferative disorders such as PTLD.[4]

The principal risk factors for the development of PTLD are the degree of overall immunosuppression and the EBV serostatus of the recipient. Additional risk factors include time post-transplant, recipient age, and ethnicity.[5]

The clinical presentation of patients with PTLD is highly variable and depends at least partially on the type of PTLD and the areas of involvement. Non-specific constitutional symptoms such as fever, weight loss, and fatigue are common. Other symptoms may be related to viral infection, lymphadenopathy, dysfunction of involved organs, or compression of surrounding structures. More than half of patients with PTLD present with extranodal masses. Involved organs include gastrointestinal tract (stomach, intestine), lungs, skin, liver, central nervous system, and the allograft itself.[6,7]

The main types of PTLD in transplant recipients include polyclonal morphologically benign lymphoproliferation (early lesions); florid follicular hyperplasia; polyclonal or monoclonal polymorphic B cell proliferations with some features of malignant lymphoma; and monoclonal proliferations, often with clonal cytogenetic abnormalities, that meet criteria for B cell or T cell lymphoma seen in immunocompetent patients, both non-Hodgkin and Hodgkin type.[1]

Accurate diagnosis of PTLD requires a high index of suspicion. The diagnosis should be suspected in a patient who has undergone allogeneic transplantation presenting with adenopathy, B symptoms (fever, weight loss, night sweats), unexplained hematologic and biochemical abnormalities, and/or signs or symptoms attributable to the infiltration of extralymphatic tissues. Radiologic evidence of a mass, or elevated serum LDH are suggestive of PTLD. Findings on positron emission tomography (PET) scanning also favor the diagnosis,[8] as well as rising EBV viral load. A tissue biopsy, preferably an excisional biopsy, with review by an expert hematopathologist, is required to ensure accurate diagnosis. Diagnosis of central nervous system or cardiac lymphoma is particularly difficult.[9]

Transplant centers have incorporated EBV monitoring into the routine evaluation of patients at high risk for PTLD so that patients can be considered for pre-emptive management of PTLD at the time of viral reactivation before the overt emergence of PTLD.

Management of PTLD has varied according to the type of lymphoproliferative disease.

Immunosuppression reduction is the main therapy. Additional therapies include immunotherapy with the CD20 monoclonal antibody rituximab, chemotherapy (R-CHOP), and radiation therapy.[10]

Prognosis varies with clonality and extent of disease with overall survival rates between 25 to 35 percent.[11] Mortality with monomorphic PTLD has been reported as high as 80 percent.[12]

***Discussion***

Our vignette highlights an important complication in the allogeneic transplant patients. Acute cellular rejection, in our patient with history of orthotopic liver transplant, required escalation of immunosuppression leading to increasing EBV viremia, likely resulting in the development of PTLD. Providers should continue to be vigilant in surveillance for the development of this diagnosis in the appropriate clinical setting.

***Figures***

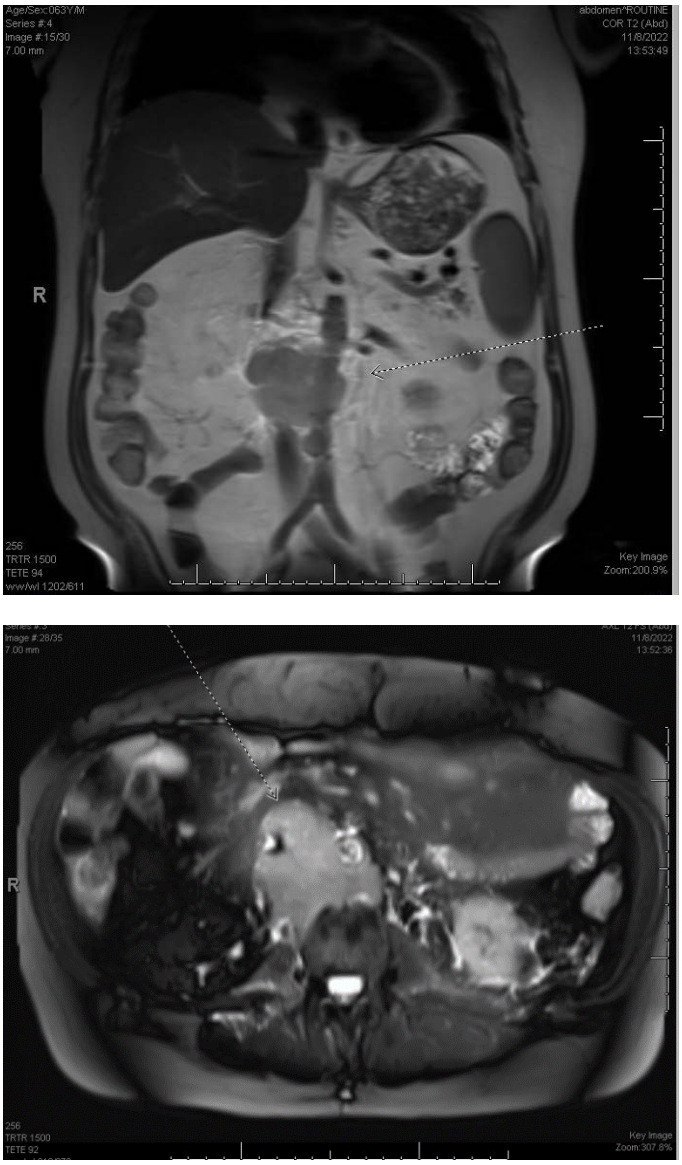


Figure 1: MRI Abdomen w/ w/o contrast (frontal and transverse). 7.9 x 7.1 cm retroperitoneal abnormality, encasing the inferior vena cava and most encasing the abdominal aorta. Findings likely represent retroperitoneal lymphadenopathy, possibly from lymphoma.

Two additional structures in the fat adjacent to the right kidney, with the larger measuring 1.6 x 1.3 cm, probably additional abnormal lymph nodes.

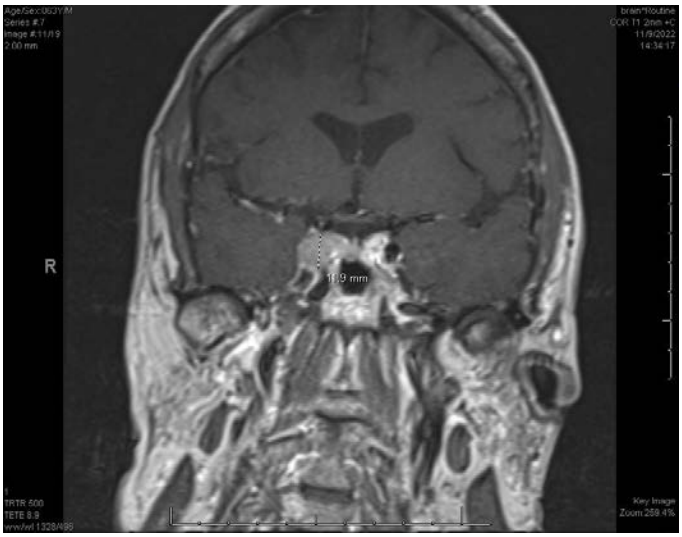

Figure 2: MRI Pituitary with contrast. 1.0 x 1.7 x 1.2 cm mass involving the right cavernous sinus and the right sella turcica. Considerations may include lymphoma/PTLD given the concurrent abdominal findings, versus other lesions in this region such as a pituitary adenoma or meningioma.

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