Successful Treatment of Primary Central Nervous System Post-transplant Lymphoproliferative Disorder after Liver Transplant using Methotrexate: A Novel Case Report

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ABSTRACT

Post-transplant lymphoproliferative disorder (PTLD) is a malignancy that occurs in 2-20% of solid organ transplant recipients. Isolated, primary central nervous system (PCNS) PTLD is exceedingly rare, with existing data limited to case reports and case series. The diagnosis of PCNS PTLD is difficult to diagnose given 1) non-specific clinical presentation and 2) burden of immunosuppression broadens diagnostic possibilities, often requiring extensive testing to reach a definitive diagnosis. We present the first known case of isolated PCNS PTLD after liver transplantation safely treated with methotrexate. Our case highlights the complex diagnostic and treatment considerations in the setting of immunosuppression and maintenance of adequate graft function.

KEYWORDS: Liver transplant; PTLD, immunosuppression; EBV

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) accounts for up to 20% of all malignancies after solid organ transplantation and occurs in 1.0-5.5% of liver transplant recipients [1]. It typically occurs within one year of transplant secondary to immunosuppression induction but can occur up to fifteen years after transplant due to the total immunosuppressive burden [2, 3]. The two most significant risk factors are previous Epstein Barr Virus (EBV) infection and degree of immunosuppression [4]. Very rarely, PTLD manifests as an isolated, primary central nervous system (PCNS) disease that is best diagnosed via brain biopsy identifying malignant lymphocytes in the central nervous system (CNS). This primary central manifestation is typically characterized by a multifocal ring-enhancing or homogenously enhancing lesion in the brain [5]. Symptoms may include sensory or motor weakness, vision loss, and/or difficulty with speech. Due to post-transplant immunosuppression, the differential diagnosis for new-onset focal neurologic deficits in these patients is broad and includes infection, medication toxicity, thrombotic events, malignancy, and others. Several case reports and case series exist of PCNS PTLD in transplant recipients [6], with very few involving liver transplant recipients [7, 8]. We present a 61-year-old male liver transplant recipient who presented with new right-sided facial numbness and was diagnosed with PCNS PTLD safely treated with methotrexate.

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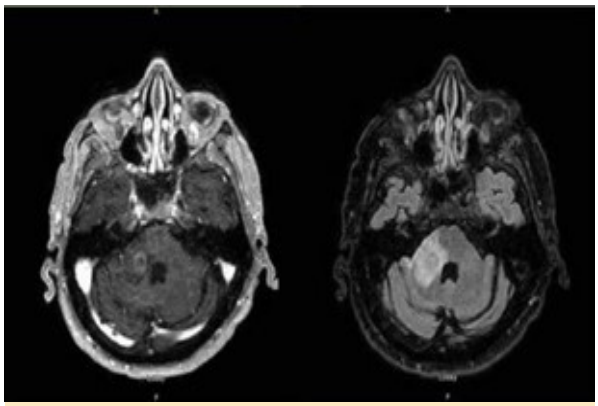

Figure 1: Initial MRI with Axial T1 3D (left) and Axial T2 Flair (right).

CASE PRESENTATION

A 61-year-old male status-post EBV positive, donation after brain death liver transplantation for decompensated alcohol-associated cirrhosis receiving tacrolimus for immunosuppression, valganciclovir for cytomegalovirus (CMV) viremia, and isoniazid (month 8 of 9) for latent tuberculosis (TB) presented for an outpatient liver biopsy 129 days post-transplant. Immunosuppression induction history included thymoglobulin, high-dose glucocorticoids, followed by maintenance tacrolimus, mycophenolate sodium, and prednisone taper. He had developed elevated liver biochemical tests with aspartate aminotransferase (AST) 91, alanine transaminase (ALT) 99, alkaline phosphatase (ALP) 103 from AST 20, ALT 35, ALP 78 four weeks earlier. Liver biopsy was planned to rule out acute graft rejection.

While in the pre-operative area, he reported a one-week history of right-sided facial numbness and was admitted for further workup. Magnetic resonance imaging (MRI) of the brain with and without contrast revealed a 1.2 x 0.8 x 1.2 cm enhancing lesion in the right brachium pontis with surrounding edema and central necrosis (Fig. 1). Computed Tomography (CT) of the chest/abdomen/pelvis did not show any abnormalities to explain the brain lesion. Cerebrospinal fluid (CSF) studies for cell count, glucose, protein, mycoplasma, borrelia, acid fast bacilli, CMV, human polyoma virus 2 (JC virus), West Nile, fungal cultures, autoimmune encephalopathy panel, and lymphoma cell markers were unremarkable. Serologies for EBV were positive. Institutional tumor board recommended brain biopsy, but the patient declined due to the need for a full craniotomy.

He was readmitted five days later, 137 days post-transplant, due to worsening headache and postural instability. Empiric treatment for fungal infection and TB was initiated, but he developed worsened confusion, truncal ataxia, and hallucinations. Positron emission tomography (PET) scan was negative for uptake outside the brain, and infectious workup including Karius testing, a proprietary test that can identify over a thousand bacteria in the blood using cell-free DNA, and blood cultures were negative. A repeat brain MRI showed an increase in brain lesion size to 3.7 x 2.9 cm with new involvement of the adjacent cerebellar white matter and brainstem - suggestive of PTLD. Brain biopsy revealed atypical perivascular and intraparenchymal lymphoid infiltrates with prominent, irregular nucleoli and positive immunostaining for EBV-encoded RNA in-situ hybridization (EBER-ISH), consistent with polymorphic PTLD (Fig. 2 and Fig. 3).

High-dose methotrexate/leucovorin was started 152 days post-transplant. Leucovorin was discontinued after methotrexate assay reached an appropriate level, and he ultimately was discharged to an acute rehab facility on methotrexate and rituximab 169 days post-transplant. Follow up MRI two months after initiation of methotrexate initiation demonstrated reduction in lesion size to 1.0 x 1.0 cm in the right pons and 0.9 x 0.5 cm in the right middle cerebellar peduncle (Fig. 4). His liver function remains intact with no evidence of hepatotoxicity secondary to methotrexate therapy.

Timeline of patient's clinical course was shown in Fig. 5.

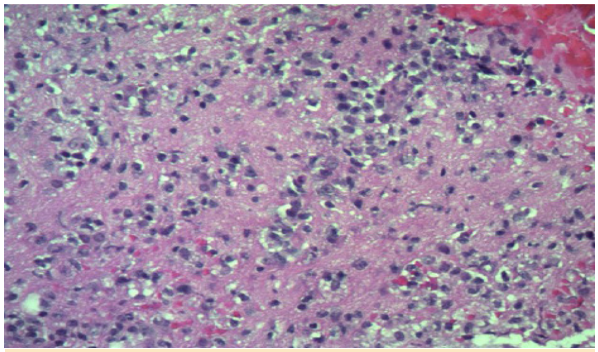

Figure 2: H&E stain with 20x magnification showing diffuse infiltrate of variable sized atypical B-cells.

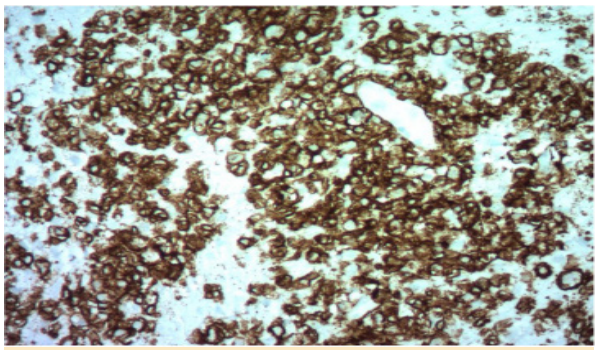

Figure 3: CD20 immunohistochemistry stain showing diffuse infiltrate of variable sized atypical B-cells.

DISCUSSION

We present the first known case of PCNS PTLD successfully treated with methotrexate after liver transplant. Treatment of PTLD includes reduction of immunosuppression. For CD-20 positive tumors, rituximab is associated with better outcomes than reduction of immunosuppression alone [9]. For systemic disease and select patients with localized disease, chemotherapy (rituximab-cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone

or R-CHOP), radiation, and surgery can be considered [9,10]. The two primary goals of therapy are eradication of the PTLD and preservation of graft function.

In our case, the tumor did express CD-20, therefore rituximab was given. However, other chemotherapies that typically treat PTLD were not used due to their inability to penetrate the CNS. Radiation therapy was also not considered for the patient at the time as it is typically reserved for CNS relapse or palliative care [10]. Treatment of PCNS PTLD using high-dose methotrexate with leucovorin has shown efficacy in renal transplant recipients [11]. Since methotrexate can cause hepatotoxicity and fibrosis after as little as two grams lifetime dose, administering high-dose methotrexate to a newly transplanted liver raised concerns among our transplant team. However, given the lack of other options for PCNS PTLD treatment, it was ultimately used.

The most significant risk factors for the development of PTLD are EBV positivity of the patient and degree of immunosuppression [4]. Our patient was EBV-positive and had received a liver graft from an EBV-positive donor. He received induction of immunosuppression with thymoglobulin, high-dose glucocorticoids, followed by maintenance tacrolimus, mycophenolate sodium, and prednisone taper. This degree of immunosuppression is comparable to most liver recipients. He also completed three months of valacyclovir and is currently continuing his one-year course of trimethoprim-sulfamethoxazole for CMV/Herpes Simplex Virus and pneumocystis pneumonia prophylaxis. Additionally older recipient age, race, and allograft type have been factors associated with PTLD risk. However, research on this topic is sparse, especially for PCNS PTLD [9].

Although the prognosis in our case is guarded and overall response is to be determined as he continues to undergo treatment, serial MRI scans since initiation of treatment show improvement in the size of the brain lesion and normalization of liver function tests.

Though uncommon, gastroenterologists and hepatologists should be aware of PCNS PTLD as a potential cause of focal neurologic deficits in liver transplant recipients. Additionally, our case demonstrates that high-dose methotrexate, despite its association with hepatotoxicity, may be a safe treatment option in liver transplant recipients.

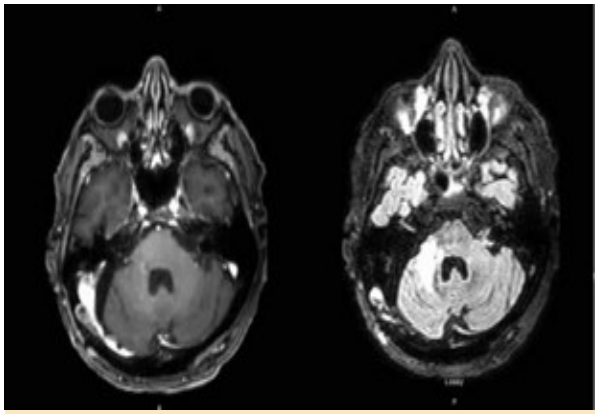

Figure 4: Post-Treatment MRI with Axial T1 3D (left) and Axial T2 Flair (right).

CONFLICTS OF INTEREST: None declared.

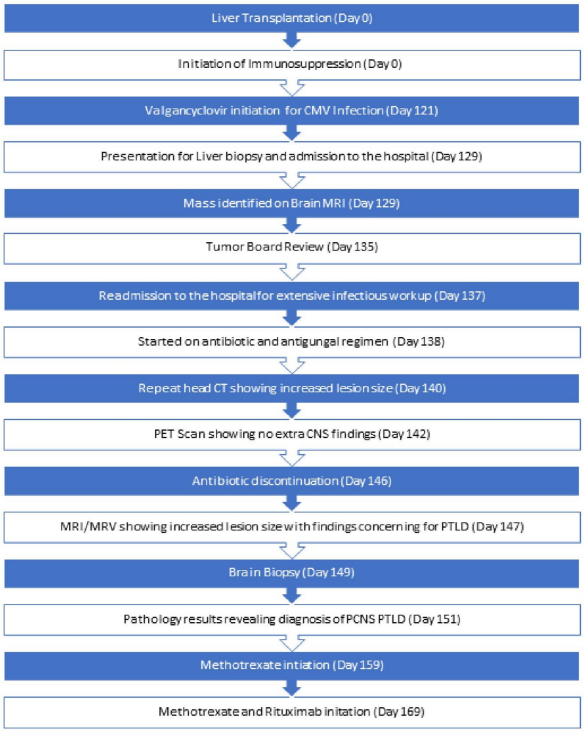

Figure 5: Timeline of patient's clinical course.

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