CASE REPORT | LIVER

Posttransplant Lymphoproliferative Disorder Isolated to the Adrenal Gland in a Liver Transplant Patient

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ABSTRACT

Posttransplant lymphoproliferative disorder (PTLD) is a serious complication that accounts for up to 20% of malignancies after solid organ transplantation. We describe a rare case of isolated PTLD in the adrenal gland occurring 7 months after liver transplant in a patient who developed a primary Epstein-Barr virus infection. He was treated with rituximab and his immunosuppression regimen was minimized. We review the incidence, pathogenesis, presentation, and management of PTLD in the liver-transplant population. Our case highlights the variation in the presentation of PTLD and the importance of a high index of suspicion among the at-risk group.

INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) occurs in an estimated 0.9–5% of the liver transplantation (LT) population and has a mortality rate as high as 50%.[1-3] The adrenal gland is a rare site of PTLD.

CASE REPORT

A 59-year-old African-American man underwent deceased-donor LT for decompensated alcoholic cirrhosis complicated by a 2.3-cm hepatocellular carcinoma (HCC) and portopulmonary hypertension. His HCC lesion had been embolized; the explant did not demonstrate additional HCC or evidence of lymphovascular or biliary invasion. The patient was Epstein-Barr virus (EBV)-seronegative prior to the LT, while the donor was EBV-seropositive.

Posttransplant immunosuppression included mycophenolate mofetil 1 g twice daily, methylprednisolone tapered over 3 months, and tacrolimus with a trough goal of 8–10 ng/mL during the first 2 months, as well as valganciclovir for cytomegalovirus (CMV) prophylaxis for 3 months. At 2 months post-LT, immunosuppression was changed to low-dose tacrolimus with a trough level of 3–4 ng/mL and everolimus with a trough level of 7–8 ng/mL to minimize nephrotoxicity.

At 3 months post-LT, primary EBV infection was diagnosed with 1,964,383 copies/mL. Liver biopsy demonstrated moderate acute rejection with concomitant EBV infection of the allograft as shown by immunohistochemistry and in-situ hybridization (Figure 1). The patient was treated with 1 g solumedrol daily for 3 days as well as 4 days of intravenous immunoglobulin. Liver function tests improved, and biopsy 3 weeks later showed resolution of rejection.
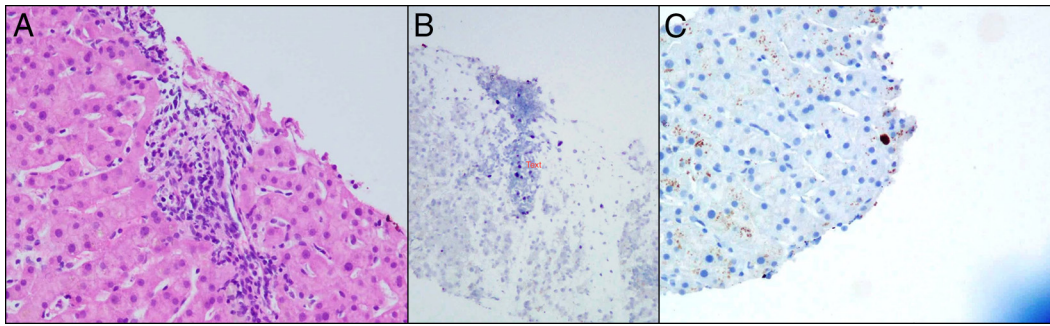
Figure 1. (A) Liver biopsy showing mild acute cellular rejection with focal portal and central vein endothelialitis and focal lymphocytic cholangitis. (B) Immunohistochemical stain for latent membrane protein-1 showing only a single positive cell. (C) Epstein-Barr virus (EBV)-encoded RNA in-situ hybridization showing scattered positive portal and rare lobular cells consistent with EBV infection.

Three months later, the patient complained of fatigue and headache. The EBV viral load was significantly elevated at 400,668 copies/mL. Positron-emission tomography-computed tomography (PET-CT) showed a new 1.9-cm fluorodeoxyglucose-avid lesion in the left adrenal gland that was concerning for metastatic HCC (Figure 2). Biopsy of the adrenal gland showed polymorphic B-cell PTLD with CD45-positive, CD20-positive, and PAX5-positive large cells with positive EBV by in-situ hybridization, as well as Reed-Sternberg cells that were CD15-negative. Liver biopsy was normal (Figure 3).

Tacrolimus was discontinued; everolimus and prednisone were continued. After 4 weekly infusions of rituximab, his EBV viral load was undetectable (<200 copies) and repeat imaging revealed no new masses or lymphadenopathy. Thus, he was scheduled to receive 4 cycles of consolidative rituximab every 21 days.[4]

DISCUSSION

PTLD represents about 20% of all malignancies in the solid-organ transplant population.[1,2] Polyclonal lesions have features of reactive plasmacytic hyperplasia, whereas monoclonal lesions may be reported as polymorphic PTLD, monomorphic PTLD, or classic Hodgkin lymphoma-type PTLD.

Monomorphic B-cell PTLD is most common. Polymorphic PTLD, as seen in our patient, demonstrates lymphocytes at varying stages of differentiation, mitotic figures, and Reed-Sternberg cells. Most cases of PTLD are associated with EBV, although PTLD has also been reported with CMV.[5] EBV-negative PTLD is less common and has a poorer prognosis.[6]

Symptoms of PTLD include fever, lymphadenopathy, diarrhea, allograft dysfunction, weight loss, and splenomegaly.[7] Imaging may show enlarged lymph nodes, splenomegaly, low-attenuating nodular lesions in the affected organ, and a porta hepatis mass with direct extension into the biliary tree, which is unique to LT patients.[8] PET-CT has been found to be more sensitive than CT in diagnosis of PTLD.[9] In LT patients, extranodal PTLD is more common, and the liver itself is involved in 21–50% of cases.[8] Risk factors include younger age, use of antibodies for immunosuppression induction, and amount of donor lymphoid tissue transplanted.[10]

Primary EBV infection in the early posttransplant period, as in our patient, carries a higher risk for development of PTLD.[2] EBV is a ubiquitous DNA herpesvirus that targets epithelial cells of the oropharynx and has a unique life cycle that can result in latent infection.[11] EBV can be transmitted to
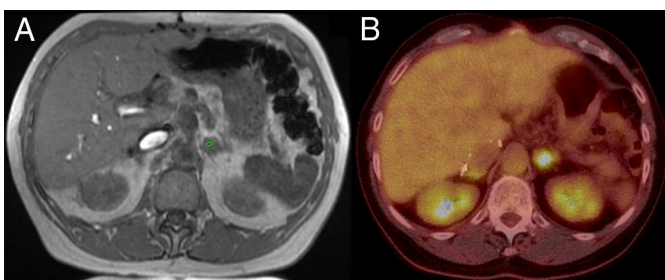
Figure 2. (A) Non-contrast abdominal/pelvic computed tomography (CT). (B) Positron-emission tomography-CT showing a fluorodeoxyglucose-avid left adrenal lesion measuring up to 1.9 cm with a max standardized uptake value of 7.0 (Deauville X).
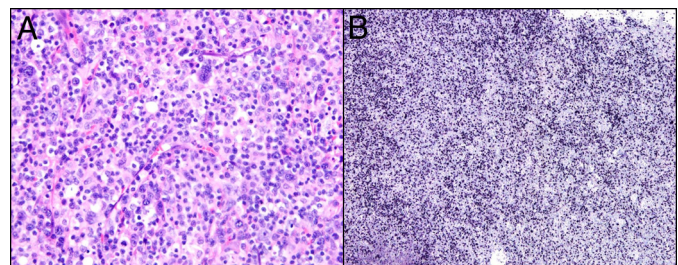
Figure 3. (A) Atypical lymphoid infiltration of adrenal parenchyma on hematoxylin and eosin staining is composed of a mixture of plasma cells, small lymphocytes, and scattered larger lymphoid cells, some resembling immunoblasts and others Reed-Sternberg cells. (B) Diffuse positive staining for EBV by EBV-encoded RNA in-situ hybridization.

seronegative patients when donors are seropositive or when non-leukoreduced blood products are used for transfusion.[7] Although testing for serological conversion is of low utility, longitudinal monitoring of EBV viral load is recommended in the pediatric population and may be useful for identifying adults at risk.[2] A rising EBV viral load should prompt further investigation for PTLD with PET-CT and, if applicable, excisional biopsy. A comprehensive staging and pretreatment workup is necessary.

Immune suppression reduction is the first step in treatment.[10,12] The specifics of immune-suppression reduction are individualized based on the transplanted organ, the extent of PTLD, and the risk of graft rejection. European and American guidelines recommend discontinuation or dose reduction of antiproliferative agents such as mycophenolate and azathioprine in limited disease.[12] In more extensive disease, the dose of calcineurin inhibitor (tacrolimus) is also reduced by 50%. Switching to a mechanistic target of rapamycin inhibitor may be considered.[6] Patients are often maintained on 7.5–10 mg/d prednisone. In critically ill patients with extensive disease, all immunosuppression except for prednisone is discontinued.[12]

Rituximab is incorporated in the first-line treatment of CD20-positive PTLD with extensive disease or limited disease if immune-suppression reduction fails.[13] Response to rituximab is approximately 44–65%, with a 1-year survival rate of 67%.[1,2] CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) should be considered in patients who do not respond to rituximab or have high-grade lymphoma or critical organ compromise; cytotoxic chemotherapy remains the only modality available to achieve remission in patients who do not respond to rituximab, but in a randomized study of CD20-positive monomorphic PTLD, patients who failed to respond to rituximab alone had worse overall prognosis.[4,14] Antiviral therapy such as acyclovir or ganciclovir is not recommended. Surgical resection or radiotherapy may be considered in some patients, although the utility of local control is unclear.[2]

Adrenal involvement usually presents in advanced stages of PTLD as unilateral involvement with diffuse enlargement of the gland. To our knowledge, only 2 cases of isolated adrenal gland PTLD in LT patients and 2 cases after allogenic hematopoietic stem cell transplantation have been reported.[15,16] Overall, adrenal involvement in the solid-organ transplant population is reported at 8%.[8]

PTLD of the adrenal gland is a rare complication of LT that can be diagnosed through careful surveillance of clinical status, EBV viral load, and appropriate imaging and pathological analysis. Treatment consists of modulation of immunosuppression and chemotherapeutic agents such as rituximab. After 4 sessions of rituximab-consolidation therapy, our patient achieved a complete response and remains in remission to date.

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