An Unusual Cause of Acute Pancreatitis in a Liver Transplant Recipient

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Abstract. Posttransplant lymphoproliferative disorder (PTLD) in liver transplant recipients is relatively uncommon, with an estimated incidence of 1%–3%. Retrospective reviews of liver transplant recipients have mainly reported posttransplant lymphoproliferative disorder affecting the liver, gastrointestinal tract, or lymph nodes. In this case report, we describe a 45-y-old female with a history of deceased donor liver transplantation for autoimmune hepatitis who had recurrent hospital admissions for acute pancreatitis. Ultimately, imaging revealed numerous complex pancreatic and peripancreatic masses, appearing to originate from pancreatic lymphoid tissue. Tissue biopsy later confirmed monomorphic Epstein-Barr virus-negative large B-cell lymphoma. Overall, PTLD involving the pancreas after liver transplantation is incredibly rare. The patient’s cumulative immunosuppression drug dose and time posttransplant were suspected to be her main risk factors, given that she had been exposed to several years of treatment with tacrolimus, azathioprine, mycophenolate mofetil, and prednisone. She was treated with rituximab monotherapy and later escalated to chemoimmunotherapy due to lack of response. PTLD involving the pancreas is an unusual cause of pancreatitis and should be considered in cases of recurrent pancreatitis in transplant recipients.

INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) in liver transplant recipients is uncommon, with an estimated incidence of 1% to 3%.1–3 The variable incidence is likely due to differences in patient populations, immunosuppression strategies, and allograft types. Risk factors include age (bimodal distribution), increased intensity of T-cell immunosuppression, viral infections, and early time after transplantation.2

We describe a liver transplant recipient who presented with recurrent, unexplained episodes of pancreatitis and ultimately was found to have pancreatic masses consistent with Epstein-Barr virus (EBV)-negative diffuse large B-cell lymphoma. PTLD involving the pancreas is an unusual cause of pancreatitis and should be considered in cases of recurrent pancreatitis in transplant recipients.

CASE DESCRIPTION

A 45-y-old female presented to the hospital with 1 wk of abdominal pain associated with poor appetite and intermittent fevers. She had 2 recent admissions for acute pancreatitis of unknown etiology, with workup negative for alcohol use, gallstones, hypertriglyceridemia, hypercalcemia, andDefine IgG4 at first use. disease. Computed tomography imaging at that time did not reveal any lesions.

Her medical history included autoimmune hepatitis for which she received a deceased donor liver transplant in 2006 later complicated by alloimmune hepatitis, as well as leukocytoclastic vasculitis of the skin. Notable medications at the time of admission included tacrolimus 3 mg BID and mycophenolate mofetil (MMF) 1000 mg BID for immunosuppression, and prednisone 20 mg daily for...
leukocytoclastic vasculitis. She had also received 2 doses of rituximab 5 mo earlier to treat vasculitic skin lesions. On presentation, she was tachycardic with a low-grade fever. Her abdominal exam revealed diffuse epigastric tenderness. Hepatic function panel was normal with the exception of an alkaline phosphatase of 379 units/L. EBV viral load detection by polymerase chain reaction (Viracor Eurofins Laboratories, Lee’s Summit, MO) was negative with a lower limit of quantitation of 49 international units/mL, and lactate dehydrogenase was elevated at 321 units/L. Lipase was also elevated at 196 units/L, although decreased from 938 units/L at the prior presentation.

Contrast-enhanced computed tomography of the pancreas revealed numerous complex pancreatic and peripancreatic masses, as well as encasement of the splenic artery and the superior mesenteric vein (Figure 1). Given the multiplicity of lesions, preserved pancreatic parenchyma, and involvement of vasculature, atypical diagnoses including lymphoma or other malignancies were favored over pancreatitis-related complications (eg, abscess or pseudocysts). She was kept nil per os, intravenous hydration was initiated, and pain was controlled with an intravenous patient-controlled analgesia pump.

An endoscopic ultrasound discovered a 5-cm heterogenous intra-abdominal lesion with mixed solid and cystic components, adjacent to the pancreatic body, without pancreatic ductal dilatation. Tissue biopsy later revealed predominantly necrotic tissue with small foci of viable large B cells (Figure 2). Considering the background of transplantation, the findings were consistent with monomorphic lymphoproliferative disorder (large B-cell lymphoma). Detection of EBV in tissue section via EBV-encoded small RNAs (EBER) and CD20 staining was negative.

Following diagnosis of PTLD, MMF was stopped, tacrolimus dose was decreased, and oral prednisone was tapered. Positron emission tomography revealed lymphomatous involvement of the pancreas, stomach, retroperitoneal lymph nodes, and bone marrow. Rituximab 375 mg/m² was initiated weekly for 4 wk. Repeat positron emission tomography following treatment showed an interval increase in size of the pancreatic masses and persistent lymphadenopathy. Treatment was escalated to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) but is currently on hold due to poor functional status.

**DISCUSSION**

We report a novel case of PTLD involving the pancreas after liver transplantation. Overall, pancreatic involvement of PTLD itself is exceedingly rare, although it is primarily documented in patients with pancreatic allografts. Similarly, retrospective reviews of liver transplant recipients have mainly reported PTLD with liver, gastrointestinal, and lymph nodal involvement. Our case was unique in that PTLD manifested as large mixed solid/cystic pancreatic and peripancreatic masses appearing to originate from pancreatic lymphoid tissue (Figure 1).

Notably, our patient lacked most traditional risk factors for PTLD. She was only 45 y old and already seropositive for EBV at the time of liver transplant. Indeed, she did have a high degree of immunosuppression, as she was on tacrolimus, prednisone, MMF, and recently, rituximab. Nevertheless, tacrolimus and MMF are relatively standard regimens for immunosuppression posttransplant, and none of these medications have definitively been linked to an increased risk of PTLD. The risk of PTLD posed by tacrolimus and azathioprine is controversial, and the contribution of MMF is unclear, with

**FIGURE 1.** Triple-phase computed tomography imaging of the pancreas at time of admission. A, Multiple complex cystic and solid masses within and adjacent to the pancreas. Note vascular involvement with encasement and occlusion of the splenic vein. B, Mass extending cranially from pancreatic tail into the lesser sac measures 6.3 × 6.1 cm. C, Mixed enhancing and hypoenhancing cystic lesion. The claw sign suggests origin from within the pancreas. Of note, the pancreatic parenchyma appears preserved.
had EBV-negative PTLD, which developed >14 y following transplantation. As rituximab targets B-cell clones, it is actually used to treat PTLD and thus is not thought to increase the risk of developing PTLD. In fact, some investigators have studied preemptive use of rituximab at the time of transplantation to prevent PTLD, primarily in hematopoietic stem-cell transplant recipients.

Ultimately, the patient's cumulative immunosuppression drug dose and time posttransplant were suspected to be the main risk factors. She had a complex immunosuppressive regimen following her transplant complicated by recurrent episodes of alloimmune hepatitis with attempts to wean immunosuppression. Prednisone was continued throughout the posttransplant period, and dose was often increased in the setting of rising liver enzymes and biopsy-proven alloimmune hepatitis. Initial goal trough level of tacrolimus following transplantation was 7–10 ng/dL, later lowered to 5–8 ng/dL in the setting of recurrent acute kidney injury. She was also on azathioprine instead of MMF for majority of the posttransplant period, initially transitioned due to pregnancy. Azathioprine doses were also frequently adjusted due to anemia. Eventually, azathioprine was switched back to MMF in the setting of worsening vasculitis. Overall, with the patient exposed to several years of treatment with tacrolimus, azathioprine, MMF, and prednisone, she was at elevated risk for a lymphoproliferative disorder. While our typical practice is to discontinue MMF 1 y following liver transplant and maintain posttransplant patients with good allograft and renal function on tacrolimus monotherapy; unfortunately, this was not possible in this patient given the aforementioned allograft, kidney, and rheumatologic issues.

Majority of cases of PTLD occur during the first year following transplantation. Jain et al documented a median time of development to 15 months in adults. Izadi and Taheri previously reported that late-onset PTLD (>1 y after transplantation) was more likely to present with disseminated disease and monomorphic lesions and had higher mortality compared with early-onset PTLD (<1 y after transplantation). Studies have also reported EBV-negative PTLD as more likely to present later and have worse prognosis. Further research remains to be done to characterize very late-onset PTLD (>10 y after transplantation). Our patient had EBV-negative PTLD, which developed >14 y following liver transplantation. Her aggressive and disseminated disease corresponds with these observations reported in the literature about EBV-negative and late-onset PTLD. She was treated initially with rituximab monotherapy, although given the worse prognosis and disseminated disease, chemoimmunotherapy with R-CHOP (often reserved for the relapsed/refractory setting) in the treatment-naive setting would have also been appropriate. In her case, this decision was made based on personal preference and concerns about her functional status.

In summary, PTLD involving the pancreas is rare but should be considered in cases of unexplained pancreatitis in organ transplant recipients, particularly those on high levels of immunosuppression.

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