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Post-Liver Transplant Lymphoproliferative Disorder at the Site of Bilio-enteric Anastomosis: A Rare Case Report and Literature Review

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1. Abstract

This is the case of a young man who underwent liver transplantation [LT] for primary sclerosing cholangitis [PSC] and experienced three episodes of treated acute cellular rejection during his follow-up. He subsequently developed obstructive jaundice, elevated liver function tests and a bilio-enteric anastomotic stricture six years after transplantation, which was detected by magnetic resonance cholangiopancreatography [MRCP] and endoscopic retrograde cholangiopancreatography [ERCP]. Tissue diagnosis from the anastomotic site indicated post-transplant lymphoproliferative disorder [PTLD], which was managed nonoperatively. PTLD is a potentially life-threatening complication following solid organ transplantation. This case demonstrates a rare presentation of PTLD occurring 6 years after LT. It is important to consider localized PTLD at the site of the bilio-enteric anastomosis as a probable cause of stricture in cases of non-specific biliary strictures, especially in patients with recurrent episodes of cellular graft rejection and high-dose maintenance immunosuppression, even long after transplantation. In these conditions, non-surgical management is often preferred.

2. Introduction

Post-transplant lymphoproliferative disorder [PTLD] is a rare but serious disorder that can occur following liver transplantation [LT] and its diagnosis and treatment could be challenging. PTLD mostly occurs within the first year after transplantation, affecting 2-4% of LT recipients, especially in pediatrics. It is linked to immunosuppressive therapy and Epstein-Barr virus [EBV] infection [1]. This report describes a case of PTLD at the site of bilio-enteric anastomosis that developed following orthotopic liver transplantation [OLT]. The condition was diagnosed and managed non-operatively. Additionally, we review the reported cases of PTLD at the site of biliary and/or enteric anastomosis following LT. The purpose of this report is to raise awareness among surgeons and physicians who deal with LT recipients that PTLD may mimic biliary anastomosis stricture.

3. Case Report

A 32-year-old man with a known history of primary sclerosing cholangitis [PSC] and medically controlled ulcerative colitis underwent OLT six years ago at our center, the Abu-Ali-Sina Organ Transplant Center in Shiraz, Iran. In June 2023, he was hospitalized with symptoms of acute onset jaundice, fever and malaise, and was diagnosed with cholangitis. The laboratory results showed leukocytosis and elevated liver function tests, including aspartate aminotransferase [AST] at 183 U/L, alanine transaminase [ALT] at 116 U/L, alkaline phosphatase [ALP] at 373 U/L, and Bilirubin at 3.8 mg/L. Additionally, a sonographic examination of the liver revealed mild increased parenchymal echotexture and intrahepatic bile duct dilatation. Treatment was initiated with a broad-spectrum intravenous antibiotic therapy consisting of Ciprofloxacin and metronidazole. The patient underwent Magnetic Resonance Cholangiopancreatography [MRCP], which showed a beaded appearance of the bile ducts consistent with the recurrence of PSC. Additionally, a stricture was observed in the site of the bilio-enteric anastomosis [Fig-1], and as a result, the patient was scheduled for Endoscopic Retrograde Cholangiopancreatography [ERCP].

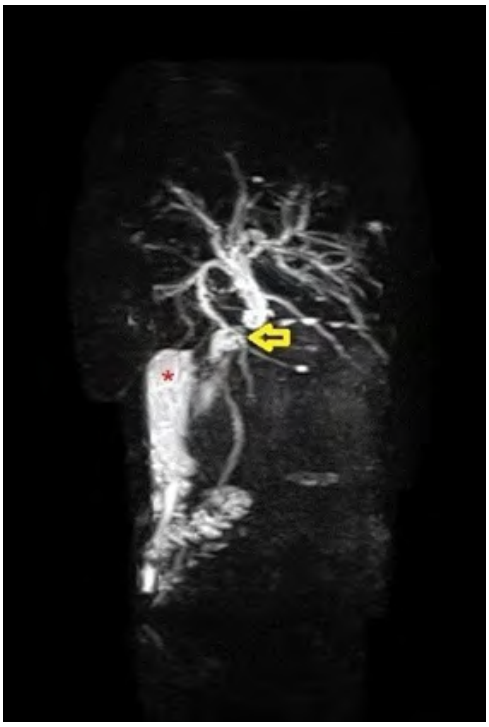

Figure 1: The Magnetic Resonance Cholangiopancreatography [MRCP] reveals intrahepatic bile duct dilatation and beading. A filling defect and stricture are indicated at the distal part of the common hepatic duct with a yellow arrow. The Roux limb of the jejunum is marked with a red star.

The patient's medical records were reviewed, which revealed that the initial induction immunosuppressive [IS] therapy after transplantation was Methylprednisolone 1 gram per day for three consecutive days. The maintenance IS regimen consisted of tacrolimus 5 mg, Mycophenolate Mofetil [MMF] 1440 mg, and prednisolone 20 mg daily. During the follow-up period, the patient experienced three episodes of elevated serum aminotransferases. A liver biopsy indicated acute T-cell mediated rejection, which was successfully treated with pulse steroid therapy [Methylprednisolone 1 gr daily for three consecutive days] in each episode [Table 1]. The recipient's preoperative workup for Epstein-Barr virus [EBV] and Cytomegalovirus [CMV] infections was negative, but data on these infections was not available for the donor. During the ERCP, a mass lesion was found at the site of the hepaticojejunostomy. The lesion was fungating, ulcerated, and friable, and the guide-wire could not be advanced into the bile duct due to a severe stricture [Fig-2]. Multiple biopsies were taken from the mass, and a percutaneous transhepatic catheter [PTC] was inserted.

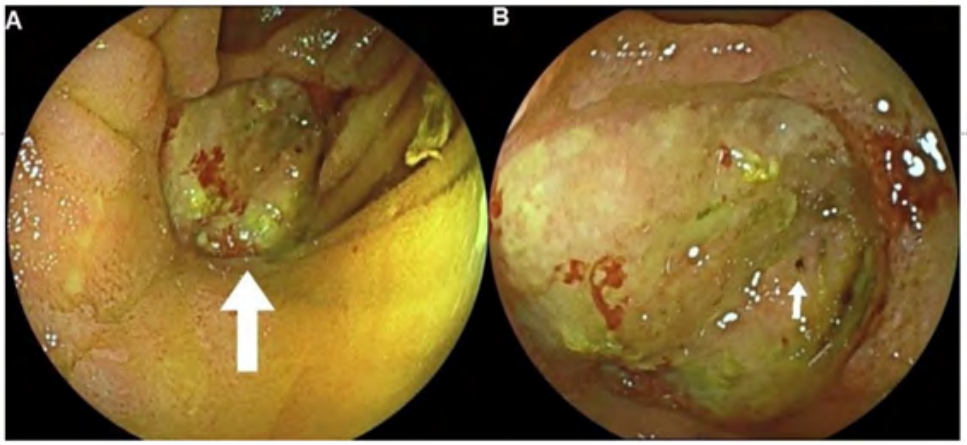

Figure 2: Endoscopic Retrograde Cholangiopancreatography [ERCP] findings; [A] A fungating, ulcerated and friable mass lesion [arrow] at the site of choledochojejunostomy that guide-wire could not be advanced into the bile duct due to severe stricture. [B] In a closer view to the mass lesion, the small orifice of bile duct is indicated by the arrow.

Table 1: The patient`s laboratory value, pathology report and management in episodes of acute cellular rejection during post-transplant follow-up period.

Date	LFT changes	Histopathology report	EBV & CMV work-up	Treatment
2018, April	AST:486 IU/L, ALT:802 IU/L, ALP:574 IU/L, Bili T:1.89 mg/dl	Acute cellular rejection RAI:9/9	EBV: ? ; CMV: Negative	Pulse steroid therapy (Methylprednisolone 1gr daily for 3 consecutive days)
2019, November	AST:234 IU/L, ALT:587 IU/L, ALP:287 IU/L, Bili T:1.7 mg/dl	Acute cellular rejection RAI:5/9	EBV: Negative; CMV: Negative	Pulse steroid therapy (Methylprednisolone 1gr daily for 3 consecutive days)
2020, July	AST:244 IU/L, ALT:471 IU/L, ALP:207 IU/L, Bili T: mg/dl	Acute cellular rejection RAI:3/9	EBV: Negative; CMV: Negative	Pulse steroid therapy (Methylprednisolone 1gr daily for 3 consecutive days)

Abbreviations: Bili T: Bilirubin total; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase; LFT: Liver function tests; RAI: Rejection activity index.

The tumor was found to have originated from the small intestinal mucosa and exhibited a slightly expansile proliferation of plasma cells and small lymphocytes in the intestinal submucosa. However, there were no significant destructive features observed in the infiltrate. Immunohistochemistry revealed a mixture of CD3/BCL-2B positive T-cells and CD20 positive B-cells, along with many polytypic plasma cells that were negative for CD56. The immunoblasts were scattered and stained with CD30. No follicular dendritic meshwork was observed with CD21. The KI-67 index was between 5-10%. The histopathology report indicated early nondestructive PTLD. For the detection of disseminated disease, computed tomography scans of the neck, chest, abdomen, and pelvis, as well as an echocardiogram and SPECT-CT, were performed. All results were negative for disease dissemination and indicated that the disease was localized to the site of choledochojejunostomy. The patient received four cycles of therapy with rituximab [an anti-CD20 monoclonal antibody] and IS medications at a reduced dose of 75% of the previous amount. The treatment with rituximab was administered intravenously at a dose of 375 mg/m3/week, and the patient tolerated it without any major adverse effects. As a result, the patient achieved complete remission. In August 2023, an ERCP was performed to evaluate the response to treatment. Significant improvement in the size and appearance of the previously identified ulcerated mass at the site of the hepaticojejunostomy anastomosis was observed [Fig-3], and multiple biopsies were taken from this area. Histopathologic examination showed no evidence of PTLD. Tacrolimus was switched to sirolimus, a mammalian target of rapamycin [mTOR] inhibitor, to prevent graft rejection. Three months after the last chemotherapy session, the patient experienced an increase in liver enzymes. Intra- and extrahepatic biliary tree on sonography and CT scan were normal. Liver biopsy showed evidence of chronic rejection and PSC recurrence in the transplanted liver, with the enzymes decreasing after treatment with a pulse of methylprednisolone. The most likely cause of graft rejection was an abrupt decrease in the dose of IS. The patient was listed for retransplantation and had undergone surgery in February 2024. During the transplantation, the roux limb of the hepaticojejunostomy was revised and distal part of it was resected and sent for pathology, which showed no evidence of malignancy detected. Currently, he is asymptomatic with normal liver function tests [AST:33 U/L, ALT:36 U/L, ALP:169 U/L, Bili:0.98 mg/L]. He is under close follow-up and taking sirolimus 2 mg, MMF 720 mg and prednisolone 15 mg daily for maintenance.

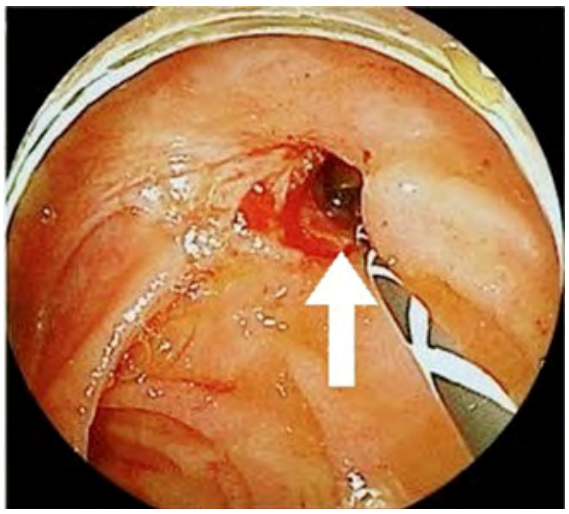

Figure 3: Follow-up Endoscopic Retrograde Cholangiopancreatography [ERCP] findings; There was significant improvement in the size and appearance of the previously identified ulcerated mass at the choledochojejunostomy anastomosis [arrow]. Multiple biopsies were taken from this area.

4. Discussion

Between 5% and 35% of OLT recipients may develop biliary problems, particularly strictures, which are classified as anastomotic or non-anastomotic. Anastomotic strictures typically occur within the first three months, and known risk factors include surgical technique, bile leak, hepatic artery thrombosis, primary sclerosing cholangitis, donation after cardiac death donors, and increased

cold ischemic time. PTLD-induced biliary stricture following liver transplantation is extremely rare. PTLD is a known entity that can occur following solid organ transplantations, typically within the first two years, due to higher levels of IS [2,3]. It may also present extranodally and is frequently associated with EBV. Extranodal diseases have been shown to be associated with poor outcomes [4,5]. In adult patients, major risk factors for PTLD include younger age, fewer human leukocyte antigen [HLA] matches, administration of antilymphocyte antibodies, hepatitis C virus [HCV] infection, EBV-seronegativity at the time of transplantation, Cytomegalovirus [CMV] coinfection, prior splenectomy, and T-cell depletion [6,7]. The patient in question was young and EBV-seronegative at the time of transplant and had been treated with tacrolimus, MMF, and prednisolone, putting him at high risk of PTLD. The clinical manifestations of PTLD vary from asymptomatic to fever, lymphadenopathy, sweating, weight loss, and local pressure effects on adjacent structures [such as bile duct stenosis and jaundice] to fulminant liver failure. In cases of nonspecific bile duct stricture following orthotopic liver transplantation [OLT], local PTLD should be suspected and investigated further with magnetic resonance cholangiopancreatography [MRCP] and endoscopic retrograde cholangiopancreatography [ERCP]. Mass lesions should be sampled for histopathological examination, which is the gold standard for diagnosis. The primary treatment for PTLD is reducing immunosuppression. Effective treatment options include rituximab monotherapy, chemotherapy, radiotherapy, and immunotherapy. However, surgical resection is still necessary for certain cases of localized disease [8]. We present a case of EBV-associated PTLD in an adult, which occurred at the site of a bilio-enteric anastomosis six years after OLT. The PTLD mimicked a biliary anastomosis stricture. PTLD at the site of biliary and/or enteric anastomosis, presenting as obstructive jaundice or a cholestatic pattern in liver function tests [LFTs], is rare. We reviewed previously reported cases in Table 2 and found only two cases of PTLD at the site of bilio-enteric anastomosis, both of which were diagnosed and managed surgically [9,10]. Doria et al. reported three cases of localized PTLD in the site of previous surgical intervention and manipulation. Two of these cases showed biliary tract involvement, specifically in the site of choledochojejunostomy and intraductal sites of longstanding catheter placement. The third case had involvement in the ileosigmoid anastomosis, which was diagnosed and managed surgically [9]. Morard et al. reported two cases of PTLD at the site of bilio-enteric and bilio-biliary anastomoses. The patients presented with cholestasis, which was diagnosed and managed surgically [10]. Baron et al. reported two cases of PTLD presenting as bile duct strictures following OLT. The PTLD was caused by external pressure and direct invasion of the bile duct wall by B-cell lymphoma. The PTLD was diagnosed and managed non-surgically. The lymphoma tissue was of donor origin, and the donors were EBV-seropositive [11]. Karb et al. described another anastomotic biliary stricture caused by a PTLD mass originating from liver segment VII and involving the bile duct [12]. Our patient had a history of three episodes of acute cellular rejection and recurrent induction immunosuppressive therapies, which is an extreme case compared to previously reported cases [see Table 2]. It appears that the donor's lymphocytes may have induced the episodes of cellular rejection, requiring intensified immunosuppressive therapy that makes the patient susceptible to PTLD. It is recommended to consider LT recipients with recurrent episodes of acute cellular rejection and intensifying IS therapies, especially at the sites of previous manipulations, as more susceptible to PTLD. In addition to reducing IS, Rituximab, an anti-CD20 antibody directed against the surface antigens of B-lymphocytes, is administered to manage PTLD after solid organ transplantations. This treatment has resulted in complete remission in up to 87.5% of cases [13]. Furthermore, mTOR inhibitors have been found to be effective not only in preventing graft rejection but also in controlling lymphocyte proliferation and preventing PTLD recurrence [14,15]. To date, our report is the only known case of PTLD at the site of bilio-enteric anastomosis following OLT that was diagnosed and managed non-operatively.

5. Conclusion

Due to the high mortality rate of PTLD and the need for early diagnosis and prompt treatment, it is important to consider localized PTLD at the site of bilio-enteric anastomosis as the probable cause of stenosis in cases of nonspecific bile duct stricture, even six years after liver transplantation. In patients with recurrent episodes of cellular graft rejection and high doses of maintenance immunosuppression following transplantation, non-surgical management is often the preferred approach. This may involve reducing immunosuppression and administering anti-CD20 monoclonal antibodies or chemotherapy to achieve a favorable response.

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8. Disclosure/Conflict of Interest

The authors declare that they have no competing interests.

9. Availability of Data and Materials

All data regarding this study has been reported in the manuscript. Please contact the corresponding author if interested in any further information.

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