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Case Report

Post-Transplant Lymphoproliferative Disorder of the Pancreas, Report of a Case Localized to the Pancreatic Head

Kossivi Dantey[1]*, Rashmi Kanagal-Shamanna[2], Maryam J Zenali[1], Andres E Quesada[3], Alfonso Quintas-Cardama[4] and Nghia Nguyen[3]

[1]*Department of Pathology, University of Vermont/ Fletcher Allen Health Care, USA*
[2]*Department of Pathology, The University of Texas, MD Anderson Cancer Center, USA*
[3]*Department of Pathology, The University of Texas Medical School at Houston, USA*
[4]*Department of Leukemia, The University of Texas MD Anderson Cancer Center, USA*

Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a rare complication of solid organ transplantation. It develops in association with immunosuppression and is usually linked to Epstein - Barr virus (EBV) infection. Risk factors for PTLD include type and duration of immunosuppression, age of the patient, and the type of transplanted organs, amongst others. This report summarizes clinico-radiologic and pathologic features in a case of pancreatic PTLD. Based on the presenting features, initial considerations in this patient included chronic pancreatitis and graft rejection. Due to intractable symptomatology, a total pancreatectomy was performed, leading to the diagnosis of polymorphous PTLD. By clinico-radiologic criteria, there can be overlapping features between chronic pancreatitis, transplant rejection and PTLD. Histologic identification of EBV in atypical lymphoid population and genomic clonality are cornerstones of diagnosis of PTLD. Control of the disease is primarily achieved by reduction or succession of immunosuppression.

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***Corresponding author**
Kossivi Dantey, Department of Pathology, University of Vermont/Fletcher Allen Health Care, Burlington, VT, 05401, Tel: 802-847-5932; Email: Kossivi.Dantey@vtmednet.org

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ABBREVIATIONS

PTLD (post-transplant lymphoproliferative disorder); EBV (Epstein-Barr virus); CMV (cytomegalovirus); US (ultrasound); CT (computed tomography); EBER-ISH (Epstein-Barr virus-encoded ribonucleic acid by in situ hybridization)

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is defined as a lymphoid proliferation developing in a solid organ or hematopoietic stem cell recipient and is usually intimately associated with EBV infection [1]. PTLD in solid organ transplant has an overall frequency of 2-10% and is seen relatively more frequently in children than in adults. The incidence of pancreatic PTLD after combined kidney-pancreas transplant is 1.0-2.0% [2,3]. Pancreatic PTLD is rare and can manifest in a variety of nonspecific ways in clinically unsuspected patients. Radiologic presentation is also non-distinct rendering histologic examination the key diagnostic parameter. Caution is also warranted in the interpretation of biopsies due to the presence of significant necrosis or non-representative sampling due to focal involvement. Herein we report a case of pancreatic PTLD in a 45-year-old man. He received a pancreas after renal transplantation and later underwent pancreatectomy for suspected allograft pancreatitis. PTLD manifested as massive enlargement, localized to the pancreas head.

CASE REPORT

A 45-year-old man with a long-standing history of hypertension and insulin-dependent diabetes mellitus, diagnosed at age 23, received a cadaveric renal transplant after having been on dialysis for years. For maintenance immunosuppression, the patient was placed on neoral (75 mg bid), prednisone (7.5 mg qd) and rapamune (2 mg qd). Status-post transplantation, his renal function remained stable with creatinine level ranging from 1.2-1.3 mg/dl; however, his diabetes was difficult to control. His glucose level fluctuated widely, ranging from 50-60 mg/dl up to 600 mg/dl, accompanied by occasional bouts of seizure. Eighteen months after renal transplantation, he received a whole-organ, cadaveric pancreas. Both the recipient and the donor were

cytomegalovirus (CMV) and EBV seropositive. Post-operatively, the immunosuppressive regimen, with variable dosage, was continued. Additionally, cytomegalovirus immunoglobulin and gancyclovir were instituted. Due to clinical suspicion for acute rejection (increased amylase and lipase, etc), thymoglobine therapy was initiated. The patient was also evaluated for acute CMV and EBV infection. Both CMV IgM and EBV capsid antigen IgM were found to be negative.

Secondary to sustained serological abnormality and unremitting abdominal pain, an exploratory laparotomy was performed, whereby the pancreatic graft was found markedly swollen. The head of the pancreas was disproportionately enlarged. Biopsies from the head of the pancreas showed abundant necrosis. The biopsies from the body and tail were diagnostic and had features of chronic pancreatitis. Ultrasound (US) (Radiograph A) and a subsequent CT scan (Radiograph B) showed heterogeneous appearing pancreas and soft tissue attenuation anterior to the transplant (8.0 x 7.0 cm), respectively. Due to intractable symptomatology and presumed graft pancreatitis, the patient underwent graft pancreatectomy. The explant showed histopathologic and molecular features consistent with focal involvement by PTLD. Subsequent CT of the abdomen and pelvis did not demonstrate any lymphadenopathy or evidence of disease at other sites. Dose reduction of immunosuppressive regimen was initiated and rituximab was instituted.

PATHOLOGIC FINDINGS

Hematoxylin and eosin (H&E)-stained biopsy sections from the pancreatic body and tail (Figure A) showed diffuse sclerosis and mild edema with acinar inflammation. There were also vascular changes in form of intimal arteritis and proliferative arteriopathy without thrombosis or fibrinoid change. The morphologic features were non-diagnostic for acute rejection. Based on the extent of fibrosis and the loss of exocrine parenchyma, a diagnosis of acute interstitial pancreatitis with severe chronic rejection was rendered. Biopsies from the pancreatic head were necrotic and non-diagnostic. The subsequent graft explant (Figure B) included the entire pancreas and a portion of small bowel (16.0 x 10.0 x 7.0 cm en-toto). The pancreatic head was globular (7.0 cm in diameter), while the body and tail had a more normal configuration. The head region was dusky, yellow and necrotic appearing. On microscopy, the body and tail showed changes compatible with those seen in the previous biopsies; however, the pancreatic head was infiltrated by a heterogeneous population of cells that included, small to large lymphocytes, numerous plasma cells and histiocytes, in an extensively necrotic background (Figures C, D). Most of the lymphocytes were of B-cell origin (CD20-positive, Figure E) with scattered CD3 positive T-cells. The atypical B cells were positive for Epstein-Barr virus-encoded ribonucleic acid by in situ hybridization (EBER-ISH) (Figure E inset). Polymerase chain reaction studies showed monoclonal B-cell receptor gene rearrangement, supporting the diagnosis of PTLD. The small bowel and a subsequently performed kidney biopsy were both negative for evidence of rejection or lymphoproliferative disorder.

COMMENT

Kidney-pancreas transplantation is the preferred modality of transplant for patients with complicated type I diabetes mellitus nephropathy associated end-stage disease and chronic pancreatitis. It can be accomplished by either simultaneous kidney-pancreas or sequential pancreas after kidney transplantation. The one-year patient survival ranges from 95% to 97%, and 1 year allograft survival rate (complete insulin independence) ranges from 78% to 85% [4,5]. The most common complications of pancreas transplantation are infections, acute and chronic rejection, reperfusion pancreatitis, vascular disease including thrombosis and infarction of the graft [6, 7]. Although in recent years, implementation of newer treatment strategies has reduced the overall complication rate, infections still remain the main cause of morbidity and morbidity in these patients [8,9].

According to the 2008 World Health Organization (WHO) criteria, PTLD is categorized into early lesions comprising plasmacytic hyperplasia and infectious mononucleosis-like PTLD, polymorphic, monomorphic (subdivided to B-cell and T/NK-cell types) and classical Hodgkin lymphoma type PTLD [10]. Overall, majority of these disorders are of B cell origin and usually harbor EBV. Risk for developing PTLD is affected by the type of transplanted organ, patient's age, duration, type and intensity of immunosuppressant, and EBV and CMV infectivity status of donor and/or recipient [11,12]. Oplez *et al* found the 5-year incidence of non-Hodgkin lymphoma to be greatest in heart-lung and lung transplant patients and the lowest in kidney followed by the pancreas transplant patients (n=200,000) [12].

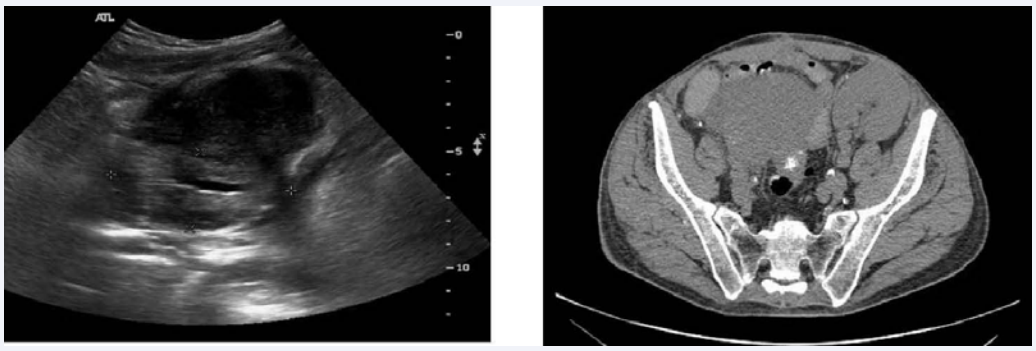

Figure 1 Radiographs A- Heterogeneous appearance of pancreas and adjacent tissue on US & B- An 8.0 x 7.3 cm area of soft tissue attenuation in the right hemipelvis, in the region of the pancreatic transplant (CT with contrast); this area corresponds to the globular necrotic pancreas head on subsequent pancreatectomy (with final diagnosis of PTLD).

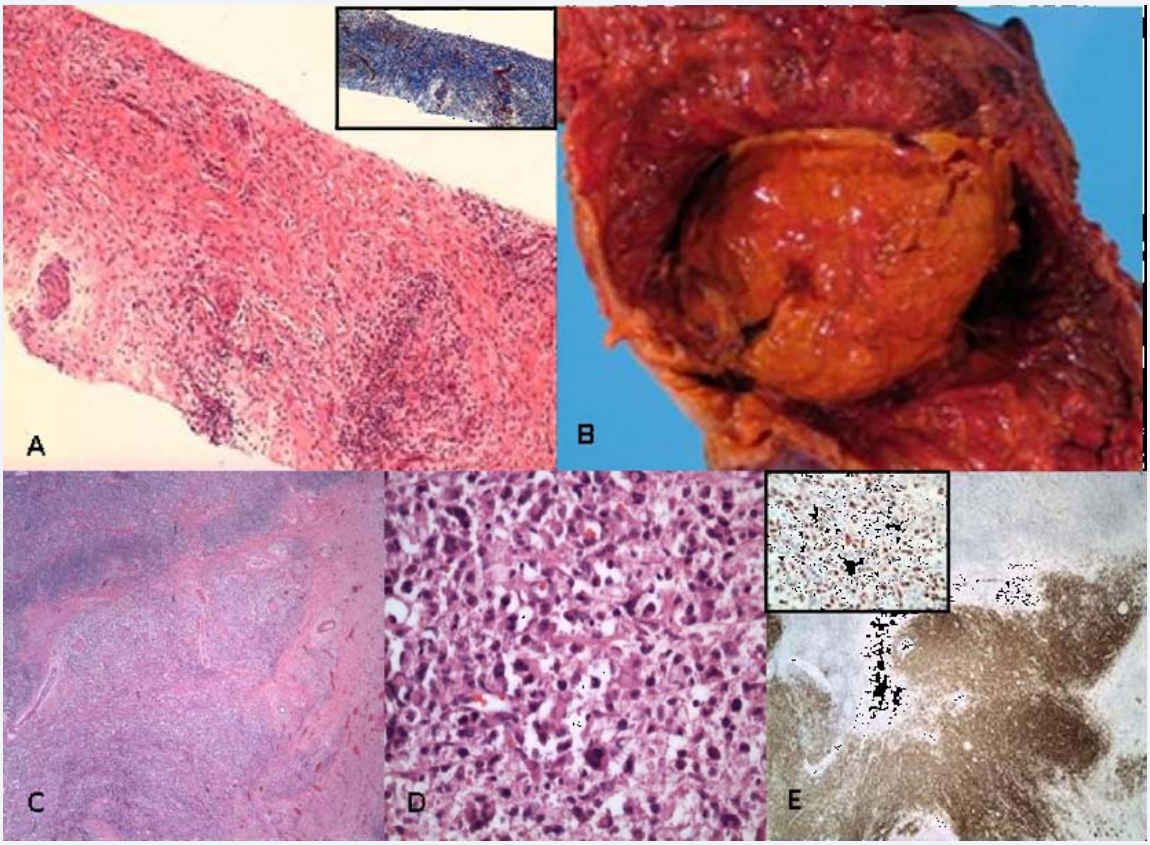

Figure 2 **A)** Initial biopsy: pancreatic body with fibrosis, mild inflammation, intimal arteritis and proliferative arteriopathy (inset trichrome stain highlights extent of fibrosis 100x). **B)** Subsequent pancreatectomy with globular and necrotic head of the pancreas explant. **C)** Tissue section of the pancreatic head with necrosis, fibrosis and cellular areas (H&E 20x). **D)** Higher magnification of the cellular areas showing a heterogeneous hematopoietic proliferation with enlarged atypical cells (H&E 400x). **E)** Cellular areas were composed predominantly of B cells (CD 20 positive 20x) and Atypical lymphoid cells showing nuclear positivity by EBER-ISH (400x).

The higher incidence of PTLD is perhaps the result of higher dosing of immunosuppressives and more intensive use of anti-T cell antibodies, in specific subsets of transplant categories. Immunosuppression is thought to contribute to the development of PTLD through decreased function of Epstein-Barr specific T-cells, which in turn lead to increased proliferation of B-cells [13].

Pancreatic PTLD can manifest in nonspecific ways and in clinically unsuspected patients, as in the reported. It can be by clinico-radiologic and even histologic features a challenging diagnosis. Commonly manifested by diffuse allograft enlargement [14,15] and non-specific serologic alteration, its distinction from pancreatitis or acute rejection can be nearly impossible [16,17], but failure to response to immunosuppressive therapy should suggest PTLD [14]. A significant increase in EBV copy number (EBV-DNA/ml) has been considered to have a high sensitivity and specificity in diagnosis of PTLD. Although no clear guideline is established as to what level of EBV is diagnostic for PTLD, a persistently low level has a high negative predictive value. Yet because not all the patients with elevated levels develop PTLD, and EBV-negative PTLDs cannot be predicted by such a test, further work up to define the role of viral load is needed [13,18].

Although most PTLD in solid organ transplants are of recipient origin, there is a preferential localization to the allograft. The reason for this is unclear; however, Bakker et al. have proposed that the allograft, or the chronic infection in the allograft may induce continuous allogeneic stimulation of the host immune system, leading to proliferation EBV infected B-cells and consequently PTLD in and around the graft [13].

In organs involved by PTLD, it is often difficult to obtain a representative and diagnostically yielding biopsy sample, as necrosis is a common associated feature [18, 19]. This limitation is yet further complicated by a non-diffuse organ involvement in a subset [14,15]. To make a diagnosis of PTLD, it is essential to obtain adequate material for complete morphologic evaluation including architecture, preferable from a non-necrotic area. Sufficient material should also be available for ancillary testing including microbiologic and clonality studies. Hence, it is recommended to obtain excisional biopsies as opposed to needle core biopsies or fine needle aspiration [13] Microscopically, PTLD is often associated with expansile or nodular inflammatory infiltrates and a prominent population of cytologically atypical B-cells. PTLD-associated inflammation usually spares the pancreatic acini and instead attacks the pancreatic parenchyma in a seemingly random manner; infiltration of peri-pancreatic soft tissue is not uncommon. In comparison, in acute rejection, there is usually a mixed population of large and small, activated-

appearing T-cells, with a minor component of plasma cells and eosinophils; inflammation usually targets and primarily damages the pancreatic acini. Endovasculitis or fibrinoid vascular change is more typically observed in acute rejection when compared with stand-alone PTLD and/or chronic pancreatitis (non-complicated with concurrent rejection) [7,18,20].

As in the reported, polymorphous PTLD is composed of a mixed lymphoid proliferation associated with destruction of pancreatic parenchyma. Atypia, necrosis and frequent mitosis are the usual associated features. Analysis of surface or cytoplasmic immunoglobulin expression can be useful to identify monotypic B cell population. Most polymorphous PTLD will show EBV latency II and III patterns, expressing EBER and EBV-LMP-1. Molecular analysis of immunoglobulin heavy chain or episomal EBV genome will frequently show a clonal population [18].

Initial EBV seronegative status and non-tacrolimus immunosuppressive regimen have been found highly associated with development of PTLD in recipients after pancreas transplantation [22]. Different strategies have been utilized to decrease the risk of developing PTLD, including serial EBV-load monitoring, immunosuppressive reduction/alteration and antiviral prophylaxis, their relative efficacy remains unknown. The primary focus in medical management of PTLD is decreasing or withdrawal of immunosuppressive [1,11,22]. Addition of rituximab (anti-CD20 antigen) has proven to be a well-tolerated and effective treatment modality in management of most PTLD [23,24]. In the current case, subsequent to pancreatectomy and reduction of immunosuppressive, rituximab therapy was instituted, and the patient's EBV load decreased beyond the critical value. There was no other organ involved by PTLD and the patient remains without evidence of recurrence.

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