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Original Report

Imaging Features of Posttransplantation Lymphoproliferative Disorder in Pancreas Transplant Recipients

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Abstract

OBJECTIVE. The purpose of this study was to describe the imaging features of posttransplant lymphoproliferative disorder (PTLD) in pancreas transplant recipients.

CONCLUSION. The prominent image finding of PTLD in pancreas transplant recipients is diffuse allograft

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enlargement, an appearance that may be indistinguishable from the image findings of acute pancreatitis or transplant rejection. However, failure of response to immunosuppressive therapy, presence of intraallograft or extraallograft focal masses, or organomegaly may suggest the diagnosis of PTLD.

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Introduction

Posttransplantation lymphoproliferative disorder (PTLD) includes a range of histopathologic abnormalities of the lymphatic system that can complicate organ transplantation. The disease spectrum ranges from benign B-cell hyperplasia to malignant lymphoma. Early diagnosis of PTLD is often difficult because the clinical symptoms may be nonspecific; however, detection of PTLD usually changes patient treatment dramatically. To the best of our knowledge, there is little description of the imaging features of PTLD in pancreas transplant recipients. Therefore, we undertook this study to better understand the imaging appearances of PTLD in the pancreas transplant recipient population.

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Materials and Methods

We performed a computerized search of our institution's pancreas transplant recipients over a 6-year period (1992-1998). The findings were then crossreferenced with histopathologic records for proven PTLD. Next, we reviewed the histologic, medical, and imaging records for each patient. Eight (2.4%) of 337 pancreas transplant recipients had developed PTLD during this period. Patients included five (2.8%) of 179 simultaneous pancreas and kidney transplant recipients, one (0.9%) of 106 pancreas-after-kidney transplant recipients, and two (3.8%) of 52 pancreas-only transplant recipients. Our study group was composed of four women and four men, ranging in age from 29 to 57 years (mean, 40 years). The onset of PTLD after organ transplantation ranged from 34 to 348 days (mean, 137 days).

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CT and sonography were performed on all eight patients in our study group, and MR imaging was performed on six of the eight patients. Although the performance of the individual imaging studies varied in time from the time of histopathologic diagnosis, all patients underwent imaging by at least one technique within 2 days of their original diagnosis. The original examinations were assessed without knowledge of the specific histopathologic findings. For this study, the dictated reports were used to establish the imaging findings and the histopathologic findings were used as the standard of reference for organ involvement.

CT for all patients in the study group was performed with either conventional or helically acquired abdomen and pelvis studies with enteric contrast media administration (collimation, 7-10 mm). One patient received an IV injection of 100 ml of iohexol (Omnipaque 300; Nycomed, Princeton, NJ). In addition, thoracic CT was performed on two patients.

All patients underwent sonography using an ATL 9 or HDI 3000 scanner (Advanced Technology Laboratories; Bothell, WA), or a Sequoia scanner (Acuson; Mountain View, CA). Imaging included a combination of gray-scale, color, and

power Doppler sonography. Linear and curved array transducers were used with frequencies ranging from 3 to 7 MHz. In addition, two patients underwent sonography of the right upper quadrant.

MR imaging of the pelvis was performed on six patients using a 1.5-T system (Signa; General Electric Medical Systems, Milwaukee, WI) with a phased array coil. MR imaging sequences consisted of axial conventional T1-weighted spin-echo (TR/TE, 714/20); respiratory triggered, T2-weighted fast spin-echo (4000/99) with chemical selective fat saturation; and a T1-weighted fast multiplanar spoiled gradient-recalled dynamic enhanced study (150/4.2; flip angle, 60°; 5 mm thickness without gap; field of view, 24 cm). After informed consent was obtained, 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) was administered by IV injection, followed by a saline flush. For the breath-held dynamic study, an initial coronal unenhanced study was performed, followed by sequential acquisitions performed immediately after the injection and then every minute for 5 min.

Results

Histopathologic Findings

Histopathologic diagnosis was made by surgical biopsy in five patients and by percutaneous biopsy in three patients. PTLD involved the allograft alone in three patients, the allograft and extraallograft tissue in three patients (liver, $n = 1$; bone marrow, $n = 1$; gallbladder, $n = 1$; lymph nodes, $n = 1$), and extraallograft tissue alone in two patients (lymph nodes, $n = 1$; liver, $n = 1$). The associated kidney allograft was involved in two of the five simultaneous pancreas and kidney transplant recipients. In patients with only extraallograft involvement, biopsy of the allograft showed no evidence of PTLD.

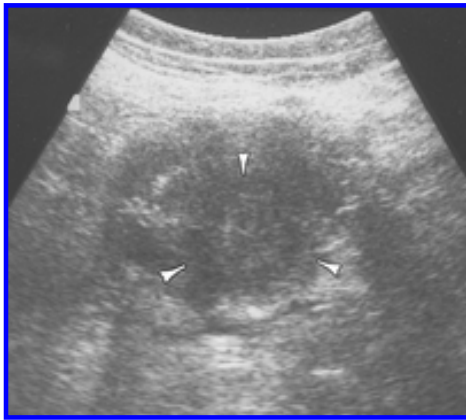
The spectrum of PTLD included polyclonal B-cell hyperplasia in six patients, polyclonal B-cell hyperplasia and B-cell lymphoma in one patient, and large cell immunoblastic lymphoma in one patient. Extraallograft disease was present in both benign and malignant grades of PTLD. All seven patients who underwent virologic studies were found to have Epstein-Barr virus antibody positive titers before transplantation.

All patients had nonspecific symptoms before diagnosis including fever, chills, malaise, nausea, and vomiting. In seven of the eight patients, mild elevation of pancreatic serum enzyme levels was noted. Explantation of the pancreas allograft was performed in seven of the eight patients after the diagnosis of PTLD was made (two patients also had explantation of the renal allograft). At follow-up (range, 3 weeks-4 years; mean, 29 months), seven patients were alive. One patient died after the explantation procedure.

Imaging Findings

Pancreas allograft disease alone.—Two of the three patients with pancreas allograft disease alone had diffuse enlargement of the pancreas allograft on CT, sonography, and MR imaging. The remaining patient had a focal solid mass in the head of the pancreas transplant that was revealed on all three imaging techniques, which was subsequently histopathologically confirmed as PTLD ([Fig. 1A](#), [Fig. 1B](#), [Fig. 1C](#)).

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Fig. 1 —54-year-old man with suspected acute rejection of pancreas and kidney allografts.

A, Transverse sonogram shows heterogeneous mass (*arrowheads*) in head of pancreas allograft. Percutaneous biopsy revealed combined B-cell hyperplasia and B-cell lymphoma.



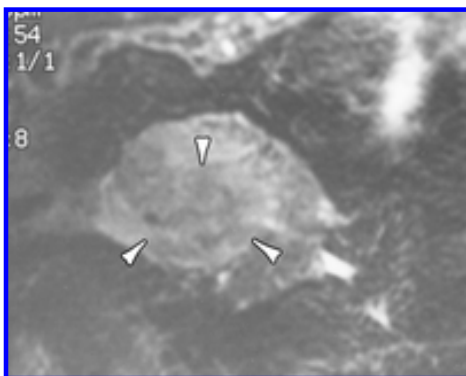
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Fig. 1 —54-year-old man with suspected acute rejection of pancreas and kidney allografts.

B, Corresponding contrast-enhanced CT scan shows poorly marginated low-attenuation mass (*arrow*) in head of pancreas allograft. Note normally enhancing renal allograft.



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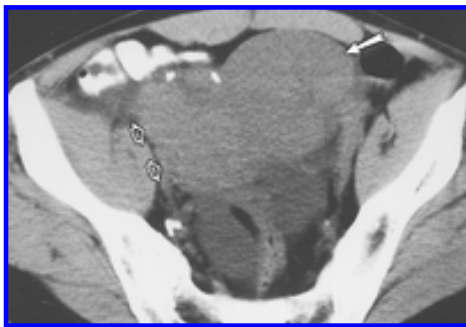
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Fig. 1 —54-year-old man with suspected acute rejection of pancreas and kidney allografts.

C, Fast spin-echo fat-suppressed T2-weighted axial MR image (TR/TE, 5161/102) shows low-signal-intensity mass (*arrowheads*) within pancreas allograft. Mass corresponds to that seen in **B**.

had histopathology). In one patient, the liver, bone marrow, and pancreas allografts were affected. This patient had an enlarged pancreas allograft on CT, sonography, and MR imaging and mild hepatomegaly on CT. A second patient had involvement of both kidney and pancreas allografts, manifesting as an enlarged kidney and pancreas on CT. However, on sonography the pancreas and kidney allografts appeared normal except for a thick-walled renal pelvis. MR imaging was not performed. Biopsy of a palpable cervical lymph node was positive for PTLD. CT images showed many small (<1 cm in diameter) lymph nodes in the abdomen. A third patient had involvement of the pancreas and kidney allografts, as well as gallbladder involvement proven surgically. On CT images, the pancreas and kidney transplants appeared diffusely enlarged ([Fig. 2A](#)); the gallbladder had a mildly thickened wall. MR images showed enlarged kidney and pancreas allografts ([Fig. 2B](#)). Sonography showed sludge and mild gallbladder wall thickening. Although the renal transplant was enlarged on sonography, the pancreas transplant appeared normal.



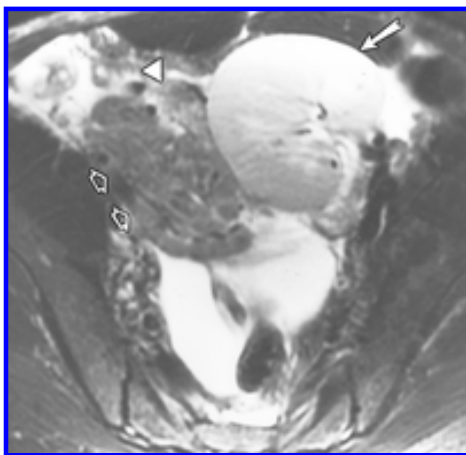
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Fig. 2. —38-year-old man with decreased urine output 14 days after transplantation.

A, Unenhanced CT scan shows closely apposed diffusely enlarged pancreas (*open arrows*) and kidney (*solid arrow*) allografts. Note ascites. Surgical biopsy revealed polyclonal B-cell hyperplasia in pancreas and kidney allografts and in gallbladder.



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Fig. 2. —38-year-old man with decreased urine output 14 days after transplantation.

B, Fast spin-echo fat-suppressed T2-weighted axial MR image (TR/TE, 6372/102) shows enlarged pancreas (*open arrows*) and kidney (*solid arrow*) allografts with normal homogeneous signal intensity. Note duodenal cuff (*arrowhead*).

Extraallograft involvement only.—Two patients had extraallograft disease only (lymph nodes, $n = 1$; liver, $n = 1$). The

first patient's CT images showed many mildly enlarged (1-2 cm in diameter) lymph nodes located in the abdomen and pelvis, particularly in the paraaortic and subdiaphragmatic regions; chest evaluation revealed no lymph node enlargement. The kidney and pancreas allografts appeared normal. Sonographic images showed a slightly enlarged pancreas allograft with heterogeneous texture. The second patient had liver involvement identified through a biopsy performed during surgery for allograft explantation. CT images showed no liver abnormality.

Discussion

PTLD is an uncommon but potentially fatal complication of organ transplantation. Its variable manifestations are detectable with histopathologic analysis and clinical assessment. The reported incidence of PTLT varies from 12% in pancreas transplants and 9% in heart and lung transplants, to 1-2% in renal and liver transplants [1, 2, 3]. Clinical symptoms range from fever and malaise similar to an influenzalike syndrome, to a fulminant and potentially fatal systemic illness. On histologic examination, PTLT exhibits a spectrum of findings ranging from benign hyperplasia to malignant lymphoma. Most of these disorders are B-cell phenotype, usually polyclonal and associated with the Epstein-Barr virus [2, 4]; although less common, monoclonal B-cell and T-cell lymphomas do occur [5, 6]. In this study, six patients had B-cell hyperplasia, one had B-cell hyperplasia and lymphoma, and one had immunoblastic large-cell lymphoma. Histopathologic diagnosis of PTLT can be difficult, because the disorder can develop rapidly and may coexist with acute rejection, a condition that may have similar histologic features [7]. The differentiation of PTLT from rejection is vitally important, because the immunosuppression therapy used to treat rejection may enhance the progression of PTLT—a potentially fatal complication. PTLT has been described by Hanto [8] as following a four-step progression from benignancy to malignancy, beginning with an uncomplicated posttransplantation infectious mononucleosis and progressing to B-cell lymphoma. Patients may have coexistent benign and malignant features as was seen in one patient in our study.

Patients with PTLT usually have Epstein-Barr virus (as seen in all seven of our patients for whom virologic data was available), Epstein-Barr virus has been strongly implicated as the cause of PTLT [2, 4, 6]. However, a direct causal link between the Epstein-Barr virus and PTLT has not been proven. The development of PTLT is also thought to be related to the use of certain immunosuppressive agents, including cyclosporine A (Sandimmune IV; Sandoz Canada, Quebec City, Quebec, Canada), Muromonab-CD3 (Orthoclone OKT3; Ortho Pharmaceuticals, Raritan, NJ), and tacrolimus (FK506; Fujisawa USA, Deerfield, IL) [1, 9, 10]. In our study, six patients received cyclosporine A, six received OKT3, and six received tacrolimus. Of the four patients who received all three medications, three developed polymorphic B-cell hyperplasia and the fourth developed malignant lymphoma.

In our study, 2.4% of all pancreas transplant recipients developed PTLT. The incidence of PTLT was much more common in pancreas-alone allografts (3.8%) as compared with pancreas after kidney (0.9%) or simultaneously placed pancreas and kidney (2.8%) transplants. To the best of our knowledge, no study has analyzed the frequency of PTLT in relation to the type of pancreas allograft transplantation. Although the sample size is small, our data suggest that patients with a pancreas transplant alone are at greater risk of developing PTLT. This trend could possibly be attributed to the fact that pancreas transplantation is associated with a high incidence of allograft rejection and steroid-resistant rejection, conditions that require large doses of immunosuppressive agents [11].

In examining the rate of occurrence of PTLT in the allograft after various solid organ transplantations, Hanto et al. [6]

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found the allograft was the site of PTLD in 37% of renal transplant recipients. Nalesnik et al. [4] reported allograft involvement in 17% of renal transplants and in 8.6% of liver transplants, and no occurrence of PTLD in heart transplants. In our study, six (66%) of the eight patients had involvement of the pancreas allograft.

The lack of specific radiologic findings contributes to the diagnostic difficulty in examining allograft recipients for PTLD. In prior series of solid organ transplants, PTLD has shown a variable imaging appearance: focal mass or masses, diffuse tissue involvement, wall thickening of the gastrointestinal tract, organomegaly, or lymphadenopathy [3, 11]. Of the eight patients in our study, five showed a diffusely enlarged allograft, a finding that may be radiographically indistinguishable from acute rejection or pancreatitis [12]. In addition, seven of the eight patients in our series developed an elevated level of serum amylase, a nonspecific finding that adds to the diagnostic difficulty. Only one patient had a focal mass involving the head of the pancreas allograft.

Our study showed that PTLD typically involved the pancreas allograft, whereas extraallograft involvement was less prominent. Of our patients with liver involvement, one presented with mild hepatomegaly and the other showed no abnormalities on CT images. Two patients had biopsy-proven lymph node involvement. One patient had palpable cervical lymphadenopathy but did not have significant abdominal or pelvic lymphadenopathy. The other patient had paraaortic and subdiaphragmatic lymph nodes that were slightly enlarged, with an average size of 1.5 to 2 cm (maximum diameter). Interestingly, no confluent nodal masses were seen, as would be expected with lymphoma involving the abdomen and pelvis. Pickhardt and Siegel [11] described abdominal manifestations of PTLD in which lymph node involvement was more commonly retroperitoneal than intraperitoneal. In their study, retroperitoneal lymph node involvement appeared as a discrete mass or as an infiltrative lesion with areas of central low attenuation consistent with necrosis.

When we compared the three imaging techniques used to assess PTLD in this study, CT of the abdomen and pelvis revealed virtually all histologically identified abnormalities. The exception was that liver and bone marrow involvement was not seen on CT images for two patients. Six of our eight patients underwent MR imaging to evaluate the allografts. The multiplanar capacity of MR imaging improved the visualization of abnormalities in some cases, but no additional findings were seen on MR imaging that were not seen with CT. In two of our eight patients, sonography failed to detect allograft involvement by PTLD.

Because of the rarity of PTLD in allograft recipients, our study is limited by a small patient population. In addition, because the study was performed at a single institution and immunosuppressive regimens may differ, institutional variation may occur. However, in our study, PTLD in pancreas allografts most commonly appeared as diffuse allograft enlargement. This appearance may be indistinguishable from the typical imaging findings of acute pancreatitis or allograft rejection. A mass lesion involving the pancreas allograft was seen in only one patient. The diagnosis of PTLD should be considered in pancreas transplant recipients who have allograft enlargement that does not respond to antiinflammatory or antirejection therapy or in whom extraallograft masses or organomegaly are present.

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