Posttransplant lymphoproliferative disorder presenting as a small bowel obstruction in a patient with pancreas transplantation alone

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Posttransplant lymphoproliferative disorder (PTLD) is a well-known complication associated with the transplant recipient. We chronicle a case of PTLD in a failed graft presenting as a small bowel obstruction in a pancreas-only transplant patient. While typical symptoms may be elusive in the complex immunosuppressed patient, graft pain along with persistent graft pancreatitis and a positive Epstein-Barr viremia should raise suspicion for an underlying PTLD.

Solid organ transplant recipients are at an increased risk for developing malignant neoplasms. More specific to the transplant population is the collection of lymphoid malignancies known as posttransplant lymphoproliferative disorder (PTLD). PTLD differs from lymphomas in immunocompetent patients in that it may present outside of nodal tissue and is frequently Epstein-Barr virus (EBV) driven (1, 2). Although PTLD in simultaneous pancreas-kidney (SPK) transplantation has been reported, little information is available on the isolated involvement of the pancreas allograft after pancreas transplantation alone (PTA). We report a case of PTLD presenting as a small bowel obstruction in a patient who underwent PTA.

CASE REPORT

A 37-year-old woman who underwent a laparoscopic Roux-en-Y gastric bypass in January 2007 developed debilitating hypoglycemia requiring in-hospital management. A thorough workup did not reveal an insulinoma but a hyperinsulin-secreting pancreatic head and tail by selective mesenteric angiogram with calcium gluconate injection. Thus, she underwent a subtotal pancreatectomy with splenectomy in September 2009. The hypoglycemia resolved temporarily. She underwent a completion Whipple procedure in December of the same year. Pathology from both specimens revealed islet cell hyperplasia.

As expected, the patient developed insulin-dependent diabetes and was approved for a PTA. She received a pancreas allograft (six-antigen mismatch) from a 24-year-old male donor in August 2011. The graft was implanted in the right retroperitoneal space with systemic venous and enteric exocrine drainage. Donor serologies were positive for cytomegalovirus (CMV) and EBV IgG. The recipient was CMV positive. Immunosuppres-

sion consisted of antithymocyte globulin induction, followed by a regimen of tacrolimus, mycophenolate mofetil, and corticosteroids. The patient had an uneventful recovery and was discharged 6 days after transplantation.

Two weeks posttransplant, she was admitted with abdominal pain, nausea, and vomiting. Additionally, she was having sporadic hyperglycemia. Serum pancreatic enzyme levels were normal, and a Doppler ultrasound of the transplanted pancreas noted venous and arterial flow. A percutaneous graft biopsy showed no rejection. Her primary immunosuppressant was changed from tacrolimus to cyclosporine, which resolved the intermittent hyperglycemia. An upper endoscopy revealed a normal gastric pouch and unremarkable Roux-Y reconstruction. Her nausea was felt to be medication related. Her symptoms resolved and she was discharged without pain or gastrointestinal complaint.

Five months later, she presented with fever and anemia. She was diagnosed with CMV viremia (3670 copies), and intravenous ganciclovir therapy was initiated. She was discharged on continued outpatient antiviral therapy and eventually returned to her clinical baseline. Seven weeks later, she was hospitalized with fever, anemia, and pain over the right lower quadrant. A repeat CMV polymerase chain reaction (PCR) test was negative, but an EBV PCR test returned positive (331 copies, IgM negative). No further antiviral treatment was given.

Eight months after transplant, she was readmitted again with right lower quadrant pain. Her serum lipase level was moderately elevated at 542 U/L, and an ultrasound once again noted patent vasculature. A computed tomography (CT) scan noted minimal edema around the graft without evidence of a fluid collection. Another allograft biopsy showed no evidence of rejection, but did note changes consistent with chronic graft pancreatitis. After empiric treatment with antibiotics, her symptoms resolved and her pancreatic enzymes normalized.

Over the next few months, she required multiple admissions for persistent graft pain. Repeat CT scans demonstrated peripancreatic

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Figure 1. CT scan of the pancreas-only transplant recipient showing (a) peripancreatic fluid around the tail of the allograft corresponding to an abscess (arrow) and (b) resulting small bowel obstruction.

inflammation consistent with graft pancreatitis, followed by the development of peripancreatic fluid suggesting an abscess. As a result, she started treatment with intravenous antibiotics. She also developed mild hyperglycemia, at first believed to be secondary to the inflammatory response. However, in the outpatient setting,

the hyperglycemia progressed and she was started on sliding-scale insulin therapy, indicating failure of the allograft.

A few days before her 1-year anniversary of transplant, the patient returned to the emergency department with abdominal pain, emesis, and a 7 kg weight loss over the previous 6 weeks. CT findings were consistent with a high-grade small bowel obstruction at the level of the pancreas transplant and a definitive peripancreatic abscess (*Figure 1*). Findings on surgical exploration were a thrombosed arterial conduit and portal vein (outflow) in addition to necrotic graft duodenum and pancreatic tail forming an abscess. The graft was removed, and immunosuppressive therapy was suspended. On pathology, the explant revealed a nonviable graft with areas containing an atypical lymphoid infiltrate consistent with PTLD, diffuse large B-cell type (CD 20⁺ and CD79a⁺). Margins were negative and the EBER (EBV-encoded small RNA) in situ hybridization test was positive, confirming an EBV-driven process (*Figure 2*). After a prolonged recovery, she was discharged home in improved condition.

On follow-up studies, a bone marrow biopsy was negative and positron emission tomography showed no residual disease. No chemotherapy was recommended as she was considered treated. She remains disease free by imaging study 18 months after graft pancreatectomy.

DISCUSSION

PTLD is a spectrum of neoplastic diseases ranging from a benign polyclonal lymphoid proliferation resembling infectious mononucleosis to a highly aggressive monoclonal process, such as diffuse large B-cell lymphoma. The exact pathophysiology of PTLD is not completely understood, but most cases (80%–90%) are of B-cell origin and are associated with an EBV infection (1). Additionally, at least 90% of PTLD cases in solid organ transplants arise from recipient cells, in contrast to the PTLD seen after bone marrow transplantation (2). The intensity of immunosuppression, including the use of muromonab-CD3

Figure 2. Histopathology of posttransplant lymphoproliferative disorder, diffuse large B-cell type. (a) Photomicrograph showing a dense population of large atypical lymphoid cells with indented, pleomorphic nuclei and conspicuous nucleoli (hematoxylin and eosin staining, 20 $\times$). (b) Photomicrograph of in situ EBV-encoded small RNA in situ hybridization test showing diffuse positive nuclear staining (20 $\times$).

(OKT3) or antithymocyte globulin induction therapy, plays a paramount role in triggering PTLD (3).

EBV is an endemic, oncogenic virus with potential to cause systemic lymphoproliferation if host immune surveillance fails. Unfortunately, a positive EBV DNA result has no prognostic value. An elevated level may be interpreted as suspicious for PTLD, but no viral load threshold has been clearly identified (1, 4). Nonetheless, viral load monitoring may be used to guide immunosuppression or track the response to treatment.

The incidence of PTLD typically peaks in the first year after transplantation, occurring more frequently in intestinal, multivisceral, and lung transplant recipients (3). Graft, central nervous system, and multiple site involvement are poor prognostic factors. Presenting symptoms of PTLD may be mild, resembling a mononucleosis-like syndrome (malaise, sweats, and fever). Although uncommon, palpable or identifiable lymphadenopathy should prompt a biopsy, as histologic analysis is key to establishing the correct diagnosis. Early stages of PTLD may be effectively treated by immunosuppression reduction or discontinuation. However, other types or advanced stages of PTLD may require chemotherapy, radiation therapy, B-cell-directed antibodies (i.e., rituximab), or surgery.

Data regarding PTLD and pancreas transplantation are sparse. However, a recent analysis by Jackson et al using the United Network for Organ Sharing database identified several factors associated with the development of PTLD: recipient EBV seronegativity, younger recipient age, white ethnicity, closer HLA matching, and an agent other than tacrolimus as the main immunosuppressive agent, the latter perhaps a contributing factor in our case. The incidence of PTLD over the 10-year review period was 1%, and patients with PTLD had a significantly lower 5-year survival rate than those without (70% vs 88%, $P < 0.001$). The type of the pancreas transplant (pancreas alone, simultaneous with kidney, or after kidney) had no association with PTLD (5).

In the largest reported single-center experience, Paraskevas et al compared the outcomes of PTLD in their pancreas transplant recipients ($N = 1357$) against liver and kidney transplant recipients. Compared with the other two groups, pancreas transplant recipients with PTLD had a significantly shorter overall survival ($P = 0.001$), with a greater mean number of organs involved at the time of presentation (3.7 vs 2.0, $P = 0.007$) (6).

PTLD in PTA has been described in three single-center experiences with all three types of pancreas transplantation (6–8). In these studies, involving 11 total PTA cases, the reported incidence of PTLD ranged from 1.0% to 8.9%. Due to low overall power, no further generalizations can be made about this subset of pancreas recipients.

PTLD in the pancreatic graft itself is not common; when present, other sites are also usually involved. As demonstrated across other solid organ transplants, disseminated disease carries a poorer prognosis than lymph node disease alone (3). Two case studies reported PTLD limited to the pancreatic allograft after SPK transplant (9, 10). In each case, the recipient had multiple admissions and a presentation that was initially thought to be graft pancreatitis. One presented with signs of

intestinal obstruction. Due to continued complications, graft pancreatectomies were performed despite functioning grafts. Both patients survived, highlighting a favorable outcome for single-site PTLD.

Only one center experience clearly described PTLD in the allograft after PTA. Of 13 total cases reported, six cases were in PTA recipients, one of whom had graft and colon involvement. This multisite patient died early from lymphoma progression (7).

Our case report describes a patient who developed CMV viremia 6 months after transplant, followed by a positive, low-viral-load EBV count. Unfortunately, the EBV viremia was not followed, and it may have been used to gauge the possibility of a forthcoming PTLD. A subsequent graft biopsy demonstrated pancreatitis, which may have masked the underlying malignancy. CT scans also revealed graft pancreatitis—as has been described in patients ultimately diagnosed with PTLD (8, 10)—rather than an overt focal mass. Persistent pancreatitis likely resulted in chronic ischemia, abscess formation, and graft failure. In our patient, PTLD was an unexpected finding on explant. As the disease was limited to the graft itself, pancreatectomy was curative without the need for further adjuvant therapy.

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