Post-transplant lymphoma of the pancreatic allograft in a kidney–pancreas transplant recipient: a misleading presentation

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Case report

A 37-year-old male patient underwent combined kidney–pancreas transplantation with an immunosuppressive treatment consisting of tacrolimus, mycophenolate mofetil and steroids, after induction therapy with anti-thymocyte globulin. The pancreas graft had intestinal drainage. Twenty-seven days post transplantation, the patient developed an episode of acute graft pancreatitis, which responded well to conservative measures (i.v. fluids, nil per orally, histamine-2 receptor blockade). On day 45, renal function was stable with a serum creatinine of 1.28 mg/dl, corresponding to a measured creatinine clearance of 57 ml/min. Because of persistent post-prandial hyperglycaemia, the addition of low-dose insulin therapy was necessary for a period of 6 weeks after transplantation.

Two months post transplantation, the patient was admitted because of diarrhoea and a rise in serum creatinine to 2.49 mg/dl. A renal biopsy showed acute cellular rejection grade Ib according to the revised Banff 2001 criteria [1]. The patient was treated with corticosteroids, resulting in a good clinical and biochemical response. However, renewed insulin therapy was temporally required during this rejection episode and was discontinued during further follow-up. Stool cultures at that time revealed Campylobacter jejuni, for which doxycycline was administered for 10 days.

Four months later, the patient presented with acute pain and swelling over the pancreatic graft. Other complaints were anorexia, weight loss and low grade fever. On clinical examination, we saw a thin patient with normal vital signs. A firm mass in the right iliac area (10 x 10 cm), painful on palpation, was present. Laboratory results showed haemoglobin levels of 10.0 g/dl—normochromic, normocytic—a white cell count of 9600/mm3—93% neutrophils—a serum creatinine of 1.4 mg/dl, urea nitrogen levels of 41 mg/dl, γ-glutamyl transferase 68 U/l, and lipase 70 U/l. C-reactive protein (CRP) levels were 65.4 mg/l. Amylase, triglycerides and calcium levels were normal. Tacrolimus blood levels were within therapeutic range (8–12 ng/ml). Proteinuria was 0.27 g/l without haematuria or bacteriuria. Screening for viral and fungal disease revealed the presence of Epstein–Barr virus (EBV) DNA viraemia [log 4.16 (=14.510) copies/ml]). At the time of transplantation, the patient tested positive for EBV serology (status of immunity).

Abdominal ultrasound showed a heterogeneous, multinodular mass (10 x 10 x 7 cm) that was partly solid and partly heterogeneous cystic. The mass could not be distinguished from the surrounding adipose tissue. Differentiation between an inflammatory process and a tumoural mass was impossible. Magnetic resonance imaging (MRI) scan of the abdomen showed a complex heterogeneous and nodular mass (9.4 cm) with compression on the pancreatic allograft and the surrounding small intestinal loops (Figure 1). The mass was iso- to hypointense on T2-weighted images and iso- to slightly hyperintense on T1-weighted images. Its vascularization originated from the right iliac vessels (Figure 2). The process could not be distinguished from the head of the pancreas nor from the transplanted afferent part of the small intestine. Reaching a conclusive diagnosis was still impossible, although an inflammatory mass with necrosis or a graft pancreatitis with pseudocyst...
formation was suggested. The differential diagnosis with a partial venous thrombosis of the afferent loop of the small intestine was hypothesized, as was a post-transplant lymphoproliferative disorder (PTLD). In the latter case, however, the mass would preferably have originated from the head of the pancreas, which seemed unlikely. The renal allograft suffered from hydronephrosis, probably caused by compression of the mass described earlier.

The tentative diagnosis of chronic/subacute pancreatitis was made and the patient was treated with i.v. fluids, nil per orally, histamine-2 receptor blockade, and placement of a nasogastric tube because of gastro-intestinal subobstruction. X-ray of the small intestine (with gastrografin) showed limited compression of the afferent intestinal loop. No leakage of contrast fluid was seen. Computed tomography (CT) scan showed a limited mechanical small bowel obstruction. Whole-body positron emission tomography after i.v. injection of 18 F-fluorodeoxyglucose (FDG-PET) showed an increased metabolic signal in the mass, but no other hot spots.

Due to lack of improvement of biochemical inflammatory parameters, broad-spectrum antibiotics (piperacillin–tazobactam) were added to the treatment. Subsequently, CRP decreased and the patient’s general well-being improved. After a short course of parenteral nutrition, the patient was able to eat again.

Because of continuous doubts about the exact characteristics of the mass, it was decided to perform a biopsy of the suspicious area. All except one fine needle biopsies consisted of necrotic debris, while the last tissue cylinder showed a mixture of necrotic debris and viable pancreatic acinar structures, surrounded by macrophages and CD20+ B cells and CD3+ T cells. Histological arguments for malignancy or fungal infection were absent.

Because of a persistent inflammatory status with the development of toxic anaemia (and the need for several blood transfusions), general malaise and pain, a pancreatic transplantectomy was planned, even though the endocrine function was normal (normal oral glucose tolerance test). After multidisciplinary discussion, a subsequent auto-transplantation of the
explanted pancreatic graft islets was proposed to the patient, if this was considered feasible after evaluation of the graft. While the explanted pancreatic tissue was sent to the islets transplantation bank for preparation, tissue cultures unfortunately showed massive growth of *Candida albicans*. Macroscopic examination of the transplantectomy specimen revealed a homogeneous, compact, yellow mass (10 × 7.5 cm), surrounding the transplanted intestinal loop, but originating from the pancreas graft rather than the intestine. While sectioning this mass, only a small rim of the remaining pancreatic tissue could be recognized. By light microscopy, large necrotic tissue areas were seen. The remaining viable pancreatic tissue was diffusely invaded by a malignant proliferation of CD20⁺ B cells, with destruction of the exocrine as well as endocrine pancreatic parenchyma. The malignant lymphoid population consisted of enlarged cells with irregular, hyperchromatic nuclei. A thin rim of amphophilic cytoplasm was visible. Mitotic figures were frequent. The diagnosis of a diffuse large B-cell non-Hodgkin’s lymphoma, type PTLD, was made (Figure 3). The tumour was positive for EBV by immunohistochemistry (monoclonal LMP-1, Dako Cytomations, Denmark, dilution 1/50) and by *in situ* hybridization [EBV (EBER) PNA probe, Dako Cytomations]. Donor origin of the lymphoid cells was not assessed; PTLD was not reported in other organ recipients from this male donor. The section margins were tumour-free as was a bone marrow biopsy, performed as part of the staging protocol. The previous renal biopsy showing acute rejection was reassessed by staining with a polyclonal anti-CD3 antiserum (T-cell marker) and monoclonal anti-CD20 antiserum (B-cell marker), but showed a mixed lymphocytic infiltrate without signs of monoclonal cell populations.

With these findings, islets auto-transplantation was no longer considered and the patient regained his diabetic state. He was subsequently treated with four weekly cycles of adjuvant rituximab (375 mg/m²), once weekly. Additionally, the patient received diflucan (i.e., later per orally) for the *Candida albicans* infection. Immunosuppression was reduced but not stopped, as the allograft kidney was still *in situ* and functioning well.

**Discussion**

Solid organ transplantation is associated with a 3–5 times higher risk of malignancy compared with the general population [2]. Beside skin cancers, PTLD is the most frequent malignancy, accounting for 15–25% of all post-transplant neoplasms [2–4]. More than 90% of PTLD is EBV related, as was the case in our patient [5]. Immunosuppressive medication impairs EBV-specific cytotoxic T-cell responses, allowing viral replication and proliferation and ultimately malignant transformation of EBV infected B-lymphocytes. Varying reports describe the type of immunosuppressive regimen, young recipient age, male gender, (Caucasian) race and simultaneous cytomegalovirus (CMV) infection as risk factors for PTLD, but the most important risk factor seems to be the EBV-seronegative status of the recipient, with a 20-fold higher relative risk in the first year post-transplantation compared with seropositive recipients [5,6]. Other cases of PTLD are EBV-negative, and the onset of these cases is distributed more evenly throughout the 10-year post-transplant period [7]. The incidence of PTLD varies with the type of allograft. The highest incidence occurs after intestinal or multi-visceral transplantation (39%), probably because of the large amounts of lymphoid tissue present and the potent immunosuppression regimens used [8]. Renal allograft recipients are the least likely to develop PTLD (<1%), while it has been described in 1–2% of liver transplant patients, in 5–10% of heart and lung transplants and in 12% of pancreas transplants [9–12]. One small study suggested a higher incidence in pancreas-only allografts (3.8%, 2/52) compared with pancreas-after-kidney transplantation (0.9%, 1/106) or simultaneously pancreas–kidney transplants (2.8%, 5/179) [13]. This might be explained by the high incidence of acute rejection in pancreas transplants, a condition that requires large doses of immunosuppression [14].

The type and the degree of the immunosuppressive regimen have been described as important risk factors in the pathogenesis of PTLD. Of particular concern is the use of calcineurin inhibitors. These agents promote the development of EBV-driven lymphoproliferation by inhibiting the maturation of T-cell-dependent

**Fig. 3.** Light microscopy of the PTLD: acini and ductuli are massively invaded by a malignant proliferation of B-cells. Left panel: haematoxylin–eosin stain; right panel: anti-CD20 (original magnification 20×).
immune responses, precluding the generation of EBV-specific cytotoxic T cells. Whether the use of triple therapy protocols (azathioprine/MMF, calcineurin inhibitors, prednisone) is associated with an increased risk of PTLD is a matter of debate, though a large study suggested that triple therapy increases the risk of PTLD 1.5-fold in the first year post-transplant, when compared with azathioprine or calcineurin inhibitor therapy [9]. Other studies failed to reveal a statistically significant increase in the incidence of early PTLD when comparing ciclosporin-based protocols with regimens including MMF [15–18]. One prospective study, in de novo renal transplant patients, suggested an equal or even lower risk of developing PTLD using MMF-based protocols compared with non-MMF-based protocols [19]. The use of ATG or monoclonal anti-CD3 antibody (OKT3) for induction or treatment of acute rejection episodes is clearly associated with an increased risk of early PTLD [20,21]. The use of Muromonab-C03 (OKT3) as an induction or anti-rejection therapy, especially when used at a cumulative dose >75 mg, increases the risk of PTLD; in the Collaborative Transplant Study, the relative risk of PTLD in the first year post-transplant was 1.8 times greater when OKT3 was used as induction (renal and heart transplants) and 4–6 times greater when used as anti-rejection therapy (only heart transplants) [9]. High doses of immunosuppression, including Antithymocyte (ATG), were used in our patient, who in addition suffered from one acute rejection episode. Symptoms of PTLD range from fever and malaise similar to an influenza-like syndrome to a potentially fatal systemic illness. Our patient presented with a picture of general malaise, weight loss and subfebrillitas. Uncommon in this case was the rapidly growing, painful, large mass, which first misled us to suppose this was an inflammatory pathology [13]. In the given context, one should also consider an acute rejection episode, although the persistent normal pancreatic function combined with a minimal increase in pancreatic enzymes made this unlikely.

On imaging, pancreatic PTLD usually presents as a diffuse enlargement of the organ, only seldom as a focal mass, as was the case in our patient [13]. Differential diagnosis with pancreatitis or acute rejection can be very difficult on a clinical basis, as is obtaining a representative fine-needle biopsy. As necrotic areas are a frequent finding in PTLD of the pancreas, biopsies can be misleading, as was the case in our patient [22].

It is difficult to identify the optimal treatment for pancreatic allograft PTLD, because large prospective controlled studies are not available. Only studies in small patient groups with a diversity of allograft types have been published. The relative importance of T-cell impairment, EBV and clonal proliferation has led to three strategies: reduction of immunosuppression, antiviral therapy and chemotherapy. Reduction of immunosuppression is the first step; patients who are unable to tolerate this have a much poorer prognosis; for 23–25% of patients this will lead to complete and durable remission of the PTLD [23]. For well-delineated and isolated PTLD, surgery or radiotherapy is useful. Acyclovir has been described to induce regression; interferon-α has both antiviral and antiproliferative activity, and durable remissions have been achieved with this compound [24–26]. Anti-B-cell monoclonal antibodies are a promising therapy: a combination of anti-CD21 and anti-CD24 antibodies was used in a multicentre trial; the overall response rate was 61% and the overall survival was 46% [27]. The humanized anti-CD20 monoclonal antibody rituximab was recently tested in PTLD patients. The largest study describes a response rate of 65% and a relapse rate of 18%, while 16% of the patients died due to infectious complications and rejection [28]. Classical chemotherapy is mostly reserved for CD20–PTLD or as second- and third-line treatment and consists of anthracycline-based regimens, which are more toxic in this type of patients with reduced renal function [29].

We opted for the removal of the graft, reduction but no withdrawal of immunosuppression and treatment with rituximab (anti-CD20 antibodies). As staging showed limited disease, we considered our patient fully treated. One year after treatment the patient remain free of disease.

Conflict of interest statement. None declared.

References


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