Renal Replacement Therapy

CASE REPORT

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Pembrolizumab-induced donor duodenum perforation after remote simultaneous pancreas-kidney transplant: a case report and literature review

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Abstract

This case report describes a patient in their 60s, a simultaneous kidney and pancreas transplant recipient, who presented with severe allograft rejection following a single dose of the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab for recurrent basal cell carcinoma (BCC) two decades posttransplant. The patient's BCC had been treated with sonidegib for 6 years, and he had been off of immunosuppression for 8 years. The patient was back on insulin therapy and had resumed maintenance hemodialysis a few months before admission. A total of 6 weeks after receiving pembrolizumab, the patient was hospitalized with abdominal pain. Imaging, followed by surgical exploration, revealed a well-circumscribed small bowel perforation corresponding to the disappearance of the rejected donor duodenal patch, which was associated with the severely atrophic and fibrotic pancreas, while the kidney exhibited gross features of rejection. Histological evaluation confirmed extensive hemorrhagic necrosis and transmural necrotizing vasculitis with thrombosis in the duodenal patch. In addition, the renal parenchyma exhibited extensive hemorrhagic necrosis and multiple vessels with thrombosis. This case underscores the risks of the rupture/leakage of donor-derived tissue triggered by immune checkpoint inhibitors, and potentially any "provoked" rejection, in transplant patients who have remaining allografts in place.

Keywords Pembrolizumab, Programmed cell death protein I inhibitor, Allograft rejection, Nephrectomy, Basal cell carcinoma

Introduction

Among organ transplant recipients, malignancies are the second leading cause of mortality after cardiovascular death [1]. Skin cancers, particularly squamous cell carcinoma and basal cell carcinoma (BCC), demonstrate the highest incidence, corresponding to 1.4 cases per 1000 transplants recipients annually [2]. Although BCC is generally treatable by local resection, recurrence, local invasion, or metaplastic transformation presents challenges, particularly in transplant recipients who have a 10 to 16 times higher incidence and recurrence rate compared with the general population [2]. Pembrolizumab, a selective anti-programmed cell death protein 1 (PD-1) humanized monoclonal antibody, has demonstrated efficacy in treating refractory BCC [3]. There is a significant risk of severe and often treatment-resistant T-cell-mediated rejection in transplant recipients, similar to what

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has been reported with other classes of immune-checkpoint inhibitors [4].

We report the case of a simultaneous kidney-pancreas transplant recipient, who was off of immunosuppression for more than 8 years after sustaining progressive graft failure. They developed bowel perforation from accelerated donor-tissue rejection after a single pembrolizumab dose for recurrent BCC treatment.

Case presentation

A patient in their 60 s, 20 years post-simultaneous kidney and pancreas transplant (SPK), presented with fatigue, confusion, and abdominal pain developed over the previous 2 months. Computed tomography (CT) revealed free air in the abdomen, indicative of bowel perforation, and the patient was transferred to our institution for further evaluation. Medical history included hypothyroidism, hypertension, insulin-dependent diabetes, and end-stage renal disease. A total of 7 years before the SPK, the patient was diagnosed with carcinosarcomatous BCC and treated with Mohs surgery. After being disease-free for 7 years, the patient underwent the SPK but experienced two BCC recurrences at 5- and 9-years posttransplant, requiring surgical excision. A total of 18 years posttransplant, magnetic resonance imaging (MRI) revealed mass-like lesions in the occipital and mastoid bones, which were treated with vismodegib for 6 years. A total of 3 months prior to presentation, the patient discontinued vismodegib and received a single dose of pembrolizumab to treat this refractory BCC. At this time, the patient had been off immunosuppression for 8 years, with nonfunctional kidney and pancreas grafts, and was on maintenance hemodialysis and insulin; 3 months after receiving pembrolizumab, the patient was admitted with presumed abdominal sepsis. Cefepime, vancomycin, and metronidazole were initiated and an exploratory laparotomy was performed. A bowel perforation was found with a 3-cm defect in the jejunum caused by the complete breakdown of the pancreaticoduodenal–jejunal anastomosis (Fig. 1A, B). A necrotic and severely atrophic transplanted pancreas stump was found, as well as a necrotic appearing kidney graft (Fig. 1A, B). A side-to-side small bowel anastomosis and pancreas–kidney graft explanation were performed (Fig. 1C).

Histological evaluation demonstrated features of severe acute rejection with mixed T-cell and antibody-mediated allograft rejection in sections of the perforated duodenal cuff, the residual pancreatic graft, and the kidney (Fig. 2A). The intestinal segment showed diffused transmural necrosis with associated serositis and mononuclear vascular and perivascular mononuclear infiltrates with intimal arteritis (Fig. 2A), and the fibrofatty tissue exhibited extensive hemorrhagic necrosis and vascular wall necrosis/thrombosis (Fig. 2B). Immunohistochemical staining showed strong immunoglobulin (Ig)M positivity in the most walls of vessels. IgG staining was negative (Fig. 2C). C4d staining was positive in necrotic vascular walls and numerous thrombi (Fig. 2D). These

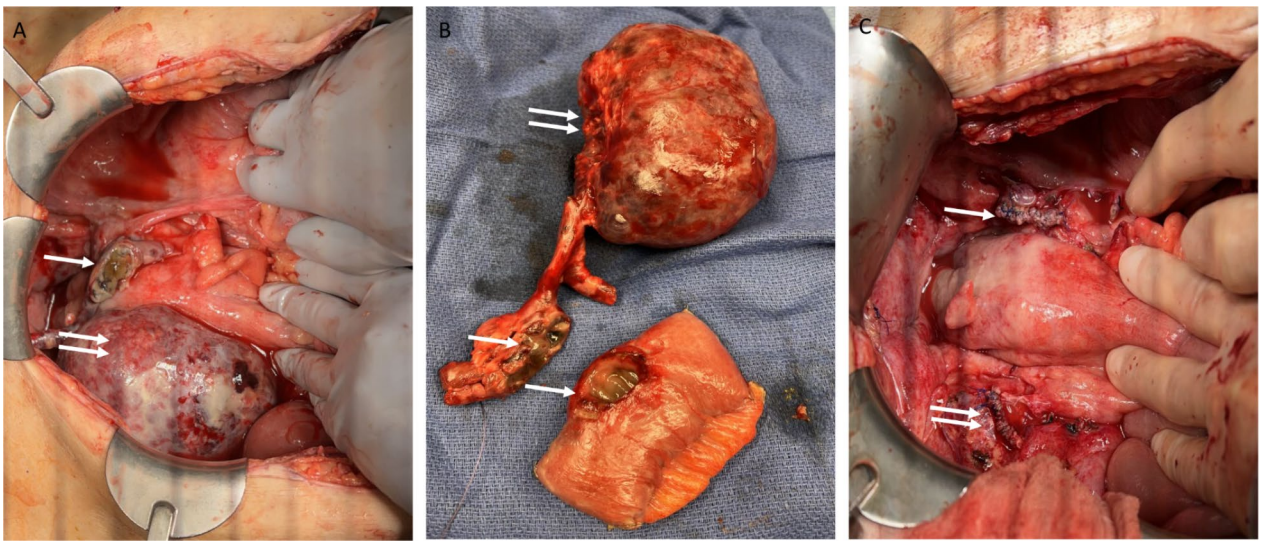

Fig. 1 **A** A single arrow shows the complete breakdown of the pancreaticoduodenal–jejunum anastomosis. The double arrows show necrotic allograft kidney. **B** A single arrow shows the complete breakdown of the pancreaticoduodenal–jejunal anastomosis site and corresponding defect left by the absent duodenal patch in the recipient's jejunum. The double arrows show necrotic allograft kidney. **C** The pelvic cavity after nephrectomy and preparing side-to-side anastomosis. A single arrow shows the oversewn right iliac vessel anastomoses site (pancreas side), and double arrows show the oversewn iliac vessel anastomoses site (kidney side)

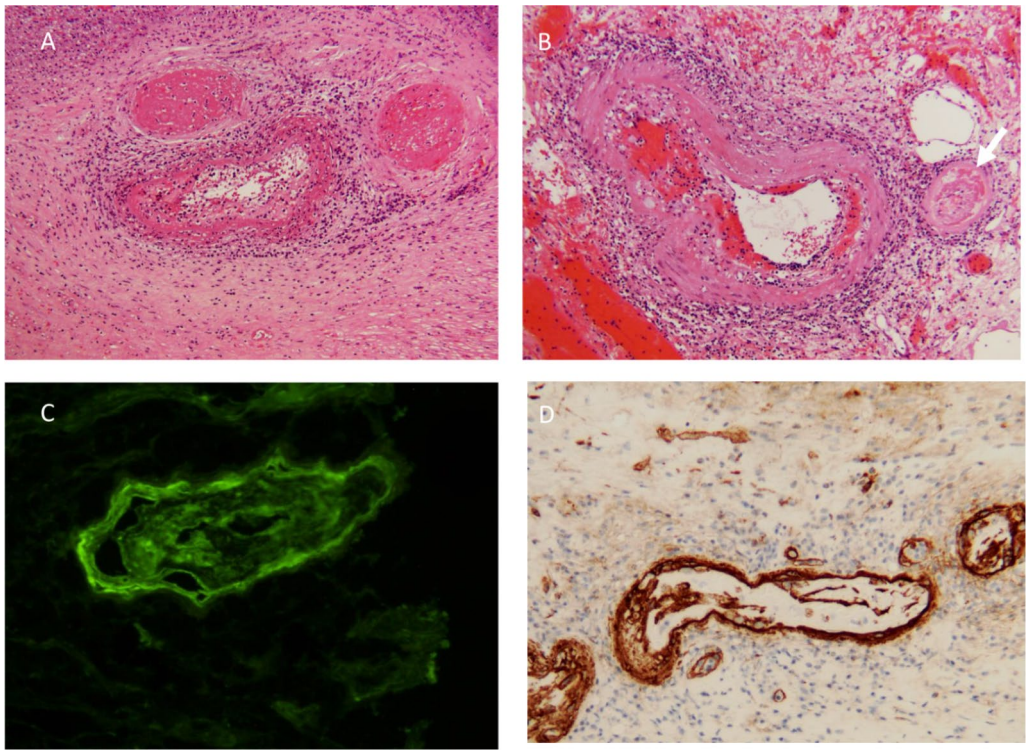

Fig. 2 **A** Duodenal cuff wall with vascular inflammation, transmural necrosis, and thrombosis. This corresponds to the area of ulceration in the gross picture. **B** Kidney: arteries with transmural necrosis/inflammation and thrombosis (arrow). **C** Kidney: positive immunofluorescent staining for IgM in the necrotic vascular walls. **D** Kidney: positive C4d immunostaining in vascular walls

findings were consistent with an acute/subacute–chronic mostly antibody mediated rejection reaction and accelerated thrombotic/necrotizing processes of the kidney–pancreas graft. The postoperative course included several complications such as ileus and slow progress due to the preoperative debilitating state. The patient was ultimately discharged home on postoperative day (POD) 42. The patient was stable at his last follow-up 1 year after his transplantectomies.

Discussion and conclusions

Posttransplant malignancies are a significant problem among transplant recipients, occurring at rates three to five times higher than the general population and can be either de novo or recurrences from either the recipient or donor [5]. Skin cancers account for 40–50% of all posttransplant malignancies [2], with nonmelanoma skin cancers, particularly squamous cell carcinoma and BCC, being the most prevalent. Risk factors including immunosuppressive therapies, advanced age, male gender, and genetic predispositions [6]. BCC is often localized and treatable with topical immune-response modifier (imiquimod or 5FU), photodynamic therapy, and surgery; its potential for recurrence, invasiveness, and metastasis poses significant challenges, particularly in chronically immunosuppressed patients in whom aggressive histological features or involvement of critical areas such as the head and neck could be life-threatening. While most advanced BCC cases harbor mutations in the hedgehog signaling pathway, newer targeted therapies such as vismodegib have shown efficacy in advanced and recurrent cases. Despite advancements, BCC remains challenging to manage when conventional therapies fail and may require an immune-checkpoint inhibitor as seen in our case [3].

Immune checkpoint inhibitors, notably PD-1 monoclonal antibodies such as pembrolizumab, represent a last-resort therapeutic option for advanced BCC in organ transplant recipients as well. While intense pembrolizumab-induced renal allograft rejection might be acceptable as a life-saving option in kidney transplant recipients (i.e., the graft can be removed, and patients can go back to dialysis) [7, 8], using immune-checkpoint inhibitors is limited in liver transplant recipients owing to the high risk of severe rejection, despite their increasing rejection control rate and improved survival in responders [9].

The use of immune-checkpoint inhibitors in transplant recipients presents a significant risk of allograft rejection. Pharmacovigilance studies and case reports highlight high rejection rates associated with

pembrolizumab and nivolumab, particularly in kidney and liver transplant patients, often leading to graft loss within weeks of initiation [7, 10, 11]. Systematic reviews confirm that anti-PD-1/programmed cell death ligand 1 (PD-L1) therapies pose a greater rejection risk compared with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, with irreversible rejection observed in some cases [4, 12]. Beyond solid organ transplants, pembrolizumab has also been implicated in corneal graft rejection, as reported in a patient who developed immune-mediated rejection 3 months after therapy initiation [13]. While corticosteroids can mitigate these effects, rejection often recurs upon discontinuation. Additionally, pembrolizumab has been linked to inflammatory complications in nontransplant settings, such as breast reconstruction [4].

In this case, a patient in their 60s, who was off of immunosuppression for 8 years, developed localized bowel perfusion as a result of complete rejection after a single pembrolizumab dose for recurrent BCC. To our knowledge, this is the first reported case describing this complication, which is specific to SPK recipients. The diagnosis was only made intraoperatively when the transplant team was called in and after the bowel perforation was repaired, highlighting the unexpected nature of this complication. In our experience, we reported another case of provoked and accelerated rejection to clear cancer in a SPK recipient that led to donor pancreas tissue breakdown and leakage [14]. In that case, a blowout of the arterial Y graft stump was noted 6 months after interleukin (IL)-2 administration and 9 years posttransplant.

In conclusion, this case underscores the possibility of the severe rejection of donor tissue and potentially life-threatening complications several years after graft acceptance in the absence of immunosuppression. Careful consideration of the risks/benefits and close monitoring of such patients requiring the stimulation of their immune system for oncologic reasons seems necessary.

Abbreviations

BCC Basal cell carcinoma
CT Computed tomography
PD-1 Programmed cell death protein 1
SPK Simultaneous pancreas kidney transplant

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None.

Author contributions

R.M. designed the study. K.S. and R.M. collected the data. K.S. and R.M. analyzed the data. K.S., C.D., and R.M. interpreted the data and wrote the manuscript. K.S. and R.M. have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

No datasets were generated or analyzed during the current study. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

Exemption was approved by the Ethics Committee of University of Maryland Medical System. Informed consent for publication of these data was obtained from the patient discussed in this report.

Consent of publication

Informed consent for publication of these data was obtained from the patient discussed in this report.

Competing interests

The authors declare that they have no competing interests.

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