Urology Case Reports 21 (2018) 89–91

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Immune system trickery and deception: Allograft-derived neuroendocrine carcinoma post kidney transplantation

Cyrus Chehroudi[a], Miles Mannas[a], Edward C. Jones[b], Christopher Nguan[a], Conrad Oja[c], Peter C. Black[a,*]

[a] Department of Urologic Sciences, University of British Columbia, Level 6 2775 Laurel Street, Vancouver, BC, V5Z 1M9, Canada
[b] Department of Pathology & Laboratory Medicine, University of British Columbia, Rm. G227, 2211 Wesbrook Mall, Vancouver, BC, V6T 2B5, Canada
[c] Department of Medical Oncology, British Columbia Cancer Agency, 13750 96 Ave, Surrey, BC, V3V 1Z2, Canada

ARTICLE INFO

Keywords:
Bladder cancer
Immunosuppression
Neuroendocrine carcinoma
Renal transplantation
Urothelial carcinoma

Introduction

Malignancy following renal transplantation is an uncommon consequence of long-term suppression of anti-tumour immune surveillance, but seems to be increasing in incidence with improved survival of renal transplant recipients.[1] The incidence of malignancy is markedly elevated in renal transplant recipients compared to the general population; however, little is known about their prognosis and the contribution of immunosuppression to disease progression. We report on the clinical course of a pancreas-kidney transplant recipient who developed invasive renal allograft-derived neuroendocrine carcinoma with rapid post-nephrectomy metastatic progression.

Case report

A 48-year-old gentleman developed gross hematuria approximately 7 years after simultaneous pancreas-kidney transplant for diabetic nephropathy. He had normal renal and pancreatic allograft function on immunosuppression with tacrolimus, mycophenolate, and prednisone. An ultrasound of both native kidneys and renal allograft was normal. Cystoscopy revealed a vascular lesion on the left lateral wall that was later resected, revealing a grade 2/3 papillary Ta urothelial carcinoma (UC).

The patient continued to have gross hematuria despite normal cystoscopy. CT urogram demonstrated hyperdense debris in the transplant collecting system suggestive of clot versus Post-transplant Lymphoproliferative Disorder (Fig. 1). Retrograde pyelogram revealed a lower pole filling defect in the transplant kidney and selective cytology showed atypical urothelial cells. Flexible ureteroscopy of the transplant kidney was unsuccessful. The suspicious upper tract lesion was biopsied percutaneously revealing mixed invasive UC with a small-cell component. Metastatic work-up at this time including MRI abdomen/pelvis and CT chest was negative.

Transplant nephroureterectomy revealed pT3 small-cell/high-grade UC and genotyping confirmed this to be of donor origin (Fig. 2). Two months post-op, the patient again developed gross hematuria secondary to a large anterior bladder tumour recurrence, which was resected and shown to be high-grade T1 disease with mixed small cell and UC features. Neadjuvant chemotherapy was deferred due to the potential risks in a transplant patient, and radical cystectomy with bilateral native nephrectomies was performed. The pathologic specimen revealed only a few foci of bladder carcinoma *in situ* and normal kidneys.

Five months after cystectomy, a surveillance CT scan revealed local recurrence in the allograft fossa, hepatic metastases, and retroperitoneal lymphadenopathy. Immunosuppression had been maintained up to this point in order to preserve pancreatic allograft function, but at this point it was discontinued. Follow-up CT scan after 3 months showed interval progression of hepatic metastases (Fig. 3). The patient's pancreatic allograft also began to fail at this point, and he was started back on insulin.

Systemic cisplatin/gemcitabine chemotherapy was initiated with complete resolution of all metastases after 6 cycles. He remained free of

* Corresponding author.
E-mail address: peter.black@ubc.ca (P.C. Black).

https://doi.org/10.1016/j.eucr.2018.09.007
Received 1 September 2018; Accepted 10 September 2018
Available online 14 September 2018

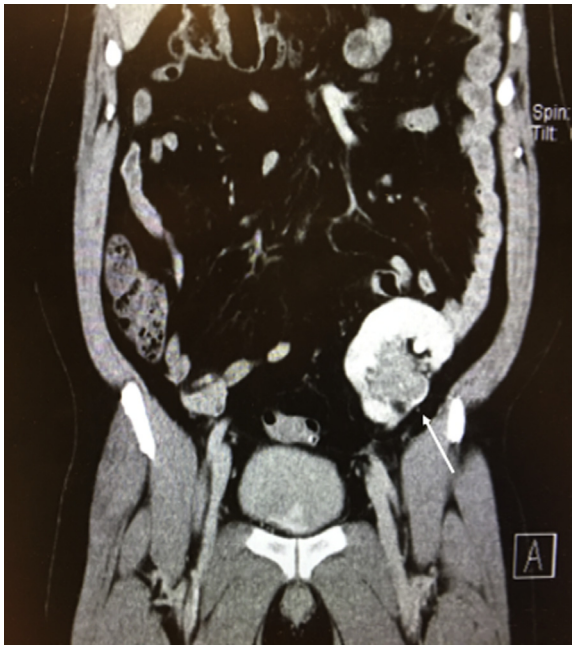

Fig. 1. CT intravenous pyelogram demonstrating a distended transplant collecting system with lobulated, hyperdense debris.

disease 12-months after completing chemotherapy.

Discussion

The incidence of any malignancy following renal transplant is estimated to be 7.5% at 3 years, while the risk of UC ranges from 0.02% to 1.0% (~3-fold that of the general population).[1] Factors associated with post-transplant UC include length of immunosuppression and origin of allograft from a deceased donor, as well as the usual risk factors.[2] No particular immunosuppressive regimen appears to be associated with heightened risk of malignancy. Most patients present with hematuria.

The literature on metastatic UC post-transplant is sparse and mostly limited to isolated case reports. Our case is unique in that it is complicated by the pancreatic allograft, aggressive histology, extensive metastatic disease, and the challenges of chemotherapy on dialysis. Most reported cases of allograft-derived UC are localized and managed by transplant nephroureterectomy with good oncological outcomes.[3] However, these patients are usually discontinued on their immunosuppression unlike our patient because of his pancreatic graft. This likely hindered his ability to mount an alloimmune response against any residual tumour post-operatively. The role of alloimmunity in the clearance of donor-origin tumours is apparent in a retrospective review of patients with allograft-derived malignancies by Penn et al.[4] It was shown that 18/33 patients with metastatic renal allograft tumour (of unspecified histology) achieved complete remission with transplant nephrectomy and discontinuation of immunosuppression. Unfortunately, it appears that the rate of immune recovery was insufficient in our case, as evidenced by the 3-month delay in the failure of his pancreatic allograft.

Unfortunately, our patient progressed to metastatic disease despite removal of the allograft and native urinary tract, and stopping immunosuppression. Cisplatin-gemcitabine was started since the tumour histology was predominately high-grade UC, and this was thought to be a more tolerable regimen in a dialysis patient. Given the challenges of dosing chemotherapy on dialysis, we avoided neoadjuvant or adjuvant chemotherapy earlier in the disease course, and in the metastatic setting opted for a trial of discontinuing immunosuppression before attempting chemotherapy. The pancreatic graft was left *in situ* as the risk of pancreatitis was outweighed by the threat of metastatic disease in

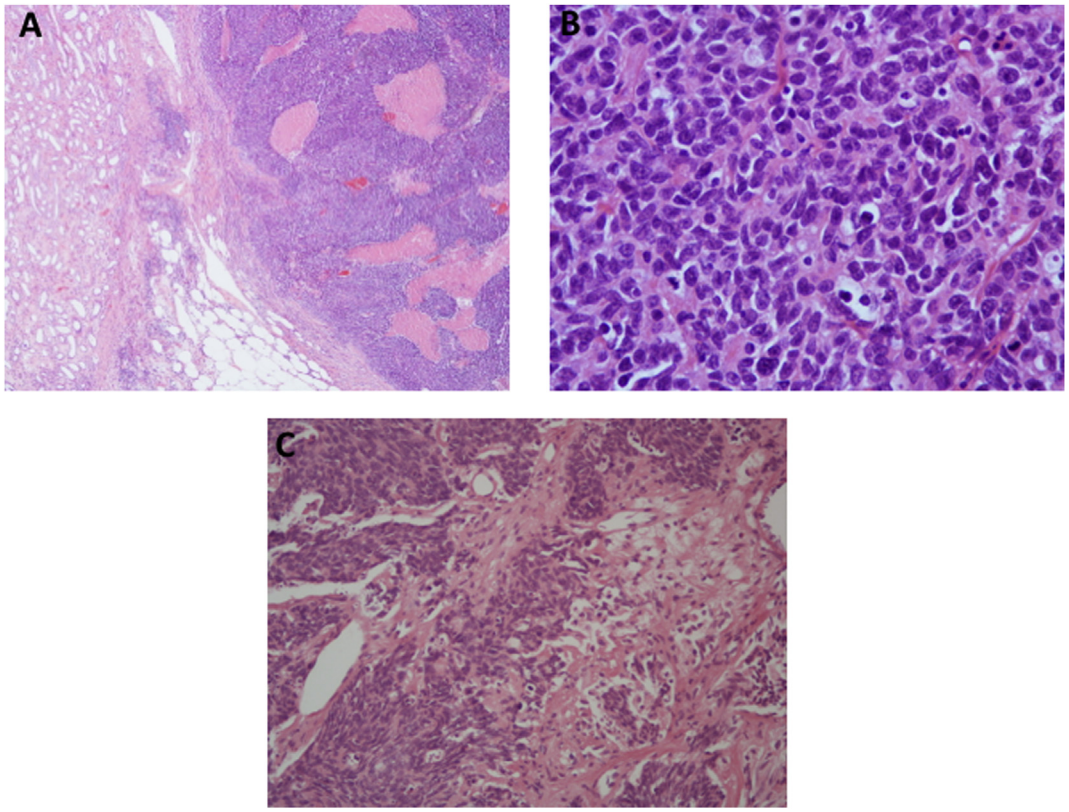

Fig. 2. Histopathology from the transplant kidney (a) demonstrating invasion of the renal pelvis (pT3) by high-grade urothelial carcinoma with interspersed neuroendocrine-appearing cells (b). Bladder tumour resection specimen post-transplant nephrectomy (c), again showing similar histologic features.

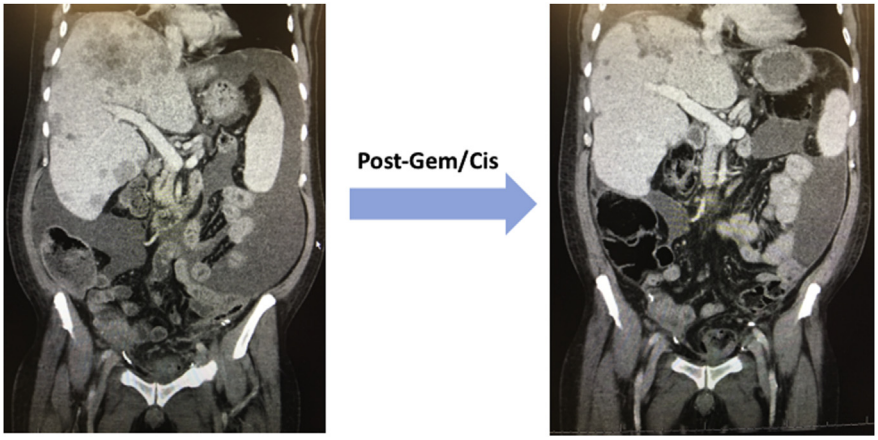

Fig. 3. CT scan showing extensive hepatic metastases at 8 months post-cystectomy and bilateral native nephrectomy.

delaying potential systemic therapy while waiting for allograft explantation.

It is well known that transplant patients are at much higher risk for progression of any malignancy.[5] In line with this, our case developed rapid recurrences and eventual progression to metastatic disease. A critical step in the management of renal transplant patients with allograft malignancy is determining the source of the index lesion. Although most urologic malignancies post-transplant are from the native tract, a donor cancer should be treated with transplant nephroureterectomy and early discontinuation of immunosuppression, if permissible.

Conclusion

In summary, we have described a case of metastatic UC in a patient with simultaneous pancreas-kidney transplant. While a relatively rare event, donor-derived malignancy is likely to be experienced at some point by renal transplant centres and requires careful management due to higher risk of progression and attention to unique factors such as alloimmunity.

Conflicts of interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eucr.2018.09.007.

References

1. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant.* 2004;4(6):905–913.
2. Master VA, Meng MV, Grossfeld GD, Koppie TM, Hirose R, Carroll PR. Treatment and outcome of invasive bladder cancer in patients after renal transplantation. *J Urol.* 2004;171(3):1085–1088.
3. Tilou X, Doerfler A, Collon S, et al. De novo kidney graft tumors: results from a multicentric retrospective national study. *Am J Transplant.* 2012;12(12):3308–3315.
4. Penn I. Transmission of cancer from organ donors. *Ann Transplant.* 1997;2(4):7–12.
5. Barrett WL, First MR, Aron BS, Penn I. Clinical course of malignancies in renal transplant recipients. *Cancer.* 1993;72(7):2186–2189.