CASE REPORT

De novo papillary carcinoma in a renal allograft: the pros and cons of immunosuppression

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Abstract We present a case of a multifocal kidney transplant renal cell carcinoma in a 35-year-old lady, presenting 16 years after kidney transplantation, diagnosed during investigation of recurrent urinary tract infections. The patient underwent a graft nephrectomy and subsequently maintained on haemodialysis. She remained disease-free after 4 years of surveillance and thus reactivated on the transplant list. This case reinforces the fact that immunosuppressive therapy has made kidney transplantation possible; however, it is accompanied by a higher incidence of malignancy. It also reinforces the importance of lifelong screening of both native and renal transplant grafts.

Keywords Kidney transplant · Allograft malignancy · Immunosuppression · Allograft nephrectomy

Introduction

The advent of modern immunosuppression has revolutionised graft and patient outcomes. Unfortunately, this improvement has been hindered by higher incidence of adverse events, which include malignancy.

Case history

A 35-year-old lady had presented with end-stage kidney disease (ESKD) of unknown aetiology at the age of 16 years. She had been maintained on peritoneal dialysis (PD) for 3 years, until she received a cadaveric renal transplant at the age of 19 years. HLA match of the graft is unknown because our centre did not employ HLA typing at the time. She had received no induction immunosuppression and her maintenance immunosuppression therapy included Cyclosporine (levels maintained between 75 and 150), and Prednisolone 5 mg once daily. Azathioprine had been stopped several years previously because of bone marrow suppression. No rescue immunosuppression had ever been required.

During her regular follow-up visits at the transplant clinic, she was noted to have recurrent symptomatic urinary tract infections which prompted further investigation of her urinary tract. At the time of diagnosis, her baseline creatinine was in the region of 250 $\mu\text{mol/L}$ (eGFR 20 mL/min/1.73 m^2) and her allograft impairment was attributed to a combination of chronic calcineurin nephrotoxicity and transplant glomerulopathy. Urine cultures revealed *Enterococcus faecalis* on one occasion, and *Klebsiella pneumoniae* twice over a 3-month period.

An ultrasound of the renal tract showed a 1.5×1.8 cm homogeneously hypo-echoic well-defined isolated nodule in the lower part of the transplanted kidney which revealed no significant internal blood flow on Doppler evaluation and no internal calcifications or cystic components (Fig. 1). A flexible cystoscopy showed a normal bladder, with atrophic mucosa and increased vasculature on the posterior bladder wall. An ultrasound-guided biopsy of the renal allograft nodule was carried out and histology revealed renal cell carcinoma (RCC), with predominantly papillary

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Fig. 1 Ultrasound showing a 1.5×1.8 cm homogeneously hypoechoic well-defined isolated nodule in the lower part of the transplanted kidney, with no significant internal blood flow on Doppler evaluation

Fig. 2 Non-contrast-enhanced CT scan showing the tumour to be well circumscribed to the lower part of the graft

components. A non-contrast staging CT scan was opted for in favour of a more revealing contrast-enhanced study to avoid contrast-induced kidney injury. Preserving the present renal function was important because at that point in time, the option of nephron-sparing surgery versus a total graft nephrectomy was still being considered as the patient was still quite keen for the former. In addition, renal carcinoma tends to metastasise mainly to bone and lung, both of which are well evaluated with non-contrast computed tomography (CT) scan. The scan showed no evidence of distant metastasis and the tumour appeared well circumscribed to the lower part of the graft (Fig. 2).

The final decision was in favour of a total graft nephrectomy with a plan to maintain the patient on long-term haemodialysis. Microscopy of the resected kidney

showed multiple foci of papillary cortical tumours. The largest solid one measuring 7 mm in diameter was present on the surface of the kidney and was well circumscribed. Both cytokeratin 7 (CK7) and epithelial membrane antigen (EMA) were positive. A second 9 mm tumour was found, and this was predominantly cystic, with papillary architecture and also exhibited foam cells within papillary cords. Several smaller incidental papillary adenomas, most of them less than 1 mm in size, were present in other areas of the kidney. The papillary tumours were considered as type one papillary carcinoma, histologically deemed to have a very low metastatic potential.

Discussion

Kidney transplantation is regarded as the best treatment option in ESRD as it conveys better overall patient survival and quality of life when compared to dialysis [1]. This has only been possible with the advent of modern immunosuppression which has revolutionised graft and patient outcomes. Unfortunately, this improvement has been hindered by higher incidence of new onset diabetes (NODAT), hyperlipidaemia, infection and malignancy.

The overall incidence of malignancy in the dialysis population is already higher when compared to the general population [2]. Moreover, malignancy in the post-transplantation period is considered to be even higher when compared to the dialysis population particularly in the second and third decades post-transplant [3, 4] (in this case, the patient presented 16 years after transplantation).

An analysis carried out by Piselli et al. concerning a cohort of post-transplant patients in Italy recognised that Kaposi sarcoma, post-transplant lymphoproliferative disease (PTLD) and solid tumours involving lip, salivary glands, kidneys, mesothelioma and testis were the most common type of malignancies [5]. The majority of renal malignancies in transplant patients arise in the native kidneys. In one study of 3568 renal transplant patients, 8 patients (0.2 %) developed RCC in the renal allograft, compared to 39 RCC in the native kidneys (1.1 %) [6]. The incidence of allograft malignancy reported by Leverage et al. is strikingly similar to that reported by Tillou et al. ($n = 41,806$; 0.19 %) in a multicentre, retrospective analysis in France [7]. Clear cell RCC is the most common subtype in the general population, whereas papillary RCC tends to be commoner in the ESKD population and kidney transplants [7–9]. RCCs associated with ESKD are characterised by multicentricity and bilaterality. In a review of published series, multifocal disease was noted in 4.3–21.4 % of RCC cases, and McHayleh et al. reported a rare case of multifocal RCC with innumerable sites within the kidney allograft [10, 11]. Multifocality of RCC occurs

independently from primary tumour size and papillary RCC is the commonest histological subtype of RCC to show multifocality [12, 13]. The incidence of multifocality is statistically higher in patients with stage pT3 than in those with stage pT1 or pT2 disease [14].

Transplant recipients have a three- to fivefold increased risk of malignancy when compared to the general population [15]. This is likely attributed to a combination of risk factors including those common to the general population and the overall immunosuppression burden. Indeed, genetic predisposition and history of pre-transplant malignancy are independent risk factors for the development of malignancy [16]. Patients with a history of invasive cancer before transplantation were found to have more than double the risk of post-transplant cancer compared with patients with no history of malignancy [14].

With regard to immunosuppressive therapy, it is rather difficult to draw conclusions on the impact of individual agents. Such studies are commonly retrospective, underpowered, inadequately randomised and with the majority of patients on combination therapies. The utilisation of lymphocyte depleting agents such as anti-thymocyte immunoglobulin (ATG) for induction or rescue therapy has been associated with increased risk of malignancies as opposed to Alemtuzumab [17, 18]. However, one has to appreciate that Alemtuzumab is a rather recent addition to our immunosuppression armamentarium when compared to ATG and up till now the evidence is rather sparse. This index case received no induction therapy. Cyclosporine (CyA) has been linked with increased risk of malignancy mostly in studies analysing its use in dermatological conditions [19, 20]. On the other hand, Tacrolimus-based immunosuppression has been associated with a higher incidence of malignancy and shorter time interval between transplantation and tumour detection [2, 21]. Fuchs et al. found no difference in the oncogenic potential between Tacrolimus and Cyclosporine [22]. Data are even more conflicting when it comes to the use of anti-proliferative agents. Some studies suggest that the use of Mycophenolate Mofetil (MMF) is associated with earlier development of malignancy when compared to Azathioprine (AZA) [23, 24], whereas another study conducted by Cherikh et al. recognised a lower incidence of PTLD with MMF [25]. Mammalian target of rapamycin (mTOR) inhibitors have been generally associated with the lowest risk. Everolimus-based immunosuppression has been linked with the least carcinogenic potential and indeed associated with resolution of some tumours [26]. Sirolimus has also been associated with reduced risk of malignancy [27]. We found no studies relating steroid use and the risk of malignancy in solid organ transplantation, this is likely to be due to the fact that steroids are used in the majority of immunosuppression protocols. Immunosuppressive drugs might

increase the post-transplant risk of malignancy by impairing immunosurveillance [28] and facilitating the action of oncogenic viruses [29]. Indeed, some infective pathogens, such as Epstein–Barr virus (EBV), human papillomaviruses (HPV) and herpes virus 8, have also been associated with increased risk of malignancy. CyA might also promote carcinogenesis through another independent mechanism. Hojo et al. found that it can promote cancer progression through direct cellular effect by inducing TGF- β production which increases cell motility and anchorage-independent growth [30]. RCC tends to be more aggressive in renal allografts, most likely because of prolonged immunosuppression [31].

Diagnosis of tumours occurring in renal transplants is usually incidental following ultrasound, or other imaging modalities, because these tumours are generally small and asymptomatic. In this index case, the tumour was detected during investigations precipitated by recurrent urinary tract infections. This is likely to have been an incidental finding, as to our knowledge, there is no significant evidence that urinary tract infection can be the presenting feature of renal carcinoma.

In the analysis performed by Tillou et al., 48 % of patients developing allograft malignancy underwent a total graft nephrectomy, 44 % nephron-sparing surgery, 6 % radiofrequency ablation and the overall estimated malignancy-free survival was 94 % [7]. Considering the patient's views and after obtaining oncologist advice, we opted for a total transplant nephrectomy instead of nephron-sparing surgery or radiofrequency ablation for various reasons. First, the allograft function was already significantly and irreversibly impaired. Second, switching to mTOR inhibitors was relatively contraindicated given the level of allograft impairment and significant proteinuria. Therefore, total allograft nephrectomy was the only way of reducing in the immunosuppression burden. Finally, papillary renal cell carcinomas have the highest potential for being multifocal. Although this decision was not taken lightly and meant that the patient would become dialysis-dependant, she has no evidence of disease recurrence after 4 years of surveillance and thus she has been reactivated on the transplant list.

Conclusion

There are several unusual features about this case—a multifocal papillary RCC in a transplanted kidney, in a female patient, diagnosed 16 years after the transplantation during investigation of recurrent urinary tract infections. Graft nephrectomy was opted for in view of an already impaired allograft function, the need to reduce the immunosuppression burden, and the fact that papillary

RCCs have the highest potential of being multifocal. The patient has no evidence of disease recurrence after 4 years of surveillance.

Immunosuppressive therapy has made kidney transplantation possible; however, it is accompanied by a higher incidence of malignancy. This case reinforces the importance of lifelong screening of both native and renal transplant grafts, given the increased risk of malignancy, the sometimes late presentation, and the aggressive course especially in allograft tumour development.

References

- Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplants, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725–30.
- Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer Incidence among US Medicare ESRD patients receiving haemodialysis, 1996–2009. *Am J Kidney Dis*. 2015; (pii:S0272-6386(15)00017-7).
- Arichi N, Kishikawa H, Nishimura K, et al. Malignancy following kidney transplantation. *Transplant Proc*. 2008;40(7):2400–2.
- Stewart JH, Vajdic CM, van Leeuwen MT, et al. The pattern of excess cancer in dialysis and transplantation. *Nephrol Dial Transplant*. 2009;24(10):3225–31.
- Piselli P, Serraino D, Segoloni GP, et al. Immunosuppression and Cancer Study Group. Risk of de novo cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009. *Eur J Cancer*. 2013;49(2):336–44.
- Leveridge M, Musquera M, Evans A, et al. Renal cell carcinoma in the native and allograft kidneys of renal transplant recipients. *J Urol*. 2011;186(1):219.
- Tillou 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):3308–15.
- Neuzillet Y, Tillou X, Mathieu R, et al. Comité de Transplantation de l'Association Française d'Urologie; Comité de Cancérologie de l'Association Française d'Urologie. Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. *Eur Urol*. 2011;60(2):366–73.
- Chen K, Huang HH, Aydin H, et al. Renal cell carcinoma in patients with end-stage renal disease is associated with more favourable histological features and prognosis. *Scand J Urol*. 2015;17:1–5.
- Crispen PL, Lohse CM, Blute ML. Multifocal Renal cell carcinoma: clinicopathological features and outcomes for tumours ≤ 4 cm. *Adv Urol*. 2008;2008:518091. doi:10.1155/2008/518091.
- McHayleh W, Morcos JP, Wu T, et al. Renal cell carcinoma from a transplanted allograft: two case reports and a review of literature. *Clin Genitourin Cancer*. 2008;6(1):53–5.
- Schlichter A, Wunderlich H, Junker K, Kosmehl H, Zermann DH, Schubert J. Where are the limits of elective nephron-sparing surgery in renal cell carcinoma? *Eur Urol*. 2000;37(5):517–20.
- Dimarco DS, Lohse CM, Zincke H, Cheville JC, Blute ML. Long-term survival of patients with unilateral sporadic multifocal renal cell carcinoma according to histologic subtype compared with patients with solitary tumors after radical nephrectomy. *Urology*. 2004;64(3):462–7.
- Baltaci S, Orhan D, Soyupek S, Beduk Y, Tulunay O, Gogus O. Influence of tumor stage, size, grade, vascular involvement, histological cell type and histological pattern on multifocality of renal cell carcinoma. *J Urol*. 2000;164(1):36–9.
- Dantal J, Pohanka E. Malignancies in renal transplantation: an unmet medical need. *Nephrol Dial Transplant*. 2007;22(1):i4–10.
- Danpanich E, Kasiske BL. Risk factors for cancer in renal transplant recipients. *Transplantation*. 1999;68(12):1859–64.
- Webster AC, Ruster LP, McGee R, et al. Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev*. 2010;20(1):CD003897.
- Puttarajappa C, Yabes J, Bei L, et al. Cancer risk with alemtuzumab following kidney transplantation. *Clin Transplant*. 2013;27(3):264–71.
- Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol*. 2003;120(2):211–6.
- Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet*. 2001;358(9287):1042–5.
- Wimmer CD, Angele MK, Schwarz B, et al. Impact of cyclosporine versus tacrolimus on the incidence of de novo malignancy following liver transplantation: a single center experience with 609 patients. *Transpl Int*. 2013;26(10):999–1006.
- Fuchs U, Klein S, Zittermann A, Ensminger SM, Schulz U, Gummert JF. Incidence of malignant neoplasia after heart transplantation—a comparison between cyclosporine A and tacrolimus. *Ann Transplant*. 2014;23(19):300–4.
- Nafar M, Einollahi B, Hemati K, Gholi FP, Firouzan A. Development of malignancy following living donor kidney transplantation. *Transplant Proc*. 2005;37(7):3065–7.
- Vegso G, Toth M, Hidvegi M, et al. Malignancies after renal transplantation during 33 years at a single center. *Pathol Oncol Res*. 2007;13(1):63–9.
- Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. *Transplantation*. 2003;76(9):1289–93.
- Donati M, Paolino G, Muscardin L, Panetta C, Donati P. Resolution of benign and malignant sebaceous neoplasms, in a renal transplant patient treated with everolimus. *Exp Clin Transplant*. 2015. doi:10.6002/ect.2014.0208.
- Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation*. 2009;87(2):233–42.
- Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs*. 2007;67(8):1167–98.
- Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. *J Am Soc Nephrol*. 2004;15(6):1582–8.
- Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature*. 1999;397(6719):530–4.
- DeLong MJ, Schmitt D, Scott KM, Ramakumar S, Lien YH. Multicentric papillary renal carcinoma in renal allograft. *Am J Kidney Dis*. 2003;42(2):381–4.