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Prolonged Survival and Preserved Renal Graft Function in a Kidney Transplant Patient With Advanced Urothelial Carcinoma Using an Immune Checkpoint Inhibitor: A Case Report

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Upper tract urothelial carcinoma (UTUC) is a rare but aggressive malignancy with an incidence of 2 cases per 100 000 people.[1] Cisplatin-based chemotherapy is the standard treatment for advanced UTUC with a very poor prognosis. The median overall survival is 6–15 mo and the 5-y survival rate is <5%.[2] Pembrolizumab, an immune checkpoint inhibitor (ICI), has been introduced for treating advanced urothelial carcinoma (UC) in cisplatin-ineligible patients.[3] However, to our knowledge, there is no report concerning treating advanced UTUC in kidney transplant patients (KTPs). Managing advanced UTUC in KTPs is a challenging problem for nephrologists and oncologists. Reducing the dose of immunosuppressants may be required to lower the risk of oncogenesis. However, this may increase the risk of acute rejection and graft loss. Furthermore, cisplatin-based chemotherapy and ICIs are associated with nephrotoxicity,[4] and ICIs may cause acute rejection and graft loss.[5]

Here, we present a case of an elderly woman KTP with advanced metastatic UTUC in the liver who has had prolonged survival without progression of malignancy. She also had a reasonably well-preserved kidney graft function for 4 y without nephrotoxicity or acute rejection while on immunosuppressants and carboplatin-based chemotherapy with pembrolizumab for 6 mo, followed by single-agent pembrolizumab for 3.5 y.

CASE PRESENTATION

A 60-y-old Thai woman with a history of using Chinese herbal medicines had end-stage renal disease from chronic glomerulonephritis of unknown etiology. After being on hemodialysis for 3 y, at the age of 63 y, she received a successful deceased donor kidney transplantation. The HLA mismatches were HLA-A = 0, HLA-B = 1, and HLA-DR = 0. The pretransplant flow panel reactive antibody test was zero reactivity for both class I and class II antibodies. The pretransplant DSA was not done because of the deceased donor kidney transplantation. She received 20 mg basiliximab on d 0 and postoperative d 4 for the induction. Her immunosuppressive regimens consisted of cyclosporine A, mycophenolate mofetil, and prednisolone. She had been doing well with good renal graft function and an average serum creatinine of 0.8–1.0 mg/dL. There was no graft rejection and no medical or surgical complications after kidney transplantation. Five y later, at 68 y old, she presented with asymptomatic microscopic hematuria and hydronephrosis of the right native kidney. A CT scan demonstrated a mass in the right renal pelvis and upper ureter of the native kidney. A bilateral retrograde pyelogram of both native kidneys revealed complete obstruction of the right upper ureter. The left pyelogram of the native kidney, renal graft pyelogram, and cystoscope were normal. According to her history of using several Chinese herbal medicines, which might contain aristolochic acid, a carcinogen for UTUC, she had a high risk of recurrent contralateral UTUC. The option of prophylactic contralateral nephroureterectomy was offered. She agreed and underwent bilateral nephroureterectomy with bladder cuff excision. The pathological reports indicated noninvasive high-grade papillary UC involving the right renal pelvis and upper ureter, with no

Received 10 February 2023. Revision received 14 May 2023.

Accepted 18 May 2023.

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All authors have contributed to the article and approved the final version submitted for publication. W.M. participated in information gathering, patient data collection, the review of literatures, drafting, and the writing of the article. S.L., T.A., and D.R. participated in the review of literatures, clinical process, data analysis, and the writing of the article.

The authors declare no funding or conflicts of interest.

Patient written informed consent was obtained, and a signed consent form was submitted for review.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001509

lymphovascular or muscular invasion. The surgical margins were free from malignancy. The pathological staging was $T_1N_0M_0$ (stage I). Despite regular surveillance for recurrence of malignancy every 6 mo, 6 y later, at 74 y old, she lost 4 kg with poor appetite and fatigue. A CT scan demonstrated multiple metastatic masses in the liver with the largest being 8 cm. A liver mass biopsy revealed malignancy and histochemistry of tumor cells stained for p63 and thrombomodulin, which was consistent with urothelial cell carcinoma. Immunohistochemistry revealed a programmed death ligand 1 (PD-L1) (22C3) tumor proportion score of <1%. To lower the risk of malignancy progression, her immunosuppressant regime was reduced by discontinuing mycophenolate mofetil. She was taking cyclosporine A 75 mg twice daily, keeping her blood cyclosporine A trough level at 80–100 ng/mL, and prednisolone 5 mg daily. She received carboplatin 300 mg (Area Under the Curve or AUC = 5 mg/mL/min), gemcitabine 1200 mg (100 mg/m^2), and pembrolizumab 200 mg every 4 wk for 6 mo, followed by pembrolizumab 200 mg monthly for 18 mo and then every 3 mo for another 2 y. A CT scan after 6 mo revealed remarkable regression of the liver masses; there was no progression of the advanced UTUC for 4 y (Figure 1). She tolerated the treatments well, and her renal graft function was relatively well preserved with an average serum creatinine of 1.2 mg/dL (Figure 2). There was no renal graft rejection despite the withdrawal of mycophenolate mofetil and no nephrotoxicity or graft rejection from pembrolizumab.

DISCUSSION

Malignancy is one of the most common causes of death in KTPs, for whom lymphoma, skin, and kidney cancers are the leading malignancies.[6] Of all kidney cancers, renal cell carcinoma is more common than UC. A Swiss single-center study found that for UC in KTPs, 92% are lower tract UC (LTUC), and only 8% are UTUC.[7] In the general population, cisplatin-based chemotherapy has been the gold standard treatment for advanced UC for the past 30 y, with very poor overall survival and significant toxicities occurring. Moreover, two-thirds of UTUC patients are cisplatin-ineligible and must receive alternative chemotherapies with poorer outcomes. In phase II clinical trials[3] conducted in 2017, pembrolizumab was proven safe and improved the short-term survival of advanced UTUC in cisplatin-ineligible patients. Pembrolizumab was also approved for cisplatin-ineligible patients regardless of PD-L1 expression in the United States.[8] The cisplatin-ineligible criteria include a solitary kidney, renal dysfunction (creatinine clearance < 60 mL/min), cardiovascular disease, hearing loss, neuropathy, and old age.[8] Our patient was cisplatin-ineligible because she was elderly (74 y old), with a solitary kidney (1 renal transplant graft). Her serum creatinine was 1.02 mg/dL (creatinine clearance of 55 mL/min). She also had cardiovascular disease with occasional congestive heart failure, and she had atrial fibrillation with a permanent pacemaker. The efficacy and safety of ICIs for advanced UTUC in KTPs are still unknown. Based on the available options in 2018, the treatment of choice for this patient was carboplatin, gemcitabine, or pembrolizumab alone. However, because of the aggressiveness of the advanced UTUC and that she was still receiving immunosuppressive treatment, we chose a combination of carboplatin, gemcitabine, and pembrolizumab for 6 mo, followed by monotherapy pembrolizumab monthly for 18 mo. Notably, she responded well with no malignancy progression. After 24 mo of treatment, we decided to continue giving the patient pembrolizumab every 3 mo because she was a very high-risk patient for the recurrence of malignancy because of receiving immunosuppressants. She was closely monitored for toxicity to pembrolizumab, and the treatment plan was subjected to being discontinued at any time, depending on her clinical status. Up to 48 mo (July 2022), she had

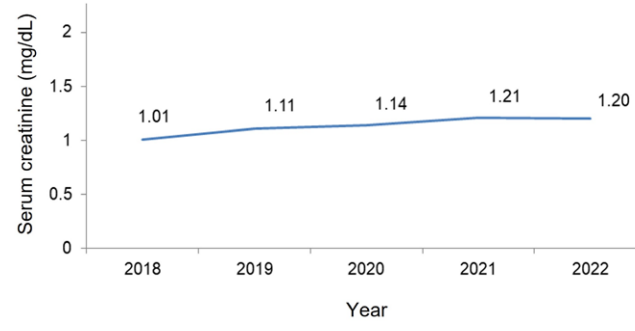

FIGURE 2. The patient's serum creatinine level from the beginning of treatment in 2018–2022.

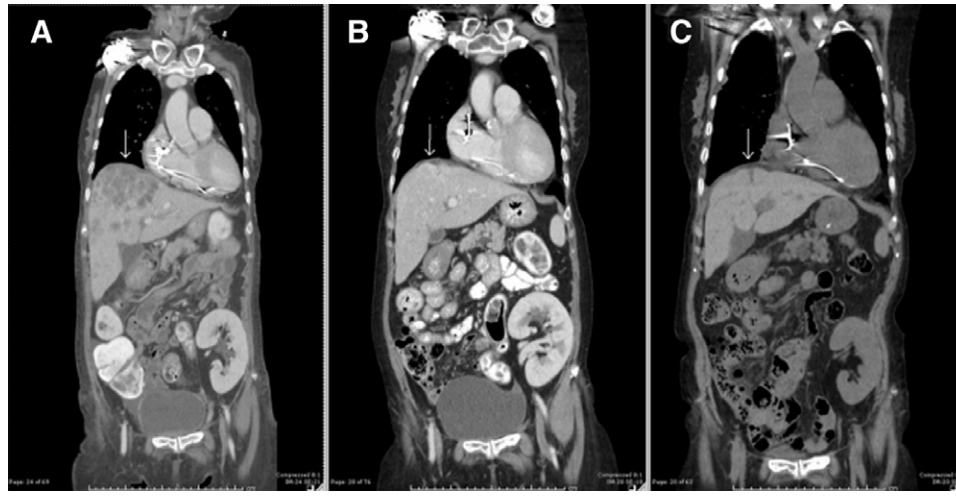

FIGURE 1. CT scan of the patient's liver masses (arrow). (A) Before treatment. (B) Six mo after treatment. (C) Four y after treatment.

well-preserved graft function. There was no UTUC progression, no nephrotoxicity, or graft rejection. However, this case report had a limitation. The DSA was not screened posttransplantation and before pembrolizumab therapy, which might help to predict subclinical ICI-derived rejection.

The mechanism behind the efficacy of pembrolizumab in this patient is unclear because her PD-L1 expression was negative. The results from a phase II clinical trial in 2017 (KEYNOTE-052)[3] demonstrated that pembrolizumab improved the clinical response in advanced cisplatin-ineligible UC patients with positive PD-L1; however, low or negative PD-L1 expression did not exclude a positive response. Moreover, in phase III studies in 2021 (KEYNOTE-361),[9] pembrolizumab did not significantly improve the survival of advanced UC. In 2020, Chiang et al[10] reported a patient with negative PD-L1 expression who responded successfully to pembrolizumab with metastatic UC that originated in a transplanted kidney. However, this patient had a transplant nephrectomy and a complete cessation of immunosuppressants.

The ICI nephrotoxicities include acute interstitial nephritis (AIN) and several types of glomerulonephritis.[4] Occasionally, the pathology may be a mixture of AIN and glomerulonephritis. The median time for AIN or glomerulonephritis to develop is 12–14 wk. The long-term effects of ICIs on kidney function are still unknown; however, some studies found a progressive decline in glomerular filtration rate over many y.[11] In addition to nephrotoxicities, ICIs in KTPs are associated with a higher risk of graft rejection and graft loss.[5] The program death-1 and the cytotoxic T lymphocyte-associated protein 4 pathways are implicated in the tolerance of transplanted organs. The blockade of these pathways, which contribute to the elimination of malignancy, may inadvertently lead to organ transplant rejection. A multicenter retrospective study on the safety and efficacy of ICIs in cancer patients with kidney transplants reported that following ICI treatment, 29 of 69 patients (42%) developed acute rejection, 19 of whom (65.5%) lost their grafts.[5] The median time from initiation of ICIs to rejection was 24 d (range 20–56 d) compared with ICI-induced AIN or glomerulonephritis, which occurred later at 12–14 wk.[4] The overall survival did not differ in patients with graft rejection versus those without rejection. However, these studies were performed in KTPs with cutaneous squamous cell carcinoma and melanoma.[5] More studies are needed to elucidate why our patient escaped the adverse effects of ICI and why her advanced UTUC responded well to pembrolizumab, despite the negative PD-L1 expression.

It is worth noting that UC is a common malignancy in some Asian KTPs, that is, Taiwan,[12] China,[13] and Thailand.[14] Chinese herbal medicines are commonly used in some Asian countries. The aristolochic acid in Chinese herbal medicines is a known carcinogen that is associated with a high incidence of recurrent contralateral UTUC. In some centers, prophylactic contralateral nephroureterectomy with bladder cuff excision was suggested for certain high-risk KTPs with UTUC, especially those with a history of aristolochic acid exposure.[15-17] In our transplant center between 1992 and 2019, UC accounted for 35% of all malignancies with high mortality, and UTUC (64%) was more common than LTUC (36%)[14] that differed from the report on Western patients (UTUC 8%, LTUC 92%).[7] This high incidence in Asian KTPs requires specific attention because the transplant societies guidelines currently do not recommend routine screening for UC in KTPs.[6,18] Therefore, these guidelines may not apply to Asian KTPs.

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