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Between the Hammer and Anvil: Resolution of unresectable muscle invasive bladder cancer in a renal transplant patient after cessation of immunosuppressive therapy

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ABSTRACT

Multimodal immunosuppression is the backbone of modern solid organ transplantation. However, immunosuppression itself is an independent risk factor for post-transplant malignancy. Although skin malignancy is the most common post-transplant malignancy, genitourinary cancers are also described. Dose reduction or cessation of immunosuppression has a beneficial role in the management of transplant patients with concomitant malignancy, but only limited data exist with respect to bladder cancer (BCa).

We describe a patient who developed metastatic muscle invasive bladder cancer (MIBC) after diseased donor kidney transplant (DDKT) who was successfully managed with dose reduction and elimination of an immunosuppression regimen.

1. Introduction

Post-transplant immunosuppressive regimens alter host immunosurveillance function, representing a risk factor for de-novo malignancy. The genitourinary tract is the second most common site of post renal transplantation malignancy, behind skin cancer, wherein renal tumors and bladder cancers hold a 15-times and 3-times higher risk than the general population, respectively.[1] Appropriate diagnosis and management is paramount, as cardiovascular disease and post-transplant malignancies are the main causes of late morbidity and mortality in the renal-transplant population.[2]

A paucity of literature exists on the management of DDKT patients with MIBC and metastatic BCa. The purpose of this case report is to present a patient with unresectable MIBC after DDKT, discuss subsequent medical and surgical management, and highlight the role of immunosuppression modulation.

2. Case presentation

A 62 year old man with autosomal dominant polycystic kidney disease (APKD) managed with bilateral nephrectomy and DDKT presented with new onset hematuria, 11 years post-transplant. His immunosuppression regimen consisted of mycophenolate mofetil (MMF) 1000 mg BID, prednisone 5mg and tacrolimus 5.5 mg, daily. His creatinine (Cr) was 4.7mg/dL (eGFR 12mL/min) elevated from a post transplant baseline Cr 1.3mg/dL (eGFR 58mL/min).

Computed tomography (CT) revealed a soft tissue mass involving the right anterolateral aspect of the bladder with new hydroureteronephrosis of the transplanted kidney (Fig. 1). Transurethral resection identified the mass was involving the ureteroneocystostomy. Postoperatively, a percutaneous nephrostomy was placed, given transplant obstruction. Pathology was consistent with high-grade urothelial carcinoma with invasion of the muscularis propria. Staging imaging was negative for nodal or systemic metastasis.

The patient was referred to a tertiary care center for remaining management. After nephrostomy, the patient's Cr improved to 2.1mg/

Abbreviations: Bladder Cancer, (BCa; Muscle invasive bladder, (MIBC); Diseased donor kidney transplant, (DDKT); Autosomal dominant polycystic kidney disease, (APKD); Mycophenolate mofetil, (MMF).

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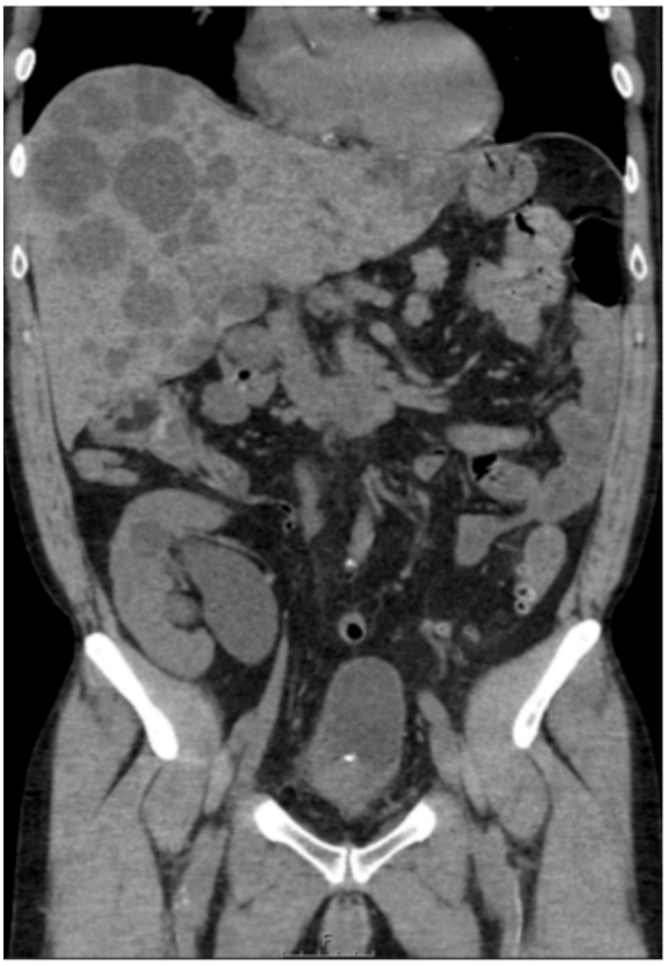

Fig. 1. CTAP demonstrates hydroureteronephrosis of the transplanted kidney from a nodular anterolateral bladder mass at time of presentation.

dL (eGFR 32mL/min). Given the patients renal insufficiency, upfront cystectomy was favored over neoadjuvant chemotherapy. Perioperatively, immunosuppression was decreased to tacrolimus 5mg daily, MMF 500mg BID, and prednisone 5mg daily.

Upon entering the abdomen for radical cystectomy, gross evidence of unresectable extravesicular disease was noted, as the tumor encased the transplanted ureter and right external iliac artery. An intraoperative biopsy of a left pelvic sidewall deposit confirmed metastatic urothelial carcinoma, staining positive for GATA3 and AE1,3 (Fig. 2). The procedure was aborted, and further discussion of systemic therapy ensued. In the setting of metastatic disease, his immunosuppression was further decreased to tacrolimus 3mg daily, MMF of 250mg BID, and prednisone 5mg daily.

The patient was started on four cycles of chemotherapy. Cycle 1 employed gemcitabine monotherapy (1000 mg/m2.) Cycles 2–4 included carboplatin (AUC 5), given the patients baseline renal insufficiency, and gemcitabine (750 mg/m2). Restaging was completed after chemotherapy, which demonstrated persistent pelvic disease (Fig. 3a).

Given persistent disease and a poor response to chemotherapy, complete cessation of immunosuppressants was decided upon for the next step in management. His only remaining suppressive medication was prednisone, 5mg daily. A repeat CT two months after tacrolimus and MMF cessation demonstrated marked improvement in fat planes and rectal wall thickening, with no evidence of metastatic disease (Fig. 3b.)

Subsequent scans for 4 years (every 2 months, lengthened to 4 months, now bi-annual) have continued to show no radiographic evidence of metastatic disease. His creatinine and eGFR remain stable at

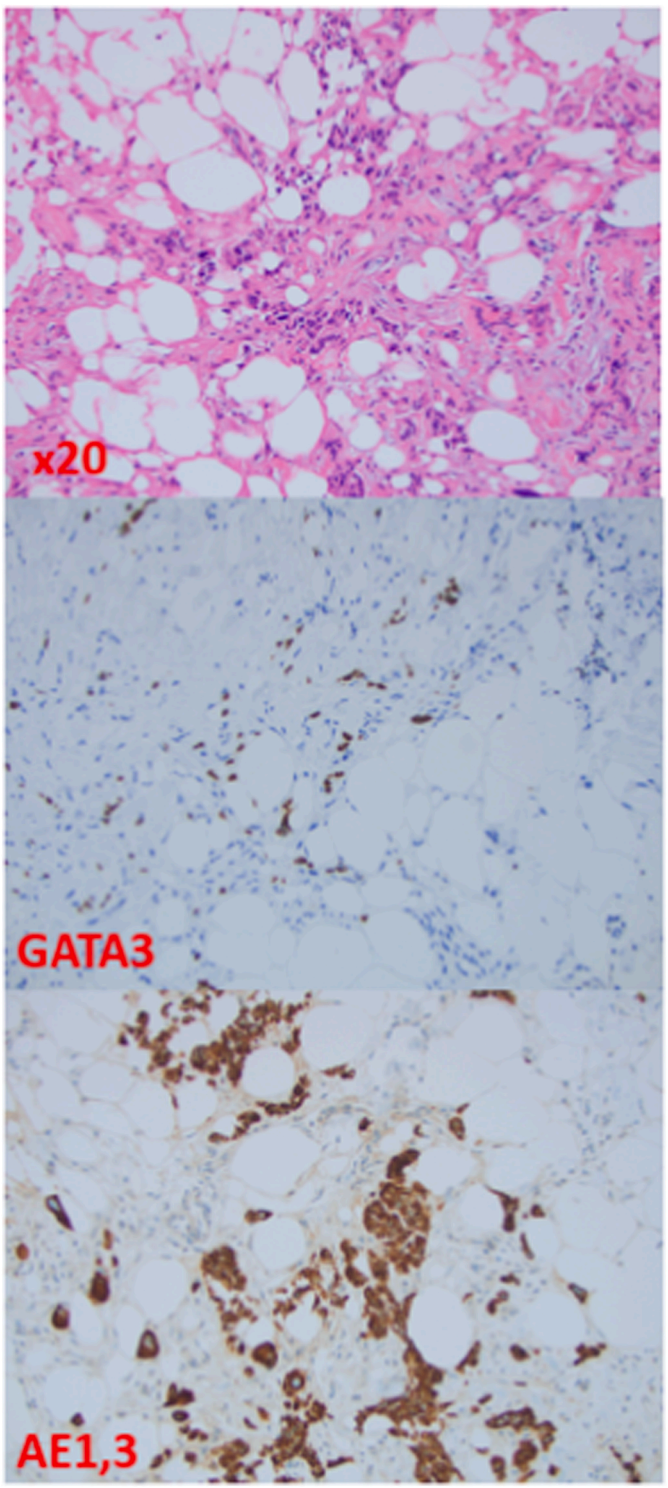

Fig. 2. Immunohistochemistry of intraoperative peritoneal deposit biopsy.

1.4mg/dL and 35mL/min respectively, with stable allograft function. The patient currently is 6 years post diagnosis, still without evidence of metastatic disease.

3. Discussion

We present a patient with metastatic MIBC post DDKT which, despite being unresectable at time of radical cystectomy, has been successfully managed with cessation of immunosuppresion and chemotherapy, with

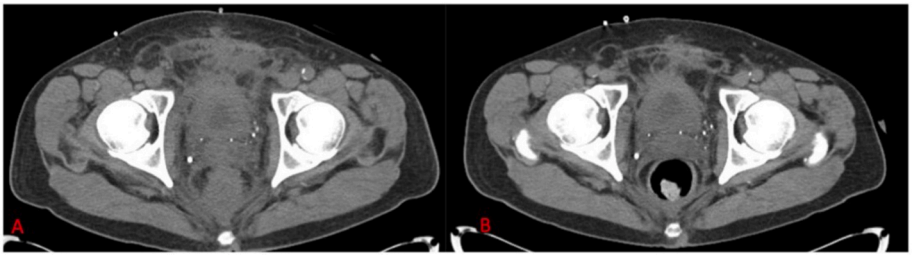

Fig. 3. (a) Persistent locally advanced pelvic disease after 4-cycles of chemotherapy **(b)** Improvement in pelvic disease after complete cessation of immunosuppressants.

regression of disease.

Genitourinary cancers have been described in increased incidence after DDKT compared to the general population.[1] Urothelial carcinoma in the DDKT population is more often high risk disease, with higher staged tumors progressing more often to MIBC.[1] Once metastatic, there is no agreed upon superior systemic therapy approach, although standard therapy with MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or cisplatin and gemcitabine have been reported. Of note, concerns of nephrotoxicity are of significant importance in the post renal transplant population.[2]

Immunosuppression, namely calcineurin inhibitors (CNI) and antimetabolite therapy, while being a hallmark of post-transplant allograft management, halts the immunosurveillance process and can increase cell growth factors such as VEGF and TGF-B.[3] Immunosuppression therefore represents a modifiable risk factor in the management of post transplant malignancy, however no protocols exist on immunosuppression modulation while balancing the risks of oncological demise and graft rejection.

Immunosuppressive regimens utilizing mammalian target of rapamycin (mTOR) inhibitors have presented promising data of adequate allograft survival along with decreased post-transplant malignancy. The CONVERT trial was a randomized trial which compared renal allograft patients on CNI to counterparts who converted from CNI to sirolimus (mTOR inhibitor) with primary endpoints of graft survival and malignancy events. Total malignancies in the conversion group were significantly lower than the continued CNI group, although the majority of these post-immunosuppression malignancies were skin based with no specific comment on urothelial carcinoma.[4]

Literature is lacking on the outcomes of graft survival after cessation of immunosuppression regimens. Retrospective data of renal transplant patients who developed secondary malignancy and subsequently underwent immunosuppression cessation or rose rejection revealed a six percent acute rejection rate, wherein all of the rejection events were reversible with steroids.[5]

A hallmark in the management of this patient was the multidisciplinary collaboration of transplant surgery, medical oncology, and urology at a tertiary care center. MIBC after DDKT is a fairly rare event, and deserves individualized and specialized management at time of presentation.

4. Conclusion

Oncologic control and preservation of allograft function are two important, yet competing, goals in the management of malignancy in post-renal transplant recipients. Here, we present a case of unresectable MIBC post DDKT successfully managed with immunosuppression cessation and systemic chemotherapy. Further experience with multidisciplinary management of such cases is necessary to compile a best practice approach to this oncologically unique and challenging patient population.

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