Letter to the Editor

Imaging misdiagnosis of urothelial carcinoma of the kidney graft as a post-transplant lymphoproliferative disorder: a case description

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Submitted Jun 30, 2024. Accepted for publication Nov 14, 2024. Published online Dec 27, 2024.
doi: 10.21037/qims-24-1323
View this article at: https://dx.doi.org/10.21037/qims-24-1323

Introduction

Due to the long-term use of immunosuppression regimens to prevent allograft rejection, solid organ transplant recipients have an increased risk of malignancy compared with the general population (1). The most common malignancies with an elevated risk in solid organ transplant recipients are non-Hodgkin lymphoma, Kaposi sarcoma, lung cancer, liver cancer, kidney cancer, and skin cancers (non-melanoma like). Additionally, kidney transplant recipients have the highest risk of developing kidney cancers (1). Kidney transplant recipients have a seven-fold risk of renal cell carcinoma and a three-fold risk of urothelial carcinoma (UC) compared with the general population (2). UC in the native urinary tract, especially the upper tract, is the most common malignancy after kidney transplantation in China, and is even more common than bladder cancer (3,4). However, reports of UC following kidney graft and ureter graft are uncommon (5,6).

A post-transplant lymphoproliferative disorder (PTLD) is a lymphoid and/or plasmatic proliferation that occurs in patients receiving chronic immunosuppression for solid organ transplantation or allogeneic hematopoietic stem cell transplantation. PTLD is one of the most common malignancies complicating solid organ transplantation (excluding non-melanoma skin cancer and *in situ* cervical cancer), and accounts for approximately 20% of all cancers (7,8). PTLD can range from benign hyperplasia and infectious mononucleosis to lymphoid malignancy (1).

The imaging manifestations of the patient described in this study include a significantly enlarged mass in the renal pelvis of the kidney graft extending to the parenchyma, and mild-moderate enhancement. The manifestations observed in this patient were similar to those of PTLD. This patient, who had UC in the kidney graft, was misdiagnosed with PTLD. Due to different therapeutic approaches for these two malignancies, prompt ultrasound (US)-guided tissue biopsy to identify cancer types is essential for accurate treatment.

Case presentation

A 56-year-old male patient with a 10-year history of diabetic nephropathy was diagnosed with chronic renal insufficiency 8 years ago, and underwent a kidney transplant 7 years ago (8 and 7 years ago in relation to the writing of this paper). One year after the kidney transplant, he had kidney graft dysfunction due to human polyomavirus [BK virus (BKV)] infection, and was treated with leflunomide and regular dialysis. Six years after the kidney transplant, the patient was hospitalized due to painless gross hematuria without any obvious precipitating factor. The US of the kidney

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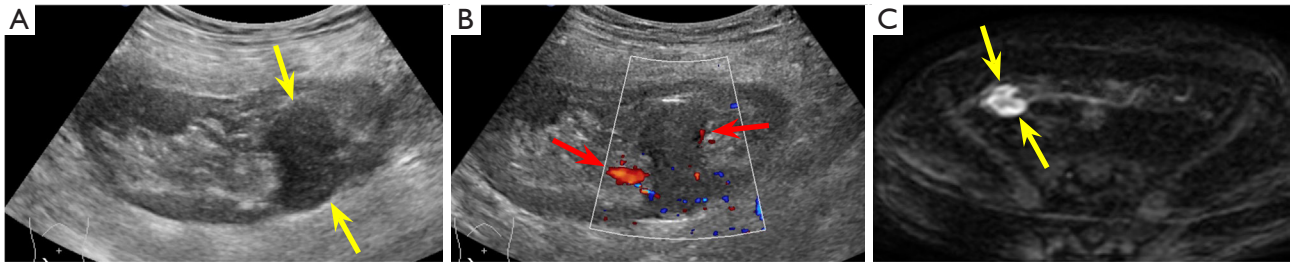

Figure 1 B-mode US, CDFI, and MRI findings of the patient at his first admission. (A) B-mode US showed a relatively well-defined hypoechoic mass located in the renal pelvis of the kidney graft, which extended into the renal lower pole parenchyma. (B) CDFI showed a small amount of blood flow signal in the mass. (C) MRI showed a round-like soft-tissue signal shadow at the lower pole of the atrophic kidney graft, protruding into the renal sinus, and a heterogeneous high signal on DWI. The yellow arrows indicate the location of the lesion. The red arrows indicate the blood flow signals in the lesion. US, ultrasound; CDFI, color Doppler flow imaging; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

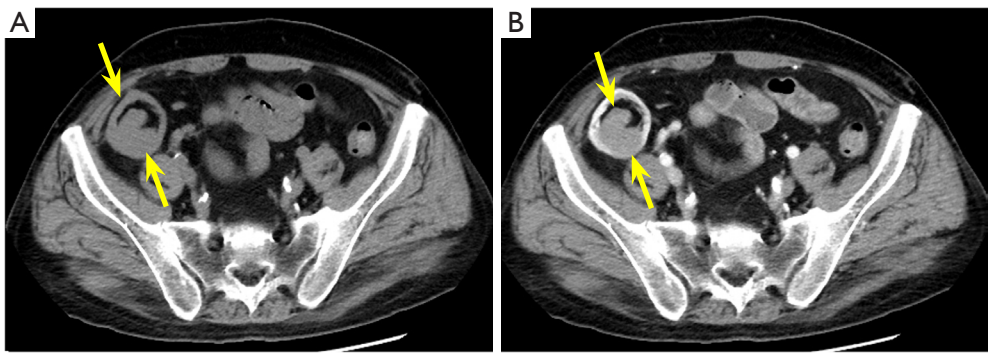

Figure 2 CE-CTU imaging confirming the solid mass. (A) The plain scan revealed an irregular occupying lesion in the lower pole of the atrophic kidney graft, involving the parenchyma and collecting system. (B) The enhanced scan showed mild enhancement of the solid mass. The yellow arrows indicate the location of the lesion. CE-CTU, contrast-enhanced computed tomography urography.

graft showed a 2.6 cm × 2.0 cm relatively well-defined hypoechoic mass located in the renal pelvis, which extended into the renal lower pole parenchyma (*Figure 1A*). Color Doppler flow imaging (CDFI) showed a small amount of blood flow signal in the mass (*Figure 1B*). Pelvic magnetic resonance imaging (MRI) revealed the same findings as previous imaging examinations, including a heterogeneous high signal on diffusion-weighted imaging (DWI), and no abnormality visible in the bladder (*Figure 1C*). Contrast-enhanced computed tomography urography (CE-CTU) revealed a 2.8 cm × 2.5 cm irregular occupying lesion in the lower pole of the atrophic kidney graft, involving the parenchyma, and mild enhancement in the collecting system (*Figure 2*). The patient refused biopsy and surgery, opting instead for regular check-ups and close monitoring.

Nine months later, the patient was re-hospitalized due to a loss of appetite and a weight loss of 5 kg. US showed a significantly enlarged mass, 5.0 cm × 4.6 cm in size, whose margin was consistent with the margin of the atrophic kidney graft without hydronephrosis (*Figure 3A*). A small amount of blood flow signal in the mass was detected by color Doppler US (*Figure 3B*). The MRI results were also suggestive of a significantly enlarged mass in the kidney graft with a heterogeneous high signal on DWI, suggestive of PTLD (*Figure 3C*). Subsequently, a contrast-enhanced ultrasound (CEUS) examination was performed to examine the perfusion pattern of the mass. After injecting the contrast agent, the edge of the mass started enhancing at 16 seconds in the arterial phase, showing hypo-enhancement during the arterial and parenchymal phases, central non-enhancement, and an early washout pattern (*Figure 4*). In summary, the results suggested a malignancy and a high

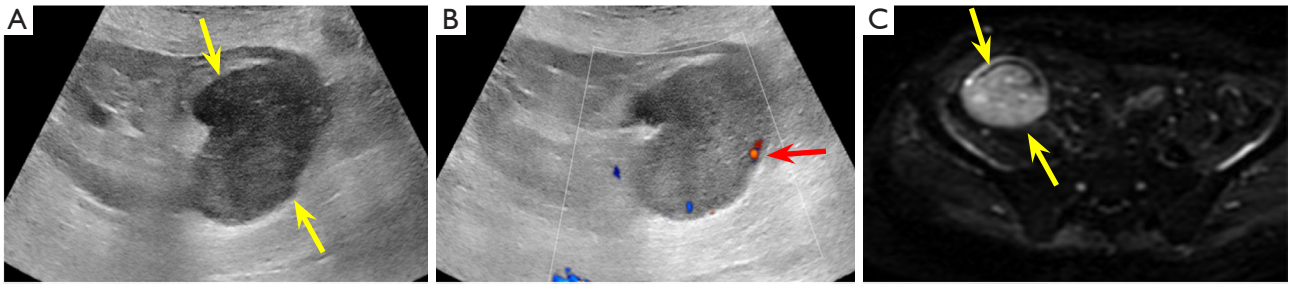

Figure 3 B-mode US, CDFI, and MRI findings of the patient at his second admission. (A) B-mode US showed that the size of the mass had gradually enlarged, and the margin was consistent with the margin of the atrophic kidney graft. (B) CDFI showed a small amount of blood flow signal in the mass. (C) MRI also showed a significantly enlarged mass, and a heterogeneous high signal on DWI. The yellow arrows indicate the location of the lesion. The red arrows indicate the blood flow signals in the lesion. US, ultrasound; CDFI, color Doppler flow imaging; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

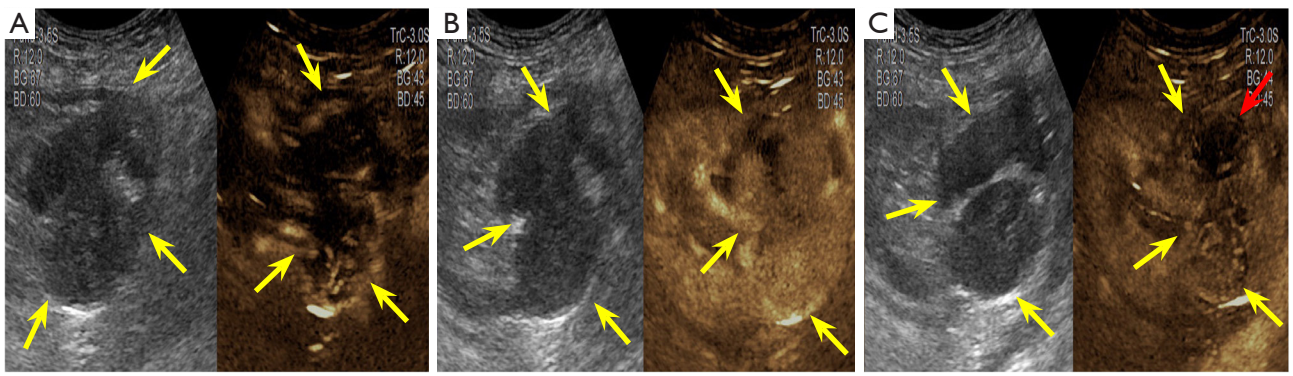

Figure 4 CEUS manifestations of kidney graft. (A) CEUS revealed that the edge of the mass started enhancing at 16 seconds in the arterial phase. (B) CEUS during the arterial and parenchymal phases revealed that the peak enhancement of this mass was the same as that of the surrounding renal parenchyma, which was called hypo-enhancement, and an irregular non-enhancement area in the mass. (C) At 1 min 49 s, CEUS revealed that the mass had an early washout pattern. The yellow arrows indicate the location of the lesion. The red arrow indicates the non-enhancement area in the mass. CEUS, contrast-enhanced ultrasound.

possibility of PTLD.

Whole body positron emission tomography-computed tomography (PET/CT) revealed a significantly high uptake mass [standardized uptake value (SUV) maximum: 19.4] in the kidney graft, but no abnormal foci of increased uptake in the scanning area bones, pelvis, and bilateral inguinal regions (*Figure 5*). Given the patient's history, a diagnosis of PTLD was considered. PTLD was suspected for a number of reasons. First, a bulky focal hypoechoic mass was detected that did not protrude beyond the contour of the kidney graft and did not cause hydronephrosis. Second, the imaging scans showed significant enlargement of this mass, and CEUS showed hypo-enhancement of the mass and an early washout pattern, indicative of malignant growth. Finally, in conjunction with the imaging findings, the patient's clinical data indicated a diagnosis of PTLD.

During the second hospitalization, a percutaneous biopsy guided by US from the renal mass of the kidney graft revealed poorly differentiated carcinoma. Radical kidney graft nephroureterectomy was then performed. The post-operative histopathological results revealed high-grade UC with necrosis, involving the renal parenchyma of the kidney graft and peri-pelvic fat, but not the renal fibrous capsule and the ureter of kidney graft. Cystoscopy showed no mass in the graft ureteral orifice, but the bladder mucosa was affected. The patient continued to receive regular dialysis but did not receive adjuvant chemotherapy or radiotherapy; no tumor recurrence was observed during the 5 months

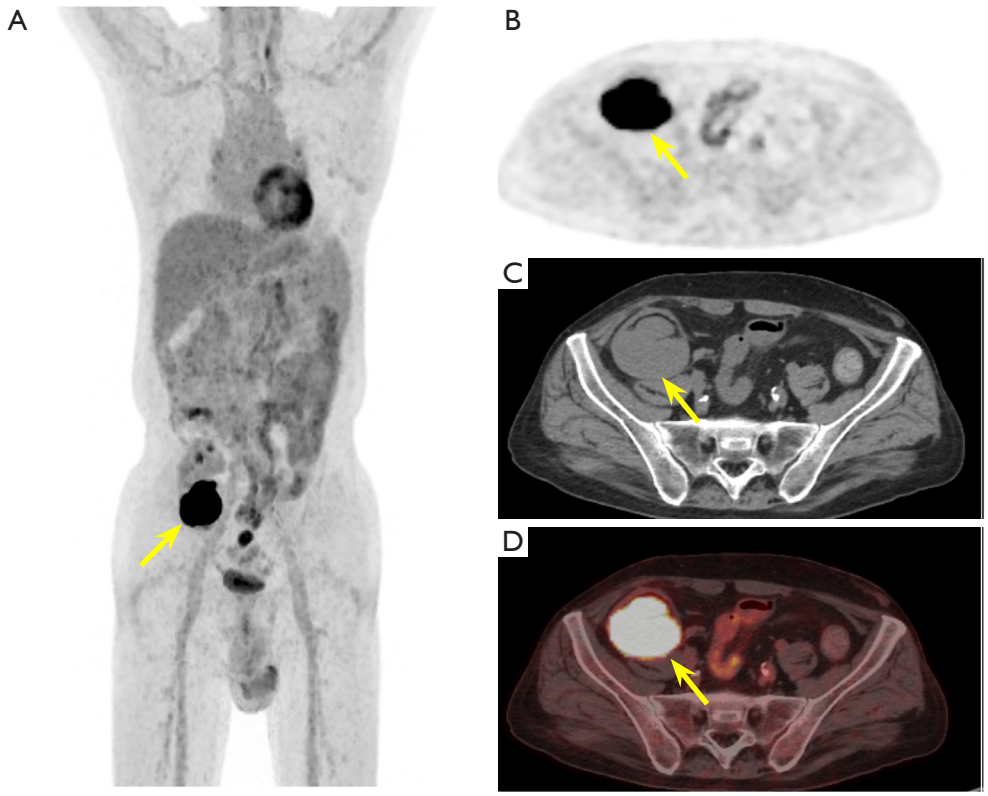

Figure 5 ^{18}F-FDG whole body PET/CT findings for the patient. (A) The MIP image showed a significantly high uptake mass in the lower pole of the atrophic kidney graft (SUVmax =19.4), and a high uptake lesion at the rectosigmoid junction (SUVmax =6.2). PET (B), CT (C), and fused PET/CT (D) of the cross section showed an abnormal FDG-avid lesion in the kidney graft. No other foci of abnormally high radioactive uptake were observed in the rest of the entire body. The yellow arrows indicate the location of the lesion in the kidney graft. FDG, fluorodeoxyglucose; PET/CT, positron emission tomography-computed tomography; MIP, maximal intensity projection; SUVmax, standardized uptake value maximum.

after the operation.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The overall level of immunosuppression is the principal factor increasing the risk of malignancy after transplantation. Notably, the incidence of PTLD is highest in the first year after transplantation, the time of most intense immunosuppression, and then falls, and rises again 5 years post transplantation (9). Kidney graft recipients receiving a low-dose cyclosporine regimen have a lower incidence of all secondary cancers, particularly skin cancers, than those receiving a normal-dose regimen (10). The risk of malignancy appears to vary depending on the immunosuppressive agents; for example, data from one series suggest that the use of tacrolimus increases the risk of malignancy following kidney transplant (11). In our case, the patient received tacrolimus-based therapy, and developed UC of the kidney graft 6 years after the kidney transplant.

Kidney transplant recipients have a three-fold greater risk for UC than the immunocompetent population, and in the East this risk can be as high as 14 folds (12). A multivariate analysis reported that the risk factors for the development of UC after renal transplantation included BKV infection and a history of smoking (13). BKV nephropathy is an important cause of graft dysfunction in kidney transplant

patients. Latent BKV infection in the urinary epithelium is known to be reactivated in immunosuppression, causing nephropathy, hemorrhagic cystitis, ureteral stenosis, and malignancy (14,15). Reactivation of BKV may contribute to tumorigenesis, mainly through the inactivation of the tumor suppressor retinoblastoma protein (pRB) and the tumor suppressor protein 53 (p53) by T-antigen (16). The patient in this case had a 20-year history of smoking, despite having quit, and a history of BKV infection with kidney graft dysfunction.

In this case, a gradually enlarging, well-defined, and homogeneous hypoechoic mass was observed in the renal pelvis of the kidney graft, extending into the renal lower pole parenchyma. This was highly similar to the US findings reported by Russ (17) of post-transplant lymphoma involving the kidney graft, but differed from the typical sonographic manifestation of UC of the renal pelvis. Generally, UC in the renal pelvis presents as a hypoechoic mass in the renal pelvis on imaging, often accompanied by hydronephrosis (which was absent in our case), and the mass typically extends into the ureter and bladder, but rarely extends into the renal parenchyma. Thus, the imaging in this case was very atypical. Additionally, the bulky focal hypoechoic mass observed in our case had edges that aligned with the renal margins, but did not cause any alteration to the renal morphology. These observations suggested a diagnosis of PTLD and represent the primary reasons for our misdiagnosis.

Due to real-time microvascular perfusion, CEUS is a remarkable technology for monitoring lesions in kidney transplants. CEUS also has no nephrotoxicity and thus is more suitable for patients with renal dysfunction. The patient in this case was already undergoing regular dialysis. During the first hospitalization, an enhanced CT scan was conducted. After each enhanced CT scan, immediate dialysis was necessary, making the entire process quite cumbersome. Thus, during the second hospitalization, CEUS was used as an alternative diagnostic tool to observe the internal structure and perfusion of the mass. CEUS enables the dynamic assessment of the vascularization, blood circulation, and contrast agent uptake in kidney graft lesions, and its specificity and sensitivity are similar to those of enhanced CT/MRI (18,19). However, unlike CT and MRI that use contrast agents in renal imaging, CEUS only produces the corticomedullary phase and nephrographic phase, and not the excretory phase. There are limited reports on the use of CEUS to detect renal pelvic UC and lymphoma, and even fewer reports exist on the use of CEUS to detect these two diseases in kidney grafts.

Distinguishing PTLD from UC using CEUS is challenging. Both diseases exhibit similar perfusion patterns on CEUS, specifically hypo-enhancement during the arterial phase (18-20). In this case, CEUS showed hypo-enhancement in the renal mass of the kidney graft during both the arterial and parenchymal phases, and an early washout in the late phase. These findings suggested malignancy only. Moreover, the non-enhancing area in the mass detected by CEUS indicated necrosis, but this observation lacked specificity. This is because necrosis can occur in almost all tumors when they reach a size of 5 cm or larger. For example, Du *et al.* reported PTLD in a kidney graft that also exhibited necrosis (18). Necrosis is rarely observed in renal pelvic UC, but in this particular case, the necrosis was relatively obvious.

The main options for the initial treatment of PTLD are reduction of immunosuppression, immunotherapy with anti-cluster of differentiation 20 (CD20) monoclonal antibody rituximab, chemotherapy, radiotherapy, or a combination of these. Conversely, radical nephroureterectomy is a standard treatment for UC in transplanted kidneys. Due to the distinct therapeutic approaches for these two malignancies, timely and accurate disease diagnosis is essential. US-guided biopsy is a well-established technique that is widely used in clinical practice. It was difficult to perform the differential diagnosis using CEUS in our case; however, CEUS can effectively distinguish solid parts from necrotic areas, thereby further improving the success rate of both biopsy and diagnosis.

Conclusions

In conclusion, the imaging manifestations of UC in the kidney graft in our case were atypical, and as a result, the imaging diagnosis was unreliable. Thus, the imaging findings had to be integrated with clinical data to make the diagnosis. More importantly, a prompt US-guided tissue biopsy had to be performed to identify the cancer types, which was essential for accurate treatment.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1323/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891-901.
2. Hickman LA, Sawinski D, Guzzo T, Locke JE. Urologic malignancies in kidney transplantation. Am J Transplant 2018;18:13-22.
3. Li S, Zhang J, Tian Y, Zhu Y, Guo Y, Wang Z, Yang Y, Ding G, Lin J. De novo upper tract urothelial carcinoma after renal transplantation: a single-center experience in China. BMC Urol 2023;23:23.
4. Du C, Zheng M, Wang Z, Zhang J, Lin J, Zhang L, Tian Y, Zhu Y. Clinical characteristics and treatment outcomes of kidney transplant recipients with de novo urothelial carcinoma: thirty years of experience from a single center. BMC Urol 2023;23:71.
5. Yu J, Lee CU, Kang M, Jeon HG, Jeong BC, Seo SI, Jeon SS, Lee HM, Sung HH. Incidences and oncological outcomes of urothelial carcinoma in kidney transplant recipients. Cancer Manag Res 2019;11:157-66.
6. Leon G, Szabla N, Boissier R, Gigante M, Caillet K, Verhoest G, Tillou X; . Kidney Graft Urothelial Carcinoma: Results From a Multicentric Retrospective National Study. Urology 2020;135:101-5.
7. Markouli M, Ullah F, Omar N, Apostolopoulou A, Dhillon P, Diamantopoulos P, Dower J, Gurnari C, Ahmed S, Dima D. Recent Advances in Adult Post-Transplant Lymphoproliferative Disorder. Cancers (Basel) 2022;14:5949.
8. Fakhri B, Fiala M, Slade M, Westervelt P, Ghobadi A. Donor-Derived Smoldering Multiple Myeloma following a Hematopoietic Cell Transplantation for AML. Case Rep Hematol 2017;2017:3728429.
9. Atallah-Yunes SA, Salman O, Robertson MJ. Post-transplant lymphoproliferative disorder: Update on treatment and novel therapies. Br J Haematol 2023;201:383-95.
10. Pham PT, Everly M, Faravardeh A, Pham PC. Management of patients with a failed kidney transplant: Dialysis reinitiation, immunosuppression weaning, and transplantectomy. World J Nephrol 2015;4:148-59.
11. Wang L, Ma K, Yao Y, Yu L, Wu J, Zhao Q, Ye Z. Carcinogenicity risk associated with tacrolimus use in kidney transplant recipients: a systematic review and meta-analysis. Transl Androl Urol 2022;11:358-66.
12. Wang Y, Lan GB, Peng FH, Xie XB. Cancer risks in recipients of renal transplants: a meta-analysis of cohort studies. Oncotarget 2018;9:15375-85.
13. Liu S, Chaudhry MR, Berrebi AA, Papadimitriou JC, Drachenberg CB, Haririan A, Alexiev BA. Polyomavirus Replication and Smoking Are Independent Risk Factors for Bladder Cancer After Renal Transplantation. Transplantation 2017;101:1488-94.
14. Kotton CN, Kamar N, Wojciechowski D, Eder M, Hopfer H, Randhawa P, Sester M, Comoli P, Tedesco Silva H, Knoll G, Brennan DC, Trofe-Clark J, Pape L, Axelrod D, Kiberd B, Wong G, Hirsch HH; . The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation. Transplantation 2024;108:1834-66.
15. Mohammadi Najafabadi M, Soleimani M, Ahmadvand M, Soufi Zomorrod M, Mousavi SA. Treatment protocols for BK virus associated hemorrhagic cystitis after hematopoietic stem cell transplantation. Am J Blood Res 2020;10:217-30.
16. Jones H, Bhakta A, Jia L, Wojciechowski D, Torrealba J. An Unusual Presentation of Metastatic BK Virus-Associated Urothelial Carcinoma Arising in the Allograft,

Persisting After Transplant Nephrectomy. Int J Surg Pathol 2023;31:1586-92.
17. Russ PD, Way DE, Pretorius DH, Manco-Johnson ML, Weil R 3rd. Posttransplant lymphoma. Sonographic characteristics of renal allograft involvement. J Ultrasound Med 1987;6:453-6.
18. Du ZS, Xie XH, Hu JJ, Fang Y, Ye L. Ultrasound for monitoring different stages of post-transplant lymphoproliferative disorder in a transplanted kidney: A case report and review of the literature. Medicine (Baltimore) 2024;103:e36206.
19. Farkas ÁZ, Török S, Kovács JB, Piros L, Végső G, Kiss G, Korda D, Bibok A, Hartmann E, Deák ÁP, Doros A. Diagnosis and Management of a De Novo Urothelial Carcinoma in a Kidney Allograft: A Case Report. Transplant Proc 2019;51:1281-5.
20. King KG. Use of Contrast Ultrasound for Renal Mass Evaluation. Radiol Clin North Am 2020;58:935-49.

Cite this article as: Xie X, Li G, Wang X, Zhang H. Imaging misdiagnosis of urothelial carcinoma of the kidney graft as a post-transplant lymphoproliferative disorder: a case description. Quant Imaging Med Surg 2025;15(1):1073-1079. doi: 10.21037/qims-24-1323