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Case Report

Neoadjuvant Nivolumab and Ipilimumab for Nonmetastatic Renal Cell Carcinoma with Tumor Thrombus

Viraj A. Master,[1] Benjamin N. Schmeusser,[1] Adeboye O. Osunkoya,[1,2] Arnold R. Palacios,[1] Eric Midenberg,[1] Lauren Yantorni,[3] Kenneth Ogan,[1] Mehmet A. Bilen[3]

[1]Department of Urology, Emory University School of Medicine, Atlanta, GA, USA
[2]Department of Pathology, Emory University School of Medicine, Atlanta, GA, USA
[3]Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, Georgia, USA

Address correspondence to Viraj Master (vmaster@emory.edu).

V. A. Master and B. N. Schmeusser are co-first authors.

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ABSTRACT

Renal cell carcinoma with level IV tumor thrombus is a condition necessitating aggressive surgical management. Many solid organ malignancies often benefit from neoadjuvant treatments for tumor debulking and improvement of surgical outcomes. However, neoadjuvant treatments for renal cell carcinoma have been limited by its resistance to traditional chemotherapy and radiation. Emerging treatment modalities, such as immunotherapies, are exciting new options that may be therapeutically effective. The combination of nivolumab and ipilimumab has exhibited success in managing metastatic renal cell carcinoma. Limited data exist for its use in nonmetastatic renal cell carcinoma with tumor thrombus. This case illustrates the use of nivolumab and ipilimumab combination therapy in delaying tumor growth, producing observable tumor thrombus histologic and radiologic treatment changes, and, most importantly, facilitating a less invasive surgical approach of a level IV renal cell carcinoma tumor thrombus.

Keywords: neoadjuvant, renal cell carcinoma, tumor thrombus, systemic therapy, nivolumab, ipilimumab, combination therapy

INTRODUCTION

Cases of renal cell carcinoma (RCC) with tumor thrombus are highly complex. If left untreated, mortality outcomes are dismal for both metastatic and nonmetastatic disease.[1,2] The surgical treatment of RCC with level IV tumor thrombus often requires aggressive maneuvers such as a sternotomy and cardiac bypass. Interest in neoadjuvant treatment options for RCC with tumor thrombus persists, although effective regimens are scarce. Here, we present a case of neoadjuvant therapy with a combination of checkpoint inhibitors, nivolumab and ipilimumab, for nonmetastatic RCC with tumor thrombus. Case details, clinical and surgical decision-making, treatment effects, and important considerations are discussed. The patient provided written informed consent to participate in this study.

CASE DESCRIPTION

A 67-year-old man presented to the urologic oncology clinic after an incidental finding on a computed tomography angiogram. A 4.3 × 3.9 × 3.7 cm partially exophytic, solid enhancing mass was seen arising from the lower pole of the right kidney with filling defect into the renal vein and inferior vena cava (IVC), suspicious for tumor thrombus (Fig. 1). Echocardiogram and ultrasound imaging confirmed the presence of a thin tumor extending from the renal mass into the IVC and culminating into a rounded thrombus in his right atrium (Fig. 2). Biopsy of the mass demonstrated clear cell RCC. Additional imaging demonstrated no evidence of metastasis.

The patient was referred to medical oncology for neoadjuvant treatment to potentially shrink the tumor and alleviate the morbidity associated with level IV

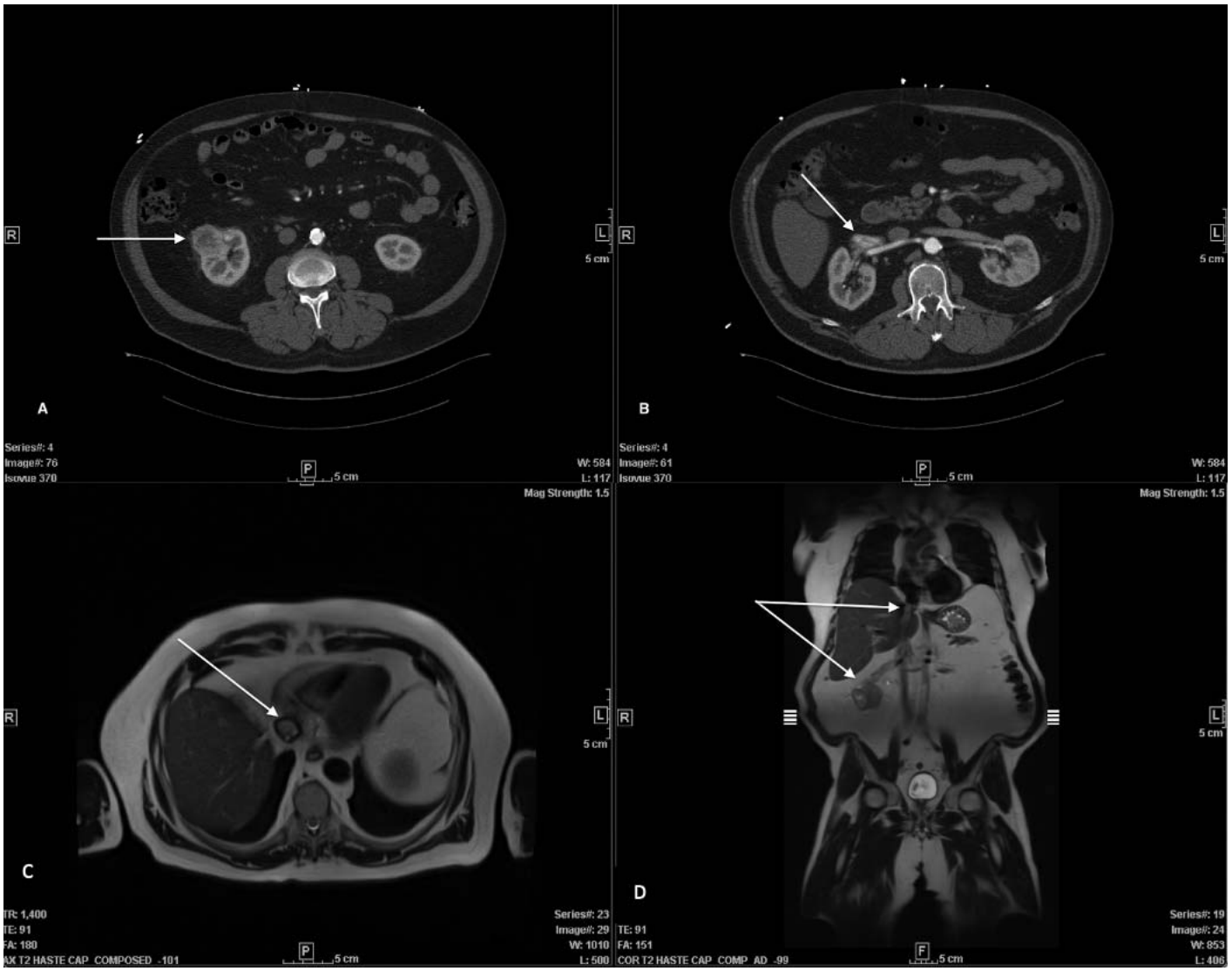

Figure 1. Imaging demonstrating evidence of RCC with tumor thrombus. (A) Contrast-enhanced CT with 4.3 × 3.9 × 3.7-cm mass in the right kidney (white arrow). (B) Contrast-enhanced CT demonstrating right renal vein defect (white arrow). (C) IVC filling defect of IVC on MRI (white arrow). (D) Coronal MRI exhibiting filling defect from lower cavoatrial junction to infrahepatic IVC, measuring approximately 5 cm in length craniocaudally (white arrows). CT, computed tomography; IVC, inferior vena cava; MRI, magnetic resonance imaging.

thrombus treatment. Dual checkpoint inhibitor immunotherapy (CII) was initiated, consisting of nivolumab (3 mg/kg/dose) and ipilimumab (1 mg/kg/dose) intravenous infusions every 3 weeks for four cycles. Repeat echocardiogram showed continued presence of thrombus. The patient then began nivolumab monotherapy (480 mg) for eight more cycles. While on the therapy, the patient did experience hypothyroidism and generalized pruritus managed well with levothyroxine and topical triamcinolone. The patient otherwise tolerated treatment well; did not experience any severe immune adverse events, renal insufficiency, hematuria, or proteinuria; and did not require systemic steroid treatment.

Following a year of CII (four cycles of nivolumab and ipilimumab, eight cycles of nivolumab), the thrombus had decreased in size but failed to regress below the right atrium (Fig. 3). Given that the patient appeared to achieve maximum benefit from the therapy, surgery was next pursued. The patient was presented with two options: a median sternotomy, atriotomy with tumor thrombectomy while on cardiac bypass, and concurrent nephrectomy and vacuum extraction of the thrombus from the IVC at the level of the renal vein. The patient opted for the latter with conversion to a more invasive treatment if necessary.

Intraoperatively, the IVC tumor thrombus was palpated through the vena cava by the surgeon, who estimated the thrombus was a cordlike structure of only 2–3 mm in thickness. An incision into the renal vein revealed a white-appearing thrombus. The tumor thrombus was

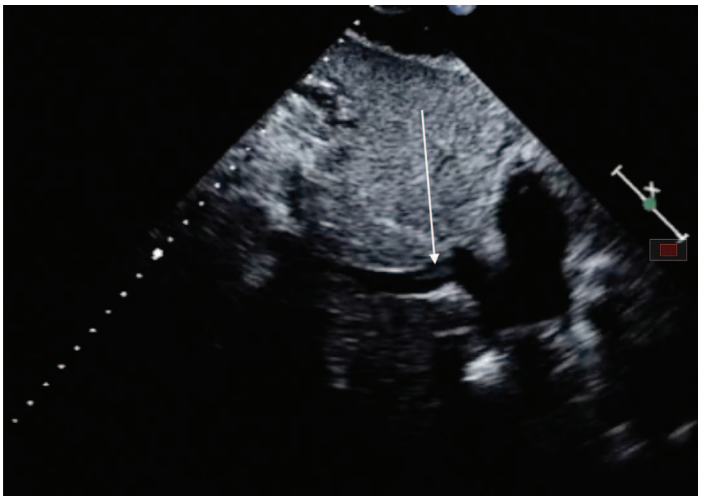

Figure 2. Transthoracic echocardiogram. Thin thrombus extending to the lower cavoatrial junction (white arrow).

grasped with a clamp, and, with steady traction, the entire thrombus was caudally extracted with minimal resistance. The vacuum device was used to remove any residual tumor and was followed by radical nephrectomy.

Histology (Fig. 4) demonstrated clear cell RCC (World Health Organization [WHO] grade 3) with viable tumor cells in the kidney and renal vein with negative margins. The IVC thrombus demonstrated therapy-related changes with no residual viable tumor and associated hyalinization, myxoid changes, and microcalcifications. This was in contrast to the primary tumor within the kidney and renal vein, which showed classic features of clear cell RCC. Final staging was pT3c pNx.

The patient is now more than a year out from surgery and has no evidence of recurrence on routine imaging. He has experienced no complications related to his surgery.

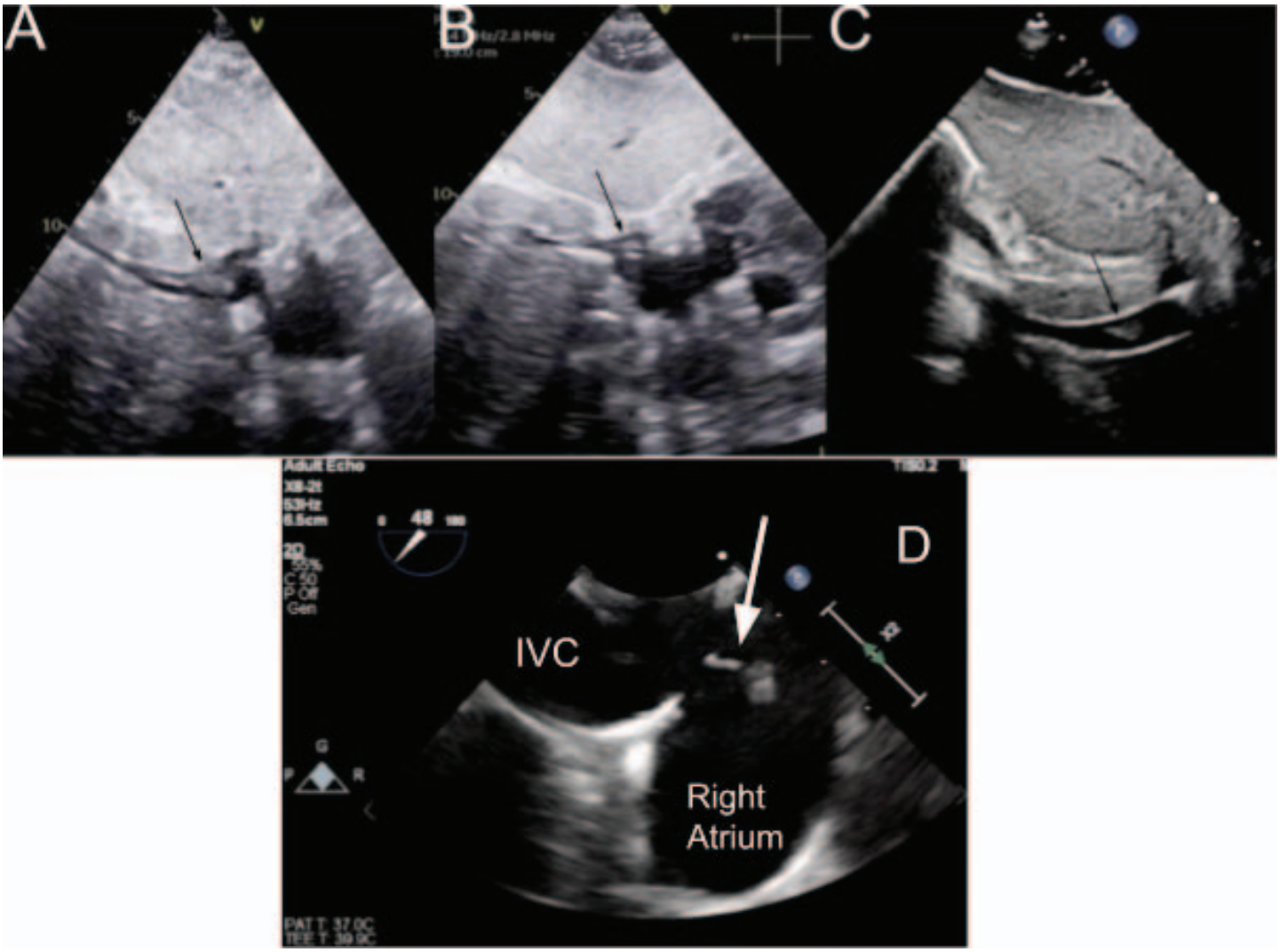

Figure 3. Echocardiograms showing IVC tumor thrombus evolution after systemic nivolumab and ipilimumab therapy. (A and B) Transthoracic echocardiogram showing tumor thrombus at 3 and 5 months after initiation of immunotherapy, respectively. Black arrow indicates presence of thrombus invasion of the IVC at the lower cavoatrial junction. (C and D) Transesophageal echocardiogram at 9 months post chemotherapy still displaying thrombus at lower cavoatrial junction, as indicated by black arrow in (C) and white arrow in (D). IVC, inferior vena cava.

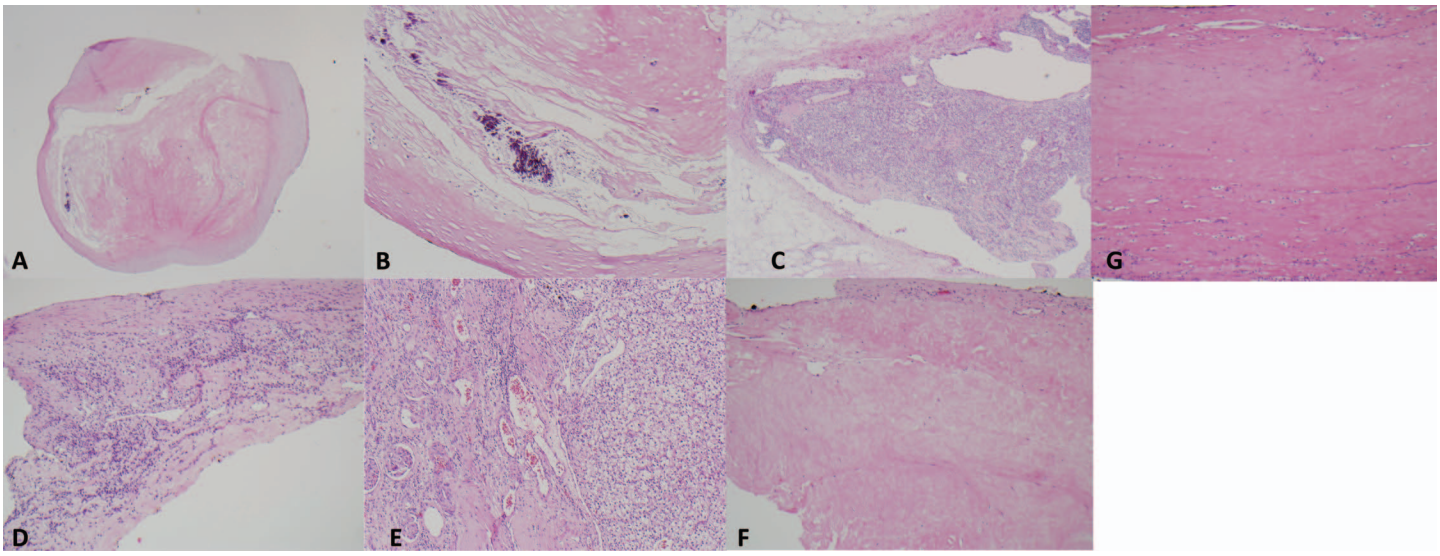

Figure 4. Histology of renal mass and IVC tumor thrombus. The IVC thrombus is negative for viable RCC tumor cells and exhibits therapy-related changes with hyalinization, myxoid changes, and calcifications (purple or red fragmented material in the larger nodule in A and B). In contrast, RCC in the renal vein is viable. (A) IVC larger nodule ×2. (B) IVC larger nodule ×10. (C) RCC in renal vein ×4. (D) RCC thrombus in renal vein lumen ×10. (E) RCC and adjacent benign kidney ×10. (F) Thrombus near RCC junction ×10. (G) Thrombus stalk ×10. IVC, inferior vena cava; RCC, renal cell carcinoma.

DISCUSSION

Nivolumab and ipilimumab combination therapy is recommended in advanced and metastatic RCC.[3] Its indication for patients with RCC with tumor thrombus is less clear and limited to a few case reports, primarily for metastatic disease.[4–9] However, to the best of our knowledge, the present case represents only the second published report for nivolumab and ipilimumab combination therapy for nonmetastatic RCC with tumor thrombus. Preoperative use of this combination resulted in posttreatment changes in thrombus histology and alleviation of surgical complexity, morbidity, and mortality associated with sternotomy and cardiac bypass. Furthermore, the regimen used in this case (four combination cycles and eight nivolumab monotherapy cycles) is unique compared with its use in other related case reports.

In many malignancies, neoadjuvant therapies are used to downstage tumors, ease surgical removal, and improve survival. However, ineffectiveness of neoadjuvant chemotherapy and radiation have limited their use in RCC.[10] Increased understanding of the ability of RCC to escape tumor immunity by altering autoantigens (i.e., downregulation of major histocompatibility complex class I molecules or changes in antigen presentation) and inducing immunosuppression via cytokines has inspired new therapeutics.[11] The emergence of novel immunotherapies has shifted the treatment paradigm and has expanded available options for neoadjuvant treatment.[12–15] For RCC with tumor thrombus specifically, neoadjuvant treatments, such as avelumab and axitinib, stereotactic ablative radiotherapy, pazopanib, sunitinib, and sorafenib, have been explored with varying efficacy in downstaging tumor staging and thrombus level.[15–20] More recently, nivolumab and ipilimumab have emerged as intriguing options in the RCC and RCC with tumor thrombus treatment arsenal.

Nivolumab is a monoclonal antibody directed against program death 1 (PD-1), inhibiting its interaction with program death ligand 1 (PD-L1). Blocking PD-1 and PD-L1 interaction effectively enhances antitumor responses and delays tumor growth.[21] Ipilimumab is a monoclonal antibody directed at cytotoxic T-lymphocyte associated protein 4 (CTLA-4), which is responsible for downregulation of T-cell responses. By disrupting CTLA-4, T-cell activation, restoration, and amplification are achieved to enhance antitumor responses.[22] Although nivolumab and ipilimumab have had positive results when used in isolation for multiple tumors, nivolumab and ipilimumab combination therapy has demonstrated increased efficacy. When compared with sunitinib in advanced RCC (Phase 3 CheckMate 214 Trial), the combination resulted in significantly higher overall survival rates when used in previously untreated advanced RCC.[23] Nivolumab and ipilimumab combination therapy is now first-line therapy for patients with advanced and metastatic RCC.[3,6,7]

Dual therapy with nivolumab and ipilimumab has been used in RCC with tumor thrombus, although primarily in metastatic disease. In several reports, neoadjuvant nivolumab and ipilimumab combination therapy resulted in various degrees of tumor thrombus regression in patients with metastatic RCC with tumor thrombus.[4,5,7–9] The use of nivolumab and ipilimumab in nonmetastatic RCC with tumor thrombus, as in this case, has been scarcely reported. In a report by Labbate et al,[6] four cycles of combination therapy followed by four cycles of nivolu-

mab monotherapy successfully downstaged a level IV tumor thrombus to level III in locally advanced RCC. Similarly, in our case, the thrombus failed to regress below the level of the hepatic veins, resulting in a negligible effect of nivolumab and ipilimumab on surgical outcome and approach. The patient still required a cardiac surgical operating room instead of a general surgical operating room, which is much more costly. Fortunately, open sternotomy was avoided in this case. The ability to grasp and cleanly pull the thrombus back in this case is abnormal because it is usually affixed to the walls of the IVC. It is additionally noteworthy that there was no malignancy histologically in the thrombus itself because this is a likely effect of the systemic therapy. The lack of malignancy identified in the thrombus but continued presence in the primary tumor is similar to the case by Labbate et al,[6] attributed to the heterogeneity of the microenvironments. Although systemic therapy resulted in no identifiable malignancy in the thrombus, surgery was still necessary to prevent thrombus dislodgement and pulmonary embolism.

These aforementioned cases demonstrate the varying success of different regimens of neoadjuvant nivolumab and ipilimumab combination therapy used in patients with RCC with tumor thrombus to help facilitate tumor thrombectomy and nephrectomy.[6–8] For metastatic disease, cytoreductive nephrectomy and thrombectomy can improve symptoms and prolong survival.[24] Moreover, 5-year survival for patients with nonmetastatic RCC with tumor thrombus is greater than 50% versus ~ 10% for complete versus incomplete resection, respectively.[24] This drastic difference in survival, highly dependent on radical surgical resection, highlights the interest in neoadjuvant treatments aimed at tumor debulking and growth restriction. However, as seen in our case, systemic therapy may fail to resolve the entirety of the tumor, emphasizing the importance of surgical intervention in patients with RCC with tumor thrombus. Furthermore, neoadjuvant immunotherapy in RCC with tumor thrombus also has the potential to prolong acceptable preoperative waiting time. Patients with high-risk RCC (i.e., T3, T4) are recommended to undergo surgery within 30 days,[25] with higher risk cases such as RCC with tumor thrombus being encouraged even sooner if possible. By allowing more time from diagnosis to operation, increased nutritional and functional status can potentially be achieved, which may have prognostic benefits for patients with RCC undergoing nephrectomy and tumor thrombectomy.[26–28]

CONCLUSION

RCC with tumor thrombus is associated with high morbidity and mortality. Neoadjuvant immunotherapy with nivolumab and ipilimumab combination therapy for RCC with tumor thrombus may decrease tumor burden and associated operative and oncologic risks. Prospective clinical trials evaluating the efficacy of neoadjuvant immunotherapy in patients with RCC with tumor thrombus should be conducted to further identify appropriate patient selection and use of such interventions.

References

1. Reese AC, Whitson JM, Meng MV. Natural history of untreated renal cell carcinoma with venous tumor thrombus. *Urol Oncol*. 2013;31:1305–1309.
2. Whitson JM, Reese AC, Meng MV. Population based analysis of survival in patients with renal cell carcinoma and venous tumor thrombus. *Urol Oncol*. 2013;31:259–263.
3. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open*. 2020;5:e001079.
4. Yoshida K, Hata K, Iizuka J, et al. Immune checkpoint inhibitor combination therapy for renal cell carcinomas with concomitant inferior vena cava thrombi. *In Vivo*. 2022;36:1030–1034.
5. Nishimura K, Miura N, Sugihara N, et al. Sequential immune-targeted surgical therapy resulted in disease-free survival in a case with advanced renal cell carcinoma. *BMC Urol*. 2021;21:124.
6. Labbate C, Hatogai K, Werntz R, et al. Complete response of renal cell carcinoma vena cava tumor thrombus to neoadjuvant immunotherapy. *J Immunother Cancer*. 2019;7:66.
7. Otsuka H, Masui K, Hosomi T, et al. Preoperative ipilimumab/nivolumab combination therapy reduced operation risk by downstaging the inferior vena cava tumor thrombus extending to the right atrium in a metastatic renal cell carcinoma: a case report. *Urol Case Rep*. 2022;40:101912.
8. Okada T, Hamamoto S, Etani T, et al. Complete response of renal cell carcinoma with an inferior vena cava tumor thrombus and lung metastases after treatment with nivolumab plus ipilimumab. *Int Cancer Conf J*. 2020;9:88–91.
9. Hayashida M, Miura Y, Noda T, et al. Complete response of metastatic renal cell carcinoma with inferior vena cava tumor thrombus to nivolumab plus ipilimumab. *IJU Case Rep*. 2022;5:268–272.
10. Makhov P, Joshi S, Ghatalia P, et al. Resistance to systemic therapies in clear cell renal cell carcinoma: mechanisms and management strategies. *Mol Cancer Ther*. 2018;17:1355–1364.
11. Jian Y, Yang K, Sun X, et al. Current advance of immune evasion mechanisms and emerging immunotherapies in renal cell carcinoma. *Front Immunol*. 2021;12:639636.
12. Deleuze A, Saout J, Dugay F, et al. Immunotherapy in renal cell carcinoma: the future is now. *Int J Mol Sci*. 2020;21:2532.
13. Martini A, Fallara G, Pellegrino F, et al. Neoadjuvant and adjuvant immunotherapy in renal cell carcinoma. *World J Urol*. 2021;39:1369–1376.
14. Sheng IY, Rini BI. Immunotherapy for renal cell carcinoma. *Expert Opin Biol Ther*. 2019;19:897–905.
15. Psutka SP, Leibovich BC. Management of inferior vena cava tumor thrombus in locally advanced renal cell carcinoma. *Ther Adv Urol*. 2015;7:216–229.
16. Hara T, Terakawa T, Hyodo T, et al. Pathological complete response of renal cell carcinoma with vena cava tumor

thrombus to neoadjuvant TKI/IO combination therapy. *Urol Case Rep*. 2021;39:101800.
17. Margulis V, Freifeld Y, Pop LM, et al. Neoadjuvant SABR for renal cell carcinoma inferior vena cava tumor thrombus-safety lead-in results of a phase 2 trial. *Int J Radiat Oncol Biol Phys*. 2021;110:1135–1142.
18. Terakawa T, Hussein AA, Bando Y, et al. Presurgical pazopanib for renal cell carcinoma with inferior vena caval thrombus: a single-institution study. *Anticancer Drugs*. 2018;29:565–571.
19. Cost NG, Delacroix SE Jr, Sleeper JP, et al. The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. *Eur Urol*. 2011;59:912–918.
20. Cai W, Huang J, Yuan Y, et al. Sunitinib or sorafenib as neoadjuvant therapy may not improve the survival outcomes of renal cell carcinoma with tumor thrombus. *Urol Int*. 2018;101:391–399.
21. Guo L, Zhang H, Chen B. Nivolumab as Programmed Death-1 (PD-1) inhibitor for targeted immunotherapy in tumor. *J Cancer*. 2017;8:410–416.
22. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol*. 2016;39:98–106.
23. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277–1290.
24. Quencer KB, Friedman T, Sheth R, Oklu R. Tumor thrombus: incidence, imaging, prognosis and treatment. *Cardiovasc Diagn Ther*. 2017;7(Suppl 3):S165–S177.
25. Martínez CH, Martin P, Chalasani V, et al. How long can patients with renal cell carcinoma wait for surgery without compromising pathological outcomes? *Can Urol Assoc J*. 2011;5:E148–E151.
26. Lawindy SM, Kurian T, Kim T, et al. Important surgical considerations in the management of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus. *BJU Int*. 2012;110:926–939.
27. Morgan TM, Tang D, Stratton KL, et al. Preoperative nutritional status is an important predictor of survival in patients undergoing surgery for renal cell carcinoma. *Eur Urol*. 2011;59:923–928.
28. Watanabe S, Ishihara H, Takagi T, et al. Impact of sarcopenia on post-operative outcomes following nephrectomy and tumor thrombectomy for renal cell carcinoma with inferior vena cava thrombus. *Jpn J Clin Oncol*. 2021;51:819–825.