Case Report

A case of clear cell renal cell carcinoma with vena cava thrombus responding to presurgical avelumab, and axitinib

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Abbreviations & Acronyms
CT = computed tomography
FDG-PET = fluorodeoxyglucose glucose positron emission tomography
IVC = inferior vena cava
MRI = magnetic resonance imaging
PD-L1 = programmed death-ligand 1
RCC = renal cell carcinoma
VEGFR = vascular endothelial growth factor receptor

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Introduction: We report a case of renal cell carcinoma with vena cava thrombus showing a marked reduction with presurgical avelumab plus axitinib, facilitating nephrectomy with thrombectomy.

Case presentation: A 50-year-old man was taken to emergent care unit due to spontaneous renal rupture and was diagnosed to have left-sided renal cell carcinoma with level IV tumor thrombus. After hemostasis was obtained via transcatheter arterial embolization, avelumab plus axitinib was introduced because upfront surgery was deemed unfeasible due to poor performance status and possible retroperitoneal tumor dissemination. After four treatment cycles, thrombus was reduced to level II, and nephrectomy with thrombectomy was performed. Histological analyses revealed massive $CD8^+$ T cell infiltration in the thrombus, suggesting immunotherapy efficacy. He has remained recurrence-free without any additional treatment for eight months.

Conclusion: For locally advanced renal cell carcinoma with vena cava thrombus, presurgical combination therapy with avelumab plus axitinib could be an option to facilitate curative surgery.

Key words: clear cell renal cell carcinoma, immunotherapy, nephrectomy, presurgical therapy, vena cava tumor thrombus.

Keynote message

- There is currently no consensus on neoadjuvant therapies for patients with locally advanced renal cell carcinoma with vena cava thrombus. Combination therapy with avelumab plus axitinib resulted in the downstaging of the vena cava thrombus and shrinkage of the renal tumor, which facilitated curative surgery.
- Immunohistochemical analyses revealed massive infiltration of CD8+ T cells within the vena cava thrombus, suggestive of the efficacy of immunotherapy.
- The association between adhesion in the retroperitoneal space and presurgical immunotherapy should be investigated further.

Introduction

RCC, when it advanced locally, often develops inferior vena cava tumor thrombus. Tumor thrombectomy accompanied by radical nephrectomy could lead to long-term survival,[1] resulting in approximately 50% five-year cancer-specific survival in patients with advanced tumor thrombus (level III or IV) but no distant metastases.[2–4] Although complete surgical resection with tumor thrombectomy could have a survival benefit, this procedure involves significant morbidity and mortality.[2] The rate of perioperative complications of vena cava thrombectomy is associated with tumor thrombus level,[5] and perioperative mortality for level IV thrombus was reported to be 40%.[6]

There is currently no consensus regarding neoadjuvant therapies for patients with locally advanced RCC developing vena cava thrombus. Presurgical use of VEGFR inhibitors might be useful by reducing the primary tumor and enabling complete tumor resection.[7] However,

the role of VEGFR inhibitors as neoadjuvant therapy for tumors with vena cava thrombus is still controversial, with conflicting results.[8–12]

Modern immunotherapy with immune checkpoint inhibitors (including the anti-programmed death-ligand 1 antibody, avelumab) has been revealed to be effective in various malignancies, including advanced RCC.[13,14] A combination of immune checkpoint inhibitors with VEGFR inhibitors is expected to have enhanced antitumor activity because VEGFR inhibitors also modulate the immune microenvironment by enhancing the infiltration of effector lymphocytes and by inhibiting immunosuppressive cells such as myeloid-derived suppressor cells.[15] Indeed, a combination of avelumab and a highly selective VEGFR inhibitor, axitinib, prolongs progression-free survival compared to sunitinib, making it one of the standard treatments for metastatic RCC.[16] Herein, we report a case of RCC with vena cava thrombus that responded profoundly to presurgical, combined immunotherapy with avelumab plus axitinib, facilitating curative nephrectomy with vena cava thrombectomy.

Case presentation

A 50-year-old man was transferred to the emergency room due to a sudden onset of left abdominal pain. CT revealed a left renal tumor surrounded by a hematoma occupying the left retroperitoneal space (Fig. 1a). The left renal tumor developed a tumor thrombus extending into the inferior vena cava (Fig. 1b,c). As the patient developed hemorrhagic shock due to spontaneous rupture of the left renal tumor, selective arterial embolization of the left renal artery was performed immediately. Follow-up CT after arterial embolization revealed no outflow of contrast medium into the retroperitoneal space, suggesting complete hemostasis. After achieving hemostasis, the patient underwent FDG-PET and MRI. FDG-PET revealed no distant metastases (Fig. 1d). MRI revealed that the protruding edge of the vena cava thrombus advanced beyond the diaphragm (level IV; Fig. 2a).

After hemostasis was achieved with arterial embolization, his Karnofsky Performance Status was 40%. Serum hemoglobin was 10.3 g/dL, corrected calcium level was 9.5 mg/dL, white blood cell count was 22.3×10^9/L, the absolute neutrophil count was 19.2×10^9/L, and platelet count was 243 000/μL. A core needle biopsy of the renal tumor was omitted to avoid further hemorrhage from the tumor. Based on the imaging studies, the patient was diagnosed with left renal RCC plus vena cava thrombus, clinical stage cT3cN0M0, which developed spontaneous rupture and retroperitoneal hematoma.

Upfront left nephrectomy with vena cava thrombectomy was deemed unfeasible because of poor performance status and the possible dissemination of cancer cells into the retroperitoneal space; therefore, we decided to introduce a combination therapy of checkpoint inhibitors and VEGFR inhibitors, following standard treatment for metastatic RCC. The combined therapy with avelumab plus axitinib was started. After two cycles, the tip of the tumor thrombus regressed from the right atrium (level IV) to the inferior vena cava below the insertion of the hepatic vein (level II; Fig. 2b), and the maximum tumor diameter was reduced by

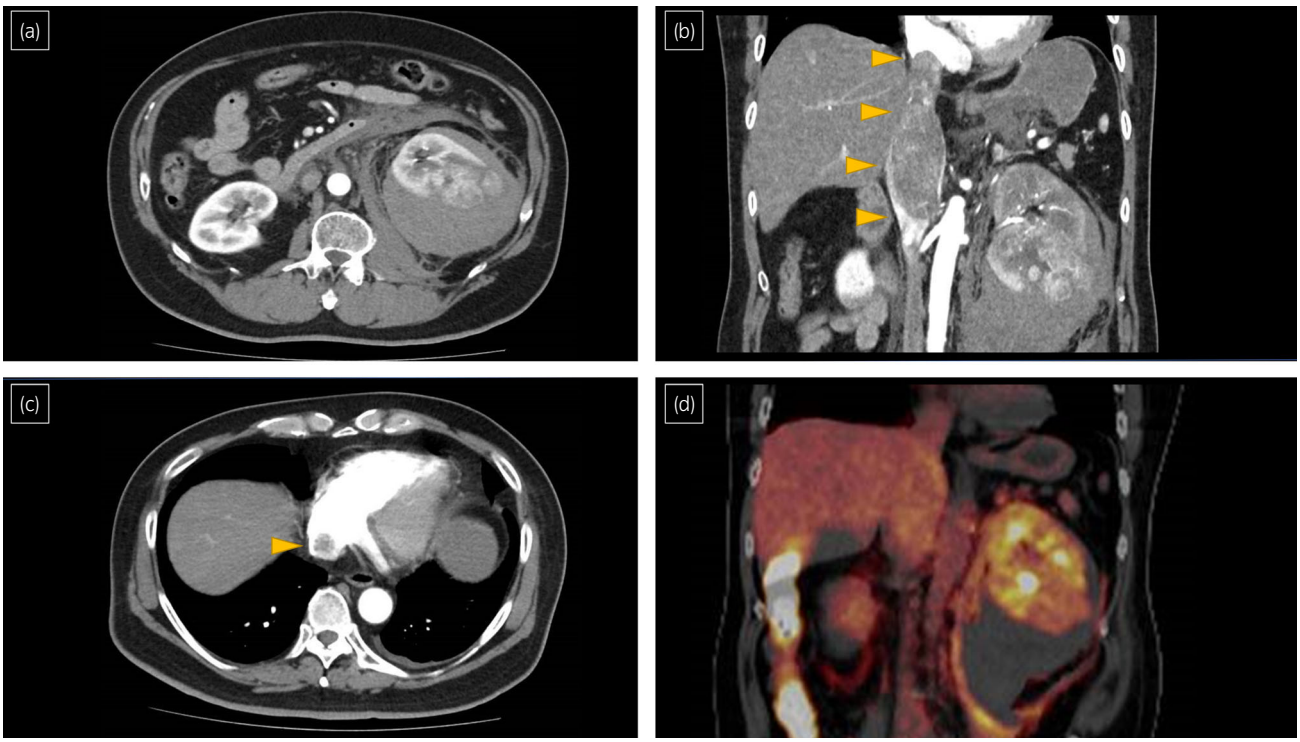

Fig. 1 Computed tomography (CT) images of the left renal tumor (a, b) and vena cava thrombus (b, c). Fluorodeoxyglucose-positron emission tomography (FDG-PET) CT imaging showing FDG uptake in the primary tumor and vena cava thrombus (d).

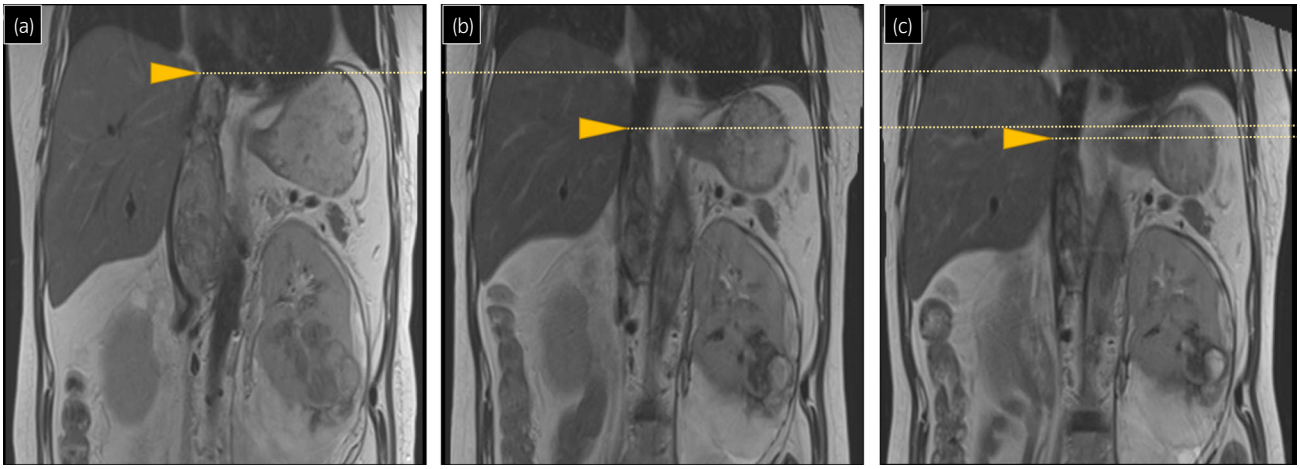

Fig. 2 T2-weighted magnetic resonance imaging (MRI) showing downstaging of the vena cava thrombus. (a) Pre-treatment, (b) after two cycles, and (c) after four cycles of the combination therapy.

40.7% from 55.3 mm to 32.8 mm. The patient received further two cycles of combination therapy, resulting in further regression of the tumor by 6.1% from 32.8 mm to 30.8 mm (Fig. 2c). The patient developed no drug-induced adverse events, and his performance status improved to 100% during the therapy.

We decided to proceed with left radical nephrectomy with vena cava thrombectomy based on the marked tumor reduction, the level-down of vena cava thrombus, and improved performance status. Dense adhesions were observed in the retroperitoneal space, possibly due to the post-hemorrhagic change or tumor dissemination at initial presentation. Due to the marked decrease in tumor thrombus level, the vena cava could be clamped below the insertion of the hepatic vein. Vena cava tumor thrombus was completely resected along with the primary left renal tumor.

Final pathologic analysis of the radical nephrectomy specimen revealed ISUP grade II (Fuhrman grade III) clear cell RCC. The resected vena cava thrombus contained areas of necrosis associated with the marked infiltration of inflammatory cells, suggesting treatment response to immunotherapy (Fig. 3a,b). Immunohistochemical analyses of viable tumors in the vena cava thrombus revealed the marked infiltration of $CD8^+$ T cells compared to the scarce infiltration of $CD4^+$ T cells (Fig. 3c,d).

The postoperative course was uneventful, and the patient was discharged 16 days after surgery. He was fully back to his activities on his first follow-up at two months. Adjuvant therapy has not been planned as there is no evidence of residual disease after curative surgery. No recurrence or metastasis was found on follow-up CT examination eight months after the operation.

Discussion

The current case initially presented with a retroperitoneal hemorrhage, which turned to be a spontaneous rupture of locally advanced RCC developing level IV vena cava thrombus. Immediate surgery was deemed unfeasible because of impaired performance status and the possibility of disseminating tumor cells, combination therapy with avelumab plus axitinib was started. The combination therapy was well-tolerated and resulted in a marked shrinkage in the primary tumor and in the vena cava thrombus (level IV to II) as well as improved performance status, which facilitated curative nephrectomy with thrombectomy. The patient remained disease-free without any adjuvant therapy thereafter. This case supports the possible role of combination therapy with immune checkpoint inhibitors and VEGFR inhibitors as presurgical therapy for patients with vena cava thrombus of RCC.

Currently, we have no standard neoadjuvant therapy for patients with vena cava thrombus of RCC. Although a case report of a complete response to neoadjuvant VEGFR inhibitor therapy for vena cava thrombus of RCC has been presented,[17] the role of presurgical VEGFR inhibitors for vena cava thrombus is still controversial with conflicting results.[8–12] Most recently, Field et al. reported that the neoadjuvant sunitinib provided a level down of vena cava thrombus in eight (42.1%) of 19 patients, as well as improved survival.[12] Possible clinical benefits from presurgical VEGFR inhibitors are thus expected; however, further clinical studies are warranted to elucidate its role as neoadjuvant therapy for RCC with vena cava thrombus.

The possible utility of modern immunotherapy with checkpoint inhibitors as presurgical therapy for vena cava thrombus has been proposed in several case reports. Labbate et al. reported a case of locally advanced RCC with vena cava thrombus who achieved a pathologically complete response after combined immunotherapy with nivolumab plus ipilimumab.[18] Similarly, Okada et al. reported a case of metastatic RCC with vena cava thrombus who underwent cytoreductive nephrectomy with thrombectomy after combined immunotherapy with nivolumab plus ipilimumab, resulting in a complete pathological response.[19]

As VEGFR inhibitors have immunomodulatory effects, combination therapy with checkpoint inhibitors and VEGFR inhibitors is expected to have enhanced antitumor effects. Bhat et al. reported a case of metastatic RCC with vena cava

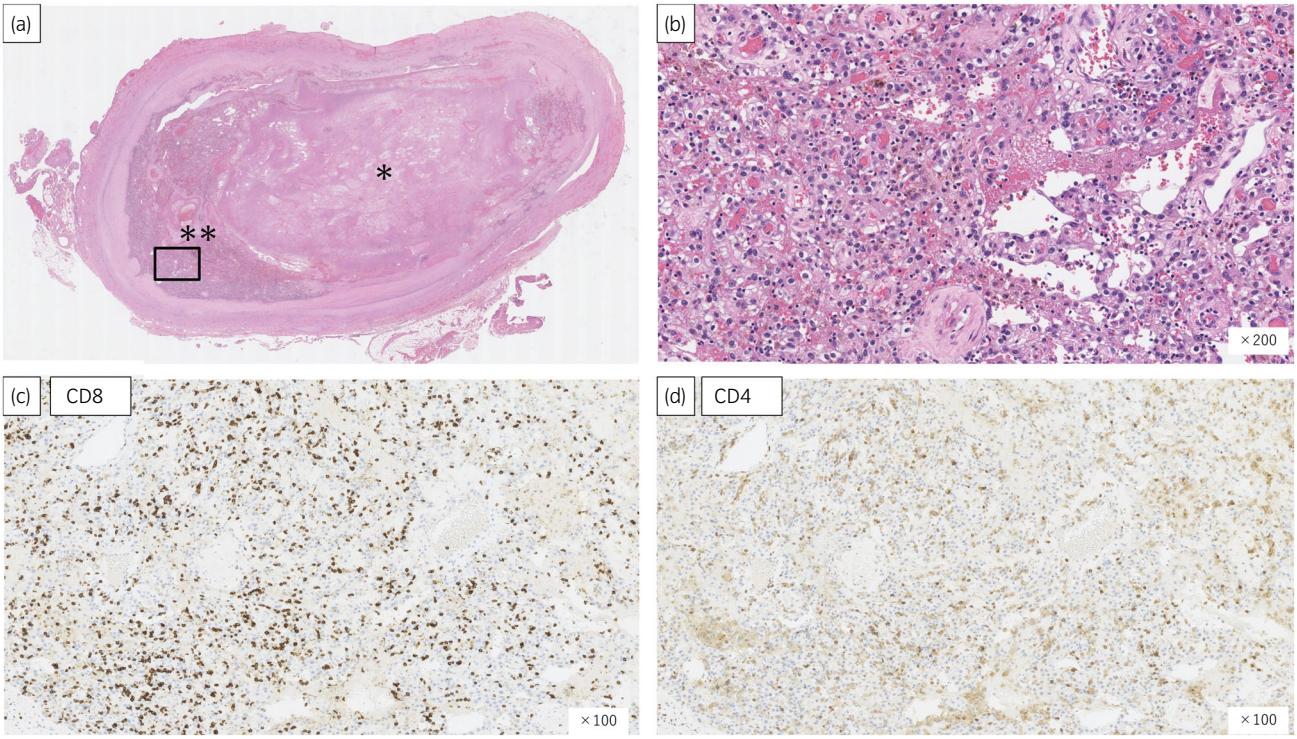

Fig. 3 Histological analyses of the vena cava thrombus. (a) Low-magnification view of the thrombus containing necrotic (*) and viable (**) lesions. Black squares indicate the areas magnified in panels (b), (c), and (d). (b) Hematoxylin-eosin staining of the viable tumor. Immunohistochemical analyses for CD8 (c) and CD4 (d) are also shown.

thrombus who experienced a marked reduction in tumor thrombus in response to nivolumab plus cabozantinib (inhibitor of VEGFR2 and other signaling pathways) and subsequently underwent cytoreductive nephrectomy with thrombectomy, resulting in long-term disease-free status.[20] This case also suggested the possible utility of combination therapy with checkpoint inhibitors and VEGFR inhibitors in a presurgical setting for vena cava thrombus of RCC. Treatment with avelumab and axitinib reduced the tumor thrombus, resulting in downstaging from level IV to level II. As surgery for level IV thrombus involves cardiovascular procedures requiring extracorporeal circulation and is associated with considerable morbidity and mortality, presurgical avelumab and axitinib undoubtedly decreased the risk of curative surgery.

Currently, there is no widely accepted strategy in selecting immunotherapy combinations or immunotherapy-VEGFR inhibitors combinations. The recent meta-analysis[21] revealed that immunotherapy-VEGFR inhibitors combinations provide superior PFS, ORR, and OS to immunotherapy combinations. However, immunotherapy combination provided the highest likelihood of OS and PFS improvement in patients with high PD-L1 expression. Considering the superior ORR, we selected immunotherapy-VEGFR inhibitors combination in this case. Unfortunately, we could not perform pretreatment tumor biopsy. The role of PD-L1 expression as a predictive biomarker should be elucidated in future trials. According to the other recent meta-analysis,[22] anti-PD-1 agents showed superior oncological outcomes to anti-PD-L1 agents. Conversely, anti-PD-L1 agents were superior to anti-PD-1 agents in their safety profiles. Considering the poor performance status, we selected the avelumab (anti-PD-L1) combination instead of the pembrolizumab (anti-PD-1) combination in this case.

In the current case, nephrectomy was quite difficult because of dense adhesions in the retroperitoneal space, although the operation was successfully completed without any perioperative complications. Although these strong adhesions could be attributed to post-hemorrhagic changes, another possibility is post-immunotherapy inflammation. Labbate et al. also reported strong adhesion after nivolumab plus ipilimumab, which warranted an intraoperative change to the planned procedure.[18] The possible association between these dense adhesions and presurgical immunotherapy may need to be studied in future trials.

In conclusion, we present the case of locally advanced RCC developing vena cava tumor thrombus, which showed a marked reduction in response to presurgical combination therapy with avelumab plus axitinib. Level-down in the vena cava thrombus as a result of the combination therapy facilitated curative-intent nephrectomy with thrombectomy. As surgery for advanced RCC with tumor thrombus is technically challenging with considerable morbidity and mortality, the utility of presurgical combination immunotherapy, which may enable curative surgery, should be further investigated.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an institutional reviewer board

Not applicable.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Registry and the registration no. of the study/trial

Not applicable.

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