



Pathological complete response of renal cell carcinoma with vena cava tumor thrombus to neoadjuvant TKI/IO combination therapy

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ABSTRACT

A 79-year-old female was diagnosed with a right renal tumor with a level II tumor thrombus of the vena cava. presurgical therapy was initiated with a combination of avelumab and axitinib for 3 months. Then, she underwent nephrectomy and thrombectomy. Histologically, the primary tumor and tumor thrombus had no viable cells, indicating that pathological complete response was achieved with presurgical tyrosine kinase inhibitor/Immuno-oncology combination therapy. An immunohistological examination showed very strong staining for tumor-infiltrating lymphocytes in the embolized area of the tumor, with CD8 predominating over CD4.

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2. Background

Presurgical therapy for renal cell carcinoma (RCC) with a tumor thrombus extending to the inferior vena cava (IVC) is attracting increasing interest, both to shrink the tumor thrombus and reduce surgical risks.

However, in the tyrosine kinase inhibitor (TKI) monotherapy era, clinical effects on RCC with an IVC thrombus were minimal in cohorts of a small number of patients. Therefore, neoadjuvant therapy for RCC using TKI monotherapy does not appear to be of clinical significance.¹

The combination of avelumab, an immune checkpoint inhibitor (ICI), and axitinib, a TKI, has recently been shown to increase the objective response rate in the primary treatment of advanced RCC. However, the clinical benefits of this combination therapy remain

unclear in cases with a tumor thrombus. We herein report a unique case in which a pathological complete response (pCR) was observed in surgical specimens of both the renal tumor and tumor thrombus after treatment with this combination therapy for 3 months.

3. Case presentation

A 79-year-old female was incidentally diagnosed with a 4.2 × 3.8cm right renal tumor with a level II tumor thrombus of the vena cava under the investigation of chest pain [Fig. 1A and B]. The contrast pattern of the tumor was suspicious for clear cell RCC. The examination for chest pain reached a diagnosis of unstable angina with severe coronary artery stenosis. Thereafter, stent placement for a narrowed coronary artery was prioritized over the treatment of the tumor. After stent placement, the patient was administered two antiplatelet drugs and, thus, was deemed unfit for surgical resection. To suppress disease progression, presurgical therapy was initiated with a combination of avelumab and axitinib. After this presurgical therapy for 3 months, the patient received 6 cycles of avelumab (10 mg per kilogram of body weight) every two weeks and 10 mg of axitinib daily, and sufficiently recovered to undergo surgery. Regarding the tumor status, reductions of 15 and 5% were observed in the primary tumor mass and IVC thrombus after treatment [Fig. 1C and D]. The patient then underwent nephrectomy and thrombectomy. She received axitinib for up to 3 days before surgery and the last administration of avelumab 7 days before surgery. Open nephrectomy and

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thrombectomy were performed. At the time of surgery, her ECOG Performance Status Score was 1 and ASA physical status was class 3.

The liver was mobilized to expose the hepatic vein by incision of the falciform, triangular, and coronary ligaments. The IVC and contralateral renal vein were mobilized to allow proximal and distal vascular control above and below the tumor thrombus. There were mild adhesions around the kidney, but structures such as renal fascia and peritoneum were preserved, and the borders of these membranes were easily detached with a little observation. Cavotomy was performed to remove the whole thrombus by making an incision in the IVC wall at the entry of the renal vein. The thrombus was smooth-surfaced, elastic hard and showed no adhesion to the IVC vessel wall. The surgical time was 4 hours and 28 minutes and blood loss was 120 cc. Fig. 2 shows an excised specimen.

The patient was discharged without any postoperative complications.

Histologically, the primary tumor and tumor thrombus had no viable cells, indicating that pCR was achieved with presurgical tyrosine kinase inhibitor/Immuno-oncology (TKI/IO) combination therapy.

An immunohistological examination showed very strong staining for tumor-infiltrating lymphocytes (TILs) in the thrombus area of the tumor, with CD8 predominating over CD4. TILs were also present in the main body of the tumor, although to a lesser extent than in the thrombus, with CD8>4 [Fig. 3A and B].

Four months after surgery, there has been no evidence of recurrence or metastasis.

4. Discussion

Few case reports showed that neoadjuvant TKI monotherapy achieved pCR of RCC with an IVC thrombus. In the ICI era, the reported number of cases with pCR after presurgical therapy with IO monotherapy has been increasing.² Labbate et al.³ recently presented a case of RCC in which pCR was achieved with IO combination therapy, and immunohistochemistry of the tumor and TILs indicated the beneficial effects of neoadjuvant IO. Therefore, expectations are increasing for the therapeutic effects of the combined usage of IO drugs. We herein present the first case report of pCR of RCC with an IVC thrombus by neoadjuvant TKI/IO combination therapy.

In this case, a pathological specimen showed very strong staining for TILs at the IVC thrombus, with CD8 being dominant.

IO drugs have been shown to exert good therapeutic effects in RCC with CD8-positive TILs. Prominent CD8-positive lymphocytic infiltration in necrotic tissue was detected in other cases of RCC that achieved a



Fig. 2. The excised specimen. The arrow symbol indicate the tumor thrombus.

complete response with IO drugs,² similar to the present case. This may show that there was a strong immune response.

Although the significance of neoadjuvant therapy for patients with RCC remains unclear, the findings of preclinical and clinical studies suggest the significantly higher therapeutic efficacy of neoadjuvant immunotherapy over adjuvant immunotherapy. In the immunotherapy era, up to 8.3% of patients with metastatic RCC have been reported to achieve pCR to nephrectomy after ICI therapy.⁴ The result of a phase 3 neoadjuvant trial with ICI monotherapy with nivolumab (PROSPER; NCT03055013) is expected.

Furthermore, in view of the response rate, combination therapy with IO drugs is expected. Based on comparisons of the response rates of these

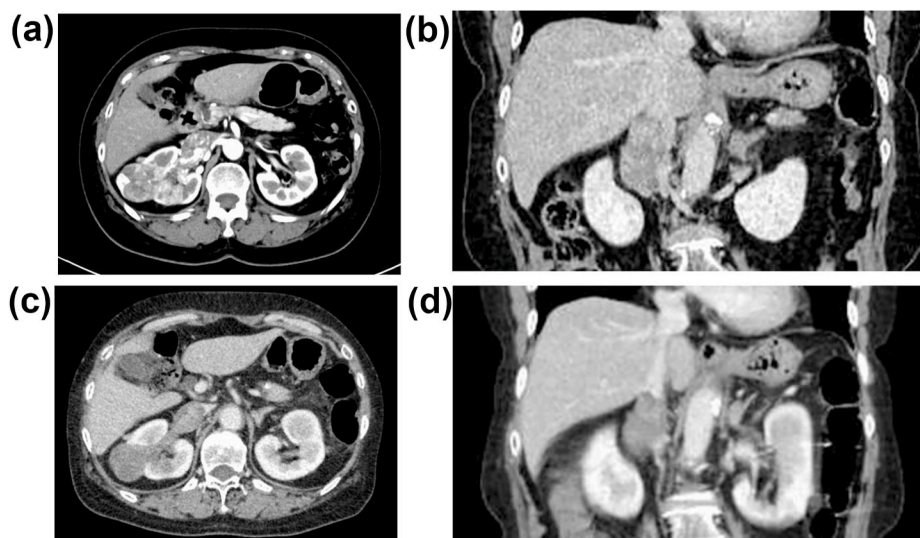


Fig. 1. Axial images of tumor thrombus pre- (A) and post- (B) immunotherapy. Coronal images of tumor thrombus pre- (C) and post- (D) immunotherapy.

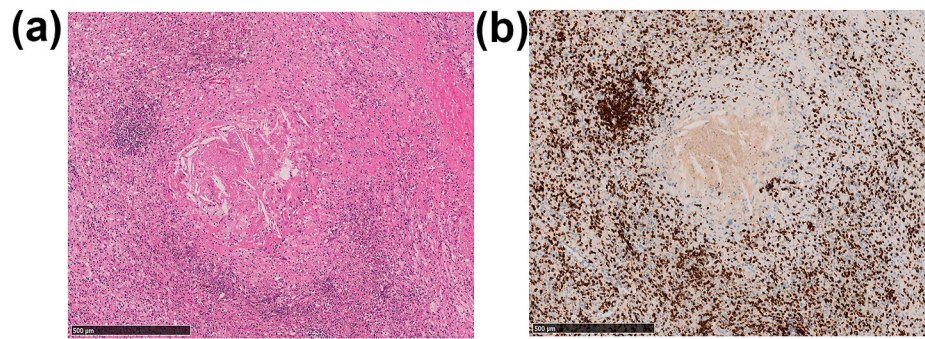


Fig. 3. H&E staining at the thrombus area of the tumor (A) and CD8⁺ TILs at the same area (B).

combination therapies in clinical trials, we consider TKI/IO to be more suitable for preoperative use. TKI/IO achieves a superior objective response rate. Preclinical data also suggest that TKI/IO exerts synergistic effects.⁵ Some phase 2 neoadjuvant trial with TKI/IO are ongoing with axitinib + avelumab (NCT03341845), axitinib + toripalimab (NCT04118855), sitravatinib + nivolumab (NCT03680521).

In addition, when comparing side effect profiles, TKI/IO has fewer severe side effects that require steroid treatment, which may reduce surgical tolerance.

5. Conclusions

We herein report a rare case of RCC that achieved pCr of both the primary tumor with IVC thrombus by preoperative TKI/IO combination therapy with avelumab and axitinib.

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Availability of data and materials

The data generated and/or analyzed during the current study are available in anonymized form upon reasonable request to the corresponding author.

Authors' contributions

TH and TT drafted the manuscript. TH, TT, TH and NJ contributed data. YN and MF provided substantial critical revisions. All authors read and approved the final manuscript. Ethics approval and consent to participate The patient provided full consent for participation and publication. Ethics approval for a case report is deemed exempt by the University of Kobe IRB.

Consent for publication

Available upon request.

Declaration of competing interest

TH, TT, TH, NJ and YN have no competing interests. MF reports research support from Mediaroid, Intuitive Surgical, Ono, Mebix, Skyjet, Rakuten Med and AIR WATER.

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List of Abbreviations

RCC: renal cell carcinoma
 IVC: inferior vena cava
 TKI: tyrosine kinase inhibitor
 ICI: immune checkpoint inhibitor
 pCR: pathological complete response
 TKI/IO: tyrosine kinase inhibitor/Immuno-oncology
 TILs: tumor-infiltrating lymphocytes