



Presurgical avelumab plus axitinib in an immunosenescent octogenarian with renal cell carcinoma invading the vena cava

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ABSTRACT

Application of immune checkpoint inhibitors (ICIs) in elderly patients remains challenging due to the scarcity of safety and efficacy data. An 84 year-old female with a right renal cell carcinoma invading the vena cava received two cycles of avelumab plus axitinib. As the thrombus showed a marked reduction, right nephrectomy and vena cava thrombectomy were performed. Pathological examination revealed intra-tumor infiltration of CD8⁺ T cells suggesting the efficacy of immunotherapy. Although immune function deteriorates with age (immunosenescence), our findings suggest that older patients may not necessarily be excluded from ICI therapy.

1. Introduction

The introduction of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of metastatic or inoperable renal cell carcinoma (RCC). However, the utilization of ICIs in elderly patients remains challenging because of limited safety and efficacy data for this population. Elderly patients are assumed to experience immunosenescence wherein the function of the immune system is less efficient than that observed in younger individuals.

Locally advanced RCC often leads to the development of a vena cava tumor thrombus. Although curative nephrectomy with caval thrombectomy is the recommended treatment, surgery is associated with substantial morbidity and mortality. Thus, presurgical therapy has been applied empirically. The efficacy of presurgical vascular endothelial growth factor receptor (VEGFR) inhibitors for a vena cava thrombus is still controversial. Recently, the efficacy of ICIs, either alone or in combination with VEGFR inhibitors, as presurgical therapy for RCC patients with a vena cava thrombus has been reported.

Herein, we report an octogenarian female patient with an RCC tumor thrombus who exhibited low levels of CD8⁺ T cells in the peripheral blood suggesting immunosenescence. The patient responded well to presurgical avelumab (anti-programmed death-ligand 1 antibody) plus axitinib (VEGFR inhibitor). Pathological examination revealed massive CD8⁺ T cell infiltration. This suggested the possible advantage of using

VEGFR inhibitors for modulating the immune microenvironment by enhancing the infiltration of effector lymphocytes.

2. Case presentation

An 84-year-old female with a history of diabetes and chronic obstructive pulmonary disease (COPD) presented to our hospital with gross hematuria. She needed home oxygen therapy for COPD and experienced difficulty in walking without help (Karnofsky performance status 60). The patient was allergic to iodinated contrast medium; therefore, plain computed tomography (Fig. 1A and B) and magnetic resonance imaging (Fig. 1C) were performed. Right renal cancer with a vena cava thrombus was detected. The superior margin of the vena cava tumor thrombus was caudal to the hepatic venous inflow, which suggested a level II thrombus (Fig. 1C). An 18F-fluorodeoxyglucose positron emission tomography-computed tomography scan (Fig. 1 D, E, F) revealed no lymphatic or distant metastasis. Thus, she was diagnosed with a clinical stage of cT3bN0M0. Considering the poor performance status, tumor biopsy was not performed.

Laboratory tests revealed anemia (hemoglobin 11.2 g/dL). According to the International Metastatic RCC Database Consortium risk classification, she was categorized into poor risk category (total score 3: treatment time, performance status, and hemoglobin). Flow cytometry for peripheral blood lymphocytes revealed decreased CD8⁺ (4.9%, reference range 17%–44%) and slightly increased CD4⁺ (58.2%,

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Abbreviations

COPD	chronic obstructive pulmonary disease
ICI	immune checkpoint inhibitor
RCC	renal cell carcinoma
VEGFR	vascular endothelial growth factor receptor

reference range 25%–56%) T-cell levels, suggesting immunosenescence. A geriatric evaluation was performed. The Geriatric 8 health status screening (8 points) suggested that she required a full geriatric evaluation. According to the Charlson Comorbidity Index, she had a high comorbidity score (8 points; age +4, COPD +1, diabetes +1, localized solid tumor +2). Comprehensively, she was diagnosed as “vulnerable,” suggesting that she required pre-habilitation to achieve treatment completion.

Considering the poor performance status, upfront left nephrectomy with vena cava thrombectomy was considered unfeasible. Thus, combination therapy of avelumab (800 mg intravenously, every 2 weeks) and axitinib (5 mg, orally, twice daily) was introduced. After two cycles of avelumab and axitinib, the vena cava thrombus shrank in diameter from 31 mm to 17 mm (–46%) (Fig. 2), and her Karnofsky performance

status recovered (score = 80).

Right radical nephrectomy with vena cava thrombectomy was performed. The vena cava was clamped below the inflow of the hepatic vein. Thereafter, the vena cava tumor thrombus was completely resected along with the primary right renal tumor. Pathological analysis revealed grade III clear cell RCC. Both primary tumor and vena cava thrombus contained necrotic tissue associated with marked infiltration of inflammatory cells, suggesting the treatment response to immunotherapy (Fig. 3A and B). Immunohistochemical analyses revealed considerable infiltration of CD8⁺ T-cells into the primary tumor and vena cava thrombus (Fig. 3 C, D), with scarce infiltration of CD4⁺ T-cells (Fig. 3 E, F). As there was no evidence of residual disease after curative surgery, the patient was followed up without any adjuvant therapy, and she remained progression-free for 15 months after surgery till the time these findings were documented.

3. Discussion

The patient was an octogenarian with a decreased performance status; thus, upfront nephrectomy with vena cava thrombectomy was unfeasible at the initial presentation. Although the flow cytometry results suggested immunosenescence, the tumor responded well to combination therapy with avelumab and axitinib. This case supports the possible role of combination therapy with ICIs and VEGFR inhibitors for

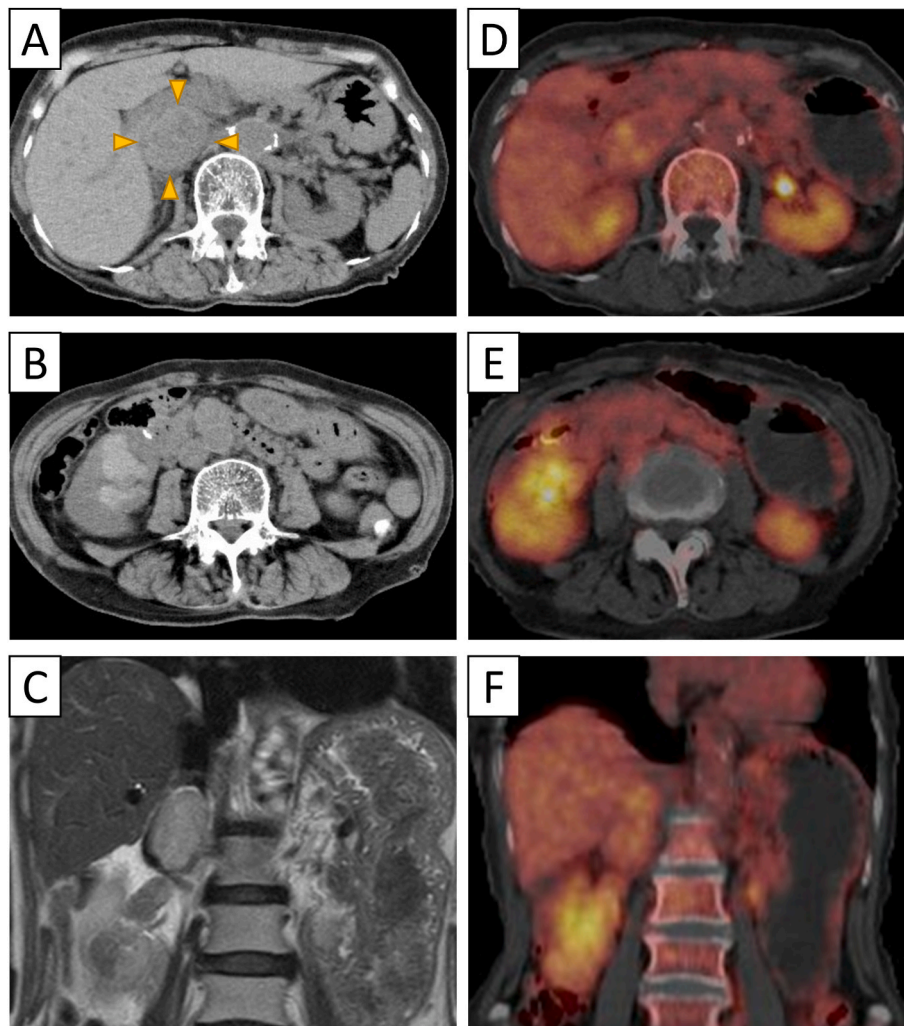


Fig. 1. Computed tomography (CT) and magnetic resonance imaging (MRI) findings of the primary right renal tumor and the vena cava thrombus. (A) Axial CT image of the thrombus; (B) axial CT image of the primary tumor; (C) coronal MRI image of the thrombus; (D) axial 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) CT image of the thrombus; (E) axial FDG-PET CT image of the primary tumor; and (F) coronal FDG-PET CT image of the thrombus.

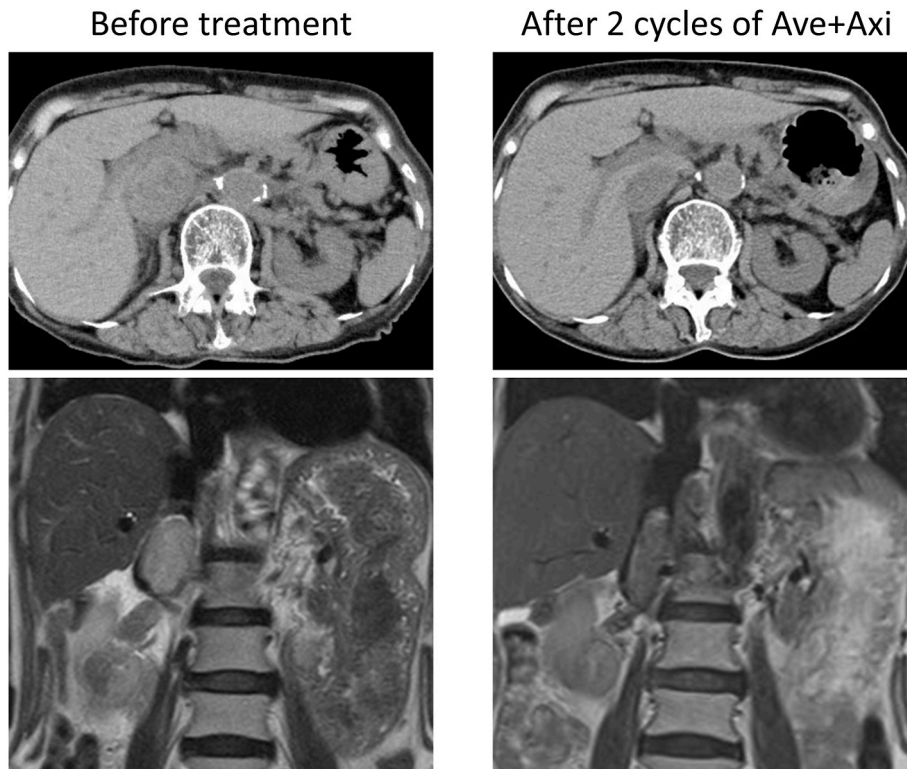


Fig. 2. Computed tomography (CT) and magnetic resonance imaging (MRI) findings of the vena cava thrombus before and after two cycles of avelumab plus axitinib therapy.

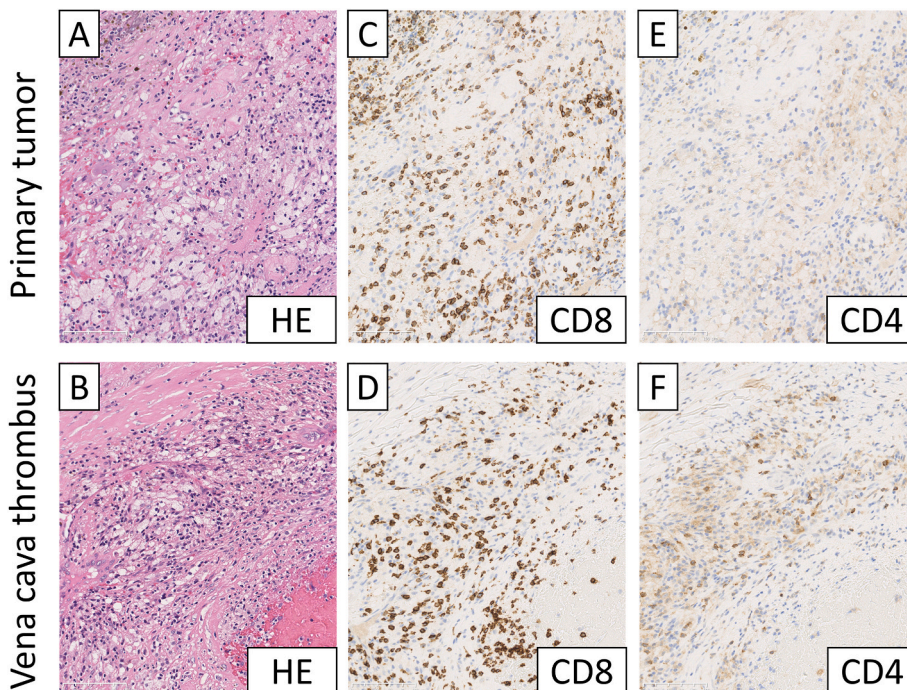


Fig. 3. Immunohistochemical analyses of the primary tumor and vena cava thrombus. (A, B) Hematoxylin and eosin staining; (C, D) CD8; (E, F) CD4.

patients with vena cava thrombus of RCC. This case also suggests that elderly patients should not necessarily be excluded from the use of ICIs.

Currently, there is no consensus regarding presurgical therapy for patients with vena cava thrombus of RCC. Several case reports have highlighted the possible role of ICIs in this setting. Labbate et al.¹ and Okada et al.² reported a complete pathological response in vena cava

thrombus after combined immunotherapy with nivolumab plus ipilimumab. Our group also reported a patient whose venous thrombus responded markedly to presurgical avelumab and axitinib.³ Most recently, Yoshida et al.⁴ reported that three of five patients treated with ICIs showed a decreased venous thrombus.

ICIs are assumed to be less effective in older patients considering

their deteriorated immune system; however, recent publications suggest that ICIs could be useful in older patients.⁵ Thus, ICIs may be administered to older patients provided that adequate geriatric assessment is performed before therapy.

In the current case, presurgical avelumab plus axitinib resulted in massive infiltration of CD8⁺ T-cells in both primary tumor and vena cava thrombus. The possible role of avelumab plus axitinib as neoadjuvant therapy for RCC is being evaluated in a phase II study (NEO-AVAX). In addition, a significant increase in CD8⁺ expression after neoadjuvant avelumab plus axitinib therapy has been reported.

4. Conclusion

In conclusion, presurgical avelumab plus axitinib can be safely administered, and it resulted in tumor reduction and a marked pathological response in an octogenarian patient.

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Approval of the research protocol by an institutional reviewer board

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Informed consent

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

Registry and the registration number of the study/trial

N/A.

Author contributions

Toshitaka Uematsu and Toshiki Kijima managed the patient and wrote the original draft. Daisaku Nishihara managed the patient. Atsuko Takada-Owada and Kazuyuki Ishida performed the pathological and immunohistochemical analyses. Takao Kamai supervised the management of the patient and reviewed the manuscript.

Declaration of competing interest

None.

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