Remarkable effect of presurgical nivolumab on originally inoperable papillary renal cell carcinoma with tumor thrombus in inferior vena cava

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Abstract

For the long-term survival of a patient with renal cell carcinoma and a vena cava tumor thrombus, total resection is desired: inoperable patients are sometimes treated with drugs. The effect of the presurgical use of nivolumab, an anti-programmed cell death 1 (PD-1) antibody drug, has been described. Our patient had inoperable renal cancer with an inferior vena cava tumor thrombus. We were able to downsize the tumor to operable size by administering nivolumab. The patient underwent a nephrectomy and thrombectomy safely. Pathological findings revealed papillary renal cell carcinoma type 2. No viable cells were identified in the removed thrombus. Anti-programmed cell death ligand 1 was expressed on the cell membrane in approximately 20% of the tumor cells, and PD-1 positive tumor-infiltrating immune cells had infiltrated particularly at the edge of the tumor. This case indicates the positive effect of the presurgical use of nivolumab for advanced papillary renal cell carcinoma.

Keywords Renal cancer · Nivolumab · Presurgical · Papillary renal cell carcinoma

Introduction

It has been estimated that 4–10% of renal cell carcinomas (RCCs) extend into the inferior vena cava (IVC), and the 5-year survival rate of RCC patients with a tumor thrombus in the IVC is approximately 50%, even though a nephrectomy and tumor thrombectomy can be performed [1]. Chemotherapy without surgical intervention is not enough to increase the survival rate of patients with this type of cancer.

It is well accepted that for patients with inoperable renal cancer, nivolumab [an anti-programmed cell death 1 (PD-1)

antibody drug] improves long-term survival and reduces tumor volume more efficiently than everolimus, a conventional drug functioning as an inhibitor of mammalian target of rapamycin (mTOR) [2]. We have expected nivolumab to be an effective presurgical drug for vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI)-ineffective cases. Here we report the case of a patient whose renal cancer and IVC tumor thrombus could be resected completely and safely after the effective reduction of the tumor volume by preoperative therapy with nivolumab.

Case report

During a checkup for anemia, a 60-year-old Japanese woman was found to have RCC and an IVC tumor thrombus. Computed tomography (CT) revealed a demarcated, bulky tumor (17.6 × 12.0 × 10.9 cm) in the patient's right kidney as well as a tumor thrombus in the right renal vein and IVC below the diaphragm (Fig. 1a). Swollen lymph nodes and distant metastases were not identified.

At admission, the patient presented with marked edema in her lower extremities. The Memorial Sloan Kettering Cancer

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Fig. 1 CT scan images showing the primary sites and tumor thrombus in the IVC. **a** Before treatment. **b** After TKI treatment for 7 months. **c** After 14 cycles of nivolumab treatment

Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk scores were intermediate. The Karnofsky Performance Scale (KPS) score was 80, hemoglobin was low (7.3 g/dL), but the patient's corrected serum calcium, lactate dehydrogenase, platelet and neutrophil were normal. Hypoalbuminemia (2.6 g/dL) was observed.

Because the tumor extended so progressively as to be inoperable, the patient was administered sunitinib (50 mg/day) as a first-line neoadjuvant treatment. Within 2 weeks of the start of this treatment, adverse events occurred: fever, hypothyroidism, diarrhea, anemia (hemoglobin 6.6 g/dL), pleural effusion, hypoalbuminemia (1.6 g/dL), and hypertension. After the patient's recovery from these events,

we switched the sunitinib to axitinib (10 mg/day). After 4 months of this treatment, the tumor size had reduced to 13.2×8.5×9.0 cm. During 5 months of treatment with axitinib, we had to reduce the dose of axitinib to 8 mg/day because of diarrhea, anorexia, and occasional dehydration shock. An examination conducted 7 month after this switch revealed that the tumor size had remained almost unchanged (12.8×8.4×8.9 cm) (Fig. 1b). At that time point, the patient had lost a significant amount of weight from 54 to 42 kg and experienced severe anorexia and fatigue (serum albumin 3.3 g/dL).

We changed the axitinib to nivolumab. A bi-weekly treatment with 3 mg/kg (120–140 mg total) of nivolumab, which was approved for the treatment of metastatic RCC in

Japan at around that time, was initiated. Patient's anorexia and fatigue then improved (serum albumin 4.5 g/dL), and no adverse events occurred. At 6 months after the start of the nivolumab treatment, the tumor size had conspicuously reduced to 9.5×6.9×6.0 cm and the thrombus had regressed to distal of hepatic vein junction (Fig. 1c). Because the primary tumor and the tumor thrombus shrank significantly, and her general condition and laboratory findings including body weight, serum albumin showed recovery, we concluded that the tumor was operable. We performed a right nephrectomy and tumor thrombectomy. After obtaining proximal and distal vascular control, the vena cava was entered. The tumor thrombus, located from right renal vein to 2 cm below the hepatic vein junction, was partly adhered to the endothelium. The vena cava wall was resected at the adhered portion and reconstructed with running non-absorbable suture without a patch. The operation time was 549 min. Intraoperative bleeding volume was 970 g and 2 units of red blood cell were transfused. The operation was performed using only the transabdominal approach.

As shown in Fig. 2a, the circumscribed, solid, grayish-white tumor measuring 6.5×6×5.5 cm was located in the upper pole of the right kidney. Histologically, atypical eosinophilic columnar cells proliferated with a papillary and sometimes tubular growth pattern. Larger nuclei pseudostratified frequently and contained conspicuous and eosinophilic nucleoli. The histologic grade was G3 according to the World Health Organization (WHO)/International Society of Urology Pathology (ISUP) grading system (Fig. 2b, c). The pathological findings indicated papillary renal cell carcinoma (pRCC), type 2, staged as pT1bcN0M0 (according to the 8th edition of the TNM classification). No viable cells were identified in the IVC thrombus. The immunohistochemical analysis revealed that anti-programmed cell death ligand 1 (PD-L1) was expressed on the cell membrane in approximately 20% of the tumor cells (Fig. 2d), and numerous programmed death-1 (PD-1)-positive tumor-infiltrating immune cells had infiltrated particularly at the edge of the tumor (Fig. 2e), despite the state of the tumor after the nivolumab treatment. The antibodies we used were rabbit monoclonal anti-human PD-L1 antibody (clone E1L3N, Cell signaling, Danvers, MA) and goat polyclonal anti-human PD-1 antibody (R&D systems, Minneapolis, MN, USA). A radiological examination 12 months after the surgery showed no recurrences or metastases.

Discussion

Nivolumab, a molecular targeted drug working as a checkpoint inhibitor, is now used as the first-line treatment for inoperable malignant melanomas and as a second-line treatment for squamous cell lung carcinomas and renal cell

carcinomas. We have reported herein a case in which the presurgical administration of nivolumab diminished the patient's pRCC and improved her preoperative systemic condition. We were thus able to perform a nephrectomy and thrombectomy safely with only a small amount of blood transfusion and without a thoracotomy.

Because the size of an IVC tumor thrombus is closely related to the frequency of surgical complications, nivolumab may reduce surgical risks, such as intraoperative excessive bleeding [3]. Nivolumab treatment may lead to a better preoperative condition and improve the anorexia and fatigue that are frequently induced by VEGF-TKIs.

It is widely accepted that, for patients with inoperable renal cancer, a VEGF-TKI such as sunitinib or pazopanib is first selected for the presurgical setting. However, some cases are problematic because of poor efficacy and/or severe adverse effects of these drugs. The Checkmate 025 trial and other research demonstrated that nivolumab is more effective for tumor response than everolimus and VEGF-TKIs in patients with advanced renal cancer [2, 4]. Though pRCC comprises about 10–15% of cases of RCC, non-clear cell subtypes including pure pRCC were excluded from the Checkmate 025 study as well as other early-phase clinical trials with nivolumab. Our patient's case indicates that nivolumab can be valuable for the presurgical reduction of pRCC.

The limitation of our case report is that we don't know the PD-L1 expression level of this tumor before the nivolumab treatment. We have no idea of the meaning of 20% positive expression of PD-L1 even after the successful nivolumab treatment. Although the expression of PD-L1 in pRCC is not so high in other reports [5], it seems too hasty to decide that nivolumab may not be so effective in pRCC cases. In RCC, the role of PD-1/PD-L1 staining to predict tumor response to immunotherapy is still an evolving field. Some reports have suggested that, unlike other tumors, in clear cell renal cell carcinoma (ccRCC) there is no significant association between PD-L1 expression and the improvement of prognosis or tumor responsiveness to nivolumab [6, 7]. These reports referred only to ccRCC, and the efficacy of nivolumab against pRCC is still unclear. There are some cases in which nivolumab was effective in inoperable pRCC [8, 9] including a case with negative expression of PD-L1 [10]. Koshkin et al. reported the clinical activity of nivolumab in patients with 41 non-ccRCC included 16 pRCC patients [11]. Partial responses were seen in 2 (14%) patients and 3 (21%) patients had stable disease. Thus, pRCC can be expected to show similar responses to nivolumab's effects compared to ccRCC, and nivolumab may be useful in the presurgical setting for patients with originally inoperable pRCC. In the future, comparative tests of nivolumab for non-clear cell RCC (including pRCC) are needed to reveal the precise effects of nivolumab on tumor response.

Fig. 2 Gross, histological, and immunohistochemical findings. **a** A well-demarcated, solid, grayish white tumor was located in the upper pole of the right kidney. **b** Low-power view ($\times 10$) of the tumor. Hematoxylin–eosin (HE) staining. **c** High-power ($\times 40$) view. HE

staining of the tumor. **d** The immunohistochemical analysis revealed PD-L1 expression in some tumor cells ($\times 40$). **e** PD-1-expressing lymphocytes had infiltrated in the tumor ($\times 40$ s)

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Ethical approval It was deemed to be unnecessary for this report.

Informed consent Informed consent was obtained from the patient.

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