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Oncology

Complete response to perioperative treatment using nivolumab for metastatic renal cell carcinoma: A case report

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CR
Complete response
CRP
C-relative protein
CT
Computed tomography
H&E
Hematoxylin and eosin
IHC
Immunohistochemistry
IHCs
Immunocheckpoint therapies
KPS
Karnofsky performance status
PD-1
Programmed death-1
PD-L1
Programmed death ligand-1
RCC
Renal cell carcinoma

ABSTRACT

We report a case of 59-year-old woman who has multiple lung metastases with renal cell carcinoma (RCC). She received neoadjuvant therapy using nivolumab following sunitinib. Thereafter, we performed cytoreductive nephrectomy and subsequently administered nivolumab. We also found a high expression of PD-L1 in tumor cell and infiltration of lymphocytes with CD8 expression by immunohistochemistry. A complete response was achieved 4 months after surgery. A perioperative treatment using nivolumab might be useful treatment for metastatic RCC.

Introduction

The efficacy of nivolumab was demonstrated by CheckMate 025 trial for metastatic renal cell carcinoma (RCC) with a reported objective response rate of 25% and complete response (CR) of 1%.[1] Recently, nivolumab and ipilimumab therapy for patients with previously untreated advanced RCC with intermediate or poor risk showed a CR of 9% based on the results of the phase III CheckMate 214 trial.[2] Therefore, treatment for metastatic RCC has been targeted at curative treatment. However, few studies reported that nivolumab was used as presurgical treatment for metastatic RCC. In this study, we report a case of CR using nivolumab as perioperative treatment.

Case report

A 59-year-old woman presented with chief complaints of fatigue, low-grade fever, and anemia. Abdominal enhanced computed tomography (CT) demonstrated a left renal tumor of 105 mm in length with extremely high-density enhancement (Fig. 1A). On chest CT, multiple lung nodules on both sides were identified. The clinical diagnosis was metastatic RCC, cT2bN0M1. Memorial Sloan Kettering Cancer Center and International Metastatic Renal Cell Carcinoma Database

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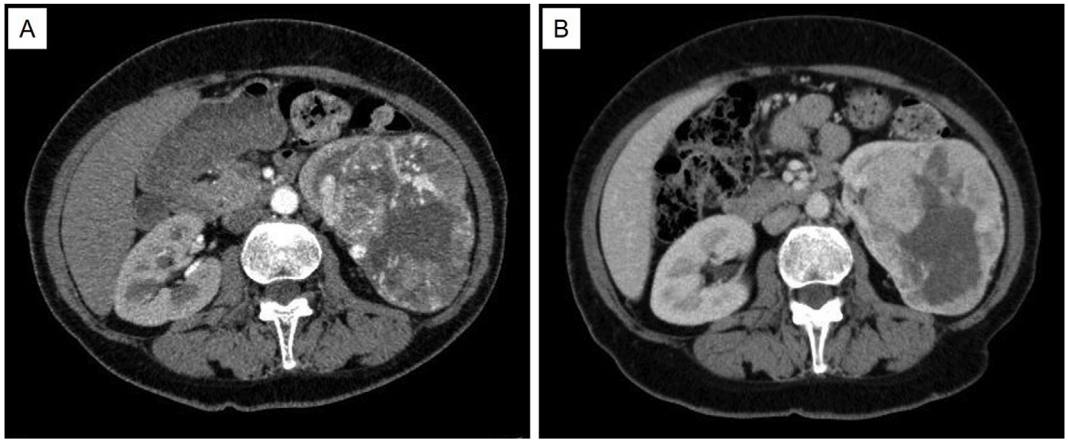

Fig. 1. (A) Contrast-enhanced computed tomography (CT) scan shows a left renal mass at the initial diagnosis. (B) After nivolumab therapy, contrast-enhanced CT shows a renal mass with enhanced wall thickening and central necrosis.

Consortium (IMDC) prognostic risk groups indicated intermediate risks. The Karnofsky performance status (KPS) was 100, and levels of platelets and C-relative protein (CRP) were extremely high, while the hemoglobin value was low.

As treatment, first, we used sunitinib as presurgical therapy instead of immediate surgery because we aimed to reduce the size of the primary tumor. After the second course of sunitinib treatment, the patient experienced fever, fatigue, and hand–foot syndrome as Common Terminology Criteria for Adverse Events grade 2, and KPS worsened from 100 to 80. CT showed stable disease of the primary tumor and lung metastasis. We considered that the effectiveness of sunitinib was not adequate because it induced several adverse events, and laboratory findings including CRP levels were not improved. As the second line of therapy, nivolumab, an immune checkpoint inhibitor, was used and administered at 3 mg/kg every other week. After four courses of nivolumab, CT showed shrinkage of lung metastases, but the primary tumor showed increased high-density enhancement at 5% (Fig. 1B). Symptoms including fever, fatigue, and hand–foot syndrome improved rapidly. We planned surgery at this timing because her KPS was improved from 80 to 100, and laboratory findings including platelet and CRP levels were also improved. We thought that we could not perform surgery safely if tumor size increases. Therefore, we performed left nephrectomy, and macroscopic findings revealed a solid, yellowish tumor measuring 11 × 7 cm in size, with necrosis in the lower pole within the resected kidney (Fig. 2). Histological findings showed pT2b, Fuhrman grades 1 and 2, and clear cell carcinoma with expanded central necrosis (Fig. 3A and B). Moreover, we performed immunohistochemical examination using a different tumor region of the Fuhrman grade. The expression of programmed death ligand-1 (PD-L1) using anti-PD-L1 antibody ([28-8] ab205921, Abcam) was negative for tumor cell with Furman grade 1, but it was positive for tumor cell with Furman grade 2. Similar results were obtained and revealed lymphocyte infiltration to the primary lesion with CD8 expression (Fig. 3C, D, E and F). The perioperative course was uneventful, and she received additional nivolumab without interruption. When eight courses of nivolumab were added after surgery, multiple lung metastases disappeared with CR. She has no signs of disease recurrence 4 months after nephrectomy and is still continuing nivolumab treatment.

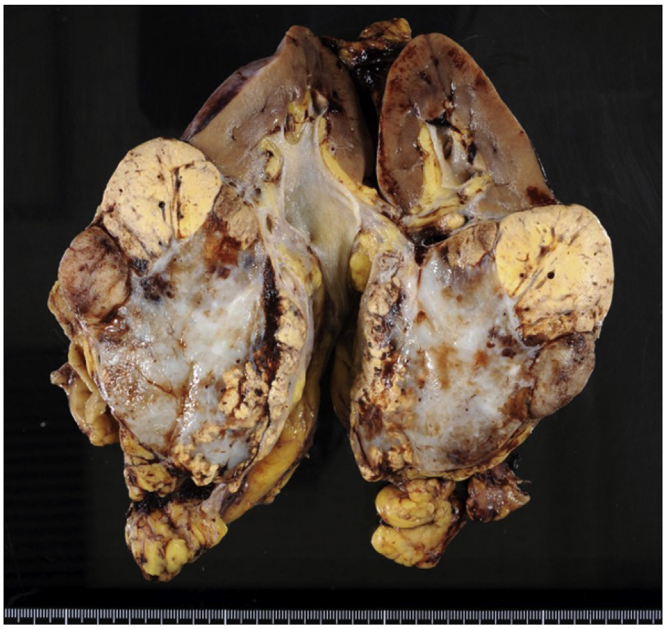

Fig. 2. Gross specimen shows a yellowish solid tumor in the lower pole within the resected kidney.

Discussion

Recently, immunocheckpoint therapies (ICTs) have changed the management of advanced or metastatic RCC. Nivolumab is a human immunoglobulin (Ig) G4 antibody targeting programmed cell death-1 (PD-1) receptor, which achieves a durable objective response in many cancers including advanced or metastatic RCC.[1] Therefore, treatment for metastatic RCC can been targeted at curative treatment. In addition, neoadjuvant or adjuvant treatment using ICTs have been suggested as the treatment option. Woldu et al. suggested the role of nephrectomy following nivolumab and demonstrated a case of CR for metastatic RCC.[3] Moreover, we previously reported a case of CR using neoadjuvant nivolumab. Our previous case showed remarkable response of the primary and metastatic sites following 16 courses of nivolumab therapy.[4] However, optional surgical timing using ICTs and risk for increased surgical morbidity were unclear. In this case, sunitinib showed no effect as first-line neoadjuvant therapy. Thereafter, mixed response for primary and metastatic lesions by four courses of neoadjuvant nivolumab as the second-line therapy was observed. As for neoadjuvant ICTs for metastatic RCC, further examination using many cases is necessary.

Nivolumab enhanced the activation of T cells and the cytocidal effect of lymphocytes. Lymphocyte infiltration was markedly observed in tumor cell which showed remarkable shrinkage during nivolumab treatment.[4] In this case, this finding was observed in tumor cell with a high-grade component than with low-grade component. Therefore, we performed immunohistochemical staining using surgical specimen and found a high expression of PD-L1 in tumor cell and infiltration of CD8-

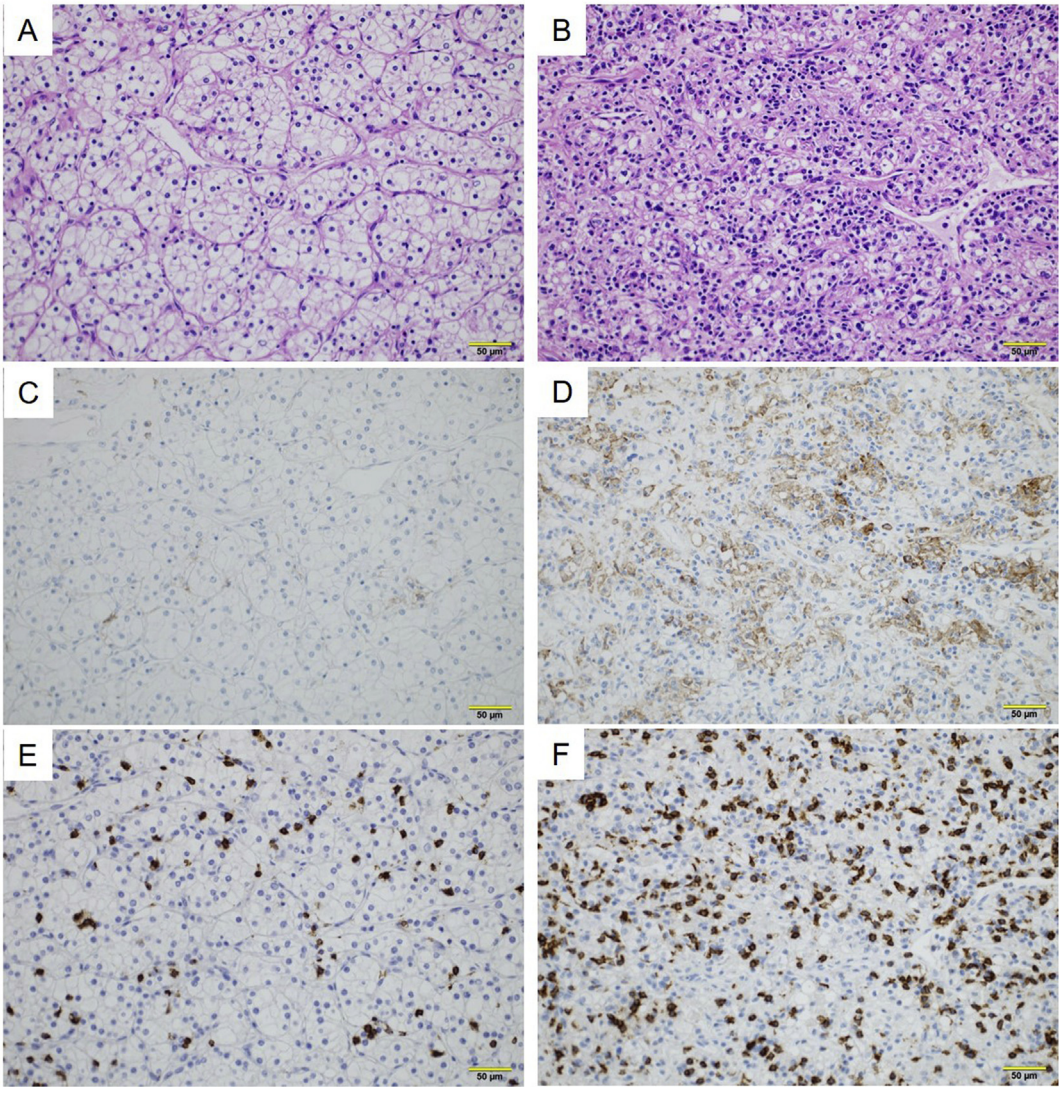

Fig. 3. Hematoxylin-eosin stain of nephrectomy specimen following nivolumab demonstrating (A) Fuhrman grade 1 and (B) grade 2 components in clear cell carcinoma. Immunohistochemical (IHC) staining demonstrates (C) the absence of PD-L1 expression of Furman grade 1 and (D) significant expression of Furman grade 2 (E) (F) IHC demonstrates lymphocyte infiltration with CD-8 expression of Furman grades 1 and 2.

positive lymphocytes with high-grade component than low-grade component. Clear cell RCC is the most common renal tumor and a paradigmatic example of a heterogeneous neoplasm.[5] In this case, this heterogeneity suggests that different responses were shown between the primary tumor and lung metastases. We also consider that the pulmonary metastasis which disappeared might have more high-grade components than the primary RCC.

In this report, we demonstrated CR using nivolumab for metastatic RCC. Our findings suggest that perioperative treatment using ICTs could be a useful treatment option for metastatic RCC.

Contribution

DI and WO drafted the report and cared for the patient. YN helped establish the pathological diagnosis. SH and YU cared for the patient and contributed to manuscript. DI and TU performed the surgeries.

Consent

Written consent to publish was obtained from the patient for the publication of this case and any accompanying images.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eucr.2019.100839.

Disclosure

The authors have no conflicts of interest to declare.

References

1. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Eng J.Med.* 2015;373:1803–1813.
2. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Eng J.Med.* 2018;378:1277–1290.
3. Woldu SL, Brugarolas J, Kapur P, et al. What is the role of nephrectomy complete response to checkpoint inhibitors? *Urol Case Rep.* 2018;14(18):60–63.
4. Ikarashi D, Kato Y, katagiri H, et al. Case of complete response to neoadjuvant therapy using nivolumab in a patient of metastatic renal cell carcinoma. *Int J Urol.* 2018;25:630–632.
5. López JI, Angulo JC. Pathological bases and clinical impact of intratumor heterogeneity in clear cell renal cell carcinoma. *Curr Urol Rep.* 2018;27(1):3 19.