Case Report

Durable response to nivolumab rechallenge in a patient with metastatic clear cell renal cell carcinoma

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Abbreviations & Acronyms
AE = adverse event
ccRCC = clear cell renal cell carcinoma
CR = complete response
CT = computed tomography
DNA = deoxyribonucleic acid
ICIs = immune checkpoint inhibitors
MM = malignant melanoma
mRCC = metastatic renal cell carcinoma
mTOR = mammalian target of rapamycin
ORR = objective response rate
OS = overall survival
PD = progressive disease
PD-L1 = programmed cell death 1-ligand 1
PFS = progression-free survival
PR = partial response
RT = radiation therapy
SD = stable disease
TKI = tyrosine kinase inhibitor
VEGF = vascular endothelial growth factor
VEGFR = vascular endothelial growth factor receptor
VHL = von Hippel–Lindau

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Introduction: While immune checkpoint inhibitors represent the mainstream treatment for metastatic renal cell carcinoma, a standardized approach following immune checkpoint inhibitors remains unclear. We report a case of metastatic renal cell carcinoma treated with nivolumab rechallenge.

Case presentation: A 60-year-old male with metastatic melanoma was referred to the urology division due to right renal cancer. He was undergoing nivolumab treatment for metastatic melanoma. Radical nephrectomy revealed clear cell renal cell carcinoma, pT3a. Two months post-surgery, multiple metastases were identified. Despite subsequent administration of interferon-α, axitinib, and temsirolimus, the metastases progressed. Consequently, nivolumab rechallenge and palliative radiotherapy were initiated, resulting in a durable response for 20 months. However, disease progression occurred, and he died of cancer 4 years after nephrectomy.

Conclusion: This is the first report of nivolumab rechallenge in metastatic renal cell carcinoma. Although the utility remains unclear, this case suggests that some patients may benefit from nivolumab rechallenge.

Key words: clear cell renal cell carcinoma, immune checkpoint inhibitors, nivolumab, nivolumab rechallenge.

Keynote message

We experienced a case of metastatic clear cell renal cell carcinoma treated with nivolumab rechallenge, which demonstrated a durable response for 20 months. Nivolumab rechallenge for metastatic renal cell carcinoma might be a beneficial option. Previous treatment lines, including TKI, mTOR inhibitors, and radiation therapy, may have affected the tumor response to nivolumab.

Introduction

Nivolumab, one of the relevant ICIs for mRCC, has demonstrated promising oncologic outcomes.[1,2] However, there are few established treatments for patients who have had a poor response to nivolumab, making subsequent treatment challenging. We report the first case of a patient with mRCC who discontinued nivolumab due to progression, underwent other therapies, and then received nivolumab rechallenge, resulting in a durable response for 20 months.

Case presentation

A 60-year-old male presented to the dermatology division with evolving nodule on his right big toe since 2011. A CT scan revealed metastases to the right inguinal to external iliac lymph nodes, brain, and right kidney (Fig. 1a), and he was diagnosed with MM, cT4N3M1, in December 2014. Following gamma knife therapy for brain metastases and systemic chemotherapy (dacarbazine+interferon-β), the primary tumor on his right toe shrunk, but lymph node metastases enlarged. Nivolumab was administered in April 2015, with 21 courses completed by September 2016. In November 2015, the primary tumor on his right toe was completely resected and MM was confirmed pathologically. In March 2016, brain metastases

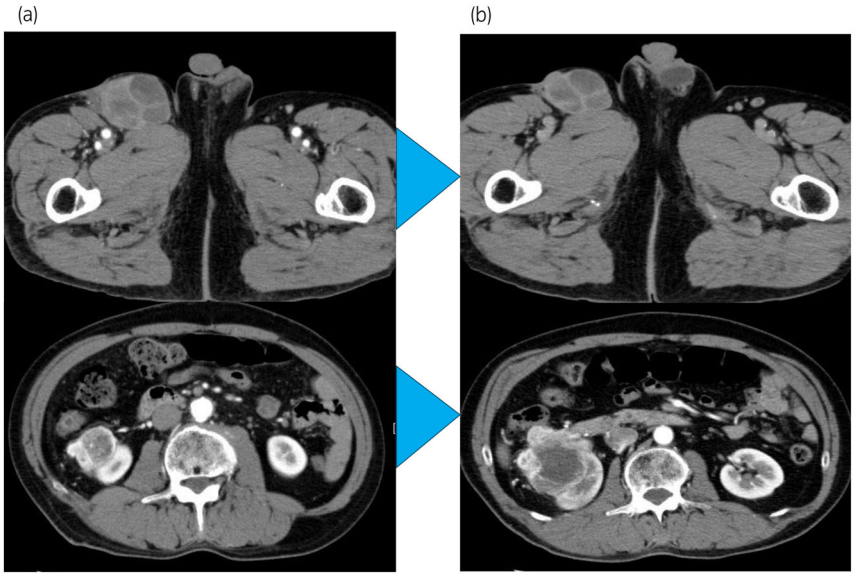

Fig. 1 CT findings before (a) and after (b) the initial nivolumab administration. (a) An enlarged right inguinal lymph node and a right renal tumor were initially suspected to be metastases of melanoma. (b) A preoperative CT showed a 52-mm right renal tumor with enhancement mainly at the peripheral lesion. The size of the lymph node metastasis remained unchanged, but the right renal tumor showed enlargement.

and lymph node metastases were evaluated as CR and SD, respectively, but the right renal tumor enlarged, and then, he was referred to the urology division. Contrast-enhanced CT showed a 52-mm right renal tumor, strongly enhanced in the early phase, and washed out in the late phase, invading the perirenal fat, suggesting ccRCC, cT3aN0M0 (Fig. 1b). In July 2016, right radical nephrectomy was performed, and pathological findings revealed ccRCC, Fuhrman grade 4, pT3a. The nephrectomy specimen was partially PD-L1 positive with little lymphocyte infiltration.

Two months after the surgery, local recurrence and multiple metastases in the lung and liver occurred (Fig. 2a). We initiated a combination treatment consisting interferon-α, cimetidine, cyclooxygenase-2 inhibitor, and renin–angiotensin system inhibitor therapy, as previously reported.[3] However, 2 months later, local recurrence, lung and liver metastases had enlarged (Fig. 2b). Axitinib was subsequently administered, and after 4 months, the lung metastases shrank. However, local recurrence and ascites, suggesting progression of liver metastasis, occurred (Fig. 2c). Temsirolimus was then administered, and 3 months later, the lung metastases showed little change, while the local recurrences and liver metastases shrunk (Fig. 2d). However, 8 months later, the liver metastases enlarged (Fig. 2e), and new left iliac bone metastasis and left adrenal metastasis occurred. A nasal tumor causing nasal stuffiness was found and was confirmed through biopsy as ccRCC metastasis. Subsequently, nivolumab rechallenge and palliative radiation (30 Gy/10 fractions/2 weeks) to the bone metastasis were started. Eleven months after these therapies, local recurrence and liver metastases had shrunk (Fig. 2f), and the nasal tumor disappeared. However, 20 months after the nivolumab rechallenge, the liver metastases grew, and portal vein invasion was newly observed (Fig. 2g). Sorafenib was administered, but was soon terminated due to liver dysfunction. Finally, he died of cancer 4 years after nephrectomy.

An autopsy revealed liver metastases, portal vein tumor embolization, pulmonary artery tumor embolization, and lymph node metastases (paracentesis, right internal iliac, and pararenal aorta). PD-L1 immunostaining of the autopsy specimen showed positivity of liver metastases, while there was little lymphocyte infiltration (Fig. 3). Concerning MM, the autopsy revealed only melanin pigmentation in the brain, with no viable melanoma cells detected.

Discussion

We present a case of mRCC that exhibited shrinkage after nivolumab rechallenge administration. To our knowledge, this is the first report of nivolumab rechallenge in a patient with mRCC who experienced progression after initial nivolumab administration. As there were no other established treatment options in Japan at that point, nivolumab rechallenge was conducted, resulting in a durable response for 20 months. Two main factors may have contributed to this favorable response.

The first potential key factor is the alteration of the tumor microenvironment. In ccRCC, the VHL tumor suppressor gene is frequently mutated.[4] The VHL gene is involved in the degradation of hypoxia-inducible factor, a transcriptional regulator of many proteins, including VEGF.[5] Recent studies have demonstrated that elevated VEGF expression can lead to immune suppression by inhibiting dendritic cell maturation, promoting proliferation of regulatory T cells, and reducing T-cell infiltration into tumor.[6–9] Additionally, mTOR inhibition induces PD-L1 expression in intratumoral vascular endothelial cells, suggesting a potential role in immune modulation.[10] Therefore, the administration of TKIs and mTOR inhibitors may modulate the tumor microenvironment, promoting antitumor immune responses. In this case, the administration of TKI and mTOR inhibitors may have altered the tumor microenvironment, triggering immune responses against the tumor cells and resulting in tumor shrinkage during nivolumab rechallenge.

The second key factor is the combination of RT with ICI and the observed abscopal effects. In this case, RT

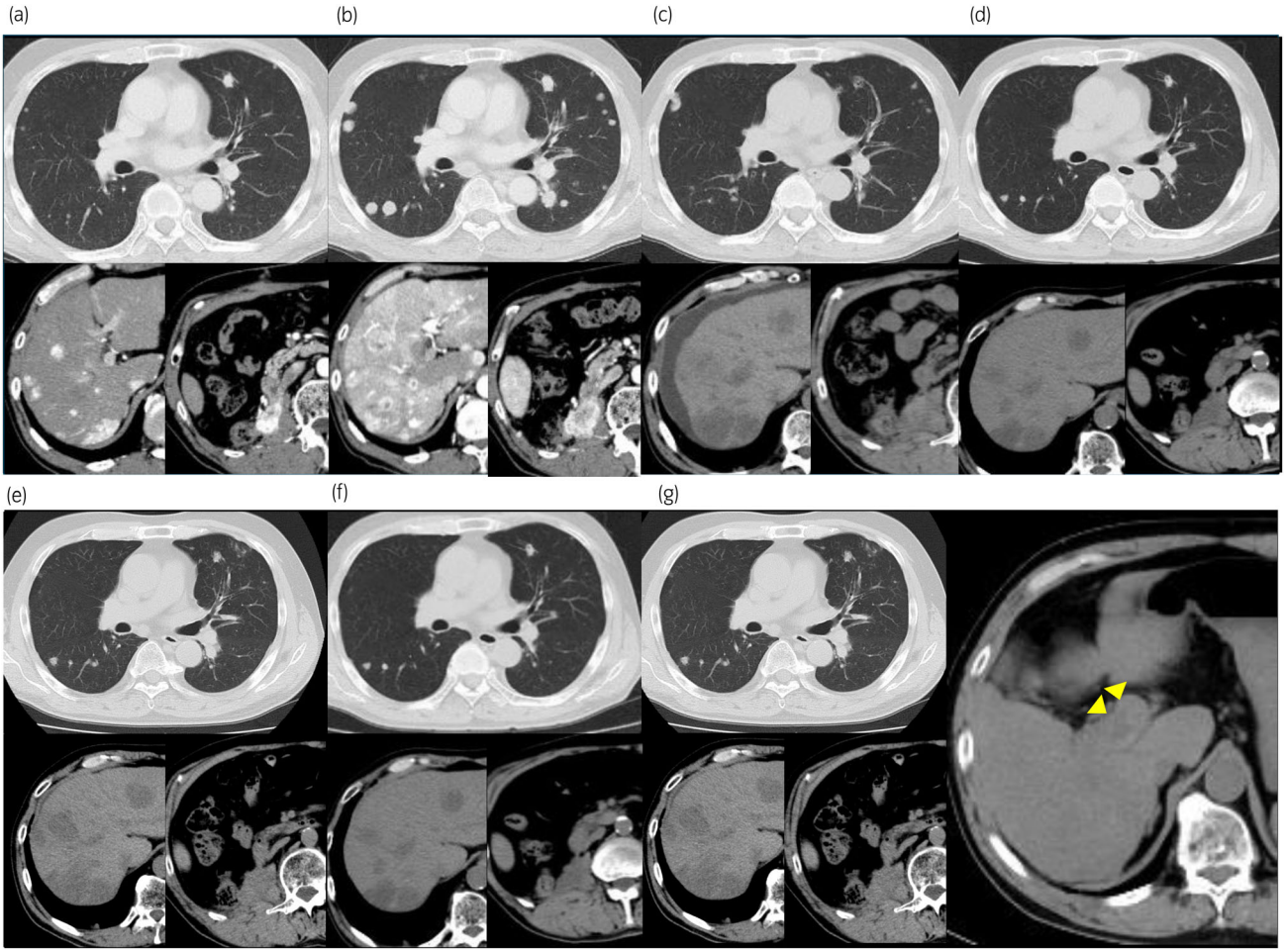

Fig. 2 CT images of the treatment course after radical nephrectomy. (a) Two months after radical nephrectomy. Local recurrence, lung, and liver metastases occurred. (b) Two months after the start of IFN-α. Local recurrence and lung and liver metastases enlarged. (c) Four months after the start of Axitinib. Lung metastases shrunk, but local recurrence and liver metastases enlarged. (d) Three months after the start of temsirolimus. Local recurrence and liver metastasis shrunk and ascites disappeared. (e) Twelve months after the start of temsirolimus. Liver metastases enlarged. (f) Eleven months after the start of nivolumab rechallenge. Local recurrence and liver metastases shrunk. (g) Twenty-one months after the start of the nivolumab rechallenge. Liver metastases grew and portal vein invasion (yellow arrowheads) was observed.

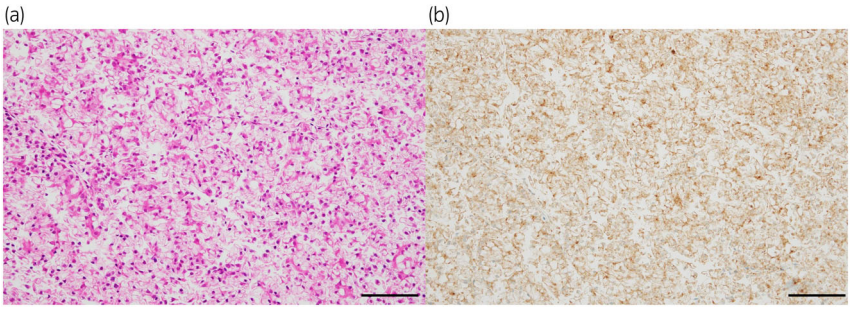

Fig. 3 Histological and immunohistochemical analyses of the liver tissue at autopsy. (a) Hematoxylin and eosin staining. ccRCC (scale bar = 100 μm). (b) PD-L1-staining positive (scale bar = 100 μm).

administered to the metastatic sites during nivolumab rechallenge may have enhanced the effect of nivolumab rechallenge. RT is a potential immunostimulatory therapy that may amplify the antitumor response when combined with ICIs.[11–13] By stimulating immunogenic cell death in the irradiated tumor, local RT can trigger systemic immunity through an in situ vaccination effect, resulting in a distant, nonirradiated site's response.[14] The mechanism of combined RT with ICI is not entirely understood, but preclinical studies have suggested that DNA damage enhances the cross-priming of naive T cells.[15,16] Hence, anti-PD-1 therapy and RT may act synergistically by promoting systemic immune responses. In this case, the combination of nivolumab rechallenge and RT to the bone metastases resulted in the shrinkage of liver metastases, potentially indicating an abscopal effect.

In this case, the initial nivolumab administration for MM showed poor effectiveness against ccRCC, but the subsequent nivolumab rechallenge for mRCC proved to be effective. The

initial ineffectiveness of nivolumab might be attributed to antigen presentation primarily related to melanoma rather than ccRCC, although the exact reason remains unclear. The prior use of VEGFR-TKI, mTOR inhibitor, and RT could have facilitated adequate antigen presentation, contributing to the subsequent efficacy of nivolumab rechallenge. Although rare, the coexistence of MM and ccRCC was reported.[17] With the expanding indications for ICIs in various cancers, similar cases may arise, warranting consideration of nivolumab rechallenge. While effective in this case, nivolumab rechallenge may not demonstrate the same efficacy in routine clinical practice and should be considered for highly selected patients.

Conclusion

We experienced a case of mRCC that progressed following the initial nivolumab administration, and the tumor shrank after nivolumab rechallenge. Although the utility of nivolumab rechallenge remains unclear, this case suggests that certain patients may derive benefits from this therapeutic approach.

Author contributions

Motohiro Fujiwara: Writing – original draft; writing – review and editing. Wataru Shimada: Writing – original draft. Minato Yokoyama: Conceptualization; supervision. Anri Koyanagi: Data curation. Hiroshi Shintaku: Data curation. Shohei Fukuda: Writing – review and editing. Yuma Waseda: Writing – review and editing. Hajime Tanaka: Supervision. Soichiro Yoshida: Supervision. Yasuhisa Fujii: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

No: M2019-172.

Informed consent

Patient written informed consent was obtained.

Registry and the Registration No. of the study/trial

Not applicable.

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