



Marked response to nivolumab combined with external radiation therapy for metastatic renal cell carcinoma: report of two cases

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Received: 11 September 2018 / Accepted: 31 October 2018 / Published online: 9 November 2018
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Abstract

Although nivolumab has been regarded as a standard agent for patients with previously treated advanced renal cell carcinoma (RCC), a significant proportion of these patients fail to achieve a response to nivolumab. In recent years, several studies have reported the favorable therapeutic impact of combined therapy with immune checkpoint inhibitors and radiotherapy on a wide variety of advanced malignant tumors, such as melanoma and lung cancer; however, the significance of this combined treatment for advanced RCC patients has not been well characterized. Here, we report two patients with metastatic RCC showing a marked response to nivolumab and external radiation therapy, including one with an abscopal response, after progression on prior treatment with multiple targeted agents. Based on the clinical courses of these two patients suggesting additive or synergistic efficacies on combining radiation with nivolumab, it might be worthwhile to consider the addition of radiotherapy for metastatic RCC patients treated with nivolumab.

Keywords Metastatic renal cell carcinoma · Nivolumab · Radiation · Abscopal effect

Introduction

In recent years, the therapeutic strategy for advanced renal cell carcinoma (RCC) has markedly changed due to the introduction of novel agents targeting immune escape by tumor cells; that is, antibody blockade of major molecules mediating immune checkpoint pathways, such as programmed death-1 (PD-1), PD-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4, has been demonstrated to have powerful antitumor activities against a wide variety of malignant tumors, including RCC [1]. Of these immune checkpoint inhibitors (ICIs), nivolumab, a human IgG4 PD-1 antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, was shown to significantly

improve overall survival (OS) in advanced RCC patients who had been previously treated with antiangiogenic agents compared with everolimus in the CheckMate 025 clinical trial [2]. Therefore, nivolumab is currently regarded as the standard of care for advanced RCC patients following progression on prior antiangiogenic therapies in major clinical guidelines [3]. However, the proportion of advanced RCC patients who favorably responded to nivolumab was reported to be approximately only 25% in a clinical trial as well as in real-world clinical practice [2, 4].

To date, a number of preclinical studies have reported findings suggesting the induction of powerful antitumor activities by combining radiotherapy and immunotherapy through various mechanisms stimulating effective immune responses [5, 6]. In clinical settings as well, there have been several studies reporting improved responses of several types of malignant tumors by combining these two therapies [7–10]. Furthermore, despite still being a rare event, the abscopal effect, a phenomenon whereby tumor regression occurs not only at the irradiated site but also in non-irradiated areas, is being increasingly observed, particularly since the recent introduction of ICIs [7, 8, 11, 12]. However, as for RCC, recognized as a highly radio-resistant tumor, limited information remains available with respect to the impact of combined therapy with ICIs and radiotherapy on the disease

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response [13]. In this report, we describe two patients with metastatic RCC who showed a marked response, including one with an abscopal response, to combined treatment with nivolumab and external radiation after progressing on targeted agents.

Case report

Case 1 A 62-year-old man with clinically localized right RCC underwent radical nephrectomy in October 2015. Pathological examination showed that the resected tumor was clear cell RCC, pT3a and Fuhrman grade 3. Ten months after surgery, right adrenal and lumbar vertebrae (L4) metastases developed, and he initially received sunitinib for 6 months, and then axitinib for 8 months. After progression on these agents, nivolumab was introduced as third-line therapy in October 2017, and external radiation with a total dose of 36 Gray in 12 fractions was simultaneously administered to the L4 lesion due to intolerable pain. Six weeks after the completion of radiotherapy, computed tomography (CT) revealed the marked regression of both metastases (Fig. 1), and its therapeutic effect was a partial response (PR), which has been maintained for 8 months to date.

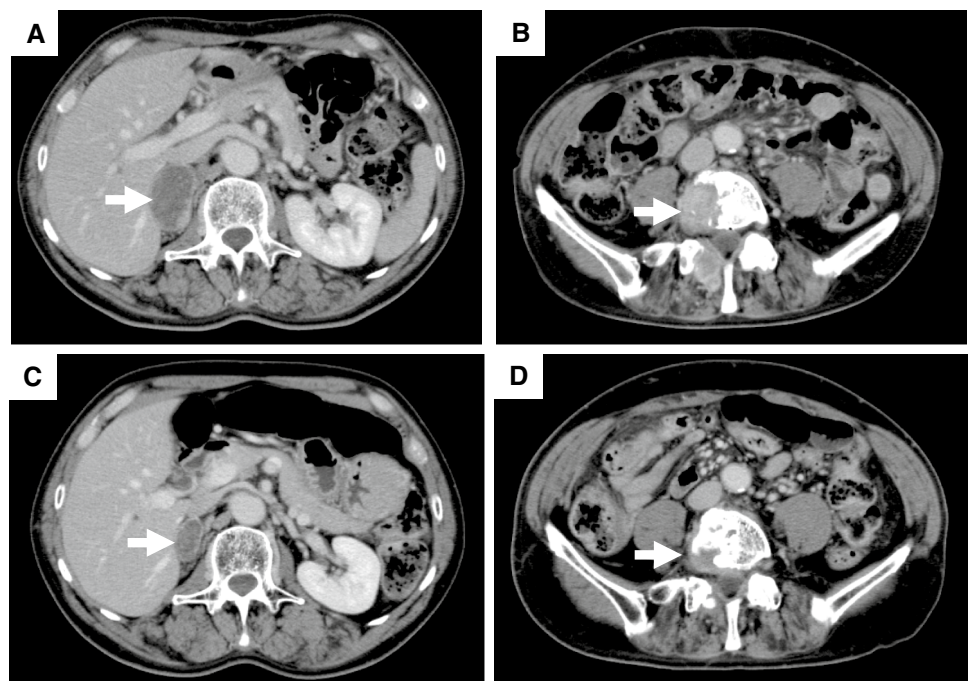
Case 2 A 71-year-old man underwent radical nephrectomy for clinically localized right RCC in June 2010, and was pathologically diagnosed with clear cell RCC, pT3a and Fuhrman grade 2. After surgery, interferon- α therapy was performed for 24 months in an adjuvant setting, metastases to left parotid gland and soft tissues then developed 33 and

37 months after nephrectomy, respectively, and both metastatic lesions were surgically removed. Furthermore, metastases to the lung, pancreas and right iliopsoas muscle were detected, and he was treated with axitinib and then sunitinib for 34 and 3 months, respectively. As third-line therapy, nivolumab was administered in October 2017. Three months after the initiation of nivolumab, CT evidently showed the progression of lung and right iliopsoas muscle metastases; however, nivolumab monotherapy was continued for further 6 weeks, and no significant changes in these metastatic lesions were observed during this interval. In March 2018, external radiation with a total dose of 66 Gray in 33 fractions was applied to the right iliopsoas muscle under continuous administration of nivolumab, considering larger tumor burden than other metastases. Six weeks after the completion of radiotherapy, shrinkages of all metastatic lesions were clearly documented on CT (Fig. 2). These effects have persisted for 5 months to date.

Discussion

The introduction of ICIs into clinical practice has revolutionized the therapeutic strategy for a wide variety of advanced malignancies, including RCC [1]. In particular, nivolumab is currently regarded as a standard agent for advanced RCC patients previously treated with antiangiogenic agents based on the results of the CheckMate 025 trial [2, 3]; however, a significant proportion of advanced RCC patients still fail to achieve a clinically meaningful response to nivolumab, and despite some patients showing a durable response to

Fig. 1 Metastatic lesions in case 1 before the introduction of combined treatment with nivolumab plus radiation (a, b) and 6 weeks after the completion of radiotherapy (c, d)



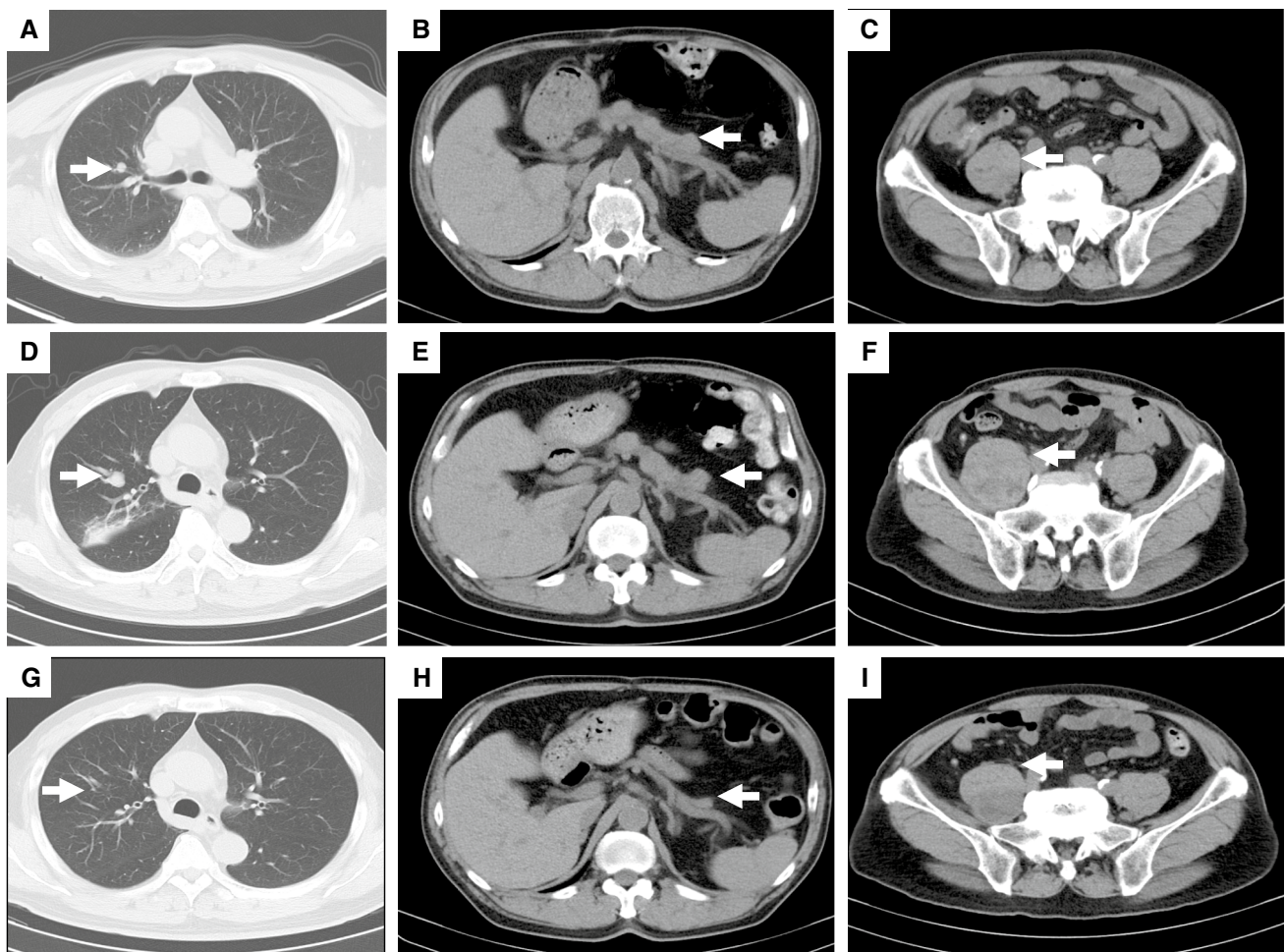


Fig. 2 Metastatic lesions in case 2 before treatment with nivolumab (a, b, c), 3 months after the introduction of nivolumab (d, e, f) and 6 weeks after the completion of radiotherapy (g, h, i)

nivolumab, the majority will ultimately develop progressive disease after an initial response [2, 4]. Considering these findings, special attention has been paid to the promising role of radiotherapy in the potentiation and modulation of tumor immunity [5, 6], suggesting the utility of adding radiotherapy to immunotherapy in the treatment of patients with advanced RCC.

In recent years, several studies have shown the significant activity of combined treatment with radiotherapy and immunological agents, particularly ICIs, against advanced malignancies [7–10]. For example, Koller et al retrospectively analyzed the prognostic outcomes in advanced melanoma patients receiving ipilimumab either alone or in combination with radiation, and showed the significantly improved outcomes, including the overall survival and complete response rate, in the combined treatment group compared with those in the ipilimumab group [9], while Fiorica et al reported significantly superior overall survival in patients with advanced non-small cell lung cancer receiving radiation

and nivolumab to that in those receiving nivolumab alone [10]. However, radiotherapy is usually applied to RCC as a palliative therapy due to its highly radioresistance phenotype, resulting in the lack of precise findings on combined therapy with radiation and ICIs for advanced RCC patients [13]. Nevertheless, simultaneous treatment of a metastatic RCC patient with nivolumab and external radiation, described for case 1 in this report, induced marked shrinkages of metastatic diseases, including adrenal and L4 lesions, suggesting that additive or synergistic efficacy by combining radiotherapy with ICIs could be expected in a certain proportion of advanced RCC patients.

In addition to local control by a direct cytotoxic effect on irradiated tumor cells, radiotherapy has also been shown to exert local as well as systemic immune-mediated antitumor activities [5, 6]; thus, radiotherapy, particularly that combined with ICIs, can induce tumor regression in lesions distant from the primary site of radiotherapy, which is known as the abscopal effect [7, 8, 11, 12]. To date, despite being

a rare phenomenon, the abscopal effect has been shown for various types of malignant tumor [11, 12]. For example, Brix et al described abscopal effects in 25–50% of patients with advanced melanoma receiving radiation plus ICIs [12]. As for RCC patients, however, only two, who showed an abscopal response to treatment with ICIs and radiotherapy, have been reported [14, 15]. Therefore, to our knowledge, case 2 may correspond to the third case with advanced RCC achieving an abscopal effect following combined treatment with ICI and radiotherapy, although it cannot be completely denied that case 2 showed the response to nivolumab after pseudoprogression, a rare event observed by administration of ICIs [16].

In conclusion, despite the rapid increase in the indications for ICIs [1], it remains to be definitively concluded whether combined treatment with ICIs and radiotherapy can improve clinical outcomes in patients with advanced malignancies, particularly those with RCC, known as one of the most representative radio-resistant tumors [7, 8, 13]. In the two cases presented in this report, however, nivolumab combined with external radiation resulted in the marked reduction of metastatic diseases, including non-irradiated lesions, after being refractory to prior treatment with multiple targeted agents. Therefore, considering the precisely clarified ability of radiotherapy to prime and modulate the immune response [5, 6], these findings suggest that the combination of radiotherapy with ICIs may further play an important role in enhancing the activity of ICIs across a broad range of malignancies.

Compliance with ethical standards

Conflict of interest Y. Matsushita, K. Nakamura, H. Furuse, K. Ichinohe and H. Miyake have declared no conflict of interest.

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