


Case Report

Radiation recall pneumonitis induced by nivolumab in a patient with renal cell carcinoma

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Abbreviations & Acronyms

CT = computed tomography
ICI = immune checkpoint inhibitor
irAE = immune-related adverse event
mTOR = mammalian target of rapamycin
PD-1 = programmed cell death-1
RCC = renal cell carcinoma
RRP = radiation recall pneumonitis
RRR = radiation recall reaction

Introduction: A radiation recall reaction in previously irradiated lungs is known as radiation recall pneumonitis. We encountered a rare case of radiation recall pneumonitis induced by nivolumab 9 months after palliative radiotherapy to the ribs.

Case presentation: The patient was a 69-year-old woman with renal cell carcinoma. She had received various drugs and palliative irradiation, which was followed by nivolumab treatment, for renal cell carcinoma. Three days after the initial nivolumab administration, she presented with respiratory symptoms. On the basis of chest computed tomography findings, she was diagnosed with nivolumab-induced radiation recall pneumonitis and treated with prednisolone (1 mg/kg). The condition resolved rapidly, and chest computed tomography 4 months after nivolumab cessation revealed interval resolution of the lung consolidation and persistent tumor shrinkage.

Conclusion: Physicians should consider the risk of radiation recall pneumonitis during treatment with immune checkpoint inhibitors in patients who have received previous thoracic radiotherapy.

Key words: nivolumab, pneumonitis, interstitial, prednisolone, radiation recall reaction, renal cell carcinoma.

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Keynote message

To our knowledge this is the first case of nivolumab-induced RRP in a patient with RCC. Most physicians other than respiratory care specialists are not familiar with RRP. Our findings indicate that all physicians should consider the risk of RRP during treatment with ICIs in patients with a history of thoracic radiotherapy and update the patient about the same.

Introduction

Nivolumab is an anti-PD-1 antibody that has been approved as an ICI for cancer therapy. Nivolumab for RCC improved overall survival in the Checkmate 025 trial.

Patients treated with ICIs can develop several adverse events based on an autoimmune etiology; these are called irAEs. IrAEs are quite different from adverse events caused by conventional cytotoxic agents, and they can potentially affect any organ. In particular, pneumonitis is a notable irAE that accounted for three deaths in an early-phase study of a PD-1 inhibitor.¹

RRP is a RRR that can occur after radiotherapy followed by administration of various anti-cancer drugs. RRR is characterized by an acute inflammatory reaction in a previously irradiated area. It can develop several weeks to months after radiotherapy completion.^{2,3}

Because RRP can have severe consequences,^{4–9} physicians should be aware of this complication while administering ICIs after radiation therapy. However, reports of ICI-induced RRP are limited.¹⁰

Here we report a rare case of nivolumab-induced RRP in a patient with RCC, in which steroid therapy was effective.

Case presentation

A 69-year-old woman visited our hospital because of unexplained fatigue. Thoracic, abdominal, and pelvic CT showed several pulmonary lesions, with the largest having a maximum diameter of 2 cm. In addition, there were several rib masses, enlarged mediastinal lymph nodes, and a 9-cm mass resembling a malignancy in the left kidney. She underwent

cytoreductive nephrectomy in July 2013. Histological examination revealed clear cell RCC.

In August 2013, first-line sunitinib was initiated. However, she still experienced fatigue, and the treatment was discontinued. Three tyrosine kinase inhibitors and two mTOR inhibitors were administered and discontinued because of adverse events, such as fatigue and anorexia, with a 3–6-month duration. In January 2016, palliative radiotherapy was

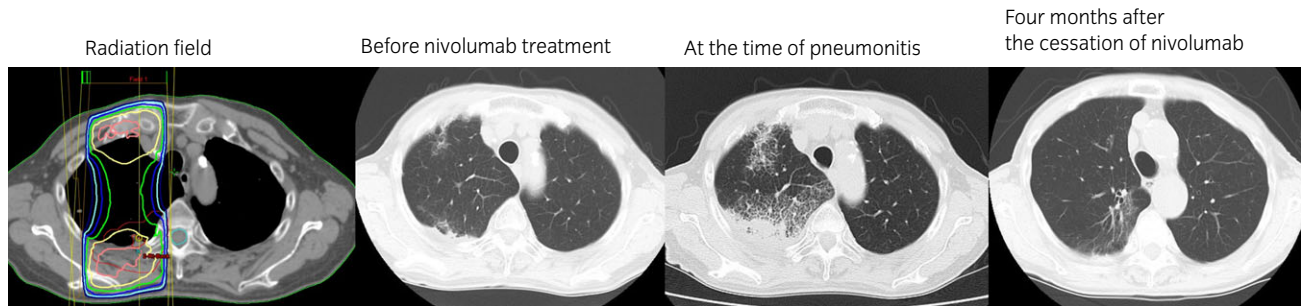


Fig. 1 Radiation field and representative images obtained before nivolumab treatment and at the time of nivolumab-induced RRP in a 69-year-old woman with RCC.

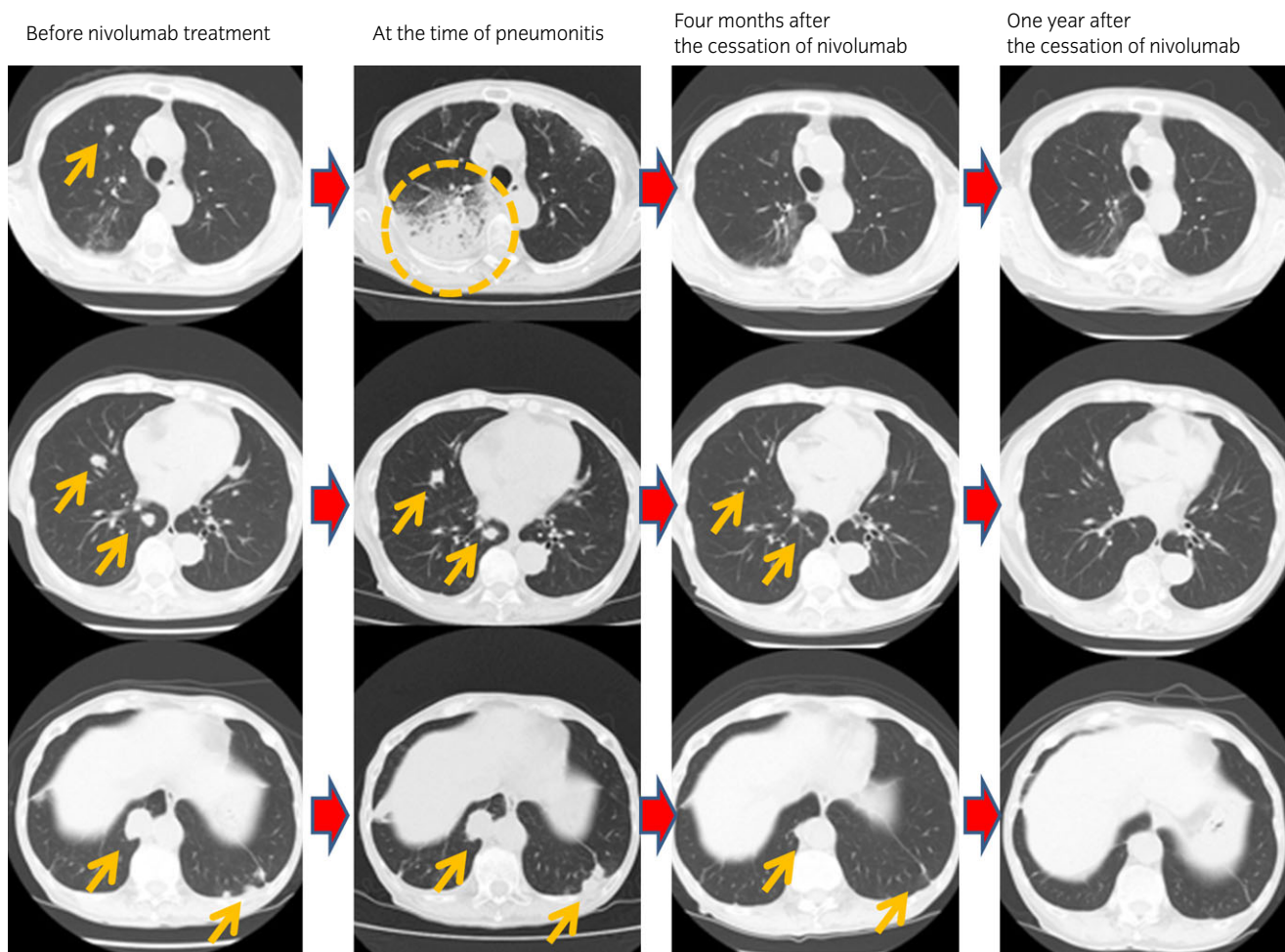


Fig. 2 Chest CT images obtained at the time of nivolumab-induced RRP and 4 months after the cessation of nivolumab in a 69-year-old woman with RCC. The image obtained at 4 months after nivolumab cessation shows interval resolution of consolidation in the right lung, along with persistent tumor shrinkage.

administered for pain control; 30 Gy in 10 fractions was delivered to the ribs. In October 2016, treatment with nivolumab (3 mg/kg) was initiated. Three days after the initial administration, she presented with dyspnea, cough, and low-grade fever. There was no increase in KL-6 or SP-D. CT showed a right lung consolidation with ground glass opacities in a previously irradiated area (Fig. 1). At that time, she was not receiving any drug, other than nivolumab, that could induce interstitial pneumonia. Accordingly, she was diagnosed with pneumonitis caused by nivolumab and radiotherapy. Oral prednisolone (1 mg/kg) was immediately initiated, and was discontinued after 4 months with gradual tapering. The patient's symptoms rapidly resolved, and follow-up chest CT 4 months after nivolumab cessation showed interval resolution of the consolidation in the right lung and persistent tumor shrinkage (Fig. 2).

Discussion

Nivolumab is an IgG4 monoclonal antibody against PD-1 that has increased the survival rate for patients with advanced RCC.¹¹ Nivolumab-induced adverse events differ from those caused by conventional cytotoxic chemotherapy; they include common side effects such as fatigue as well as distinct irAEs.¹² IrAEs are triggered by activation of the autoimmune system by T cell activation and include dermatitis, endocrinopathies, and pneumonitis. Pneumonitis constitutes the major and most common toxicity caused by ICIs.^{1,10,12} Therefore, with the increasing use of ICIs, diagnosis and proper management of irAEs is important.

When radiotherapy is followed by the administration of an anticancer agent, the subclinical damage caused by irradiation is unmasked and clinically manifests as RRR. The skin is the major site of RRR, which is known as RRP when it occurs in previously irradiated lungs. RRP induced by chemotherapy is diagnosed on the basis of previous thoracic radiotherapy, radiographic abnormalities, and the clinical presentation. Symptoms appear within days or weeks after administration of the antitumor agent, and RRP can develop several weeks to months after radiotherapy completion.^{2–5,13} Antitumor agents that can cause RRP include anthracyclines, taxanes, gefitinib, erlotinib, gemcitabine, and sunitinib.^{5–9} For this patient, (i) no imaging and clinical symptoms were observed for 9 months after radiotherapy (radiation pneumonitis typically occurs within 6 months after radiotherapy); (ii) acute interstitial pneumonia began 3 days after nivolumab administration; (iii) the damaged area was consistent with the radiation field; (iv) the patient exhibited improvement upon PSL treatment after discontinuation of nivolumab; and (v) the patient had not been treated with other suspect drugs. From these points, the patient was diagnosed with RRP.

The etiology of RRR remains unknown. One hypothesis is that the precipitating agent participates in lethal damage accumulated by the stem cell population in a previously irradiated area.¹⁴ Another hypothesis constitutes hypersensitivity to cytotoxic drugs by radiation-induced injury.⁸

The management of RRR depends on the severity of symptoms. Withdrawal of the administered agents may lead

to spontaneous improvement in RRR in some cases,³ while steroids may be needed in patients with severe pneumonitis. Ding *et al.* reported relief of symptoms and radiological chest abnormalities after withdrawal of the administered agent, combined with steroid administration in all 12 patients with RRP.⁴

Although RRP occurred in our case, it showed a significant response against pulmonary metastasis from RCC. In previous studies, irAEs were associated with a durable response to ICIs in melanoma patients.^{15,16} Moreover, immunotherapy-related thyroid dysfunction and dermatitis have been associated with a clinical benefit of ICIs in patients with nonsmall cell lung cancer.^{17–19} Moreover, pneumonitis has been associated with a clinical benefit.²⁰ Further studies should investigate the relationship between pneumonitis and therapeutic effects in patients with RCC.

To our knowledge, this is the first case of nivolumab-induced RRP in a patient with RCC. Most physicians other than respiratory care specialists are not familiar with RRP. Our findings indicate that all physicians should consider the risk of RRP during treatment with ICIs in patients with a history of thoracic radiotherapy.

Conflict of interest

The authors declare no conflict of interest.

References

- Topalian SL, Hodi FS, Brahmer JR *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* 2012; **366**: 2443–54.
- Azria D, Magne N, Zouhair A *et al.* Radiation recall: a well recognized but neglected phenomenon. *Cancer Treat. Rev.* 2005; **31**: 555–70.
- Burris H, Hurtwig J. Radiation recall with anticancer agents. *Oncologist* 2010; **15**: 1227–37.
- Ding X, Ji W, Li J, Zhang X, Wang L. Radiation recall pneumonitis induced by chemotherapy after thoracic radiotherapy for lung cancer. *Radiat. Oncol.* 2011; **6**: 24.
- Award R, Nott L. Radiation recall pneumonitis induced by erlotinib after palliative thoracic radiotherapy for lung cancer: cancer report and literature review. *Asia Pac. J. Clin. Oncol.* 2016; **12**: 91–5.
- Schweitzer VG, Juillard GJ, Bajada CL, Parker RG. Radiation recall dermatitis and pneumonitis in a patient treated with paclitaxel. *Cancer* 1995; **76**: 1069–72.
- Ma LD, Taylor GA, Wharam MD, Wiley JM. “Recall” pneumonitis: adriamycin potentiation of radiation pneumonitis in two children. *Radiology* 1993; **187**: 465–7.
- Schwarte S, Wagner K, Karstens JH, Bremer M. Radiation recall pneumonitis induced by gemcitabine. *Strahlenther. Onkol.* 2007; **183**: 215–7.
- Seidel C, Janssen S, Karstens JH. Recall pneumonitis during systemic treatment with sunitinib. *Ann. Oncol.* 2010; **21**: 2119–20.
- Shibaki R, Akamatsu H, Fujimoto M, Koh Y, Yamamoto N. Nivolumab induced radiation recall pneumonitis after two years of radiotherapy. *Ann. Oncol.* 2017; **28**: 1404–5.
- Motzer RJ, Escudier B, McDermott DF *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N. Engl. J. Med.* 2015; **373**: 1803–13.
- Michot JM, Bigenwald C, Champiat S *et al.* Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur. J. Cancer* 2016; **54**: 139–48.
- Choi YW, Munden RF, Erasmus JJ *et al.* Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. *Radiographics* 2004; **24**: 985–98.
- Kitani H, Kosaka T, Fujihara T, Lindquist K, Elkind MM. The “recall effect” in radiotherapy: is subeffective, repairable damage involved? *Int. J. Radiat. Oncol. Biol. Phys.* 1990; **18**: 689–95.

- 15 Downey SG, Klapper JA, Smith FO *et al.* Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin. Cancer Res.* 2007; **13**: 6681–8.
- 16 Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin. Cancer Res.* 2016; **22**: 886–94.
- 17 Hasan Ali O, Diem S, Markert E *et al.* Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer. *Oncoimmunology* 2016; **5**: e1231292.
- 18 Osorio JC, Ni A, Chaft JE *et al.* Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small cell lung cancer. *Ann. Oncol.* 2017; **28**: 583–9.
- 19 Teraoka S, Fujimoto D, Morimoto T *et al.* Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. *J. Thorac. Oncol.* 2017; **12**: 1798–805.
- 20 Fujimoto D, Yoshioka H, Kataoka Y *et al.* Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: a multicenter retrospective cohort study. *Lung Cancer* 2018; **119**: 14–20.