

of cancers, possibly from the blockade of the negative immunomodulatory response.^{4,5} Few reports of the abscopal effect in UC exist⁶ and, to the best of our knowledge, this case is the first report of abscopal effect in both renal pelvic cancer and UC in the ICI era. As there is more interest in the role of ICIs for UC management, trials are needed to determine whether they provide survival benefit.

Our patient received two types of chemotherapy before RT administration, and there are several points for discussion. One is that the combination of three different therapies (chemotherapy, ICI, RT) may have caused the abscopal effect. Further trials are required to assess this theory. Another is that the chemotherapy contributed to the release of tumor antigens. However, the fact that shrinkage occurred only after the initiation of RT led us to assume that the RT was responsible for the observed shrinkage of the non-irradiated lesions.

To the best of our knowledge, there is no concrete definition of the “ICI and RT combination” to date. For other types of malignant tumors, several sequences have been reported in which the abscopal effect was observed, but it remains unclear whether RT before, concurrent with, or after drug administration is the most effective.^{7–9} This case involved “sequential therapy with ICI followed by RT,” but the optimal time window for RT and/or ICI chemotherapy is beyond the discussion of this case. Future clinical trials using ICI/RT combination will hopefully further clarify optimal sequential rationale.

Conclusions

In conclusion, we observed a possible abscopal effect due to RT in a patient with UC after ICI treatment. The combination of RT and ICIs may highlight a new strategy for the treatment of metastatic UC.

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Editorial Comment

Editorial Comment to Possible abscopal effect in urothelial carcinoma of the upper urinary tract after treatment with immune checkpoint inhibitors

The abscopal effect was first described in 1953 by Dr Mole as “an effect of ionizing radiation at a distance from the irradiated volume but within the same organism,” and it now refers to shrinkage of non-irradiated primary and/or metastatic

Disclosure of ethical statement

All informed consent was obtained from the patient. This work was conducted in accordance with the Declaration of Helsinki.

Conflict of interest

The authors declare no conflict of interest.

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lesions following radiotherapy.¹ Although the precise mechanism of the abscopal effects remains unclear, an increasing number of recent reports in the immune checkpoint inhibitors era support that activation of the immune system and modulation of the tumor microenvironment by radiation and immune checkpoint inhibitor therapy likely plays important roles in this treatment effect.²

In this issue of *IJU Case Reports*, Ishiyama *et al.* reported the case of a patient with renal pelvic cancer who had recurrence after radical nephroureterectomy.³ After gemcitabine

and cisplatin combination chemotherapy followed by pembrolizumab immune therapy, the patient underwent radiation therapy to treat the local recurrence lesion and for pain relief.³ With dramatic symptom relief, computed tomography demonstrated a reduced size of the irradiated and multiple non-irradiated lymph nodes.³ The authors considered this case to be an abscopal effect after treatment with an immune checkpoint inhibitor and they concluded that this combined and/or sequential administration of an immune checkpoint inhibitor and radiation therapy may become a new metastatic urothelial cancer treatment strategy.³

Based on the promising anti-tumor efficacy and a manageable safety profile, pembrolizumab therapy has been rapidly introduced and the paradigm of medical treatment for metastatic urothelial cancer is dramatically changing in clinical practice in Japan.⁴ In addition to the agent's intrinsic efficacy, the abscopal effect that is induced by radiation therapy is recognized in various malignancies in this immune checkpoint inhibitor era, although the incidence and radiation characteristics including dose, fraction, and timing required for its occurrence remain unknown.² In a single institutional retrospective study, Trommer *et al.* investigated the characteristics of the abscopal effect among the 126 patients who received an immune checkpoint inhibitor and radiation therapy. Twenty-four of these patients had eligible non-irradiated lesions and an abscopal effect was observed in seven patients (29%, malignant melanoma: $n = 3$, non-small cell lung cancer: $n = 3$, renal cell carcinoma: $n = 1$).⁵ This suggests that the abscopal effect might not be a rare event in the immune checkpoint inhibitor era.⁵ When the precise mechanism and

the optimal radiation characteristics are revealed, the abscopal effect may be incorporated into the treatment strategy as an important option in metastatic urothelial cancer.

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