



Oncology

Abscopal effect following checkpoint inhibitor therapy and localized radiotherapy for metastatic clear cell renal cell carcinoma: A case report

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ABSTRACT

We present the case of a 64-year-old patient with metastatic renal cell carcinoma, who experienced disease progression despite undergoing multiple lines of systemic therapy, including immune checkpoint inhibitors (ICI). Two months after stereotactic radiosurgery to his brain lesions and while the patient was not on any systemic therapy, restaging scans demonstrated a dramatic near complete regression of the primary renal lesion and metastatic sites, which was attributed to the abscopal effect, mediated by the exposure to ICI and radiotherapy. While its mechanisms are not fully understood, it is believed to stem from the tumor immunosuppression and immunogenicity induced by radiation.

1. Introduction

Renal Cell Carcinoma (RCC) represents 2 % of global cancer diagnoses and causes over 100,000 deaths per year. A third of the patients have metastatic disease at the time of the initial diagnosis.^{1,2} The histology, stage, and grade at presentation may predict the prognosis, recurrence rate, and treatment response.³ The management of metastatic RCC (mRCC) is mainly with systemic therapy with ICIs and anti-angiogenesis agents, given alone or in combination.⁴ However, despite the growing treatment landscape, most patients progress on systemic therapy with limited treatment options.

Radiation therapy is another treatment modality in RCC with an emerging critical role in the treatment paradigms of RCC. Contrary to the initial beliefs that radiation carried toxic side effects and that RCC was radioresistant, it has proven to be an integral part of the management of RCC patients, extending the duration or helping defer the initiation of systemic therapy.^{5,6} The abscopal effect (ab- 'position away from' and scopus 'target') is thought to induce an immune-mediated regression of non-radiated metastatic lesions.^{7,8} The cases where this effect is witnessed are very rare, especially before 2014, with less than 50 reported cases of the abscopal effect. In the past few years, there has

been a slight increase in its occurrence, probably due to a potential augmentation from the increased use of immunotherapy agents.^{9,10}

Herein, we report the case of a 64-year-old male with metastatic clear cell RCC (mccRCC) who experienced disease progression at several metastatic sites despite undergoing multiple lines of systemic therapy, including ICIs and targeted agents (Fig. 1), but eventually had a dramatic disease response, which was attributed to the abscopal effect from radiation therapy. This report represents a small contribution to the limited number of cases of the abscopal effect in several metastatic cancers, including mRCC. Reporting these cases may generate interest in researching the possible advantages of local radiation therapy for patients who are undergoing immunotherapy treatment.

2. Case presentation

Our patient, a 64-year-old male, initially presented to the Emergency Room in late 2018 with worsening shortness of breath, fatigue, and lower back pain. Upon examination, he was found to have a left-side pleural effusion and a left renal mass suspicious for RCC. He had recently stopped smoking after a 35-pack-year smoking history. Thoracentesis was performed which yielded 5 L of pleural fluid and the

Abbreviations: RCC, renal cell carcinoma; mRCC, metastatic renal cell carcinoma; mccRCC, metastatic clear cell renal cell carcinoma; ICI, immune checkpoint inhibitors; CT CAP, Computed Tomography Scan of the Chest Abdomen and Pelvis; SBRT, Stereotactic Body Radiation Therapy; anti PD-1, anti-Programmed Cell Death Protein-1; SRS, Stereotactic radiosurgery).

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patient was eventually taken for a bronchoscopy and biopsy which confirmed the diagnosis of mcrRCC. Shortly after, he was started on first-line systemic therapy, consisting of a double ICI combination with ipilimumab plus nivolumab, and after completing the induction phase, he continued on maintenance therapy with nivolumab until mid-2020, when it was discontinued due to progressive disease evaluated with a CT scan of the chest, abdomen, and pelvis (CT CAP). He then received VEGF-TKI (Vascular endothelial growth factor-tyrosine kinase inhibitors) treatments with pazopanib followed by cabozantinib, which were both discontinued due to disease progression. In 2021, he started treatment with fourth line therapy with the mTOR (mammalian target of rapamycin) inhibitor everolimus, which was also discontinued after 6 months because a repeat CT CAP showed progressive disease.

At this juncture and after failing multiple lines of therapy, the medical oncology team discussed the limited treatment options after failing four prior lines of therapy, but the patient was keen to consider further therapy. In view of this, he was offered pembrolizumab plus lenvatinib, which demonstrated anti-tumor activity in patients with mRCC post prior anti PD-1 (Programmed Cell Death Protein 1) treatment failure.¹¹ Shortly after starting this combination, he received stereotactic body radiation therapy (SBRT) to symptomatic bone lesions at the second and fourth lumbar vertebrae with 5 fractions. Restaging CT CAP in June 2022, 3 months after starting pembrolizumab plus lenvatinib, demonstrated further disease progression at multiple sites, including a large destructive lesion in the left femur. Systemic therapy was discontinued, and he underwent a wide excision of the left proximal femur in July 2022 and the pathology results revealed ccRCC. In August 2022, he presented with word-finding difficulty and facial drop with evidence of new brain metastatic lesions. In view of these new findings, he underwent stereotactic radiosurgery (SRS).

Restaging CT CAP performed after he completed the brain lesions management and while he was off systemic therapy for about four months demonstrated a remarkable improvement in the non-irradiated lesions (Fig. 2). A previously seen left renal lower pole mass (3.7 × 2.7 cm) was now CT occult. There was a decrease in the size of a left pulmonary upper lobe mass from 5 × 2 cm to 3 × 1 cm (Fig. 2B and 2E) and other pulmonary metastatic nodules also decreased. Furthermore, numerous lytic osseous metastases appeared to be smaller. Metastases that were previously seen on the pancreatic head measuring 1 cm and on the right adrenal gland measuring 3.2 cm (Fig. 2A) were no longer visible (Fig. 2D). Additionally, two facial lesions in the patient's chin and right cheek (Fig. 3A), which were biopsied in May 2022 showing RCC histology, and had been present throughout the treatment, had now completely resolved (Fig. 3B). This dramatic tumor response represents an abscopal effect in response to the radiation treatment he received after stopping immunotherapy.

3. Discussion

This case report presents a rare case of an unexpected metastatic disease regression in a patient with mcrRCC which occurred after subsequent treatment with anti PD-1 ICI and radiotherapy, highlighting the synergistic effect of radiation and immunotherapy in inducing an abscopal effect, in particular the distant treatment response occurring

four months after the patient received the last dose of immunotherapy, followed by radiotherapy.

Historically, RCC was considered to be radioresistant based on early in vitro studies and in clinical studies of patients receiving adjuvant conventional fractionated radiation.^{5,12} However, subsequently it was demonstrated that higher doses of radiation can overcome the inherent radioresistance of RCC.¹³ Recent advances in radiation therapy technology have enabled the precise targeting of tumors with highly conformal radiation beams. The introduction of sophisticated imaging methods, along with innovative techniques like SBRT has expanded the clinical applications of radiation therapy.⁵

Radiation therapies are used for the treatment of multiple cancers, and they can be delivered systematically or locally. Systematic radiation is safe and effective in limiting the progression of mRCC in selected cases, without significant negative effects on the patient's quality of life. SBRT has been shown to defer the initiation of systemic therapies when started after nephrectomy or it can be used when systemic therapy breaks are preferred.^{6,14,15}

Radiotherapy can promote cell apoptosis which in turn induces an immune-mediated regression of non-irradiated lesions, a process known as the abscopal effect. It was first described by Dr. Mole in 1953 as "an action at a distance from the irradiated volume but within the same organism".⁷ Now, it describes the regression of non-irradiated tumor lesions after radiotherapy. The abscopal effect is very rare, with less than 50 cases reported before 2014. It has been reported in multiple cancer histologies, including RCC, melanoma, pancreatic cancer, breast cancer, hepatic cancer, and colon cancer.^{8,10,16} A slight increase in its occurrence has been noticed in the past few years, probably by a potential augmentation from the widespread use of ICIs.

The abscopal effect mechanisms are not understood clearly and completely, and a general agreement is yet to be achieved. However, the most convincing and backed-up hypothesis describes it as a product of immune activation initiated by damaged DNA. Radiotherapy is thought to induce DNA damage and cell apoptosis, a process that releases cytokines, which in turn initiate a signaling cascade that stimulates T-cells, which can express their action in distant parts of the body that haven't been radiated.^{9,17}

The median time to notice the abscopal effect after the administration of radiotherapy is two months, based on a systematic review of 46 reported cases. The reviewed cases were from 1969 to 2014 and showed that the median radiation dose needed to achieve this effect was 31 Gy units (Gy) with only five of the patients having received immunotherapy.⁹

Our case demonstrates a marked interaction between radiotherapy and immunotherapy in mRCC to induce distant tumor response mediated by the abscopal effect. Recent trials demonstrated synergy of combining SBRT with immunotherapy in mRCC. In the RADVAX study, SBRT was combined with ipilimumab plus nivolumab in patients with mcrRCC. The study included a total of 25 patients and the objective response to this combination was 56 % with a median progression free survival of 8.2 months.¹⁸ The ECOG-ACRIN group is currently running the phase 3 trial SOAR to investigate the activity of combining SBRT with standard of care immunotherapy in patients with oligometastatic RCC (NCT05863351).¹⁹

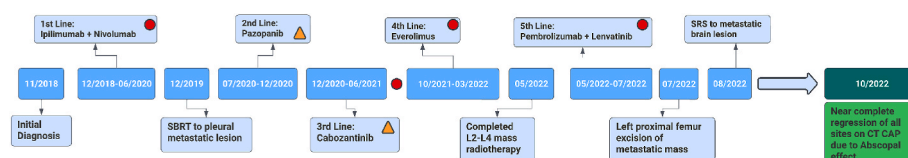


Fig. 1. Chronological overview of treatment interventions and outcomes.

This illustrates the key milestones, interventions, and clinical responses observed throughout the treatment period. Legend: Circle (red) = Disease progression on CT CAP; Triangle (orange) = Treatment discontinued due to toxicity or side effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

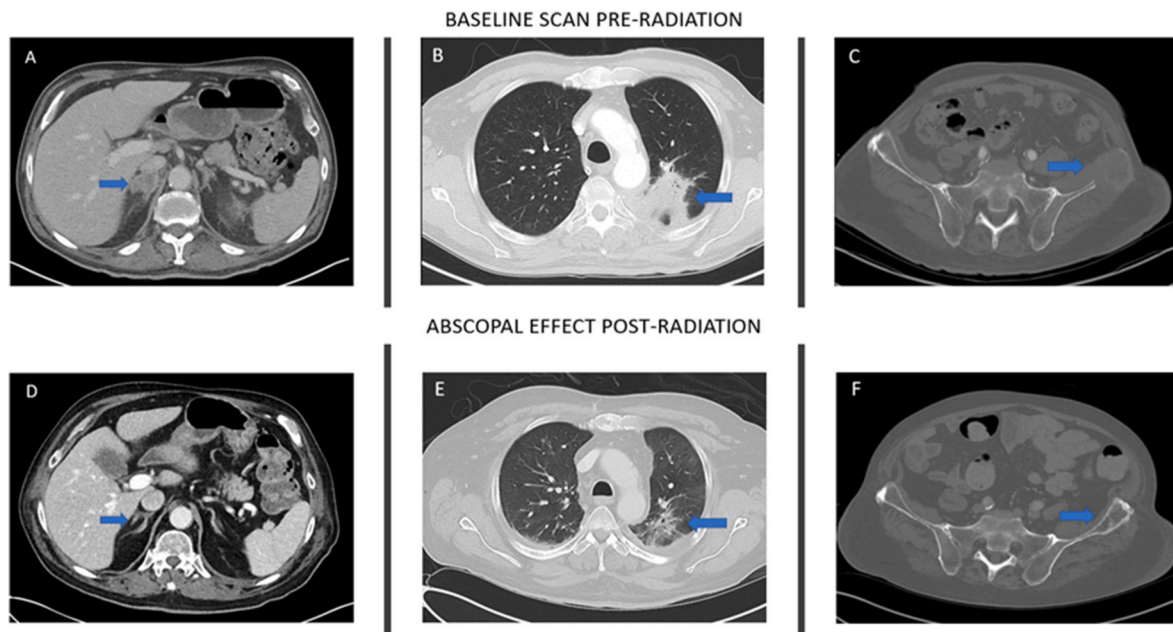


Fig. 2. Abscopal effect as a response to radiation therapy in mRCC.

A CT CAP before receiving SRS to the brain lesions, showing disease progression (parts A, B, and C), and the demonstration of the post-radiation abscopal effect (parts D, E, and F). Axial CT through the abdomen demonstrates a right adrenal metastasis (arrow) (part A). Axial CT through the chest demonstrates a left pulmonary upper lobe mass (arrow) (part B). Axial CT also demonstrates an osseous metastasis with soft tissue component located in the pelvis (arrow) (part C). Follow-up CT CAP shows a complete radiographic response with resolution of visible sites of disease in the abdomen and pelvis (parts D and F), and a decreased size of the pulmonary mass (part E).



Fig. 3. Abscopal effect with complete resolution of facial metastatic lesions.

Two facial lesions in the patient's chin and right cheek (part A), which were biopsied showing RCC histology, and had been present throughout the treatment, had completely resolved as a result of the post-radiation abscopal effect (part B).

4. Conclusion

The latest developments in cancer therapy with the widespread use of immunotherapy and radiotherapy highlight the need to explore the underlying mechanisms of the abscopal effect in greater detail. This research could support the future development of innovative interventions.

CRedit authorship contribution statement

Ardit Feinaj: Conceptualization, Visualization, Writing – original draft. **Evan Fox:** Investigation, Visualization, Writing – review & editing. **Victoria Sinibaldi:** Investigation, Writing – review & editing. **Lawrence Kleinberg:** Investigation, Writing – review & editing. **Yasser Ged:** Conceptualization, Investigation, Supervision, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to improve readability and correct grammar or spelling errors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors have no conflict of interest to disclose.

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