


## CASE REPORT

# Extracranial abscopal effect induced by combining immunotherapy with brain radiotherapy in a patient with lung adenocarcinoma: A case report and literature review

Xinqing Lin<sup>1\*</sup> , Tingting Lu<sup>2\*</sup>, Zhanhong Xie<sup>1</sup>, Yinyin Qin<sup>1</sup>, Ming Liu<sup>1</sup>, Xiaohong Xie<sup>1</sup>, Shiyue Li<sup>1</sup> & Chengzhi Zhou<sup>1</sup>

<sup>1</sup> State Key Laboratory of Respiratory Disease, National Clinical Research Centre for Respiratory Disease, Guangzhou Institute of Respiratory Health, Department of Respiratory and Critical Care Medicine, First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China

<sup>2</sup> Department of Neurology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

## Keywords

Abscopal effect; brain metastasis; immunotherapy; lung cancer; radiation therapy.

## Correspondence

Chengzhi Zhou, Guangzhou Institute of Respiratory Health, State Key Laboratory of Respiratory Disease, First Affiliated Hospital, Guangzhou Medical University, 151# Yanjiang Road, Guangzhou 510120, China.

Tel: +86 20 8306 2888

Fax: +86 20 8306 2729

Email: doctorzcz@163.com

\*These authors contributed equally to this work.

Received: 25 January 2019;

Accepted: 1 March 2019.

doi: 10.1111/1759-7714.13048

Thoracic Cancer **10** (2019) 1272–1275

## Abstract

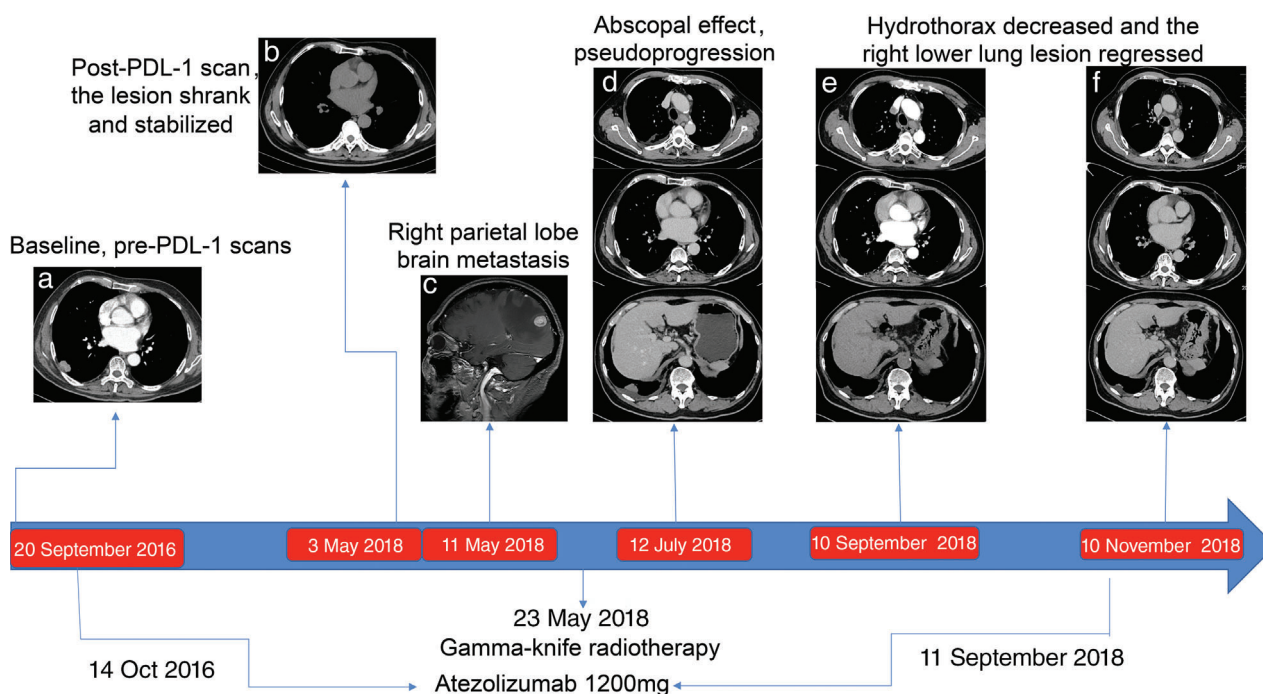
An extracranial abscopal effect induced by brain radiotherapy is particularly unusual because of the brain's distinctive immune microenvironment. We report a case of an extracranial abscopal effect in a 71-year-old male patient with lung adenocarcinoma treated with atezolizumab and later combined with brain radiation for brain metastasis. The subsequent abscopal effect first manifested as pseudoprogression of the primary lesion in the lung before remission was confirmed. This case suggests that immunotherapy increases the chance of an abscopal effect occurring after radiation therapy for brain metastases in patients with primary tumors with low immunogenicity.

## Introduction

An abscopal effect refers to the regression of non-irradiated metastatic lesions at a distance from the primary site of irradiation.<sup>1</sup> Prior to the wide application of immunotherapy, the abscopal effect was rarely observed. The central nervous system (CNS) had been considered to have immune privilege. Regular immune responses are limited in the CNS. We report the first case of an extracranial abscopal effect after stereotactic brain radiotherapy as second-line treatment with atezolizumab in a patient with lung adenocarcinoma.

## Case report

In April 2016, a 71-year-old male patient was diagnosed with poorly differentiated adenocarcinoma in the right lobe of the lung (stage IV) without driver gene mutations. After six cycles of treatment with nedaplatin and paclitaxel, the primary tumor enlarged, indicating the failure of first-line chemotherapy (Fig 1a). Atezolizumab monotherapy (1200 mg, every 3 weeks) was introduced on 14 October 2016. The primary tumor and mediastinal lymph nodes were reduced (Fig 1b); however, the patient developed a headache, and metastasis in the right parietal lobe was



**Figure 1** Chest computed tomography (CT) and cranial magnetic resonance imaging. (a) A CT image taken before immunotherapy shows a lesion in the right lower lobe of the lung. (b) After immunotherapy, the CT shows that the lesions in the lung have reduced and stabilized. (c) Brain metastases in the right parietal lobe and peritumoral edema. (d) Newly developed nodules in the basal segment of the right lower lobe of the lung and a small amount of pleural effusion on the right side, considered pseudoprogession. (e,f). CT images show that the pleural effusion and the lesions in the right lower lobe have reduced.

detected on 11 May 2018 (Fig 1c). Given that the primary tumor can still benefit from immunotherapy, atezolizumab was continued. Brain X-knife stereotactic radiotherapy was commenced on 23 May 2018 (48Gy/8F, 6Gy/F, 3F/W). In July, the patient developed a cough and shortness of breath. A new nodule in the basal segment of the right lower lung was detected. The subpleural lesion in the basal segment of the left lower lobe was slightly enlarged, with a small amount of pleural effusion on the right side (Fig 1d). Atezolizumab treatment was continued and follow-up computed tomography scans in September and November 2018 showed that the nodules in the basal segment of the right lower lung had shrunk, the number of subpleural lesions in the basal segment of the left lower lung had reduced, and multiple lymph nodes in the mediastinum had become smaller (Fig 1e,f). An abscopal effect in the lung induced by the localized brain radiotherapy was considered. Brain magnetic resonance imaging revealed that the primary metastases at the parietal lobe had disappeared. However, multiple other metastases and a peritumoral edema emerged in the right frontal lobe and left cerebellar hemisphere. Nonetheless, after continued X-knife radiotherapy, these new intracranial metastatic lesions regressed.

## Discussion

Lung cancer is the leading primary tumor that tends to metastasize to the brain.<sup>2,3</sup> Radiation therapy is currently the most widely adopted method to treat brain metastases. To date, an extracranial abscopal effect caused by radiotherapy for brain metastases in lung cancer has not been reported. In our case, a complete response was achieved in the primary tumor after 19 months of immunotherapy before brain metastasis developed. After 50 days of radiation treatment for the metastatic brain lesion, the lesions in the lung enlarged. Two months later, the lesions in the lung had shrunk, suggesting that the prior change in the lesion was pseudoprogession. We believe that the localized radiotherapy at the brain induced an abscopal effect in the lung. This is the first report of an abscopal effect manifesting as early pseudoprogession in the lung.

An immune-mediated response is considered one of the most critical mechanisms of an abscopal effect.<sup>4</sup> Radiation induces the immunogenic cell death of cancer cells, during which various cytokines and signals are released. These cytokines and signals alter the tumor microenvironment and promote the influx of immune cells to lesion sites through antigen-presenting cells (APC) that specifically recognize tumor-specific antigens released by the dead

**Table 1** Characteristics of the abscopal effect induced by radiotherapy in the brain

No.	Primary tumor	Gender	Age	Therapy before RT	RT type	RT dose, Gy/fractions	Site of abscopal effect	Time of abscopal effect (months)	Publication year
1	Melanoma <sup>16</sup>	M	44	Ipilimumab plus temozolomide	WBRT	30/10	Lung, liver,	2	2014
2	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	WBRT	30/10	Liver metastases	1 (1–4)	2014
3	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	WBRT	30/10	Pelvic relapse	1 (1–4)	2014
4	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	WBRT	30/10	Liver, bilateral axillary and right ovarian metastases	1 (1–4)	2014
5	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	WBRT	30/10	Lung, cutaneous, lymph nodal and abdominal metastases	1 (1–4)	2014
6	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	SRT	24/1	Cutaneous metastases	1 (1–4)	2014
7	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	SRT	20/1	Liver metastases	1 (1–4)	2014
8	Melanoma <sup>9</sup>	NA	NA	Ipilimumab	SRT	24/1	Lung metastases	1 (1–4)	2014
9	Melanoma <sup>17</sup>	F	50	IL-2	WBRT		Pulmonary, retroperitoneal, and mesenteric nodes	5	2015
10	Colorectal cancer, adenocarcinoma <sup>15</sup>	F	74	No	WBRT	30/10	Lung	2	2018

NA, not available; RT, radiotherapy; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

cells.<sup>5</sup> However, between 1969 and 2014, there were only 46 case reports of abscopal effects caused by radiotherapy monotherapy,<sup>6</sup> indicating that radiotherapy alone was not sufficient to induce effective antitumor immunity. Two factors are currently considered to be critical for the occurrence of an abscopal effect: first, sufficient CD8+ T cells for activation in the immune system; and second, the production and presentation of tumor-associated antigen by APC to CD8+ T cells, which then produce specific killer T cells for the cancer cells at the primary and metastatic locations. Immunotherapy can liberate and activate CD8+ T cells from an immunosuppressed state, thereby increasing the probability of abscopal effects.<sup>7,8</sup> Reports of abscopal effects have increased along with the development of combined radiotherapy and immunotherapy, but these have mainly occurred in patients with highly immunogenic melanomas.<sup>9–13</sup>

The brain was previously considered an organ with immune privilege because it is difficult for nascent tumor-associated antigens to travel across the blood-brain barrier (BBB).<sup>14</sup> The occurrence of brain metastasis or the administration of radiation treatment often implies BBB opening. Antigens and cytokines produced during radiotherapy can cross the BBB. However, in clinical practice, an abscopal effect induced by localized brain radiotherapy rarely occurs, possibly because the BBB influences the amount of newly released tumor antigens and partially restricts the entrance of APCs into the brain. To date only 10 melanoma cases<sup>9</sup> and one intestinal cancer case<sup>15</sup> with brain metastases have been reported (Table 1). Both whole-brain radiotherapy and stereotactic radiotherapy can induce extracranial abscopal effects. The time to induce an abscopal effect via radiation can vary, generally from one to five months. Most of these patients had undergone

immunotherapy before radiotherapy. Our case indicates that abscopal effects can be induced even at tumor sites with low immunogenicity if radiotherapy is combined with immunotherapy.

An extracranial abscopal effect could be induced by combining brain radiotherapy with immunotherapy in poor immunogenic lung cancers with brain metastasis. Prospective studies are needed to confirm these preliminary results.

## Acknowledgments

This study was supported by the Open Project Program of State Key Lab of Respiratory Disease (SKIRD-QN-201720), the Special Fund Project of Science and Technology in Guangdong Province (2017B020247038) and the National Natural Science Foundation of China (81701172).

## Disclosure

No authors report any conflict of interest.

## References

- 1 Mole RH. Whole body irradiation; radiobiology or medicine? *Br J Radiol* 1953; **26**: 234–41.
- 2 Schouten LJ, Rutten J, Huvneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002; **94**: 2698–705.
- 3 Khasraw M, Posner JB. Neurological complications of systemic cancer. *Lancet Neurol* 2010; **9**: 1214–27.
- 4 Demaria S, Ng B, Devitt ML et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is

- immune mediated. *Int J Radiat Oncol Biol Phys* 2004; **58**: 862–70.
- 5 Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellos-Hoff M, Formenti SC. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. *Oncoimmunology* 2014; **3**: e28518.
  - 6 Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer* 2016; **40**: 25–37.
  - 7 Shaverdian N, Lisberg AE, Bornazyan K *et al.* Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 2017; **18**: 895–903.
  - 8 Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. *J Hematol Oncol* 2018; **11**: 104.
  - 9 Grimaldi AM, Simeone E, Giannarelli D *et al.* Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. *Oncoimmunology* 2014; **3**: e28780.
  - 10 Twyman-Saint Victor C, Rech AJ, Maity A *et al.* Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 2015; **520**: 373–7.
  - 11 Koller KM, Mackley HB, Liu J *et al.* Improved survival and complete response rates in patients with advanced melanoma treated with concurrent ipilimumab and radiotherapy versus ipilimumab alone. *Cancer Biol Ther* 2017; **18**: 36–42.
  - 12 Aboudaram A, Modesto A, Chaltiel L *et al.* Concurrent radiotherapy for patients with metastatic melanoma and receiving anti-programmed-death 1 therapy: A safe and effective combination. *Melanoma Res* 2017; **27**: 485–91.
  - 13 Roger A, Finet A, Boru B *et al.* Efficacy of combined hypofractionated radiotherapy and anti-PD-1 monotherapy in difficult-to-treat advanced melanoma patients. *Oncoimmunology* 2018; **7**: e1442166.
  - 14 Ishiyama H, Teh BS, Ren H *et al.* Spontaneous regression of thoracic metastases while progression of brain metastases after stereotactic radiosurgery and stereotactic body radiotherapy for metastatic renal cell carcinoma: Abscopal effect prevented by the blood-brain barrier? *Clin Genitourin Cancer* 2012; **10**: 196–8.
  - 15 Chuang CH, Hsu JF, Shen YT, Yang CJ. Regression of a metastatic lung mass after receiving whole brain irradiation: Can the abscopal effect cross the blood-brain barrier? *Asia-Pac J Clin Oncol* 2018; **14**: e548–50.
  - 16 Thallinger C, Prager G, Ringl H, Zielinski C. [Abscopal effect in the treatment of malignant melanoma]. *Hautarzt* 2015; **66**: 545–8. (In German.)
  - 17 Okwan-Duodu D, Pollack BP, Lawson D, Khan MK. Role of radiation therapy as immune activator in the era of modern immunotherapy for metastatic malignant melanoma. *Am J Clin Oncol* 2015; **38**: 119–25.