CASE REPORT

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

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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.1 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...
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 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 pseudoprogression. 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 pseudoprogression in the lung.

An immune-mediated response is considered one of the most critical mechanisms of an abscopal effect. 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

Discussion

Lung cancer is the leading primary tumor that tends to metastasize to the brain. 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 pseudoprogression. 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 pseudoprogression in the lung.
However, between 1969 and 2014, there were only 46 case reports of abscopal effects caused by radiotherapy monotherapy, 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. 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.

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). 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 and one intestinal cancer case 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.

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### Disclosure
No authors report any conflict of interest.

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### 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   | Melanoma16   | M      | 44  | Ipilimumab plus temozolomide | WBRT   | 30/10                | Lung, liver,             | 2                             | 2014             |
| 2   | Melanoma5    | NA     | NA  | Ipilimumab        | WBRT   | 30/10                | Liver metastases        | 1 (1–4)                      | 2014             |
| 3   | Melanoma5    | NA     | NA  | Ipilimumab        | WBRT   | 30/10                | Pelvic relapse           | 1 (1–4)                      | 2014             |
| 4   | Melanoma5    | NA     | NA  | Ipilimumab        | WBRT   | 30/10                | Liver, bilateral axillary and right ovarian metastases | 1 (1–4)                      | 2014             |
| 5   | Melanoma5    | NA     | NA  | Ipilimumab        | WBRT   | 30/10                | Lung, cutaneous, lymph nodal and abdominal metastases | 1 (1–4)                      | 2014             |
| 6   | Melanoma5    | NA     | NA  | Ipilimumab        | SRT    | 24/1                 | Cutaneous metastases    | 1 (1–4)                      | 2014             |
| 7   | Melanoma5    | NA     | NA  | Ipilimumab        | SRT    | 20/1                 | Liver metastases        | 1 (1–4)                      | 2014             |
| 8   | Melanoma5    | NA     | NA  | Ipilimumab        | SRT    | 24/1                 | Lung metastases         | 1 (1–4)                      | 2014             |
| 9   | Melanoma17   | F      | 50  | IL-2              | WBRT   |                      | Pulmonary, retroperitoneal, and mesenteric nodes | 5                             | 2015             |
| 10  | Colorectal cancer, adenocarcinoma15 | F | 74  | No               | WBRT   | 30/10                | Lung                   | 2                             | 2018             |

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