Case Report
Abscopal effect of local irradiation treatment for thymoma: a case report

Song Guan1*, Hui Wang2*, Xiu-Heng Qi3, Qian Guo3, Hong-Yan Zhang1, Huan Liu1, Bao-Jie Zhu1

Departments of 1Radiotherapy, 2Respiratory and Critical Care Medicine, 3Oncology, Hebei Petrochina Central Hospital, Langfang 065000, China. *Equal contributors.

Received August 14, 2019; Accepted May 6, 2020; Epub May 15, 2020; Published May 30, 2020

Abstract: Introduction: With the rapid development of immunotherapy in recent years, growing clinical evidence suggests that a combination of radiotherapy and immunotherapy could improve the abscopal response rates and increase survival. However, observations on abscopal effects in patients receiving radiotherapy alone are still very rare. This study reports a rare case of a patient with type B3 thymoma with multiple lung metastases, who received localized irradiation. Case presentation: A 76-year-old Chinese woman was admitted to our hospital in November 2017, and her physical examination revealed a thymus mass with multiple lung metastases. Although the left lower lobe lesion was slightly larger than before, the patient presented with regression of the non-irradiated metastases after treatment with radiotherapy alone. Conclusion: This patient experienced an apparent regression of metastatic mass, suggesting a radiation-induced abscopal effect.

Keywords: Abscopal effect, radiotherapy, thymoma, lung metastases, anti-tumor response

Introduction

As one of the main means of cancer treatment, radiation therapy has been mainly employed to control and eradicate local lesions due to the significant limitation of normal tissue toxicity [1, 2]. However, evidence from clinical and experimental data has suggested that the response to radiation may not only be locally, but also invoked by local irradiation at a distance from the irradiated site, which is called the abscopal effect [3]. The abscopal effect, which was first described by Mole [4] in 1953, is a rare phenomenon. Although this remains obscure, the biological mechanism underlying this effect has been considered to be involved in the secretion of effector cytokines, immunogenic cell death, and the release of new antigens recognized by the adaptive immune system [5, 6]. With the rapid development of immunotherapy in recent years, growing clinical evidence suggests that a combination of radiotherapy and immunotherapy could improve the abscopal response rates and increase survival. However, observations of abscopal effects in patients receiving radiotherapy alone are still very rare [7]. A recent literature review of abscopal effects of radiotherapy alone reported that there were only 46 cases between 1969 and 2014, despite the millions of patients being treated worldwide [8]. Furthermore, it has been considered that radiotherapy rarely produces a protective immunological effect, which may be correlated to the immune dysfunction of cancer patients. At present, it has been mainly reported that the abscopal effect may be observed in patients receiving radiotherapy alone for several immunogenic tumors, including renal cell carcinoma, hepatocellular carcinoma and malignant melanoma. However, clinical reports related to thymoma are extremely rare. The present report describes the abscopal effect of topical irradiation, without any combination therapies, in order to treat lesions distant from the irradiated sites in a patient with type B3 thymoma, and discuss the potential implications for clinical research.

The present study presents a rare case with type B3 thymoma with multiple lung metastases, who received localized irradiation to target the primary thymic lesion.
Case presentation

A 76-year-old Chinese woman was admitted to our hospital in November 2017. The patient had no complaint of any discomfort, but the physical examination revealed a thymus mass with multiple lung metastases. This patient was in good health, and had no underlying diseases. However, the enhanced computed tomography (CT) scan revealed an invasive thymoma (measuring approximately 6.5×4.8 cm) with multiple lung metastases and lymph node metastases, which invaded the ascending aorta and pericardium structure. Furthermore, the biopsy disclosed a type B3 thymoma. The patient was advised to refine the tumor markers for the subsequent evaluation of the outcome of treatment, but the patient refused. The patient had no complaints of chest distress, cough, myasthenia, or other related discomfort after admission, and the PS score was 0. Considering the above and the large local lesion with multiple lung metastases, the patient was recommended to receive systemic chemotherapy combined with palliative radiotherapy. However, the patient only agreed to receive palliative radiotherapy. Hence, three-dimensional conformal radiation therapy (3D-CRT) with a dose of 66 Gy in 33 daily fractions was performed from January 10, 2018 to March 2, 2018. In the CT scan performed in the middle of the radiation therapy, an obvious regression of the thymic lesion and lung metastases in the non-irradiated area was surprisingly revealed, even though the left lower lobe lesion was slightly larger than before (Figures 1-5). At two months after radiation therapy, the CT scan revealed that the thymic lesion and most of the lung metastases continued to shrink. However, regrettably, the...
Irradiation treatment for thymoma

Figure 3. The CT scan assessment of tumor burden before and after treatment. A: The pretreatment CT scan revealed multiple metastases in the upper lobe of both lungs; B: The follow-up CT scan during treatment revealed a significant regression in the upper lobe of the right lung, and the lesions in the upper lobe of the left lung disappeared; C: The CT scan at two months after treatment; D: At five months after treatment, there was a complete response in the upper lobe of both lungs.

Figure 4. The CT scan assessment of the tumor burden before and after treatment. A: The pretreatment CT scan revealed a thymus mass measuring approximately 6.5×4.8 cm with mediastinal lymph node metastases; B: The follow-up CT scan during treatment revealed that the thymus mass and lymph node metastases were significantly smaller than before, and the thymus mass was approximately 5.7×3.6 cm; C: The CT scan at two months after treatment revealed that the thymus mass continued to shrink to approximately 2.7×2.2 cm, and the lymph node metastases almost disappeared; D: The CT scan at five months after treatment revealed that the thymic mass was slightly smaller than before, which measured approximately 2.4×1.5 cm.

Discussion

Although the left lower lobe lesion was slightly larger than before, the present patient presented with regression of non-irradiated metastases after treatment with radiotherapy alone. Considering that the overall tumor burden was significantly reduced, the present case is an example of what has been called the abscopal effect induced by local radiotherapy. Although the biological mechanism underlying this effect is yet to be fully understood, this has been considered to be the change in immune pattern caused by the local radiotherapy, which enhances the immunological effect of the body’s immune system on distant tumor lesions. It has been reported in literature that the median time from radiation therapy to a documented abscopal response is five months (range: <1-24 months), and that there would be a median time of 13 months before disease progression.
Irradiation treatment for thymoma

occurs, or the reported follow-up ends (range: 3-39 months) [9]. The present case revealed an abscopal effect at one month after the radiotherapy started, which is earlier than that in previous reports.

Preclinical and clinical reports have shown that local irradiation produces both positive (immune stimulatory) and negative (immune suppressive) immune-mediated effects. This can both induce the regression of established metastases through the abscopal effect, and increase the development of distant metastasis. Radiation can also damage normal immune cells, and inhibit the proliferation and activation of T lymphocytes, causing impaired immune function. Meanwhile, the upregulation of TGF-β facilitates the growth and survival of regulatory T cells (Tregs) with immunosuppression. In addition, radiation therapy can also recruit circulating tumor cells to irradiated tissues, and the mechanism behind this may include immunosuppression after radiotherapy, radiation-mediated local tissue and/or vascular injury, and cytokine production, thereby facilitating tumor recurrence and metastasis [10]. It is noteworthy that a conventional radiation field usually includes the thymus and hematopoietic bone marrow, which further weakens the patient’s immune system. This may be one of the reasons why the abscopal effect of thymoma is rare.

In opposition to these immunosuppressive effects, local radiotherapy can also stimulate immune responses by causing DNA damage responses and immunological events, including anti-tumor immune mechanisms and inflammatory reactions, which are interconnected. Ionizing radiation can not only damage tumor cells, but also induce the release of some special “danger signals”, such as the following: (1) Calreticulin: The radiation-induced translocation of calreticulin to the surface of carcinoma cells, which acts as a phagocytic signal for dendritic cells [11]; (2) The release of high mobility group box-1 protein (HMGB-1): HMGB-1 arising from dying tumor cells can promote DC activation and elicit immune responses, and its interaction with TLR4 can also influence the processing and presentation of tumor antigens [12]; (3) The release of ATP: A cell-cell signaling factor that can trigger DC activation, and the priming of interferon-γ (IFNγ) producing CD8+ T cells [12]. These “danger signals” provide a potent ‘eat me’ signal for specialized antigen-presenting cells, particularly for dendritic cells. In addition, irradiated dying tumor cells release large amounts of tumor-associated antigens (TAAs) that can potentially be exploited to stimulate robust tumor-specific immune responses [13]. Meanwhile, the activation of the mTOR pathway by radiation is critical for the radiation-enhanced CTL killing, and radiation-induced increase in MHC class I levels leads to the enhanced susceptibility of tumor cells to lysis by CTL. Furthermore, the localized irradiation of the tumor results in the increase in IFN-γ production, which plays a key role in T cell traf-
Irradiation treatment for thymoma

ficking to the tumor microenvironment through the upregulated expression of adhesion molecule VCAM-1, and promotes effective T cell function.

The CT scan of the present case in the midterm of radiotherapy revealed the regression of lesions out of the radiation field. Although the left lower lobe lesion was slightly larger than before, the overall tumor burden was significantly reduced, suggesting that the local radiotherapy induced a relatively effective systemic anti-tumor immune effect. However, regrettably, at 2-5 months after treatment, although the primary lesion was still gradually regressing and most of the lung metastases markedly regressed, the left lower lobe lesion progressively increased, and new metastases appeared, suggesting that the anti-tumor immunity induced by radiotherapy was gradually weakening. This appears to confirm the view of Levy et al. [14], who reported that radiation alone can rarely induce a long-term abscopal effect.

At present, there is a growing consensus that combining radiotherapy with immunotherapy provides an opportunity to boost the abscopal response rates, extending the use of radiotherapy to treat both local and metastatic diseases. Compared with radiotherapy alone, radiotherapy combined with anti-PD-1/PD-L1 immunotherapy significantly improves local tumor control, long-term survival, and the protection against tumor re-challenge [15]. Weichselbaum [16] further advanced the hypothesis that combination therapy may be a general strategy for patients with metastatic cancer. However, a number of studies still need to be explored, such as radiotherapy dose, fractionation, timing and irradiated site, and so on. It appears that radiation-induced tumor immunity is not associated with proton therapy, when compared with conventional photon therapy [17]. SBRT or hypofractionation may be a more appropriate radiotherapy model for combination therapy, since it can increase immunogenic cell death [18]. Pike et al. [19] further illustrated that prolonged courses of extracranial radiation have the potential to cause severe and prolonged lymphopenia, which is associated with poorer survival in patients treated with immune checkpoint inhibitors (ICI).

In addition, there may be different thresholds in different tumors, in which a lower threshold may lead to a suboptimal dose, while a higher threshold may make immunosuppression dominant [20]. Therefore, Bristow et al. [21] advanced the study of precision radiotherapy to achieve the individualization of radiation dose prescriptions on the basis of the genetic and biological features of each tumor, and the surrounding normal tissues. Furthermore, for patients with advanced cancer, single treatment appears to be insufficient, and often needs to be combined with multiple treatments. Therefore, determining how to screen the best population and optimize the best treatment pattern is one of the urgent problems that needs to be solved.

The limitation of the present report was that due to poor compliance and heavy economic burden, the patient refused any hematologic-al examination and follow-up treatment, and a biopsy of the growing lesion could not be obtained for further pathological diagnosis. Therefore, the patient’s immune status and outcome could not be accurately evaluated, and the investigators could not help the patient gain further benefits on survival and life quality. In addition, due to poor compliance, the patient did not receive a review on time after the radiotherapy to evaluate the outcome, which may also lead to a certain bias in the evaluation of the patient's status and outcome. Furthermore, as a preliminary study, there was insufficient data about the tumor markers and systemic chemotherapy, and the pathologic examination of the left lower lobe lesion, which should be further investigated in the future.

Conclusion

The abscopal effect is a relatively rare phenomenon. In the present case, the patient did not receive any systemic treatment. After the routine radiotherapy for the primary thymic lesion, the irradiated lesion subsided, and multiple lung metastases in the non-irradiated areas markedly regressed, which may be attributed to the abscopal effect. Although the mechanism behind this is not fully understood, some evidence suggests that the mechanism behind this is correlated to radiation-induced
Irradiation treatment for thymoma

immune system activation. However, radiotherapy alone is rarely able to induce a sustained and effective abscopal effect. Therefore, determining how to induce the abscopal effect more effectively and maintain a long-lasting effect would be the key research directions in the future.

Acknowledgements

The authors thank the patient for her participation and her agreement to publication of the report.

Disclosure of conflict of interest

None.

Address correspondence to: Xiu-Heng Qi, Department of Oncology, Hebei Petrochina Central Hospital, No. 51 of Xinhua Street, Guangyang District, Langfang 065000, China. Tel: +86-0316-207-7202; E-mail: xiuhengqi1081@163.com

References


Irradiation treatment for thymoma

