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Systematic review of case reports on the abscopal effect

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A B S T R A C T

Radiation therapy is a highly effective local treatment for cancer. However, sporadic events of tumor regression in unirradiated fields, known as abscopal effect, have been observed for decades. This abscopal effect has more recently been postulated to be a result of antitumor immune response induced by radiation therapy. With the advent of modern immunotherapy, the potential for immune activation by radiation therapy defines a novel role for radiation therapy in systemic disease. In this context, we have searched documented cases abscopal effect of radiation therapy in literature. A total of 46 reported cases have been identified from 1969 to 2014 with median radiation dose of 31 Gy, median follow-up of 17.5 months, and median documented time to notice the abscopal effect was 2 months. This review systematically summarizes all clinical case reports of abscopal effect to gain insight into this uncommon but important phenomenon.

Introduction

Radiation therapy is known to be a highly effective local treatment for cancer and an integral part of multidisciplinary approach to cancer care. The mechanism of radiation is mainly through the damage of DNA inside cancer cells within the target. However, although uncommon, an effect has been described in distant sites away from the irradiated areas. This phenomenon is called “abscopal effect,” which was first described in 1953.[1] The word is derived from Latin, literally translated as shooting target that is away. The immune activation by radiation therapy has been postulated as the dominant mechanism of this phenomenon.

In this review, we systematically identified all available reported clinical cases of abscopal effect to describe clinical presentation, treatment, and biological findings in each case. Toward this end, we identified all case reports of abscopal effect through MEDLINE search. Different terms were used in our search, including “abscopal,” “non-targeted irradiation,” “non-targeted radiotherapy,” and “distant bystander.” During the process of reviewing the reports, any identified articles referenced were included as well. Most of the identified reports were in English and the remaining non-English articles were translated. Only clinical case reports were selected and reviewed with no exclusion criteria applied.

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Results

A total of 46 reported cases in 31 articles were identified; those patients were reported from 1969-2014. Case reports are summarized in the Table. The median reported age was 64 years (age range: 28-83 years). There were 5 patients with immunotherapy treatment during radiation therapy, 4 of which had melanoma. The median reported radiation dose was 31 Gy (range: 0.45–60.75 Gy) with median dose per fraction of 3 Gy per fraction (range: 0.15-26 Gy). In all, 20 patients were treated for metastatic sites. The median reported follow-up was 17.5 months (range: 1.5-120 months). The median documented time to notice the abscopal effect was 2 months (range: 0-24 months) and the median documented time to progress at the site of abscopal effect was 6 months (range: 0.7-14). Pathologic or laboratory studies were done in 7 patients before or after radiation treatment; they will be discussed in detail.

Hepatocellular carcinoma

Ohba et al[2] reported a 76-year-old man with a previously heavily treated liver with multiple persistent lesions. The patient developed vertebral bony metastasis 2 years after the last liver-directed therapy. Palliative radiation was prescribed to control the pain in the involved vertebra to a total dose of 36 Gy. External beam radiotherapy (EBRT) palliated his symptoms and his α-fetoprotein (AFP) decreased. Imaging studies showed a resolution of the bony lesion and regression of the liver lesions to a very small size 10 months after treatment. A retrospect analysis on stored serum was done to measure levels of IL-1β, IL-2, IL-4, IL-6, tumor necrosis factor (TNF)-α, and hepatocyte growth factor. There was a marked increase in the level of TNF-α after radiation to a peak of 102 pg/ml (preradiation level: 37.8 pg/ml). There was also an increase in IL-2 from 1260-1630 pg/ml after radiation.

Similarly, a report from Korea[3] described regression of liver disease and all bony metastatic sites after completion of palliative radiation to a skull lesion. After he was diagnosed with metastatic hepatocellular carcinoma, the 65-year-old male patient refused any traditional therapy and instead started ingesting a mushroom called Agaricus (*Phellinus linteus*) for 18 months. The patient developed painful skull lesions and was treated with palliative radiation to a dose of 30 Gy. Within 3 months, the liver disease and other untreated lesions began to regress; the response lasted for 9 months before stabilization. This was associated with the normalization of AFP level during the same period. The proposed explanation for this marked response was the possible immune modulation due to the mushroom *Phellinus linteus*.

In another report,[4] the dominant mass in the right lobe of the liver was treated in a patient with bilobar hepatoceullerlaur carconoma. The patient, 79 years of age, had a selective transcatheter arterial embolization and localized EBRT to a dose of 48 Gy to the disease in the right lobe only. His bilobar disease regressed on his 5-month follow-up CT scan.

Okuma et al[5] described a 63-year-old male patient with hepatocellular carcinoma who underwent extended right hepatic lobectomy. During the follow-up, he developed a single right lower lobe lung metastasis and a single mediastinal lymph node metastasis. EBRT was delivered to the mediastinal lymph node with a dose of 60.75 Gy, using 2.25 Gy per fraction, with no other therapy administered. In addition to the reduction of the lymph node size on follow-up scans, there was also spontaneous shrinking of the lung metastasis (which was outside the radiation field), as well as a dramatic decrease in serum AFP. In the 10-year follow-up, the patient had no recurrence in the thorax.

Adenocarcinoma

A 37-year-old female patient with papillary adenocarcinoma of unknown origin presented with involved lymph nodes in the bilateral neck, right axilla, and mediastinum, as described by Ehlers and Fridman.[6] Radiation with 40 Gy was delivered using anteroposterior/posteroanterior (AP/PA) fields to treat the bilateral neck and supraclavicular regions to palliate symptoms caused by the bulky $8 \times 5\ cm^2$ cervical lymph node. The primary treated neck nodes had a partial