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Case of Abscopal effect with Metastatic Non-Small-Cell Lung Cancer

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Abstract

The abscopal effect is originally defined as the observational effect of radiation therapy at site distant to the treated field. Recently systemic effects of local radiotherapy including hyperthermia and immunotherapy have received attention as a new therapeutic modality. We report a case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. Patient was treated with fractional radiotherapy, modulated electro-hyperthermia (oncothermia) and granulocyte-colony stimulating factor (GM-CSF).

Key words: Abscopal effect, Radiotherapy, Hyperthermia, GM-CSF, Non-small-cell lung cancer

Introduction

During the last decade, there has been an amazing progress in cancer research and treatment in the world and also in Korea. Nevertheless, the overall 5-year survival rate of lung cancer patients in 2001 - 2005 period was still 15.6% in South Korea. This type of cancer is usually diagnosed in advanced stage, consequently the overall survival did not show noticeable improvement, [1].

Poor performance status and/or multiple co-morbidities limit the treatment options for elderly patients [2]. Their poor prognosis is commonly accompanied with a common refusal of cytotoxic chemotherapies even adequate chemotherapy would be available with acceptable expected tolerance **[2]**. Options about the actual cancer treatments are deeply affected by subjective opinion of patients and their family members, who are avoiding the treatment-related several side effects [3]. In such cases radiotherapy could be considered as curative or palliative treatment option [4].

The newly available orally administered medicaments for non-small-cell lung cancer (NSCLC) are frequently refused also due to the requested co-payment and the lack of enough proper evidences [5].

According to our common knowledge the local therapy of radiation is not available in cancer patients with multiple metastatic lesions. However, systemic, so called abscopal effect, is observed [6] outside the treated field of ionizing radiation [7], but it is generally under-recognized in the clinical practice [**6**]. The first published observation on systemic effect of local radiotherapy was made by R.H. Mole, who proposed the term "abscopal effect" in 1953 [8]. It is originally defined as the systemic effect of radiation therapy observed in distant tumors from the site of irradiation field. It is suggested that the abscopal effect relates to immune response mediated by cytokines, but the mechanism remains unclear because this phenomenon is so rare and poorly understood in clinical practice, showing many controversies also [9]. Sometimes it is used complementary to other type of local therapies including surgery, hyperthermia and immunotherapy [10]. These complementary applications have recently received attention as new therapeutic facility [11].

Case reports on abscopal effect were published in various malignancies including lymphoma, malignant melanoma, chronic lymphocytic leukemia, adenocarcinoma of the esophagus, papillary adenocarcinoma, and hepatocellular carcinoma. However, according to our knowledge, there is

no report regarding NSCLC [12], [13] with abscopal effect, however some pulmonary applications were experienced [14], and clinically applied [15], [16].

In our present paper we assumed the possible boosting of abscopal effect of radiotherapy in combination of modulated electro-hyperthermia **[10]** and immunotherapy. Case of abscopal effect was observed in a patient with multiple metastatic NSCLC, treated with 3-D Conformal Radiation therapy (3DCRT), electro- hyperthermia (oncothermia) and granulocyte-colony stimulating factor (GM-CSF).

Case description and applied methods

A 72-year-old male patient was diagnosed with unclassifiable NSCLC by other hospital in July 2009. The classification of the tumor at first diagnosis was cT2N2M0, stage IIIB. Despite of the advanced case the patient refused any treatment. Five months later (December 2009), he visited outpatient department of complementary and alternative medicine with complaints of hemoptysis and dyspnea on exertion gradually worsened 4 weeks before. He was referred to medical oncology department and admitted for re- evaluation.

Staging work-up including chest CT and PET scans showed 9.5cm sized cavitary mass at right middle lobe with multiple regional and metastatic lymph nodes. He had no co- morbidities and no medical history (see Figure 1.). However, he still refused chemotherapy and together with his family members requested other possible treatment options.

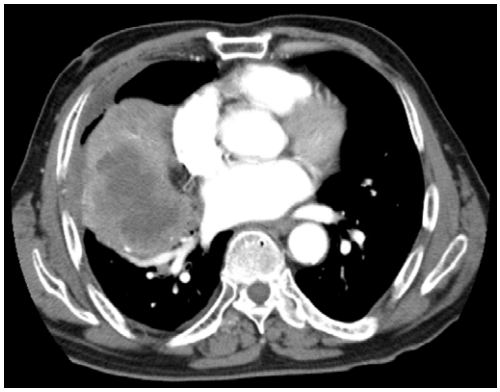
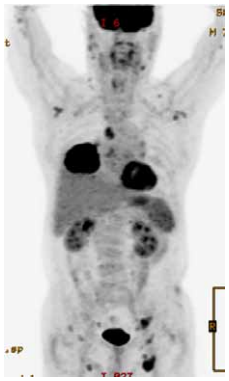
a.)  b) 

Figure 1. CT CT chest scan (a) and whole body FDG-PET scan (b) of the patient. About 9.5 cm sized huge lung mass with central necrosis was detected in right lower lobe and the mass had a hypermetabolic walled cavity. Multiple metastatic lesions were also showed in both of neck, axillas, inguinal regions and mediastinum including right hilum

In these circumstances we made radiotherapy in combination with oncothermia and GM-CSF expecting to induce abscopal effect. Local field radiation therapy to lung mass was delivered at a dose of 1.7 cGy in 28 daily fractions for 5-6 treatments in a week. It was followed by oncothermia after radiation 3 times a week (see Figure 2.). After 2 weeks of treatment, GM-CSF (250 microgram, Leukine®, USA) was administered subcutaneously once a day for 10days.

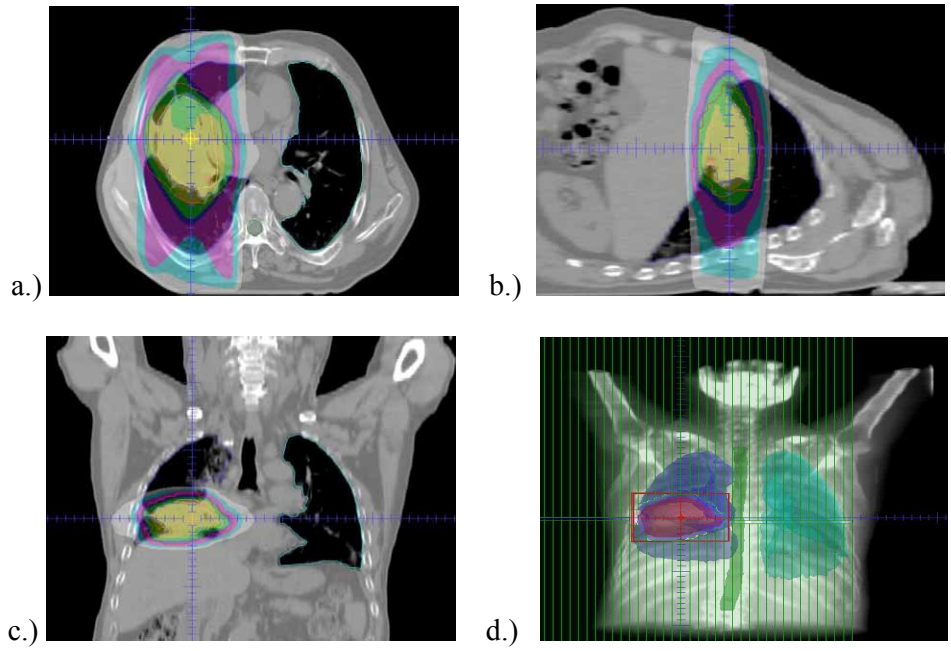


Figure 2. Multi-leaf collimator (MLC) shaping surrounding target and radiation dose distribution in 3 directions for a patient with metastatic non-small-cell lung cancer. Scheme of the axial (A), sagittal (B) and coronal (C) images show the radiation dose distribution for lung mass of primary site. The isodose distribution of individual colors showed as yellow (100%), Green (95%), blue (90%), magenta (70%), cyan (50%) and white (30%) associated to prescribed dose. (D) MLC shaping in anterior beam's eye view

Oncothermia is an emerging method [17], having positive studies [18], and its radiotherapy application is established, [19]. It is a loco-regional deep heating with RF- conductive current by modulated 13.56MHz radiofrequency current [20], having definite synergy of the heat and applied electric field, **[10]**. Hyperthermia can also enhance the immune reactions with increase of natural killer cell activity and distribute tumor- specific antigens on the surface of tumor cells [21].

According to preliminary data of clinical study designed **[11]**, GM-CSF in dose 125 IJg/m^2 was given subcutaneously for 14 days after one week of radiotherapy. The result supported that using GM-CSF was feasible and its effect enhanced the immune therapy.

GM-CSF was also evaluated to detect its immunostimulatory and antitumor effects in breast cancer and melanoma as neoadjuvant or adjuvant treatment complementary with chemotherapy or applied as monotherapy [22], [23]. In these studies, GM-CSF was administered for 10 to 14 days and the results were encouraging and promising.

Results and discussion

Treatments were provided without any complications. Patient presented no severe adverse effects except grade 1 fatigue at the end of treatment period. By follow-up process, just after finishing radiation treatment series PET scan showed nearly complete remission in multiple metastatic lymph nodes, which were distantly away from radiotherapy field (see Figure 3.).

Figure 3. FDG PET scan at the end of radiotherapy combining with hyperthermia and GM-CSF. The image shows excellent response in lung mass of primary site which was irradiated and complete remission in all metastatic lesions which were outside the radiation field

Evaluating the case we think that the activated immune response was the key factor of the present result. We think, oncothermia had parallel effects in our case, by local oxygenation had sensitized more the local radiotherapy effect, as well as the immune response was more activated by its electric field process [**10**]. Furthermore, probable the granulocyte-colony stimulating factor (GM-CSF) promoted the growth and differentiation of dendritic cells which is one of the most promising approaches in cancer immunotherapy. We suppose the radiotherapy combined with oncothermia and GM-CSF can be feasible and more effective than the radio-monotherapy is [**6**].

Patient was satisfied and discharged with successful response. The follow-up of the patient is continuing.

Conclusion

Our case describes a successful abscopal effect with local radiotherapy in combination with oncothermia and GM-CSF immune-stimulation. This attempt seemed to be more effective in immune response than radiotherapy alone. Our present report orients our attention to make further observations of the phenomenon in similar cases when its application is requested. Further studies on the abscopal effect are necessary to evaluate the significance of this cancer treatment option.

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