Case Report — The Eurasian Journal of Medicine — EAJM 2011; 43: 115-8

Hyperthermia in the Treatment of Post-Actinic Osteosarcomas: Our Anecdotal Experience

Göğüs Duvarı İrritasyonuna Bağlı Osteosarkom Tedavisinde Hipertermi: Anekdotal Deneyimimiz

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Abstract

Irradiation-induced sarcomas are a late sequelae of irradiation therapy. Most sarcomas have been reported to occur after exposure to a radiation dose of 55 Gys and above, with a dose ranging from 16 Gys to 112 Gys. These tumours are very aggressive and an early detection is needed for a timely intervention. Surgery is only effective treatment for local control instead chemotherapy is a valuable tool for systemic control of disease. Irradiation therapy use is controversial because of its side effects on a site previously irradiated. Irradiation therapy combined with hyperthermia is a new treatment that overcomes these problems without limiting the effect of radiation therapy. It may become a tool for local control of the unresectable tumours or an adjuvant treatment of the surgery. In this report we present a rare case of irradiation-induced recurrent osteosarcoma involving the chest wall that was treated with surgical resection followed by radiation therapy combined with hyperthermia as an adjuvant treatment of the surgery.

Key Words: Hyperthermia, Radiation, Sarcoma

Özet

Işınlama-kaynaklı sarkomlar radyoterapinin geç bir sekelidir. Çoğu sarkomun, 16 Gy ile 112 Gy arasında değişen bir dozu ile, 55 Gy ve üstünde bir radyasyon dozuna maruz kaldıktan sonra oluştuğu bildirilmiştir. Bu tümörler son derece agresiftir ve erken teşhis, zamanında müdahale için gerekli olmaktadır. Cerrahi, kemoterapiden farklı olarak sadece yerel kontrolü için etkili bir tedavi değildir aynı zamanda sistemik hastalığın kontrolü için değerli bir araçtır. Işınlama tedavisi kullanımı önceden ışınlanmış bir bölgenin tekrar ışınlanmasındaki yan etkileri nedeniyle tartışmalı bir konudur. Hipertermi ile kombine ışınlama, radyasyon tedavisinin sınırlanması olmadan bu sorunların üstesinden gelindiği yeni bir tedavi yöntemidir. Rezeke edilemeyen tümörlerin lokal kontrolü veya cerrahi bir adjuvan tedavi için bir araç haline gelebilir. Bu yazıda, cerrahi rezeksiyonu takip eden radyasyon tedavisi ile göğüs duvarının tekrarlayan bir osteosarkomunun cerrahinin adjuvan tedavisi olarak bir hipertermi ve ışınlama ile birlikte yapılan radyoterapiyi takiben cerrahi rezeksiyonla tedavi edilen nadir bir olgu sunuyoruz.

Anahtar Kelimeler: Hipertermi, Radyasyon, Sarkoma

Introduction

In 1902, Frieben [1] reported the first case of a tumor caused by prolonged exposure to ionizing radiation. He described a technician who tested Roentgen tubes and, after 4 years of exposure, developed a squamous carcinoma of the hand. Subsequently, many other cases have been published.

Our case involves a recurrent radio-induced osteosarcoma of the chest wall in a patient who, 13 years prior, underwent radiation therapy for a right breast cancer.

Case Report

The proposed case concerns a 57-year-old patient who, 13 years earlier (when she was 44 years old) underwent a right radical mastectomy and subsequent radiotherapy for ductal carcinoma of the right breast infiltrating the chest wall.

After 11 years, when the patient was 55 years old, she draw our attention because a radio-induced osteosarcoma of the anterior thoracic wall had occurred (Figure 1) without systemic diffusion. We performed a thoracectomy consisting

Received: May 10, 2011 / **Accepted:** June 21, 2011

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doi:10.5152/eajm.2011.25

of a partial resection of the sternum and the placement of orthopedic cement and prosthetic mesh.

After 2 years, a chest-computed tomography showed a recurrence of the osteosarcoma in the right sterno-clavicular region without other diffusion. We then performed a right anterior re-thoracectomy (with removal of the pre-existing dual mesh prosthesis and orthopedic cement), a resection of the middle 1/3 of the clavicle and adjacent segments of I-II-III ribs, a wall reconstruction with prosthetic dual mesh reinforced with a titanium plate (Figure 2) and a myocutaneous pedicle flap obtained from latissimus dorsi.

The histological examination documented a fibroblastic and chondroblastic osteosarcoma appropriately distant to all the excision margins.

The patient was discharged on postoperative day seven after a short period of hospitalization in intensive care.

The patient also underwent postoperative radiotherapy combined with hyperthermia.

Five months after the surgery, the clinical and instrumental control showed effective consolidation of the chest wall and good trophism of the flap without recurrence.

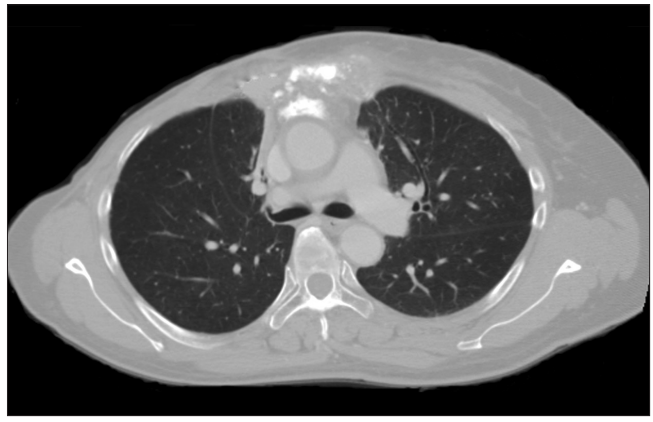

Figure 1. *Computed tomography shows the retrosternal mass.*

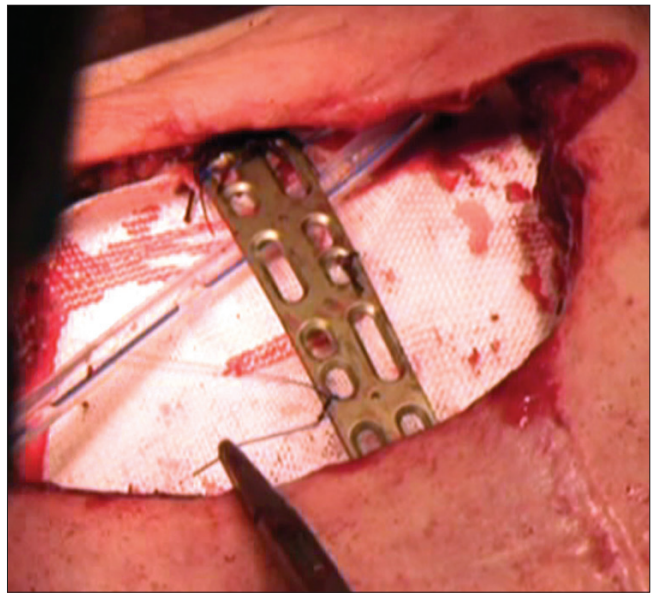

Figure 2. *This intraoperative photo shows the chest wall reconstruction with prosthetic dual mesh reinforced with a titanium plate.*

Discussion

Ionizing radiations can induce tumors in almost every tissue, but the most frequently induced neoplasms are osteosarcomas and leukemias [2].

The higher incidence of bone sarcoma compared to soft-tissue sarcoma is due to the higher absorption of radiation by bone [3, 4].

The incidence of irradiation-induced sarcomas ranges from 0.03% to 0.8% [4, 5], and the highest incidence is reported following exposure to 55 Gys with a range between 16 Gys and 112 Gys [4-7].

The radio-induced osteosarcoma is a late complication of radiation therapy. The medical literature reports a latent period after irradiation ranging between 3 months and 53 years, with an average ranging between 10 and 20 years [3, 4, 6]. It seems that age, sex, histology of the primitive tumor, dose and the mode of exposure do not have an impact on the induction of this type of tumor [3].

Post-irradiation osteosarcoma presents two peaks of incidence related to age: a first peak between 10 and 19 years, including patients irradiated in childhood, and a second peak after 50 years, including patients irradiated during adulthood [4]. These data are in contrast to the typical age of onset of primitive sarcoma, which occurs in the third or fourth decade of life [4].

The diagnosis of osteosarcoma is performed with clinical observation and radiological and histological investigations. In 1948, Cahan and colleagues [7] proposed the criteria for the diagnosis of post-irradiation osteosarcoma, which were subsequently modified in 1971 by Arlen [5, 8] as follows: 1) history of irradiation, 2) onset of cancer at the irradiated sites, 3) latency intervals of at least 5 years, and 4) histological diagnoses of osteosarcoma.

Some authors emphasize [9] the diagnostic importance of 18-fluorodeoxyglucose positron emission tomography (PET) imaging in providing detailed information about osteosarcoma staging and grading to evaluate the treatment and to detect a recurrence. The recent combination of PET and computed tomography (PET-CT) is a very important tool for monitoring the patients who are at risk and for providing an early diagnosis of post-irradiation osteosarcoma [4].

Thallium-201 scintigraphy is helpful in monitoring the effectiveness of neoadjuvant chemotherapy for osteosar-

coma because this investigation allows accurate evaluation of tumor necrosis [10].

The Cooperative Osteosarcoma Study Group reported that the standardized therapeutic management of primitive osteosarcoma includes neoadjuvant multidrug chemotherapy with doxorubicin and methotrexate followed by wide resection of the primary tumor, which is still considered the only definitive treatment to ensure local tumor control. Postoperative chemotherapy reduces the incidence and delays the occurrence of systemic diffusion [11].

Some authors [4] reported that it is not possible to expose the patients affected by a post-irradiation tumor to radiation therapy because of its side effects on a previously irradiated site, but a recent study proposes the use of radiotherapy combined with hyperthermia to overcome these problems without limiting the therapeutic effect of radiation therapy. Hyperthermia is a potent sensitizer of cell destruction by ionizing radiation; however, the precise mechanism of heat-induced cell death is unknown. It seems that the radiosensitization observed is due to the fact that heat is a pleiotropic damaging agent, which alters cell components to varying degrees, damages protein structures, and modifies the DNA response to damage. Thus, hyperthermia influences several molecular parameters involved in sensitizing tumor cells to radiation and can enhance the potential of targeted radiotherapy. Therefore, radiotherapy combined with hyperthermia may become a tool for local control of an inoperable tumor or an adjuvant therapy in the context of surgery [12, 13].

Prognosis is correlated with the site and the possibility of successful radical surgical intervention. Therefore, osteosarcoma of the limbs will have a better prognosis because it is possible to amputate the limb, which in turn allows for radical surgery. In contrast, the osteosarcomas of the head and neck have a more ominous prognosis because the anatomical site is not suitable for a radical resection [14]. Usually therapeutic management in post-irradiation osteosarcoma cases is more difficult than in primitive osteosarcomas because it is not typically possible to administer the typical chemotherapy used to treat primitive sarcomas because the general conditions of patients does not allow it. Furthermore, it is not possible to expose patients to radiation therapy because of its side effects on a site that has already been irradiated [4, 8, 14]. More frequently, post-irradiation osteosarcoma is poorly differentiated and therefore inherently more aggressive [4]. Immunosuppression due to the primary cancer and/or its treatment may further worsen the prognosis. Therefore, the prognosis of post-irradiation osteosarcoma is worse than the prognosis for primitive osteosarcoma, as the overall survival at 5 years for post-irradiation osteosarcoma is 10-30% [4] compared to 60% for primitive osteosarcoma [11].

Ours is a typical case of post-actinic osteosarcoma that occurred 11 years after radiation therapy and then relapsed after 2 years in a patient, on both occasions without systemic metastases. The patient was otherwise in good clinical condition. Given the resectability of the site, despite the surgical and oncologic complexity of the case, we decided to proceed to surgery in both cases.

The first time, we decided to avoid radiation therapy for a site affected by a neoplastic complication induced by radiotherapy. Because the second time was a recurrence, we decided to attempt radio-hyperthermia (for the first time in our experience), and we obtained a satisfactory result (to date, at five months).

Irradiation-induced sarcomas are very aggressive tumors, which often escape early detection and prevent a timely therapeutic intervention. About 60% [4] of cancer patients will undergo radiation therapy for therapeutic or palliative purposes. Considering the average increase in life and survival, the incidence of oncologic radio-induced disease is likely to increase.

Currently, there are no preventive measures to protect this category of patients [4]. Therefore, we believe that it is only possible to make an early diagnosis with close radiographic follow-up of the patients at risk, for example with PET-CT, which seems to facilitate early and accurate diagnosis [9].

In agreement with other authors, we consider that surgical resection is the only treatment to ensure local tumor control and support the use of chemotherapy as an important tool for the systemic control of the disease [11].

A recent study proposed radiotherapy combined with hyperthermia. Hyperthermia is a type of cancer treatment in which the body tissue is exposed to high temperatures to damage and kill cancer cells; it enhances the effect of radiotherapy and then allows radiation therapy to be performed at lower doses, reducing its side effects without reducing its effectiveness [12, 13]. Radiation therapy combined with hyperthermia may become an important tool for the local therapy of unresectable osteosarcomas or an adjuvant treatment in the context of surgical resection.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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