



Case Report

Bilateral Breast Cancer After Prophylactic Bilateral Pulmonary Irradiation

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Abstract

The purpose of this article is to report a new case of a probably radio–induced bilateral breast cancer occurred after prophylactic bilateral pulmonary irradiation in the treatment of osteosarcoma. A 42–year–old woman, treated at the age of 12 years for osteosarcoma at the right lower limb with chemotherapy (methotrexate, adriamycin and cisplatin) followed by non–conservative surgery and adjuvant radiotherapy. Eighteen years after,

she developed her first breast cancer, and five years later, her second contralateral breast cancer. The patient was treated for her two non–metastatic cancers and is currently in complete remission.

This publication adds to several previous publications the very probable effect of ionizing radiation in the occurrence of secondary cancers.

Keywords: Breast Cancer; Bilateral; Radiotherapy; radio–induced; pulmonary irradiation.

Introduction

The first cases of radiation–induced cancers were published five years following the discovery of radioactivity. The rates might exceed 5% and even approached 20% in some series ⁽¹⁾. After Hodgkin’s disease, breast cancer has been widely studied in literature ^(2–5), unlike those occurring after prophylactic lung irradiation, particularly in the context of the management of primary bone tumors such as Ewing’s sarcoma ⁽⁶⁾.

We report a new case of bilateral breast cancer, probably radio–induced, occurring to a prophylactic pulmonary irradiation on a patient treated for osteosarcoma of the lower limb.

Observation

A 43–year old single female patient, with no medical or surgical history or family antecedent that had been treated for non–metastatic right lower limb osteosarcoma at the age of 12. The treatment consisted of neoadjuvant chemotherapy (CT) based on methotrexate, adriamycin and cisplatin, followed by a non–conservative surgery, then a prophylactic bilateral pulmonary irradiation at the dose of 20 Gy. Eighteen years later, during a routine medical examination, a suspicious nodule on the left breast was found. After exploration, including mammogram that showed a suspect image classified BIRADS 4, we discovered that it was an infiltrating ductal

carcinoma of 3 cm of long axis, ranked T4bN0M0, which was estrogen and progesterone receptor–negative, HER–2/neu protein was not performed. The treatment of the left breast tumor consisted on a neoadjuvant chemotherapy followed by radical mastectomy with axillary lymph node dissection. The final histological examination showed a viable tumor residue of 30x15 mm long axis, infiltrating the skin, without histological positive lymph nodes in five nodes removed.

Adjuvant chemotherapy was performed, followed by irradiation of the chest wall, the internal mammary nodes and above the left supraclavicular nodes to a dose of 50 Gy on 25 fractions. Five years later, the patient developed a second suspect breast nodule in the remaining breast of 3 cm, classified T4bN1M0. The biopsy showed that it was an invasive ductal carcinoma, grade II SBR with positive hormone receptor.

The treatment consisted on neoadjuvant CT followed by radical mastectomy and axillary lymph node dissection. The final histological examination was in favor of a

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mucinous carcinoma of 35 mm, three of the five nodes removed were invaded. Adjuvant CT was prescribed, followed by whole-breast, internal mammary and right supraclavicular nodes irradiation to a dose of 54 Gy, 2 Gy/fraction, 5 fractions/week. Five years after her second breast cancer, the patient is in complete remission.

Discussion

In recent decades, and thanks to advances in medicine and science, a continuous rise in the rate of survivors after pediatric cancer has been observed⁽⁷⁾. Among these cancers, osteosarcoma is the most common primary malignant bone tumor among teenagers, aged between ten and twenty years. This tumor is characterized also by the high frequency of occurrence of lung metastases⁽⁸⁾.

To limit these lung metastatic relapse, an early prophylactic lung irradiation has been part of the adjuvant treatment of osteosarcoma, similar to a treatment of Ewing's sarcoma. However, this attitude is no longer recommended in the treatment of non-metastatic osteosarcoma (level of evidence C) for two reasons: on one hand, the absence of significant gain in terms of overall survival and disease-free survival, and on the other hand, the potential complications of such irradiation⁽⁹⁾.

The effects of chest irradiation, especially in the context of mantle irradiation, on patients surviving after treatment of their Hodgkin's disease at their young age, have been extensively studied^(5,10). These effects include the major risk of developing radio induced breast cancer. In fact, 18–20% of adult women who survived after childhood cancer, particularly Hodgkin's disease, and who were treated with medium or high dose (≥ 20 Grays) thoracic irradiation, developed breast cancer⁽¹¹⁾.

A cohort study conducted by Taylor AJ. et. al. on 383 British women survivors after treatment of their Hodgkin's disease, proved that the cumulative risk of developing breast cancer after 25 years, especially in patients who have a supra diaphragmatic radiotherapy, was 12.2%⁽²⁾. The risk of mammary carcinogenesis radiation would increase, according to Kenney LB. et al. in family history of breast disease and thyroid disease⁽¹²⁾.

Moreover, many authors have shown that the risk of developing radio induced breast cancer is inversely related to the age of the radiation exposure. It would be 6 times more if the patient is treated at the age of 30 and 60 if she is treated at the age of 16. It is probably related to the existence, at that age, of a large number of stem cells, a high rate of proliferation, and a greater hormonal promotion⁽¹³⁾. This will explain the increasing breast sensitivity to radiation starting from very low doses of 0.09 to 0.11 Gy.⁽¹⁴⁾

According to M. Tubiana, the risk of breast cancer is increasing when the cumulative doses exceed 500 mGy. This confirms the additive effect of very low doses in breast radio carcinogenesis among girls and young women⁽¹⁵⁾. This notion, widely proven in the literature, formed the basis of recent studies. They are delivering distressing messages, namely the criminalization of radio diagnostic examinations and especially scannographic in increasing the total accumulated doses⁽¹⁶⁾.

Until now, few studies have focused on studying the quantitative correlation between the estimated dose level received by the growing cell and the probability of occurrence of radio-induced cancer^(17,18,19). Indeed, Inskip PD. et al⁽¹⁷⁾. showed that women, who received 40 Gy total dose in the breast have a relative risk of developing breast cancer, 11 times more than non-irradiated. This risk is estimated to be 6.2 if the dose exceeds 40 Gy, whereas it is 2.6 if it is less than 40 Gy dose⁽¹⁸⁾. The risk is also closely related to the size of the range. Indeed, a wide irradiation, including the mantle, is purveying of 3.2 higher risk of cancer than just mediastinal irradiation⁽¹⁹⁾.

From a radio biological point of view, there is a linear relationship between the prescribed dose (between 1 mGy and 100 Gy) and the number of DNA double strand breaks and between these breaks and the observed biological effect, including cancers⁽²⁰⁾. Among the repair systems of DNA, we note the homologous recombination, controlled by the tumor suppressor genes, such as BRCA1 and BRCA2, which is an important parameter in cell radiosensitivity⁽²¹⁾. The kinetics repair of these breaks, are relatively long and dependent on the size of the breaks and the cell type⁽²²⁾.

Moreover, the combination of radiotherapy and chemotherapy was more inductive to secondary solid tumors than radiotherapy alone. This is explained by the potentiating effect of certain chemotherapy drugs, including anthracyclines such as doxorubicin⁽²³⁾. However, this is not the case of alkylating agents, which seem even having a protective effect, especially if the number of treatments is increased.

However, it is important to note the increasing potential of bilateral radio-induced mammary cancers⁽²⁴⁾. According to Deniz K. et al⁽¹⁸⁾, this risk is approximately 20%, with respect to a risk of 2 to 11% for the general population⁽²⁵⁾. In a recently published multicenter study of Cutuli B. et al, among 189 patients have been treated for Hodgkin's disease in childhood; 25 of them (13.2%) have developed bilateral breast cancer, metachronous in 88% of cases⁽²⁶⁾.

Some factors are strongly associated with an increasing risk of contralateral breast reached. Among these factors,

we mainly include the young age of women at the time of treatment of the first cancer (35–40 years), family history of breast cancer, a first lobular breast cancer (in situ or invasive), and multifocal or multicenter breast cancer (27).

Therefore, and in view of the literature, it appears that the detection of second cancers, especially breast ones, must be an indisputable imperative in monitoring all irradiated patient, especially at an early age (28). The Children Oncology Group (COG) developed in 2003, the Long–Term Follow–Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer, and recommended annual mammography screening from the age of 25 years or 8 years after thoracic irradiation, at medium or high dose (≥ 20 Gy) (29). In 2008, the COG, the American Cancer Society, and the United Kingdom Department of Health recommended breast MRI in addition to annual mammography in the detection of radiation–induced breast cancers (4, 30).

Conclusion

Therapeutic advances in the treatment of paediatric cancers have led to prolonged remissions or even cures. The study of the fate of these patients and long–term survivors is important. Indeed, the whole thoracic irradiation at a young age, especially in the treatment of Hodgkin’s disease or osteosarcoma, is associated with an increasing risk of developing breast cancer, which is the fear of all radiation oncologists. This motivates us to benefit from a plan of common screening radiation–induced cancers.

This study has been reviewed by the appropriate ethics committee, and therefore, has been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki. The patient gave his informed consent prior to his inclusion in the study.

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