

CASE REPORT

Reirradiation in a patient with breast carcinoma after Hodgkin's lymphoma*Reirradiação em paciente com cancro da mama tratada por linfoma de Hodgkin***André Filipe Pinheiro Figueiredo¹, Diogo de Carvalho Miranda e Silva Delgado², Vera Margarida de Azevedo Andrade Arnaut Mendonça³, Marília Maria Liberato Jorge Lemos⁴**

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ABSTRACT: The long-term survival of the Hodgkin's lymphoma patients treated at an early age with chemoradiotherapy is raising awareness for the late effects of this treatment. Radio-induced breast cancer is one of the described risks and occurs almost exclusively after a period of 10 years. Well-established risk factors include the diagnosis in the 10-16 age group, the use of extended-field radiation therapy and an increase in radiation dose. Conservative breast surgery with adjuvant radiotherapy is feasible, but dose-reduction techniques to organs at risk should be considered, given the previous irradiation. We report a clinical case of a secondary breast cancer in a patient who underwent chemoradiotherapy, with mantle field radiation therapy, for supradiaphragmatic Hodgkin's lymphoma at youth. After multidisciplinary discussion and given the patient's willingness to preserve the breast, she was treated with conservative breast surgery and adjuvant radiotherapy.

Keywords: Radiation-induced malignancies; Breast cancer; Hodgkin's lymphoma.

RESUMO: A sobrevida longa das pacientes com linfoma de Hodgkin submetidas a quimiorradioterapia numa idade precoce tem evidenciado os efeitos tardios deste tratamento. O desenvolvimento de cancro da mama radio-induzido é um dos riscos descritos, ocorrendo quase exclusivamente após um intervalo de 10 anos do tratamento. A idade ao diagnóstico entre os 10-16 anos, a radioterapia de campo amplo e um aumento da dose prescrita são os fatores de risco estabelecidos. A cirurgia conservadora da mama com radioterapia adjuvante é exequível, mas, dada a irradiação prévia, devem ser equacionadas estratégias de redução de dose nos órgãos de risco. Apresenta-se o caso de cancro da mama secundário numa paciente submetida em jovem a quimiorradioterapia, com técnica de irradiação em manto, por linfoma de Hodgkin supradiaphragmático. Após discussão multidisciplinar e dada a vontade da paciente em preservar a mama, foi tratada com cirurgia conservadora e radioterapia adjuvante.

Palavras-chave: Tumores radio-induzidos; Cancro da mama; Linfoma de Hodgkin.

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INTRODUCTION

Radiotherapy is required in at least 40% of all curative therapeutic strategies in oncology¹. In Hodgkin's lymphoma treatment, in association with chemotherapy, it leads to an overall and relative survival of 89.6% and 94.3% at 5 years, respectively². Given the higher incidence of Hodgkin's lymphoma in the 20-40 age group, the late effects of the treatment are of particular concern^{3, 4}. The irradiation field for supradiaphragmatic disease includes organs at risk such as the heart, esophagus, lungs and thyroid and, particularly in the case of female patients, the mammary glands. Risks include cardiovascular disease, endocrinopathies and the development of secondary tumors⁵. Secondary breast cancer in patients treated at a young age (≤ 30 years) is the most common secondary tumor⁴, with a risk of death from breast cancer twice as high as patients with spontaneous breast cancer⁵.

CLINICAL CASE

A 47-year-old female patient with a history of Nodular Sclerosing Hodgkin lymphoma, stage IIA, presented as a left cervical adenopathy at 19 years old. She was treated with chemotherapy (4 cycles of ABVD regimen) followed by mantle field irradiation, which included cervical, axillary and mediastinal regions (with consequent irradiation by unquantified dose in the

mammary glands bilaterally), with telecobalt therapy, with the total treatment dose at point A of 35.6 Gy¹ (2.5 Gy per fraction prescribed to the skin per session). ¹ Gray: unit of ionizing radiation dose in the International System of Units corresponding to the energy absorbed per unit mass

The patient had smoking habits since she was 19 years old, quantified in 21 UMA. She had a history of 3 pregnancies (the first at 29 years old) and was premenopausal. She used oral contraceptives for 14 years and posteriorly placed a copper intrauterine device. She had no family history of cancer, namely breast cancer.

She underwent routine mammograms irregularly. In December 2014, a suspicious lesion in the upper quadrants of the left breast appeared on a mammogram. The patient had occasional complaints of a "stinging" sensation in her left breast. On physical examination, a suspicious hardened area was palpable in the upper-outer quadrant. Suspicious lymph nodes were also palpable in the ipsilateral axilla. Mammography showed a dense area with a spiky appearance in the upper-outer quadrant of the left breast (BI-RADS V). On ultrasound examination, a solid lesion with irregular edges and 18 mm of greatest diameter was observed (BI-RADS V) (Figure 1). The patient was submitted to a core needle biopsy guided by ultrasound. In magnetic resonance imaging (MRI) evaluation, the lesion measured approximately 20x11 mm, 0.5 cm from the skin, 7 cm from the nipple and 7 cm from the chest wall (Figure 2). In ipsilateral axillary region, three pathologic lymph nodes, varying in size between 17 and 20 mm, were seen. A surgical clip was placed in primary tumor.

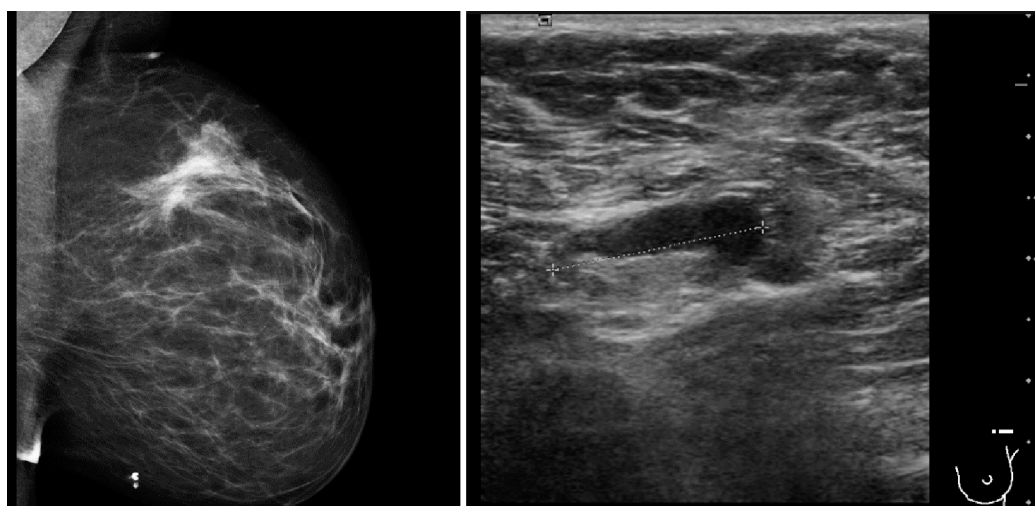


Figure 1: Breast mammography (left) and breast ultrasound (right) at diagnosis

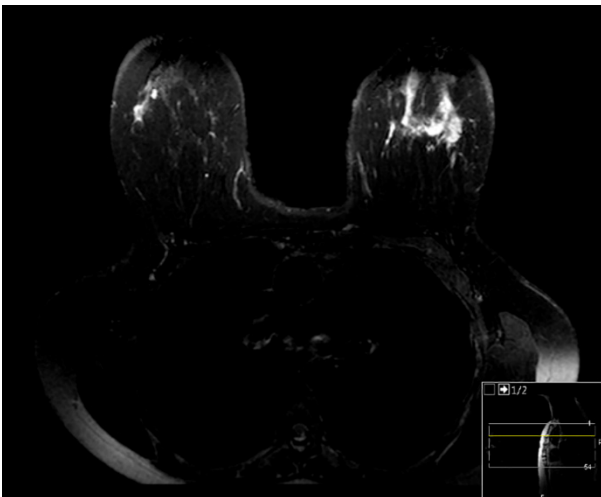


Figure 2: Breast MRI at diagnosis, using the SPAIR fat suppression technique

Biopsy revealed an invasive carcinoma NST (of no special type), grade 2, in about 80% of the sample, with estrogen receptors with moderate intensity marking in 80% of tumor cells and progesterone with strong intensity marking in 90% of tumor cells, HER2 negative status (1+) by immunohistochemistry, with a proliferative index (Ki-67) of 85% and negative p53 expression, classified as a luminal B molecular subtype. The fine-needle aspiration cytology of one of the pathologic lymph nodes revealed the presence of metastasis compatible with breast carcinoma.

Computed tomography (CT) of the chest and abdominal ultrasound did not found distant metastasis.

The clinical stage was defined as IIB (cT1c cN1 cM0).

The therapeutic strategy was decided by a multidisciplinary team and took into account the patient's desire to preserve the breast. It was highlighted that even after mastectomy, the patient probably needed post-mastectomy radiotherapy (particularly targeting the high-risk lymph node regions, taking into account the presence of axillary metastasis), and so the mastectomy did not eliminate posterior re-irradiation. It was also highlighted that breast reconstruction after mastectomy is concerning in a previously irradiated patient, with high rates of postoperative complications. The patient didn't have any late skin toxicity from previous irradiation, which gave support to a conservative strategy. The patient was warned of the risks of re-irradiation, including the possible poor cosmetic result, and with the agreement of the medical team choose a breast conserving surgery.

Neoadjuvant chemotherapy was initiated with four dose-dense cycles of doxorubicin and cyclophosphamide (AC regimen) followed by twelve cycles of paclitaxel, with good overall tolerance. After six weeks, she underwent a left breast tumorectomy with ipsilateral axillary lymph node dissection. The anatomopathological result of the surgical specimen showed a residual invasive carcinoma with 9 mm of greatest diameter, with a distance of 1 mm to the closest margins (upper and posterior). Of the twelve lymph nodes removed, one had micrometastasis. The pathological staging was ypT1bN1mi.

After eight weeks, the patient received 3D conformal radiation therapy (3D CRT) targeting the left breast and the high-risk lymph node regions with a dose of 50 Gy, followed by a boost in the tumor bed, completing the total prescribed dose of 66 Gy, 2 Gy per fraction (Figure 3).

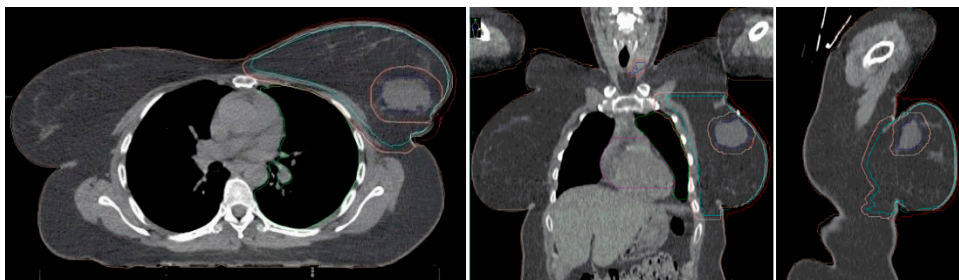


Figure 3: Target volumes and organs at risk delineation in axial, coronal and sagittal sections (from left to right, respectively)

The patient presented grade 2 radiodermatitis in the inframammary fold, axillary and supraclavicular region, treated with oral non-steroidal anti-inflammatory drugs and application of Mepilex® Lite dressing.

She was under hormone therapy with tamoxifen for two years, followed by letrozole after menopause, which she has maintained since then with good tolerance.

One year and six months after the end of radiotherapy, the patient complicated with deep vein thrombosis of the left upper limb. She started anticoagulation with

low-molecular-weight heparin (LMWH), with clinical improvement.

At the date of the last follow-up visit, two years and six months after radiotherapy, the patient was asymptomatic and in the MRI assessment she did not present any suspicious lesion. On physical examination, an area of telangiectasias, edema and fibrosis of the left breast were observed. She maintained an ipsilateral upper limb edema, but with preserved joint mobility (Figure 4).



Figure 4: Photographic records of the patient in a follow-up visit showing edema and fibrosis of the left breast and ipsilateral upper limb (left) and telangiectasias in left axillary region (right)

DISCUSSION

The update of the Late Effects Study Group in Hodgkin's lymphoma showed that the increase in the relative risk of breast cancer in patients that underwent radiotherapy at young ages (≤ 30 years) occurs after 10 years, with a median time of 18,1 years. Age at diagnosis is one of the main risk factors, particularly the interval between 10-16 years, given the greater radiosensitivity of the mammary gland cells at the time of puberty⁴.

The role of chemotherapy in the carcinogenesis of these secondary tumors is controversial. Even if the risk of secondary tumors also increases in patients undergoing chemotherapy alone⁶, in studies of chemoradiotherapy versus radiotherapy alone, the combined therapy seems to confer a decrease in this risk⁷. The likely cause is the induction of premature menopause by the use of alkylating agents that reduces the risk of developing hormone-dependent tumors⁸.

In 2016, Conway et al.⁹ demonstrated that the volume of the irradiation field is a significant risk factor. In this study, the mantle field irradiation increased the risk of secondary breast cancer by 2.9 ($p = 0.004$) and 3.3 ($p = 0.01$) in comparison to patients undergoing chemotherapy only and a smaller volume irradiation field, respectively.

In the past, as exemplified by our case, patients underwent radiotherapy using the classic mantle field technique, which includes cervical, axillary and mediastinal lymph node regions. Subsequently, a smaller volume irradiation field became standard and included only the lymph node regions with documented disease – involved field radiotherapy. In the last decade, the use of positron emission tomography by computed tomography (PET-CT) allowed the irradiation targeting only the involved lymph nodes. However, the fusion of PET-CT images with radiotherapy planning CT is compromised, since they are usually obtained in different positions. An adaptation of this technique has gained popularity and includes the location of the lymph nodes initially involved, but not the entire lymph node region – involved site radiotherapy¹⁰.

The telecobalt therapy unit in which our patient underwent treatment is outdated and the use of 3D CRT with a linear accelerator is the standard nowadays¹⁰. Nieder et al. published a comparison of dosimetric studies between the following techniques: two opposite antero-posterior

and postero-anterior fields, four fields with 3D CRT and seven fields with intensity-modulated radiation therapy (IMRT). The coverage of the target volume was similar between the different techniques, but the use of IMRT allowed better spare of the heart and a decrease of the higher doses in the breast and lung parenchyma. Even though heart sparing irradiation with IMRT may contribute to the reduction of late cardiovascular toxicity, the benefit in the breast and lungs parenchyma is more controversial given the irradiation of a greater volume with lower doses that can be carcinogenic. Age, cardiovascular comorbidities, administration of cardiotoxic chemotherapy, individual anatomy of the patient and family history of cancer, are factors to consider when deciding on the most appropriate radiotherapy technique¹¹.

Krul et al. described a linear increase in risk with increasing dose with an adjusted odds ratio of 6.1% by Gray¹². In our case, the total dose received > 30 Gy was probably a major risk factor.

In comparison to spontaneous tumors, Alm El-Din et al.¹³ found a higher incidence of bilateral tumors, however with the same pathologic characteristics. In contrast, Horst et al.¹⁴ settled that these secondary breast cancers are usually more aggressive, often triple-negative (estrogen and progesterone negative receptors and HER2 negative status).

The carcinogenesis of radiation-induced tumors is linked to DNA damage and probably to DNA repair defects present in genetic polymorphisms of some patients. For example, Best *et al* identified two variants on chromosome 6q21 that induce a minor expression of PRDM1 that downregulates pro-proliferative genes such as MYC. The presence of this polymorphism increases the risk of secondary tumors in children undergoing radiation, but not in adults, which supports the hypothesis of genetic susceptibilities that are particularly relevant at younger ages¹⁵. Nevertheless, mutations in the tumor suppressor genes TP53, BRCA1 and BRCA2 are not more frequent in survivors of Hodgkin's lymphoma with secondary tumors¹⁶.

The follow-up in our case was not in agreement to current guidelines. All patients with ≤ 40 years old at the time of chest and / or axillary irradiation should start annual mammograms 8 to 10 years after treatment or at age 40 (whichever comes first). Patients with ≤ 30 years old should start annual breast MRI^{3,10}. The use of both imaging modalities improves sensitivity in the diagnosis

from 70% to 95%¹⁷.

According to Watson et al.¹⁸, the tolerance of chemotherapy in the treatment of breast cancer in patients that already did chemoradiotherapy for Hodgkin's lymphoma seems to be similar to patients without previous chemotherapy treatments, so a conventional chemotherapy protocol should be the choice. In our case, the patient showed good tolerance to chemotherapy.

Given the previous irradiation of thoracic and axillary region, radical mastectomy is often the surgical option to avoid re-irradiation of the same region. However, even after radical mastectomy, the patient can benefit from adjuvant radiotherapy to the chest wall and lymph node regions to increase loco-regional control of the disease. In patients that choose to have breast reconstruction surgery, this may be particularly problematic considering the rate of postoperative complications of up to 69%¹⁹.

Haberer et al.²⁰ analyzed a significant group of cases treated with breast-conserving surgery and showed the feasibility of this treatment strategy, without compromising loco-regional control, therefore should be considered in patients who wish to conserve the breast, as our patient. However, the authors recommended strategies to spare organs at risk, highlighting the use of unconventional positioning as lateral or ventral decubitus position, deep inspiration breath-hold technique or breathing-synchronized irradiation²⁰. There are also promising results with the use of intraoperative partial breast irradiation in women who had previously been irradiated^{21,22}. However,

the feasibility of the patient positions and advanced techniques described above have to be assessed on a case-by-case basis, as there may be anatomical or compliance limitations.

In a study of seventy-one Hodgkin's lymphoma survivors treated for secondary breast cancer, mostly with mastectomy, Wolden et al.²³ reported a similar prognosis compared to the general population, with 10-year overall survival rate of 88% for stage I. In this study, only two patients were treated with breast-conserving surgery, one of which developed soft tissue necrosis in the breast due to re-irradiation.

CONCLUSIONS

Chemoradiotherapy is the standard treatment for localized Hodgkin's lymphoma, associated with overall survival gain. Given the higher prevalence of this disease at younger ages, the late effects of this treatment are of particular concern and need tailored surveillance. We highlight the risk of radio-induced tumors, particularly the most common secondary breast cancer. The age at diagnosis, the volume of the irradiation field and the prescribed dose are established risk factors. Breast conserving surgery with adjuvant radiotherapy is feasible, without compromising local control, even though therapeutic decision must always be personalized and changes in the patient position and use of advanced radiotherapy techniques must be considered.

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