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Effective management of a patient with secondary male breast cancer after neck radiotherapy for tonsillar lymphoma

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► ***Case report***

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ABSTRACT

Recent advances in surgical techniques, chemotherapy and radiotherapy led to significant increase in the number of long-term cancer survivors, but on other hand with increased probability of adverse effects, including the development of a secondary malignant neoplasm. This is especially important to consider when there is the need to provide treatment recommendations for patients undergoing radiotherapy keeping in mind the potential risks of toxicity associated with possession of specific genetic variants. We reported the clinical case of a patient in whom rare malignancies associated to genetic mutation have been treated and managed in the best way thanks to the support of radiotherapist. In particular a male patient with positive family history of BRCA2 mutation, developed breast cancer after radiotherapy for a rare tonsillar non-Hodgkin Lymphoma. We highlight that the knowledge of all aspects of the diseases, of all treatments secondary effects, in particular of ionizing radiation in patients with potential genetic risk of toxicity, allowed an optimal management of the case.

INTRODUCTION

Radiotherapy (RT) is an integral part of cancer management, with more than 50% of all patients undergoing radiation treatment [(1)]. However, the management of patients' candidate to RT is often complicated because RT represents only one of the therapeutic options available, so patients are not strictly managed by the radiotherapist, but by clinicians, who are not expert about the effects of ionizing radiations and their management. In fact, although the progress in the fight against cancer, many patients treated with RT suffer from adverse effects, including the risk of a secondary malignant neoplasm [(2)].

Ionizing radiation works by causing damage to the DNA of the target cell, but healthy tissues affected by the radiation can also suffer the same damage. Healthy tissues are capable of repairing radiation damage, but this possibility depends on many factors, including the presence of genetic mutations [(3)].

In organizing a RT plan, it is important to know all the disease characteristics in order to prepare an optimal treatment planning, but also patient clinical conditions are essential to evaluate the possibility to perform RT, defining its modalities.

We therefore report a clinical case of a patient treated for rare tonsillar lymphoma, for whom the medical history allowed to identify the predisposing factors for the onset of a secondary Male Breast Cancer (MBC). In particular the knowledge of positive family history of BRCA2 mutation and previous chemotherapy (CHT) and irradiation fields of previous radiotherapy allowed to establish a targeted follow-up in order to promptly treat MBC.

Case presentation

A 59-year-old male patient was referred to the radiotherapy department for the treatment of a B-cell High-grade Tonsillar Lymphoma with a positive left submandibular ipsilateral lymph node of 2.5 cm diameter. The patient gave his informed consent for the scientific use of medical data. He already completed 4 cycles of rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) CHT.

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The RT treatment was performed on oropharynx and neck lymph node levels with Linear Accelerator (Unique™, Varian Medical System, Palo Alto, CA, US) for a total dose of 30 Gy in 15 daily fractions (5 fractions per week). Analyzing the dose distribution from the MIM Maestro ® software (MIM Software Inc., Cleveland, OH, US) in the first head and neck RT plan, the breasts, received a mean dose of 61.8 cGy (max 513.9 cGy, min 9.6 cGy). In terms of relative biological efficacy dose, the breast had received 74.2 mSv from the first head and neck treatment alone (figure 1).

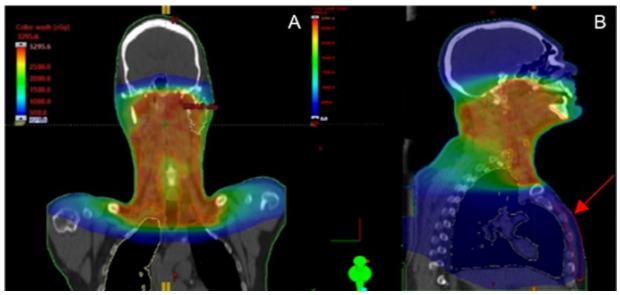

Figure 1. Head and neck treatment plan. **(A)** Dose distribution from the coronal image. **(B)** Dose distribution from the sagittal image with breast contours, included in the distribution dose field, indicated by a red arrow.

During the preliminary visit, the patient reported a family history of oncological disease, in particular, the diagnosis of breast cancer to his sister at the age of 43 with the BRCA2 mutation.

In the following 5 years, the patient performed a six-monthly follow-up according to the current guidelines without signs of recurrence [4].

After that, considering the oncological familiarity, the previous R-CHOP CHT, and breast involvement in the irradiation field, the patient was advised to perform periodic six-monthly breast ultrasound and prostate-specific antigen (PSA) dosage.

After 6 years after the end of RT, the breast ultrasound showed a solid lesion with irregular margins in the right breast. The patient was direct to perform first a lymphoscintigraphy for the detection of sentinel lymph node, then he underwent total mastectomy with axillary lymphadenectomy (figure 2).

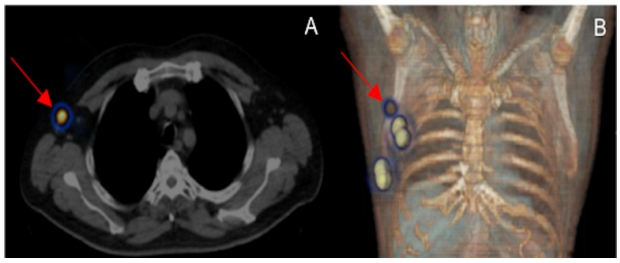

Figure 2. Lymphoscintigraphy with 99mTC-nanocolloid from the right breast. The axial image **(A)** and the volumetric reconstruction **(B)** show the presence of the sentinel lymph node in the right axilla, indicated by a red arrow.

The pathology exam showed ductal infiltrating carcinoma, grade 3, with deep vascular infiltration and skin infiltration. The presence of metastasis in the sentinel lymph node led to axillary lymphadenectomy: four axillary nodes were positive for metastasis. Estrogen Receptor 90%, Progesteron Receptor 90%, Ki67 16%, Her2 neg = pT4b pN2a. At genetic screening, the patient was also found to be a carrier of BRCA2 mutation.

After surgery, the patient underwent adjuvant CHT according to the schedule of Epirubicin and Cyclophosphamide for 4 cycles and concomitant starting of anti-estrogen therapy for 5 years.

After that, RT treatment was performed on the chest wall and supraclavicular nodes area with Linear Accelerator for a dose respectively of 50 Gy and 40 Gy in 25 daily fractions (5 fractions per week) (figure 3).

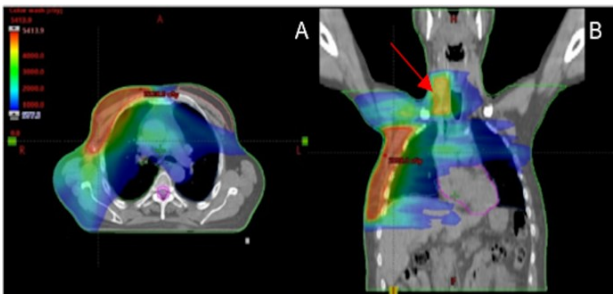

Figure 3. Right chest wall and ipsilateral supraclavicular nodes area treatment plan. **(A)** Dose distribution from the axial image. **(B)** Dose distribution from the coronal image with the right supraclavicular nodes area, indicated by a red arrow, which received a lower dose considering the previous treatment dose overlap.

One year after the end of chest wall RT, the patient performed 18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) (Discovery 710, GE Healthcare, Milwaukee, WI, US) scan to follow both breast cancer and lymphoma and it showed the absence of relapses (figure 4).

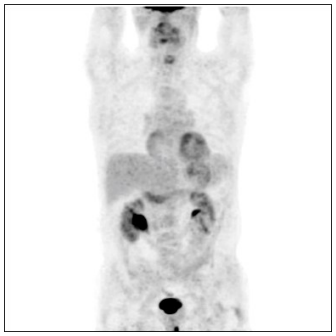

Figure 4. 18F-FDG PET/CT. The maximum intensity projection (MIP) of the PET shows the physiological distribution of 18F-FDG.

DISCUSSION

Tonsillar tumors are relatively common primary carcinomas of the head and neck district and are mostly represented by squamous cell carcinomas followed by non-Hodgkin Lymphoma (NHL) [5]. Primary extranodal NHL of the head and neck

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account for 10-20% of all non-Hodgkin's lymphomas. Treatment policies for primary extranodal lymphomas included RT with or without CHT for limited-stage disease and aggressive CHT with or without RT for advanced-stage disease.

In recent years, an increasing number of studies reported a trend in developing a secondary tumor in patients who underwent combined CHT and RT, representing a matter of debate. This condition belongs to the evidence that the combination of RT and CHT is more inductive to secondary solid tumors than RT alone. This is explained by the potentiating effect of CHT drugs such as anthracyclines (e.g. doxorubicin). Conversely, alkylating agents, seem to have a protective effect, especially if the number of treatments is increased [6].

Several studies reported an increased overall risk of secondary cancer after treatments for NHL [7- 9]. Sacchi and colleagues reported the onset of secondary cancer in almost 7% of patients with indolent NHL with a median estimate of 52 months. Interestingly, in their study, the risk was increased significantly in the male population and patients between 45-64 years old, and the cumulative incidence of secondary cancers continued to increase throughout follow-up [9].

In the clinical case we presented, the age of the onset, as well as the latent time of secondary cancer, are in line with the literature.

The growing interest and knowledge about the detection of secondary neoplasms require a personalized screening program for higher-risk patients to prevent or promptly diagnose secondary tumors.

Nowadays, according to the European Society for Medical Oncology (ESMO) guidelines, the follow-up recommended for patients with NHL consists of a careful history and physical examination every 3-6 months for the first three years, then once a year with attention to the development of secondary tumors or other long-term side-effects of CHT. In addition, is common practice a computed tomography scan examination at 6, 12, and 24 months after the end of treatment [4].

One other important aspect concerns the importance of good clinical practice and the value of the doctor-patient relationship that allows patient medical history “depth-learning”.

RT is an essential component of cancer therapy in almost all oncologic diseases. This highlights the importance of using the best data available to provide treatment recommendations for patients who require RT but have an increased risks of toxicity considering the possession of specific genetic variants. For this reason, our clinical case patient was advised to perform periodic six-monthly breast ultrasounds for an accurate follow-up.

MBC is a rare tumor, accounting for ~0.6% of all breast cancers and <1% of all cancers in men [10]. Its pathogenesis is not clear and known risk factors include genetic defects (BRCA2), estrogen–androgen imbalance, radioactive injury, and testicular disease (cryptorchidism, orchitis, or orchiectomy) [11].

Moreover, a family history of breast cancer increases the risk of MBC, with a relative risk of 2.5; 20% of affected men have a first-degree relative with breast cancer, especially in the early onset [12, 13]. Notably, in the setting of the early onset, Rosenblatt and colleagues showed that the odds ratio of developing breast cancer was greater in men with first-degree relatives who developed mammary neoplasm before the age of 45, than in men with older first-degree affected relatives [14].

In clinical practice, genetic counseling is therefore recommended in all MBC patients, especially when the mutation in relatives is not already known.

Inherited germ line mutations are a likely etiology for 4% to 40% of MBC compared to 30% to 86% of female breast cancer [13]. Estimates of the lifetime risk of developing MBC range from 1% to 5% for BRCA1 mutation carriers and 5% to 10 % for BRCA2 mutation carriers, compared to 0.1% in the general population [15].

BRCA1 plays a key role in DNA double-strand breaks (DSBs) repair pathways in the late S and G2 phases of the cell cycle, allowing the cell to repair DNA damage before proceeding to the next phase of the cell cycle while the functions of BRCA2 are largely limited to DSBs repair by promoting the mechanism of homologous recombination [3, 16].

It has been hypothesized that patients with breast cancer and BRCA1/2 mutation may be more vulnerable to side effects of radiotherapy (especially at lower doses) than those without mutation, considering the lack of homologous recombination leading to inadequate repair of double-stranded DNA breaks [16].

The individual risk of the described patient in our case is increased by the combination of BRCA-2 mutation and the diffuse RT dose to the breast from the previous treatment, which could have played a role in oncologic promotion, in a baseline condition of weak DNA repair capability represented by the BRCA2 mutation.

The time latency of 5 years between first RT and secondary malignancy is well within the expected range of latency described in Hodgkin’s disease after initial RT [17].

MBC has many similarities with female one, but the rarity of the disease precludes large clinical trials, to define standard treatments.

All pathological subtypes of breast cancer in women can be developed in men, with invasive ductal carcinoma accounting for most cases (93.7%), followed by papillary carcinoma (2.6%), medullary carcinoma, tubular carcinoma, mucinous carcinoma, metaplastic carcinoma, inflammatory breast cancer, and Paget disease [10].

MBC is burdened by a poor prognosis. Giordano et al, reported that MBC had a later age of onset

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compared to female disease, and it is often diagnosed at an advanced stage often presenting ductal histology, and ER/PR-positive status [10, 18].

Research directed at MBC has been limited compared to female breast cancer, so management of MBC has mainly relied on adopting clinical practices developed to treat female breast cancer patients: surgery, RT, CHT, and endocrine therapy [19- 21].

Men are more likely than women to undergo mastectomy and to receive adjuvant radiotherapy, as our patient.

About the axilla dissection, according to the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) practice guidelines for lymphoscintigraphy, sentinel lymph node localization and biopsy are now the standard of care for staging the axillary lymph nodes in breast cancer patients with clinically negative axillary lymph node involvement [22]. Sentinel lymph node is preferred because of a strong reduction in treatment-related morbidity compared to axillary dissection [23].

The choice of CHT in men is made on the same risk factors valid for women (including tumor size, nodal involvement, hormone receptor status, HER2 status, and the underlying biology of cancer) [24].

Although new therapeutic approaches, disease recurrence remains one of the main adverse predictors of prognosis in MBC [25, 26].

The role of whole-body imaging, especially 18F-FDG PET/CT, in the management of MBC, has been poorly reported due to the rarity of MBC. Among the current literature, some studies have shown that 18F-FDG PET/CT is a powerful tool in the restaging setting and treatment response assessment in MBC patients, especially in the recurrence scenario, and could be essential to delineate the correct therapeutic approach and to predict the prognosis [27- 29].

In the specific setting of disease recurrence, Vadi and colleagues showed that 18F-FDG PET/CT was able to detect recurrence (both local and distant) in 82.6% of patients and a significant number of patients had distant metastases (65.2%) underlining its good diagnostic utility in MBC [30].

Secondary malignancies are important causes of morbidity and mortality in patients with oncologic disease treated with RT. Some histotype and genetic mutation may predispose patients to even greater risk of secondary malignancies with an even worse prognosis.

We reported the clinical case of a patient in whom rare malignancies associated to genetic mutation have been treated and managed in the best way thanks to the support of radiotherapist.

We conclude that the knowledge of all aspects of the diseases and all treatments secondary effects allowed optimal management of the patient.

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***Authors' contribution*:** FT conceptualization; ARP methodology; EM resources; MM clinical and radiological support; AS data curation and supervision; CA writing-original draft preparation, AS review and editing, MP project administration. All authors have read and agreed to the published version of the manuscript.

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