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Double Breast Neoplasia: RH+, HER2- Metastatic Left Breast Cancer and Triple Negative Metastatic Right Breast Cancer: Case Report

Imane Chahbounia[1*], Saida Lamine[2], Khaoula Alaoui Slimani[2], Omar Ait Sahel[2], Rachid Tanz[2], Hassan Errihani[2], Mohammed Ichou[2]

[1]Medical Oncology Department, Mohamed V Military Instruction Hospital, Rabat, Morocco
[2]Medical Oncology Department, National Institute of Oncology, Rabat, Morocco

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***Corresponding author:** Imane Chahbounia
Medical Oncology Department, Mohamed V Military Instruction Hospital, Rabat, Morocco

Abstract **Case Report**

Breast cancer is the most common cancer in women, and the proportion of metastatic cancer is not negligible; either metastasis of a cancer that was initially localized, or metastatic disease from the outset. The case of double breast neoplasia is not exceptional; but when faced with two breast cancers, both metastatic, and with different molecular profiles, several questions arise. Case report: We report the case of a diabetic patient with localized RH+, HER2- left breast cancer treated with surgery and adjuvant chemotherapy in 2003, which became metastatic to the lung in 2022, and for which the patient received hormone therapy + anti CDK4/6. In the same month as the pulmonary lesions were discovered, a right breast cancer was diagnosed, biopsied as triple-negative; this metastasized to the brain in 2024. Conclusion: the problem in this case concerns the rarity of occurrence of two metastatic breast cancers for the same patient, the complexity of therapeutic management, and makes us think about intra-tumoral heterogeneity in breast cancer.

Keywords: Treatment, bilateral breast neoplasia, metastasis, heterogeneous cancer.

INTRODUCTION

Breast cancer is a major public health problem worldwide, with incidence rising steadily over time due to the increasing prevalence of various risk factors. According to the International Agency for Research on Cancer, breast cancer ranks first in terms of frequency among all female cancers, and fifth in terms of mortality [1].

Breast cancers are classified (according to hormone receptor and HER2 receptor) as: RH+ HER2- cancer, triple-negative cancer or HER2+ cancer.

Prognosis may vary according to the presence or absence of receptors, but also according to the stage of the disease; thus, metastatic disease may have a severe prognosis than localized disease. And therapeutic management will depend on a number of factors, including molecular classification and stage [2].

Therapeutic management can become more complicated in case of double breast neoplasia, especially in advanced stages [3].

In this context, we report the case of a patient who has two breast cancers: a RH+, HER2- left breast cancer localized in 2003 that became metastatic in 2022; and a triple-negative right breast cancer localized in 2022 that metastasized in 2024.

CLINICAL OBSERVATION

This is a 63-year-old patient, followed for type 2 diabetes on metformin, hypothyroidism on levothyrox and followed since 2003 for localized left breast cancer RH+ HER2-, operated (conservative surgery) and treated with adjuvant chemotherapy.

19 years later (in 2022), during surveillance, a nodule was discovered in the right breast, which was subsequently operated on (mastectomy + curage). Pathological anatomy: invasive ductal carcinoma, receptor-negative (RH-, HER2-), SBR grade III, 3N+/23N, absence of vascular emboli and peri-nervous sheathing.

A cervico-thoraco-abdomino-pelvic CT scan performed in the following weeks showed suspicious

secondary pulmonary nodules and mediastinal adenopathies.

On PET scan: multiple pathological hypermetabolic lung parenchymal and subpleural foci in both lungs, associated with large pathological hypermetabolic mediastinal and left pulmonary hilar lymph node foci (Figure 1).

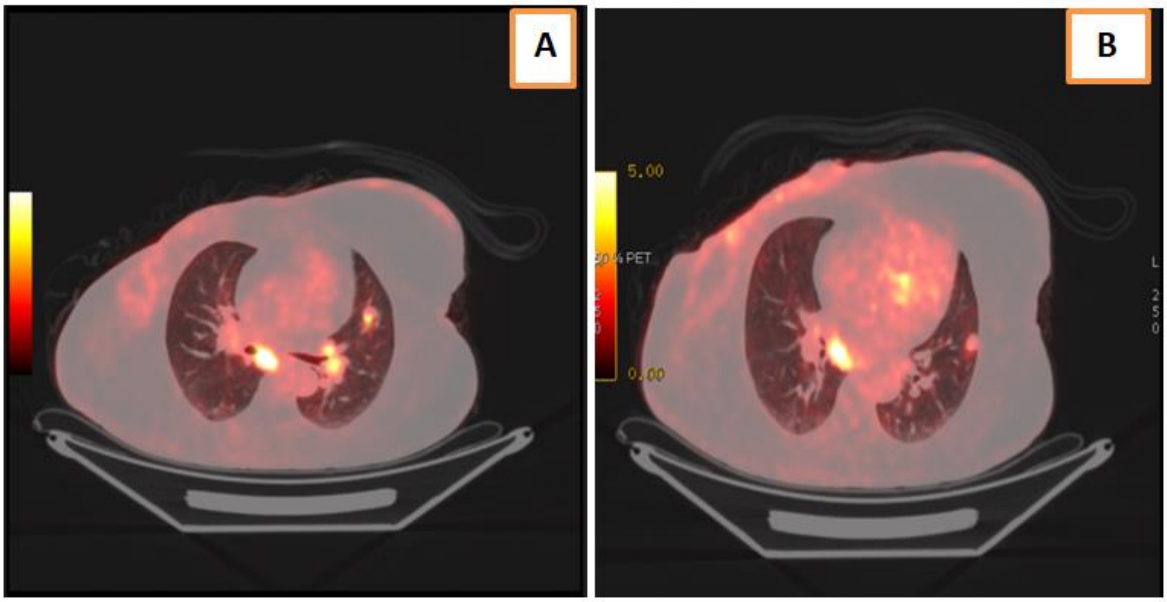

Figure 1: A) PET-CT axial section showing a pathological hypermetabolic pulmonary nodule of the left lung (lingula), and left pulmonary hilar and subcarinal lymph node hypermetabolism; B) PET-CT axial section showing a pathological hypermetabolic subpleural lung nodule (in the left lower lobe)

A lung biopsy was performed, with an anatomopathological study in favor of a pulmonary localization of a poorly differentiated carcinomatous process, and immunostaining supported the diagnosis: RH+, HER2-. It was therefore a metastasis of the RH+, HER2- cancer diagnosed in 2003.

The patient has been on aromatase inhibitors + palbociclib since February 2022. In view of the progressive onset of right-hemiparesis, brief loss of consciousness and cognitive impairment (with dysphasia, dyslexia, memory and attention problems), a cerebral CT scan was ordered in January 2024: left capsulo-lenticular intra-parenchymal lesion with subfalcoral involvement, giving rise to the 1st suggestion of a secondary location.

Cerebral MRI identified a 32*28mm left paraventricular lesional process (Figure 2).

We completed the investigations with a biopsy of the thalamic process and an anatomopathological study, the results were as follows: morphological appearance and immunohistochemical profile compatible with a brain metastasis of the patient's known breast carcinoma; hormone receptors were negative, as were HER2 receptors (Herceptest score = 0).

The patient received stereotactic radiotherapy to the brain (+ corticosteroids) in the month following this diagnosis, which was beneficial, and helped her to recover her autonomy and higher brain functions. The bone scan was without abnormality.

So this patient has had two breast cancers, both metastatic:

- A left breast cancer localized in 2003 RH+, HER2- becoming metastatic to the lung in 2022.
- A right breast cancer localized in 2022 triple-negative, becoming metastatic to the brain in 2024.

Following the recommendations of international scientific societies, and after a medical staff meeting, we proposed to put the patient on a treatment that targets both metastatic cancers at the same time.

For the triple-negative metastatic cancer, we asked for PDL1 status, which came back at 0%, so we decided on chemotherapy alone, which would also target the second cancer: weekly Paclitaxel 90mg/m² D1 D8 D15 (D1 = D28).

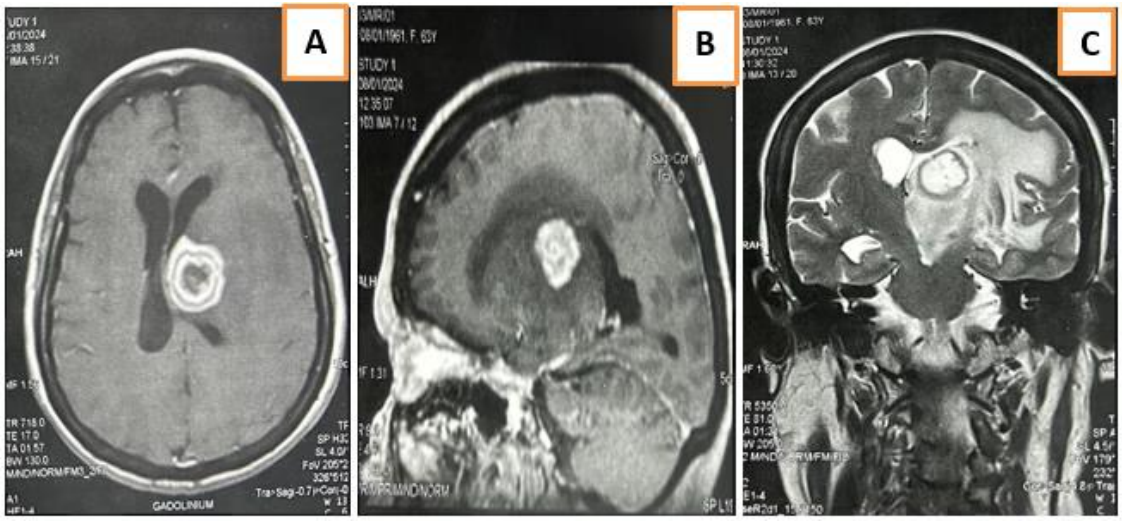

Figure 2: Cerebral MRI showing an intra-axial deep white matter process, oval and well-defined with regular contours (A+B), T2 iso signal (C), necrotic center enhanced peripherally after Gadolinium injection (A), associated with peri-lesional glove finger edema, exerting a mass effect (A); (A) Axial T1 section (Sat Fat) with Gadolinium injection; (B) T1 sagittal section (Sat Fat) with Gadolinium injection; (C) Frontal T2 section

DISCUSSION

In advanced stages of RH+, HER2- breast cancer, hormone therapy is the preferred option whatever the line of treatment, except for visceral crisis where a rapid tumor response requires chemotherapy, oligometastatic disease where multimodal management can be envisaged, and de novo metastatic inflammatory breast cancer.

In first-line treatment, hormone therapy is generally not prescribed on its own, but in combination with targeted therapy, in particular anti CDK4/6, thus improving progression-free survival and overall survival, but requiring toxicity management [4].

For patients who have not received adjuvant hormonal therapy for more than 12 months, or who have never received it, aromatase inhibitors are combined with anti-CDK4/6; in the opposite case (if adjuvant hormonal therapy is recently received): fulvestrant is used instead of aromatases inhibitors [5].

In premenopausal women, ovarian suppression is necessary, either by ovarian function suppression (OFS) or ovarian ablation. Bilateral oophorectomy provides more rapid estrogen suppression than gonadotropin-releasing hormone agonists [6].

For the second line of therapy, and after progression with aromatase inhibitors and a CDK4/6 inhibitor, determination of somatic mutations in PIK3CA, estrogen receptor 1 (ESR1) and germline mutations in BRCA1/2 is recommended, and treatment will follow. Chemotherapy is indicated in subsequent lines [7, 8].

Unlike metastatic RH+ HER2- breast cancer, the main treatment for metastatic triple-negative cancer is not hormone therapy, but rather chemotherapy, immunotherapy and/or targeted therapy [9].

In first-line treatment, establishing PD-L1 status and searching for the BRCA germline mutation is essential to optimize therapeutic management. If PD-L1 positive (CPS greater than or equal to 10%), the preferred option is pembrolizumab in combination with chemotherapy (paclitaxel, nab-paclitaxel or gemcitabine + carboplatin); the atezolizumab + nab-paclitaxel combination also remains valid [6].

In the case of BRCA germline mutation with negative PDL1 status, the preferred options are olaparib or talazoparib, or carboplatin-based chemotherapy [10].

If PDL1 status is negative in the absence of BRCA germline mutation, the preferred option depends on previous treatment exposure, disease presentation and patient considerations. Taxane monotherapy is the most frequent option, anthracyclines are an option in cases of no prior exposure or if rechallenge is possible. In case of imminent organ failure, combination therapy is preferred based on a taxane and/or anthracycline combination and including bevacizumab [6, 11].

When it comes to triple-negative or RH+, HER2- metastatic breast cancer, management is generally straightforward. But when we're dealing with two cancers, affecting both breasts, treatment decisions become more difficult.

Double breast neoplasia is a rare situation; almost all breast cancers are unilateral, with bilateral breast cancer affecting around 1-3% of all those diagnosed.

Bilateral breast cancer can be classified as synchronous (coexisting) or metachronous (existing at

different times). Synchronous cancers are those in which both breast tumors are diagnosed within three to six months. Cancers are said to be metachronous if the second breast cancer is diagnosed three months after the primary one; as in the case of our patient, who developed the second cancer almost 19 years after the first [12].

Synchronous bilateral breast cancer is rarer than metachronous cancer [13]. The fundamental question to answer in the case of cancer of both breasts: what are the risk factors?

A genetic mutation can increase the risk of developing tumors in both breasts. Other possible factors include diagnosis of the first cancer at a young age, a family history of breast cancer, a history of breast complications and obesity [1].

In terms of prognosis, median survival in bilateral breast cancer is multifactorial, and may depend on the size of both tumors, hormone and HER2 receptors, proliferation index, lymph node invasion and the metastatic or localized stage of both cancers [2].

Double breast neoplasia remains a rare disease entity, especially when both cancers are metastatic; so the management and therapeutic decision can only be taken in a multidisciplinary concertation meeting.

CONCLUSIONS

Given its rarity, this described case of "metastatic double breast cancer" calls for further, ongoing scientific research in all directions: surgery, chemotherapy, targeted therapy and immunotherapy.

Our patient's clinical observation brings us to a new debate: is the late onset of a second breast cancer a true primary? or just a metastasis of the first, changing its molecular profile?

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