CLINICAL CASE

BILATERAL BREAST CANCER, THERAPEUTIC APPROACH

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Abstract

We present a rare case of breast neoplasm, synchronous (simultaneous) bilateral breast cancer, methods of diagnosis, multimodal treatment and the standard follow-up program. Bilateral breast cancer is a rare entity, with an incidence between 0.3 and 12%, representing 1 to 2.6% of all breast cancers. Bilateral breast cancer is defined as the presence of cancer cells in both breasts at the same time or at a distance of up to 3 months from the identification of the first tumor (synchronous), or metachronous if it occurs after more than 3 months from the identification of the primary tumor. There is not a general agreement regarding the optimal treatment. The prognosis is considered more severe than that of a unilateral neoplasm and the patients are treated more frequently by undergoing bilateral mastectomy rather than conservative surgery. We present the case of a 57-year-old patient diagnosed by clinical and imaging investigations (mammography, MRI) with bilateral breast tumor formations. The 57-year-old patient was referred to our clinic for a bilateral synchronous breast pathology. The pathological examination of the biopsy revealed bilateral invasive ductal breast cancer, with an intermediate histological grade G2, ER +, PR +, HER2 - (score 0 ASCO-CAP). Therefore, the diagnosis was simultaneous bilateral breast cancer, a rare entity which represents the real bilateral cancer of the breast. Neoadjuvant therapy was started and then Madden modified radical mastectomy was performed. The histopathological examination confirmed the invasive ductal carcinoma in the left breast - pT1cN1aG2 and in the right breast- pT1cN0aG2. Considering that it is a rare variant of breast cancer, with a severe prognosis, the presented case reflects the current diagnostic and treatment approaches, and the gaining of better long-term results are ensured by a correct multidisciplinary approach.

Keywords*: bilateral breast cancer, breast neoplasm, ductal breast cancer*

Introduction

Bilateral breast cancer is a rare entity, with an incidence between 0.3 and 12%, representing 1 to 2.6% of all breast cancers. Bilateral breast cancer is defined as the presence of cancer cells in both breasts at the same time or at a distance of up to 3 months from the identification of the first tumor (synchronous), or metachronous if it occurs after more than 3 months from the identification of the primary tumor. There is not a general agreement regarding the optimal treatment. The prognosis is considered more severe than that of a unilateral neoplasm and the patients are treated more frequently by undergoing bilateral mastectomy rather than conservative surgery.

Presentation of case

In this article we present the case of a 57-year-old patient, who was hospitalized for tumoral formations in both breasts. The patient is a smoker (20 packs per year) and has high blood pressure. Personal history: menarche at 14 years old, 4 misscarriages, no births and menopause at 47 years old. She has no family history of breast or genital cancer.

The patient came for a clinical examination having a painful sensation and paresthesia in both breasts. During the examination we have detected a painful formation in the upper external quadrant of the left breast.

Bilateral breast ultrasound examination of the right breast reveals: glandular tissue moderately represented, dilated galactophorous ducts; a formation which replaces normal tissue 1.43 / 0.81 cm, imprecisely delimited, star-shaped, with architectural distortion and microcalcifications, well vascularized, localized at 11 mm depth and 6 cm from the nipple. In the left breast: glandular tissue moderately represented, dilated galactophorous ducts; a formation which replaces normal tissue 2.08 / 1.48 / 1,7 cm, imprecisely delimited, star-shaped, with architectural distortion and microcalcifications, well vascularized, localized at 12 mm depth and 4 cm from the nipple. In conclusion, ultrasound examination reveals: type 2 mammary gland; microcystic adenosis; bilateral formations which replace normal tissue - BIRADS score 5.

Bilateral mammography reveals: breasts with a fat-glandular structure, without asymmetric density. The left breast presents in the upper external quadrant a star-shaped opacity with a diameter of 1cm, with some microcalcifications included - BIRADS score 5.

Bilateral breast MRI with intravenous contrast: type 1 mammary gland, formations which replace normal tissue in both breasts, bilateral axillary lymphadenopathy with a reactive character, BIRADS score 5 (Figure 1).

It is recommended to obtain a biopsy specimen from the tumor formations which was identified clinically and radiologically, because the radiologic features affirm a high risk of malignancy.

A TRU CUT biopsy of both tumor formations was performed.

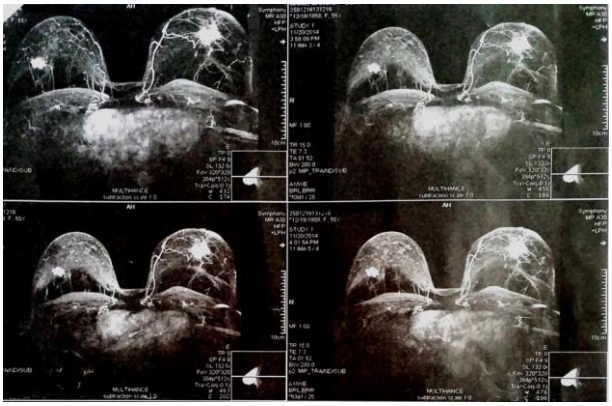

Figure 1 - Bilateral breast MRI

The histopathological and immunohisto-chemical examination of the biopsy pieces: bilateral invasive ductal breast carcinoma, intermediate histologic grade (G2) (Nottingham score 6: Ft=3, A=2, M=1); with a nonextensive component (1%) of ductal carcinoma in situ; absent lymphovascular invasion (LV0); undeterminable perineural invasion (PNX); A molecular luminal subtype; existing hormonal receptors (100% estrogen receptors, 95% progesterone receptors); negative HER2 (score 0, ASCO-CAP 2013); low proliferation index (Ki67 10%).

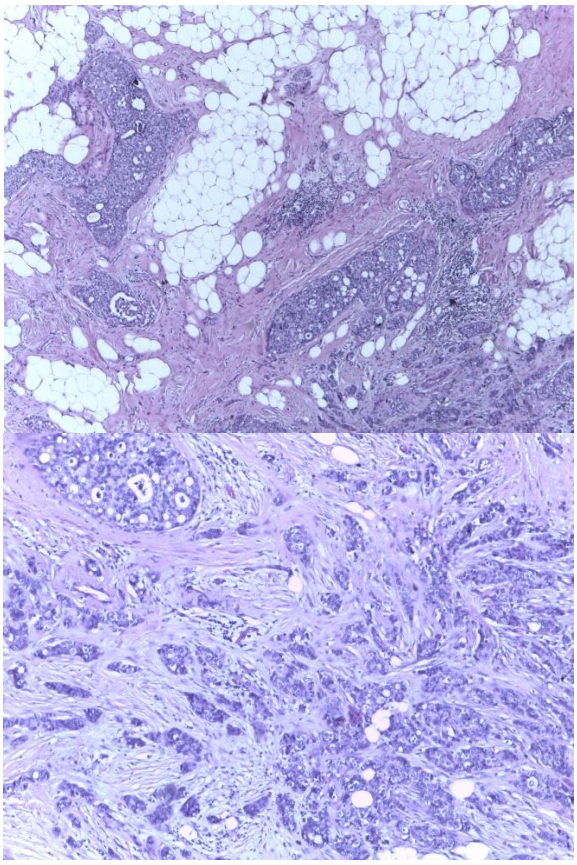

Figure 2 - microscopy hematoxyline – eosine (HE) 5x, 10x, left breast

Considering the limits of biopsy sample and the phenotypic heterogenity, the pathologist recommended histopathological and immunohistochemical revaluation of the surgical resected pieces to define the morphology of cancer, grading of tumors, the prognosis and morphological status markers HER2/neu. Immunohistochemical positivity for hormonal receptors requires evaluation for an oncological management and antihormonal treatment.

The neoadjuvant treatment consisted of 4 series of 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC).

After 6 weeks, a bilateral Madden modified radical mastectomy was performed (Figure 4), and also histopathological examination of the resected pieces, which confirmed the diagnosis of invasive ductal breast carcinoma, pT1c,N1a,G2 in the left breast (Figure 2, 3) and pT1cN0aG2 in the right breast (Figure 5).

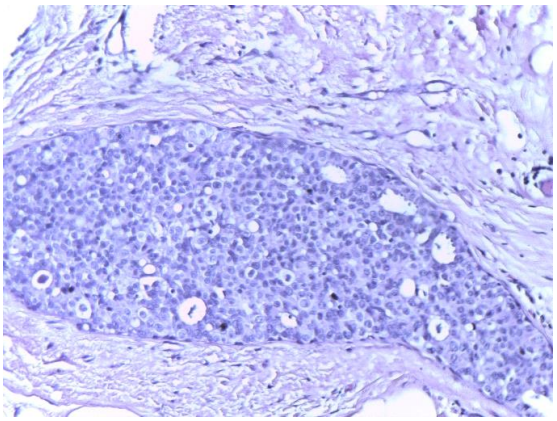

Figure 3 - microscopy HE 20x, left breast – detail – intracanalicular proliferation

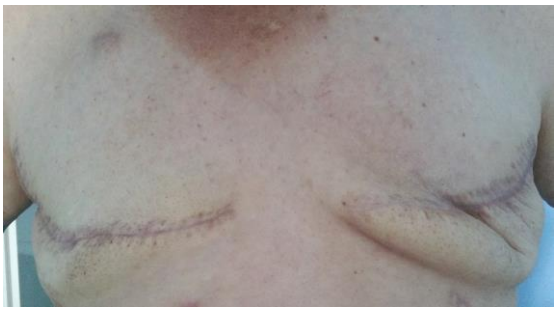

Figure 4 - Postoperative aspect

The patient received standard chemotherapy (4 series of Taxol and Endoxan), radiotherapy and adjuvant hormone therapy (Tamoxifen), and entered in a standard follow-up programme.
6 months cranian thoracic abdomino-pelvic CT scan shows no signs of metastasis.

A breast reconstructive procedure is planned.

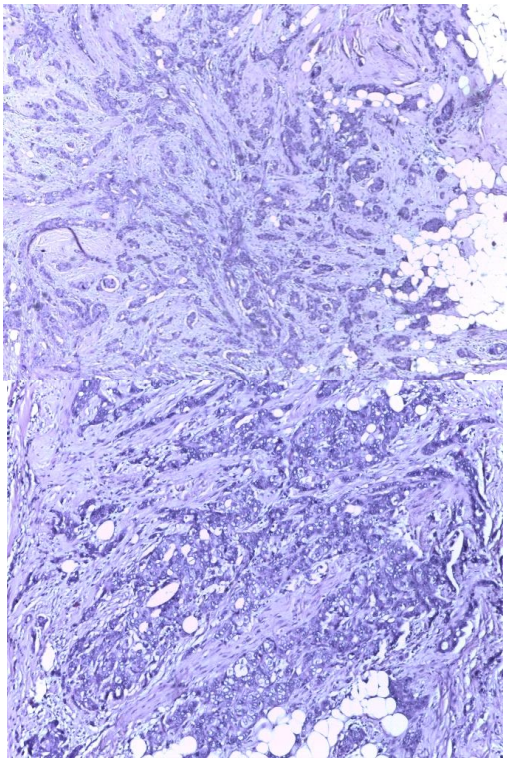

Figure 5 - microscopy HE 5x, 10 x, right breast

Literature review

According to the latest report of the International Agency for Research on Cancer, Globocan 2012, breast cancer represents the first position in the world in the incidence of neoplastic diseases (25.1%) and the second position (14.7%) in terms of cancer mortality among women [1]. According to the same study in 2012, in Romania, in a female population of 11,017,000 women, 8,981 new breast cancer cases of 35,611 cancers among women were registered, resulting a incidence of 24.96%.

Synchronous bilateral breast cancer is a rare entity, with an incidence between 1 and 3% of all breast cancers [2]. This happens because there is a small difference of time to define the synchronous and metachronous types of breast cancer. According to Hartman et al 2007, the diagnosis of a second tumor within 90 days since the first appearance of the first tumor, is called synchronous breast cancer [3], the simultaneous tumors are diagnosed at the same time, and the metachronous tumors are those occurring after 90 days. In case of simultaneous detection the most advanced tumor is described as the dominant and determine the clinical

stage, but the less advanced tumor is considered contralateral. By synchronous and metachronous cancers the first diagnosed tumor is considered the primary, and the other is contralateral. Yet this description is irrelevant in terms of treatment and prognosis, because the histopathological and immunohistochemical type of tumors is important [4].

The etiology of synchronous breast cancer is still unknown, but it seems that its appearance and development have a multifactorial etiopathogeny. Among the risk factors associated to unilateral and synchronous breast cancer are: female gender, existing family history, existing breast lesions, medical history of genital and breast cancer, age, gynecological, physiological disorders [5,10,12]:

- Gender : female/male ratio: 100/1;
- Existing family history: if a first degree relative has developed the neoplasia until the age of 60 years, the risk of breast cancer is 4-6 times higher;
- Existing breast lesions: benign tumors and inflammatory or traumatic injuries can be favorable conditions for the development of cancer;
- Gynecological physiological disorders: nulliparity, abortions (especially repeated miscarriages), dysmenorrhea, refusing lactation, late menopause;
- Age: according to Roder et al the risk of synchronous bilateral breast cancer increases with age (21), at patients with a mean age of 44.83 ± 9.67 years [12].

From the histological point of view, an increased risk of contralateral breast cancer is present at primary lobular breast cancer. This may reflect the fundamental differences of biological and/or etiological behavior of the tumors originated in the lobular differentiated cells versus those with ductal origin. It was found that an initially lobular breast cancer component, regardless of whether it was invasive or in situ, was associated with an almost 2 times higher risk of developing a contralateral breast cancer [6,7].

Synchronous tumors have similar biological behaviors [4]:

- Similar histological appearance;
- Cellular differentiation with favorable tumor grading (G1, 2) at more than 2/3 of cases;
- Positive expression of hormones estrogen and progesterone receptors;
- Low peritumoral vascular invasion (PVI) and Ki-67 expression;
- Low tumoral volume.

Because of the fact that they have similar biological behaviors, some authors explain the etiopathogeny of synchronous bilateral cancers through the hypothesis of multicenter cancer, which may present an intense proliferative activity, and of metachronous bilateral cancers, by lymphatic spread, the second being actually a metastasis of the first cancer [4].

Differentiation criteria of bilateral primitive tumors and contralateral metastases are:

- histopathological: the presence of an in situ component or a better histological differentiation of the subsequent tumor or different histological tumors in the two breasts;
- chronological: the absence of lymphatic or hematogen metastases and/or long time interval between the detection of those two localisations.
- In order to discriminate against mono or biclonal origin of the two tumors, the best is the molecular exploration [8]. Carcinomas were classified as de novo carcinomas or metastases relying on the three levels of concordance:
- molecular tumor affected markers were considered concordant if 50% or more of the same markers had a mutation;
- there exists a copy of the same affected gene;
- there is an acquired mutation due to the temporal sequence.

In patients with synchronous bilateral breast cancer, the molecular analysis revealed discordant mutations in all cases, supporting de novo diagnosis of primary bilateral breast carcinomas. At patients with lymph node metastases, the primary breast carcinoma and the metastases share the same mutations revealing a metastatic lesion. However, when metastases are metachronous detected, the clone can undergo a genetic alteration under the influence of environmental factors, including under the influence of radiotherapy [5,8,10].

Besides the hereditary or acquired genetic changes and mutations underlying neoplasms, a main role in the pathophysiology of breast cancer, and more so in the case of synchronous bilateral breast cancer, have estrogens and progesterons [4,9,10,11].

Estrogens, by their effect of stimulating the proliferation of breast epithelium, are increasing the chance of a DNA replication resulting carcinogenic mutations. Among the risk factors above mentioned are also the precocious menarche, the irregular ovulation and the late menopause, factors that are increasing the time of exposure to estrogens. According to Coradini et all [11], most or even all of the synchronous bilateral breast cancers have estrogen receptors. This was not demonstrated in case of progesterone receptors, their appearance in synchronous cancers being variable, without any statistical significance.

It was found that both long time survival and recurrence-free interval are not different in bilateral or unilateral breast cancer [12]. They decrease if cancer occurs at a younger age, premenopausal, if the patient has associated diseases and if the interval between the two locations is shorter (in case of the metachronous cancers). Also, it has been observed that the risk of mortality at persons with metachronous cancer discovered in less than 5 years after the first tumor is significantly higher than of those with synchronous cancer. Those who have positive HER2 have a higher mortality risk than those with negative HER2 [9,12].

It was observed that bilateral mastectomy for prophylactic purposes is very efficient for the removal of oncological risk of the female population with demonstrated genetic risk. This is followed by bilateral breast reconstruction with autologous tissue, by rearrangement of myocutaneous flaps attached to rectus abdominis muscle [4].

The treatment of synchronous bilateral breast cancer is multimodal combining surgery, chemotherapy, radiotherapy, hormonotherapy and immunotherapy and is customized depending on the patient, the size of the tumor, the axillary lymphatic invasion, the existence of hormone receptors, the histological type, the tumor stage and the menopausal status [10].

Multicenter unilateral breast cancer poses a higher risk of bilateral developing, representing a formal contraindication of breast conservative surgery. For simultaneous or synchronous tumors, possible curable, bilateral mastectomy rather than conservative surgery is traditionally preferred [4].

Irradiant treatment is based on radiosensitivity of the mammary epithelial cells. It can be preoperatively administered to decrease the tumor volume, to sterilize peritumoral or multicentric localizations and to decrease the tumor stage, to reduce the risk of metastasis, and also postoperatively, to sterilize the remaining tumor tissue in surgically inaccessible regions and to reduce the risk of local recurrence [10].

Chemotherapeutic agents are used to prevent recurrences and metastases by destroying the migrated cells during surgery or radiotherapy to decrease the preoperative tumor volume and to provide palliation of extended unresectable tumors and metastases. The most used chemotherapeutic agents are combinations as Cyclophosphamide, Methotrexate-Fluorouracil, Cyclophosphamide-Doxorubicin-Fluorouracil, Cyclophosphamide-Doxorubicin-Paclitaxel[10].

It is focused on hormone-dependent tumors with estrogen or progesterone receptors and intended to modify the patient's hormonal environment. For this purpose are administered postmenopausal hormone antagonists (Testosterone), selective antagonists of estrogen receptors (Tamoxifen), aromatic inhibitors of estrogen synthesis (Exemestane, Anastrozole), or Gonadoliberine analogs (Goserelin) pre-menopausal, or surgical or radiological oophorectomy [10].

In the case of tumors which have HER2 receptors, monoclonal antibody therapy (Trastuzumab - Herceptin) is indicated [10].

Discussions

It is recommended to perform a detailed medical history, clinical examination and mammography to follow breast cancer. Clinical examinations should be performed every 3 months in the first 3 years, then every 6 months for the next 4 to 5 years and annually thereafter. For women who have undergone a breast conservative surgery, a post-treatment mammography should be performed one year after the initial mammography and then at least 6 months after completed radiotherapy. Thereafter, unless otherwise indicated, mammography should be annually performed.

If a bilateral mastectomy was performed, as it is preferable for simultaneous or synchronous tumors, it stands to reason that mammography is pointless, and the main tracking method is clinical examination. In case there is any suspicion after the clinical examination, it is recommended to perform a complete blood count, a biochemical examination of blood, a thoracic cardiopulmonary radiography, an abdominopelvic ultrasound, a bone scintigraphy, CT or MRI to discover possible metastasis [13].

Conclusions

During a clinical examination by breast palpation, a painful formation in the upper external quadrant of the left breast was detected. As a consequence of this, bilateral breast ultrasound examinatin and bilateral mammography were performed and bilateral mammary tumor formations were noticed. The pathological examination of the biopsy revealed bilateral invasive ductal breast cancer, with an intermediate histological grade G2, ER +, PR +, HER2 - (score 0 ASCO-CAP). Therefore, the diagnosis is simultaneous bilateral breast cancer (the same with synchronous), a rare entity, which represents the real bilateral cancer of the breast. Neoadjuvant therapy was started and then Madden modified radical mastectomy was performed. The final histopathological examination confirmed the invasive ductal carcinoma in the left breast - pT1cN1aG2 and in the right breast - pT1cN0aG2. The patient received chemotherapy, radiotherapy and adjuvant hormone therapy, and entered a standard follow-up program.

Sychronous bilateral breast cancer is rare and the treatment is multimodal depending on the patient, the size of the tumor, the axillary lymphatic invasion, the existence of estrogen or progesterone receptors, the histological type, the tumor stage and the menopausal status.

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