

Rare Metastasis of Invasive Lobulillary Breast Cancer to Endometrium / Myometri: Case Report.

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1. Abstract

We present a clinical case of unusual course, with a diagnosis of endometrioid adenocarcinoma with myometrial involvement due to multifocal carcinoma of lobular carcinoma of the breast, which is not the most common histological subtype of breast carcinoma, but the most frequent histological type that causes gastrointestinal, gynecologic, and peritoneal metastases. Although female genital tract metastases are clinically important, they are rare, more so metastatic breast cancer metastatic to the uterus, these lesions may present insidious symptomatology and disguise primary cancer. In postmenopausal women, abnormal menstruation should alert physicians to consider the possibility of primary and secondary neoplasms improving the timely diagnosis and treatment of this pathology. It should also be considered that patients with breast cancer who have received tamoxifen may develop not only primary endometrial cancers but may also sometimes present uterine metastases.

2. Introduction

Breast cancer, in women, is commonly the most diagnosed cancer worldwide. 24.2%, meaning approximately one in four of all new cancer cases diagnosed in women worldwide are breast cancer; moreover, this type of cancer is the most common cancer in 154 of the 185 countries included in GLOBOCAN 2018; for the same source, breast cancer is also the main cause of cancer death in women (15.0%) [1].

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Genital metastases from breast carcinoma are rare. Although lobular carcinoma is not the most common histologic subtype of breast carcinoma, it is the most frequent histologic type causing gastrointestinal, gynecologic, and peritoneal metastases [2]. Uterine metastases constitute approximately 4% of genital tract metastases, with 47% of cases involving the breast as the primary site [4].

while cases of metastases from the breast to the uterus have been reported in the world literature, endometrial affectation by such metastases is extremely rare. Therefore, it is presented for consideration the case of a patient diagnosed with endometrioid adenocarcinoma with myometrial involvement by multifocal carcinoma of type lobular carcinoma of the breast.

3. Clinical Case

It is presented the case of a 63-year-old female patient with a history of G3P3A0V3, essential arterial hypertension, type II diabetes mellitus and moderate obesity (BMI: 39.95 Kg/Mt²), menarche: 12 years old and last menstruation at 39 years, who consults the gynecology service for intermittent postmenopausal vaginal bleeding of 4 months of evolution, with transvaginal ultrasound reported in the institutional medical history with uterus in AVF of 92x54x52 mm, with endometrium of 21.5 mm, it is considered that there is endometrial thickening and therefore biopsy curettage is ordered, which is not practiced to the patient. Additionally, she presents results of mammography of 2015, reported with focal asymmetry with specular contour in the right upper interquadrantic line

BIRADS V (Figure 1). She has a breast ultrasound where a solid nodule is reported in the right upper interquadrantic line, with lobulated contour, moderately defined BIRADS IVB. A trucut needle biopsy guided by breast ultrasound was ordered, which was reported as a tumor lesion of small undifferentiated cells arranged in nests in a desmoplastic stroma, suggesting incisional biopsy and/or immunohistochemistry.

Subsequently, she was taken to right quadrantectomy, with pathology report (Q.16.4213) as infiltrating lobular carcinoma, nuclear grade 1, tumor size 1.5 x 1 cm. In-situ (Focal) lobular carcinoma with free resection margins (Figure 2).

The patient has positive estrogen receptors (95%), positive progesterone receptors (70%) and negative Her-2 neu. Tamoxifen 20 mgs per day was prescribed for two years, treatment that she received intermittently, with periodic control by oncological surgery with normal mammograms.

In the last years, she consults the gynecology service due to postmenopausal vaginal bleeding of long evolution, requesting a biopsy curettage, which is reported (EM19-6152): morphological findings suggestive of adenocarcinoma; then MRI of pelvis and abdomen contrasted reported as studies without significant findings (Figure 3).

Extension studies are performed: ultrasound scan of the urinary tract showed no masses and normal chest x-ray. She was presented to the gynecologic oncology medical Board, where it was determined to schedule an endometrial protocol with freezing biopsy. The procedure is performed which freezing biopsy report (M2004775) is reported as positive for malignancy and, the immunohistochemical profile report (EM20-3540) describes endometrium with malignant epithelial tumor lesion and infiltrated in the myometrium of non-cohesive atypical cells. With diagnosis: endometrioid type endometrial adenocarcinoma, myometrial metastatic lobular carcinoma of mammary origin, estrogen receptor positive (61-70%), progesterone receptor positive (1-10%), HER-2 oncoproteins: negative (0%) and KI67 15%.



Figure 1: Mammography: focal asymmetry with spiculated contour in the right superior interquadrantic line BIRADS V.

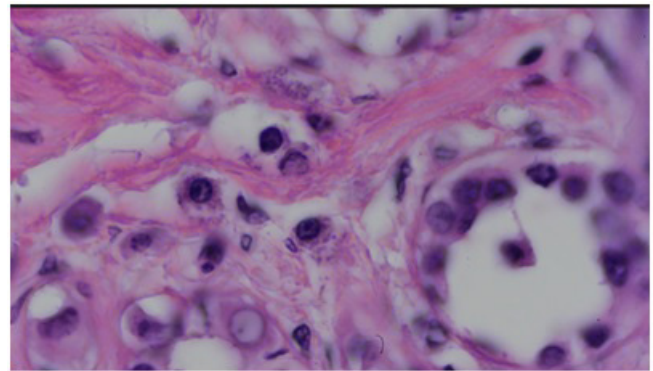


Figure 2: Right quadrantectomy pathology report: infiltrating lobular carcinoma, nuclear grade 1.



Figure 3: MRI of pelvis and abdomen contrasted reported as studies without significant findings.

4. Discussion

In postmenopausal women with vaginal bleeding, the existence of endometrial carcinoma should be suspected. An endometrium thickness of more than 10 mm strongly suggests carcinoma. Patients with 2 or more risk factors, among which are: Diabetes mellitus, Obesity, chronic unopposed estrogen exposure, Tamoxifen use (5), must be included in a follow-up program from the age of 45 years. In the clinical case presented there are postmenopausal patients, obese, diabetic, with intermittent vaginal bleeding, who received tamoxifen for breast cancer, events presented as risk factors for endometrial cancer.

Metastases from primary extragynecological sites to the uterus are rare, with the breast and colon being the most common sites. Ovarian tumors are the most common gynecologic primary site to metastasize to the uterus. Studies conducted by Mazur et col. studied 325 cases, during the period 1980 to 1981, of anatomical location of metastases in the uterine body, in which it was concluded that the involvement of the endometrium itself explained for 3.8% of the cases, both the myometrium and the endometrium 32.7% and the myometrium only 63.5%. Of the cases of metastases limited to the endometrium, lobular carcinoma is the predominant one [6].

Invasive ductal carcinoma and invasive lobular carcinoma are the two most frequent histological subtypes of breast cancer. Invasive ductal carcinoma represents approximately 76% of all breast cancers, while invasive lobular carcinoma represents 8% [7]. Despite its lower incidence, infiltrating lobular carcinoma is the histologic subtype that most frequently produces metastasis to the female genital tract. It has been proposed that this phenomenon is due to the small size of the tumor cells of the infiltrating lobular carcinoma and to the loss of expression of its cell-cell adhesion molecule E-cadherin, which generates alterations in cell adhesion [7]. The present clinical case shows the aforementioned: the patient has a history of infiltrating lobular breast cancer 5 years ago, with intermittent vaginal bleeding with irregular treatment with tamoxifen.

For the study of diagnostic images for this pathology, MRI is the most frequently used imaging technique since it has a good sensitivity to assess myometrial and cervical involvement. Besides, it can assess the presence of pathological pelvic and/or para-aortic lymphadenopathies. Although it has its limitations, it is the test with the best performance despite its high cost [8].

For the histopathological diagnosis of endometrial cancer, it is considered necessary to take endometrial tissue samples guided by hysteroscopy. However, in hospitals where this resource is not available, biopsy curettage is used as in the clinical case presented. From the etiopathogenic point of view, two different types of endometrial adenocarcinoma are considered. A hormone-dependent variety or type I, preceded by hyperplastic lesions, and a non-hormone-dependent variety or type II, not linked to hyperplastic lesions, with a poor or scarce degree of cellular differentiation. Type I is associated with women with hyperestrogenism and obesity, and the prognosis is good as they are tumors of low histological grade, endometrioid, with minimal endometrial invasion and infrequent genetic changes; type II evolves with higher aggressiveness due to a higher probability of deep myometrial invasion, genetic changes, and high histological grade, being debatable the relationship between this and the risk factors [9, 5]. In the clinical case the diagnosis is corroborated by biopsy curettage in which it is reported as adenocarcinoma, the study of the freezing of the surgical procedure: total hysterectomy and bilateral salpingo-oophorectomy: positive for malignancy. With the immunohistochemical profile: endometrial adenocarcinoma endometrioid type, additionally the patient presented is obese in management with nutrition and dietetics.

There are different markers to consider in metastasis of primary breast cancer to the uterus, but Estrogen Receptors (ER), Progesterone Receptors (PR) and HER2 are the ones that have been found to be of clinical relevance at the time of treatment. ER is found to be 80% positive and has two types of receptors: ER-a and ER-b, so estrogen acts through these two receptors. ER-a is also influenced by growth factors such as HER-2 [10]. In the clinical case presented, the immunohistochemistry of the initial breast

lobular carcinoma was found positive estrogen receptors (95%), positive progesterone receptors (70%), additionally, the immunohistochemistry reports on endometrial tumor strong expression for estrogen and progesterone receptors. While in the myometrial component a mild to moderate intensity for these same receptors and in the diagnosis is highlighted as myometrial metastatic lobular myometrial carcinoma of mammary origin.

HER2 is a protein member of the growth factor receptor family. It is normally present in the cell membrane fulfilling functions in growth, survival, repair and proliferation cell growth and division. The increase of its presence is defined as an overexpression, which generally occurs as a result of an increase in the number of copies (amplification) of the gene that encodes it, the HER2/neu gene, located on the long arm of chromosome 17 [11]. Patients with breast cancer who present amplification of this gene generally present a more aggressive form of cancer, in addition to a higher resistance to conventional treatments [12]. In the pathology report of the quadrantectomy, total hysterectomy, and bilateral salpingo-oophorectomy, the Her-2 were negative.

The morphologic features of primary endometrial and myometrial tumors and metastatic breast lesions present a significant diagnostic challenge, especially since both cell types are likely to demonstrate positivity for hormone receptors [7].

The biomarker Gross cystic disease fluid protein 15 (GCDFFP-15), protein inducible by a synonym of prolactin which was originally detected in the cystic fluid of cystic mastopathy, it is not expressed in ductal epithelium or lobular normal, but in apocrine metaplasia of the breast. Apart from breast cancer, only very few tumors, such as prostate cancer and carcinomas of the skin appendages, express GCDFFP-15. Therefore, it is very specific and is frequently used as an immunohistochemical marker for the evaluation of a possible mammary origin of metastatic carcinoma of unknown primary site [13]. Another important sensitive marker for mammary origin is GATA-3, which are transcription factors, corresponding to a family of proteins characterized by their ability to bind to the GATA DNA sequence (where G is guanine, A is adenine and T is thymine). It is expressed in a large proportion of invasive breast cancer cases, especially in the luminal subtypes [14]. In the immunohistochemistry report of the bilateral hysterectomy and salpingo-oophorectomy of the clinical case presented shows in the endometrial component absence of expression for GATA-3 and GCDFFP-15. On the contrary, in the myometrial component, it shows a strong labeling for these 2 biomarkers.

Often the interval between the primary tumor and the appearance of uterine metastases is years, and in this case the disease-free period can be 5 years. Uterine metastases are usually a manifestation of disseminated disease, but in some cases the uterus may be the only site of tumor metastasis [5, 6]. This was evidenced in the clinical case.

Tamoxifen is the most widely used oral medication against breast cancer. It is a non-steroidal medication that acts as a Selective Estrogen Receptor Modulator (SERM) in the breast, which represents an excellent option for the treatment of breast cancer with positive hormone receptors. Paradoxically, it acts as an estrogen agonist, mainly in the endometrium, favoring epithelial thickening. Tamoxifen is metabolized by a variety of enzymes in the liver, including CYP2D6. Genetic polymorphisms affecting the activity of this enzyme could explain why some patients have a better response to tamoxifen than others. There is an additional risk of endometrial cancer associated with the use of tamoxifen as a treatment for breast cancer because this medication triples the risk of endometrial cancer and increases the possibility of developing benign endometrial lesions. In the clinical case presented, the patient receives this treatment after the surgical management of breast cancer and even though there was monitoring by oncologic surgery, no symptoms of vaginal bleeding due to oncologic surgery were reported, but there is evidence of consultations to the gynecology service in different institutions for vaginal bleeding, with the order of biopsy curettage

In a study to assess the risk of endometrial cancer after adjuvant tamoxifen treatment for breast cancer patients in Taiwan. A total of 74,280 breast cancer patients between January 1997 and December 2004 were included in the study; 39,411 received tamoxifen treatment and 34,869 patients did not. A total of 222 patients developed endometrial cancer, and of these, 153 (69%) were observed in patients with tamoxifen treatment and 69 (31%) in patients without tamoxifen use. Logistic regression analysis showed that tamoxifen usage, and age older than 35 years were significantly correlated with the development of endometrial cancer ($p < 0.001$ and $p = 0.002$, respectively). Concluding that there is an association with a significant higher risk of developing endometrial cancer in patients with breast cancer who received tamoxifen [15].

The treatment of endometrial cancer in early stages is basically surgical and is based on total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Although the latter has been shown to have more prognostic value in several studies, and when the pelvic nodes are negative, para-aortic lymphadenectomy should not be performed due to the low risk of metastasis [16]. In the clinical case, the patient was considered to have stage IA1 of the International Federation of Gynecology and Obstetrics (FIGO, by its initials in Spanish), as she had endometrial involvement and $< 50\%$ of the myometrium, without intraperitoneal involvement

5. Conclusion

Although female genital tract metastases are clinically important, they are rare, more so metastatic breast cancer metastatic to the uterus, these lesions may present insidious symptomatology and disguise primary cancer. In postmenopausal women, abnormal menstruation should alert physicians to consider the possibility of

primary and secondary neoplasms improving the timely diagnosis and treatment of this pathology. It should also be considered that patients with breast cancer who have received tamoxifen may develop not only primary endometrial cancers but may also sometimes present uterine metastases.

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