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Case Report

Endometrial tubal metaplasia in a young puerperal woman after breast cancer

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Abstract: Introduction: Tamoxifen is the usual endocrine (anti-estrogen) therapy for hormone receptor-positive breast cancer in pre and post-menopausal women. Previous studies have suggested an increased prevalence of endometrial diseases after treatment with tamoxifen. Case presentation: The authors report a case of 38-year-old woman with diagnosis of endometrial polyp and tubal metaplasia, during puerperium and after micropapillary ductal breast cancer surgery, 5 years of tamoxifen treatment, spontaneous pregnancy without complications and full-term vaginal delivery. Conclusion: Tamoxifen is a safe and reliable treatment of breast cancer, but data suggest an association with endometrial polyps, hyperplasia, metaplasia and carcinoma. One of the most common types of endometrial metaplasia is ciliated tubal metaplasia. It is generally known that endometrial tubal metaplasia is a benign disease. However studies propose endometrial tubal metaplasia to be a potential premalignant endometrial lesion and its association with endometrial hyperplasia and well-differentiated endometrioid carcinoma. We propose close monitoring of patients taking tamoxifen and prompt evaluation of any uterine bleeding or pelvic complaint or abnormal TVUS images.

Keywords: Breast cancer, endometrial polyp, tubal metaplasia, tamoxifen

Introduction

Breast cancer patients have an increased risk of endometrial pathology [1]. Tamoxifen (TAM) is both an antagonist and an agonist of the estrogen receptor [2]. In breast tissue it acts as an antagonist of the estrogen receptor. It is currently used in the adjuvant therapy and chemoprevention of both early and advanced ER+ (estrogen receptor positive) breast cancer in pre and post-menopausal women [3]; FDA approved tamoxifen for the prevention of breast cancer in women at high risk of developing the disease [4]. It has been further approved for the reduction of controlateral breast cancer [5]. In other tissues such as the endometrium, it acts as an agonist, and thus may be characterized as a selective estrogen-receptor modulator [2]. In some women it has been associated with endometrial pathology. Previous studies have suggested an increased prevalence of endometrial polyps, hyperplasia, metaplasia and carcinoma after treatment with tamoxifen [1].

Endometrial polyps are the most common endometrial pathology described in association with tamoxifen exposure [6]. In our case it has been identified a tubal metaplasia (TM) on an endometrial polyps. Metaplasia is adaptive disorder involving a newly acquired morphology and function. The most common types of endometrial metaplasia are ciliated tubal metaplasia and mucinous metaplasia [7]. Tubal (or ciliated cell) metaplasia of the endometrium is Characterized by ciliated, secretory and intercalary cells, resembling the Fallopian tube [7].

Case report

We described a 38-year-old woman with a spontaneous pregnancy and a full-term vaginal delivery, after breast cancer and tamoxifen treatment, referred to our hospital for abnormal vaginal bleeding. She hasn't history of fever or pelvic pain and before the delivery her mestruation was regular. In 2008, at the age of 32 years, she received a diagnosis of micropapillary ductal carcinoma of the right breast.

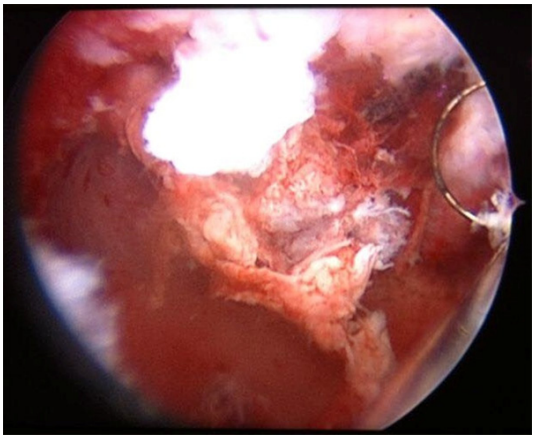

Figure 1. Endometrial formation of about 14 mm, visualized during operative hysteroscopy.

Histopathological analysis revealed a 19 × 20 mm invasive carcinoma with no lymph node metastasis, no metastatic disease and it was staged pT1cN0M0. The tumor was estrogen receptor and progesterone receptor positive. The human epidermal growth factor receptor 2 (HER2/neu) was negative. The patient underwent right quadrantectomy with axillary lymph node dissection and after she performed treatment with radiotherapy for 1 month and tamoxifen for 5 years. During and after tamoxifen treatment the patient had regular menstruations and carried out periodical follow up visits and investigations that showed there wasn't disease relapse and endometrial alterations. In 2014, four months after the end of treatment with tamoxifen, she had a spontaneous regular pregnancy, without complications. Successfully, after a vaginal delivery, during puerperium and breastfeeding, the patient had an abnormal vaginal bleeding that proceeds for two months. Due to these bleeding the patient was admitted to Sant'Andrea Hospital, University of Rome Sapienza. It was performed a gynecological examination and transvaginal ultrasound (TV-US), that reveal an endometrium with a hyperechogenic formation of 14 mm in diameter. CEA, APF, CA125, CA19, 9, CA15, 3, bHCG were at normal levels.

She underwent a diagnostic and successfully operative hysteroscopy. On examination the uterine cavity appeared to be occupied by a formation of about 14 mm, like a placental remnant, that was removed and analyzed (**Figure 1**). Histopathological analysis revealed an endometrial polyp with tubal metaplasia and necrotic-hemorrhagic characters.

Discussion

Breast cancer means an increased risk of endometrial pathology that may be linked to a hyperestrogenic state and genetic predisposition [1]. Tamoxifen is the most widely used antiestrogen drug in adjuvant therapy for receptor-positive breast cancer in pre and post-menopausal women that acts as an ER agonist and stimulates endometrial proliferation [2]. It could produce an increased risk of endometrial polyps, hyperplasia, metaplasia, adenocarcinoma and sarcoma, but this process is unknown [1]. An increased risk of endometrial carcinomas has been reported in breast cancer patients during or after tamoxifen therapy; the relative risk is estimated to be two- to four-fold, especially in postmenopausal patients [8]. The association between TAM long term use and p53-overexpression in endometrial tumors is supported by Bergman studies [9], whereas Ferguson et al observed that p53 expression in these patients was the same of non-TAM-users [10]. However in women, the influence of duration of tamoxifen treatment on the pathogenesis of endometrial disease has not been confirmed. Several studies have documented that risk of endometrial cancer increases with longer duration of tamoxifen use compared with non-users. Long-term tamoxifen users have a worse prognosis of endometrial cancers, which seems to be due to less favorable histology and higher (stage III and IV) [9]. However, the benefit of tamoxifen on breast-cancer survival far outweighs the increased mortality from endometrial cancer [9]. Literary studies showed that women who develop endometrial cancer following a diagnosis of breast cancer had an increased probability of high-risk histological subtypes, independent of TAM use [10]. Our patient had a breast cancer about 8 years ago that was treated with surgery and a 5-years-hormonal therapy with tamoxifen. She carried out a careful follow up with vaginal ultrasound and breast controls that were normal. Her menstruation was normal. She has a spontaneous regular pregnancy, without complications and a vaginal delivery. During the puerperium, after abnormal vaginal bleeding she received a diagnosis of endometrial polyp with tubal metaplasia.

Metaplasia is adaptive disorder involving a newly acquired morphology and function. Endometrial metaplasia is a condition characterized by an increased proliferation of homolo-

gous or heterogonous cells that substitute epithelial and stromal elements. Epithelial metaplasia is more frequent than stromal [11].

The most common types of endometrial metaplasia are ciliated tubal metaplasia and mucinous metaplasia [7]. The pathogenesis of metaplasia may be identified in genetic mutations or hormonal unbalanced action that can occur during endometrial growth.

It has a heterogeneous pathway; it has been observed in benign pathologies hormonally related such as polyps or patient with intrauterine device and in benign elements of adenocarcinoma [7]. The types of endometrial metaplasia most frequently associated with malignancy risk are mucinous, ciliary and tubal ones [7]. A histological diagnosis of endometrial tubal metaplasia need the presence of ciliated columnar cells with bland round nuclei and eosinophilic cytoplasm, similar to the cells normally seen lining the fallopian tube [12]. Studies in literature are poor. It is generally thought that endometrial tubal metaplasia is a benign disease. However some studies propose endometrial tubal metaplasia to be a potential premalignant endometrial lesion and its association with endometrial hyperplasia and well-differentiated endometrioid carcinoma [13]. Endometrial cancer is the most common malignancy of women in developed countries, and its incidence is rising among pre- and postmenopausal women. Risk factors of endometrial cancer include: obesity,early menarche or late menopause, null parity, family history of endometrial cancer, radiation exposure, polycystic ovarian syndrome, unopposed oestrogens therapy, diabetes mellitus, hypertension, chronic diseases of the liver and biliary tract, Lynch syndrome type II, breast cancer, ovarian cancers, long-term use of tamoxifen [14].

The higher risk of endometrial disorders and cancer described in women with a history of breast cancer suggests the need to apply effective strategies for the monitoring, diagnosing and treating these pathologies in an early stage. Several approaches have been proposed for screening abnormal endometrial proliferation or endometrial cancer in females with a history of breast cancer. Transvaginal ultrasound has improved the measurement and characterization of the endometrium in a variety of clinical situations, even in association with sonohysterography [1]. However the use of hysteroscopy with biopsy, even though it's an invasive procedure, is confirmed as an indispensable, sensitive and specific method to assure a definitive diagnosis of endometrial pathologies and establish the more specific treatment [1]. In our case the presence of an abnormal uterine bleeding must questioning us about the investigations and exams that must be performed to leave out every possible endometrial premalignant lesion and allow a targeted treatment and diagnosis.

Close monitoring of patients taking tamoxifen is needful. Our case, considering the clinical history, the rapid formation of metaplastic polyp after precedent negative breast and endometrial follow up, showed that is necessary apply prompt evaluation and careful investigations of any uterine bleeding or pelvic complaint or abnormal TVUS images. In fact, it's necessary not underestimate symptoms and ultrasound images and only hysteroscopy with biopsy allowed us to make an early diagnosis and a timely treatment. Therefore, the potential premalignant role, the rapid clinical evolution and a possible association with endometrial carcinoma of tubal metaplasia in a young patient with a previous breast cancer suggest the need to continue a careful valuation and follow up.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure of conflict of interest

None.

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