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Metachronus endometrial carcinoma in a seventy five year old woman with carcinoma of the left breast treated with tamoxifen

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Abstract

Background: A second cancer is a different type of cancer than the original cancer. It is diagnosed after a completed treatment for the first cancer. Second cancers occur in only one to three percent of survivors. The level of risk is very small. In general, greater numbers of cancer survivors are living longer due to improvements in treatment. Whether or not a second cancer develops is dependent on many factors. These include the age of the patient when treated, the treatment received, the genetic make-up and family history. The actual number of people who will get a second cancer is relatively small. Each cancer survivor's experience is unique.

The aim of this report is to call attention to what might be an emerging place of secondary malignancies in cancer survivors in our setting.

Method: We report a case seen in our practice of a seventy five year old woman who was treated for invasive ductal carcinoma of the left breast and developed invasive endometrial carcinoma about 4 years later.

Conclusion: There is a need to be on the lookout for possible second malignancies in cancer survivors. Examination and tests for second malignancies should be part of the routine follow up procedures in this group of patients.

Keywords: *Second malignancy, tamoxifen, breast and endometrial cancer*

Résumé

Contexte: Un deuxième cancer est un autre type de cancer que l'original du cancer. Il est diagnostiqué après un traitement terminé pour la première le cancer. Deuxième cancers surviennent dans seulement un à trois pour cent des survivants. Le niveau de risque est très petite. En général, un plus grand nombre de survivants du cancer vivent plus longtemps, en raison des améliorations du traitement. Qu'il s'agisse ou non d'un deuxième cancer développe est tributaire de nombreux facteurs. Cela inclut l'âge du patient lors d'un traitement, le traitement reçu, la génétique et l'histoire familiale. Le nombre réel de personnes qui obtiendront un deuxième cancer est relativement faible. Chaque survivant du cancer l'expérience est unique.

L'objectif de ce rapport est d'appeler l'attention sur ce qui pourrait être une nouvelle place de tumeurs malignes secondaires de survivants du cancer.

Méthode: Nous signalerun cas observé dans notre pratique de soixante cinq ans femme qui a été traitée pour invasif carcinome canalaire du gauche breastand envahissantes développés endomètre environ 4 ans plus tard.

Conclusion : Il est nécessaire d'être à l'affût d'éventuelles tumeurs malignes secondaires de survivants du cancer. Examen et essais de tumeurs malignes secondaires devrait faire partie de la routine procédures de suivi dans ce groupe de patients.

Introduction

A second cancer is a new cancer or malignancy that differs histologically, or molecularly, from the previously diagnosed cancer in a patient. Second malignancy is a recognized sequalae of many of cancer treatment modalities including chemotherapy and radiation therapy. However, not all second cancers are as a result of previous cancer treatment. Cancer is a relatively common disease worldwide.

In the year 2000, Globocan estimated that there were 22.4 million people living with cancer out of which about 10 million were new cases [1]. With this number, it is not unlikely that some individuals will develop another malignancy in addition to a previous one. In addition, many cancer etiological factors can lead to different cancer types. Continued exposure to such aetiological factors may therefore lead to the development of new cancers. One of the difficulties in the management of a second cancer is therefore in determining whether a particular second cancer is treatment related or not.

With the improvement in cancer treatment modalities, cancer survivors are becoming a large epidemiological group and many of them are living for longer period. Since carcinogenesis often takes a long time, it is estimated that there will be more cases of second malignancies in previously treated patients than we were seeing before.

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In this report, we present the occurrence of a second malignancy in a patient treated previously for breast cancer who developed an endometrial malignancy about four years after the initial diagnosis.

Case report

The patient is a 75-year old female retired teacher who was first seen at the referral clinic, Lagos University Teaching Hospital (LUTH), where she presented with a 3 months history of bloody nipple discharge with an associated lump on the left breast. There was no ulceration of the nipple or the breast mass. She had no family history of breast or other cancers. She attained menarche at 17 years and menopause at 50 years. She is Para 3^{+1} with two children alive. Her menstral periods were regular 28-day cycle and last 3 days. She breastfed all her children for at least a year. She was not a known hypertensive or diabetic, there was no history of oral or any contraceptive use and no history of benign breast lesion. She neither drank alcohol nor smoked cigarette. There was no history of previous mammography.

When she was examined there were no significant findings in all the systems. Vaginal examination revealed no abnormality. Laboratory tests showed normal haematological and radiological parameters. An incisional biopsy was done and the result of the biopsy came out as an invasive ductal carcinoma. She had a Left extended simple mastectomy on 7th of September, 2007. The histology report of the surgical specimen confirmed invasive ductal carcinoma SBR grade III. The patient was commenced on tabs tamoxifen 20mg daily.

She was thereafter referred to us at the University College Hospital (UCH) Ibadan on the 23rd of November, 2007 for chemo-radiation therapy. A general physical examination was done in our clinic with no significant findings. The chest wall mastectomy scar showed no loco regional recurrence and there were no axillary or supraclavicular nodes enlargement. She had a full blood count, electrolyte, urea and creatinine, chest x-ray and retroviral screening done which were all within normal limits. Abdominopelvic ultrasound showed a uterus with normal outline measuring 9.2cmx4.3cm, endometrial plate measures 2mm and no mass was seen within it.

She was thereafter planned for external beam irradiation 45Gy in 12 alternate daily fractions to the left chest wall over 4 weeks between 11/12/07 and 21/1/08 concurrently with chemotherapy; Intravenous Adriamycin 50mg/m2 and cyclophosphamide 1g 3weekly for 6 courses. She had the chemotherapy between 7/12/2007 and 16/05/2008 with no adverse side effects.

Patient was thereafter repeatedly seen on follow up visits in our clinics with good disease control. She used tamoxifen for 2 years and 4 months and stopped on her own volition.

During one of the follow up visits on 10/11/2011, about 4 years after her last treatment and 2 years 4 months after she stopped using the tamoxifen, she presented to the clinic with complaints of spontaneous bleeding per vagina. There was no trauma preceding the onset and it was not associated with foul smelling watery discharge. There were no episodes of dizziness or fainting attacks. Digital and speculum vaginal examinations showed atrophic vulva and a 2cm mass on the cervix which is hard and fixed to the underlying tissue. The vaginal wall was smooth and there was no contact bleeding.

She was seen by the gynaecologist who examined and did a EUA (Examination under Anaesthesia) with endometrial and cervical biopsy. Histology report revealed moderately differentiated adenocarcinoma of the endometrium.

Abdominopelvic ultrasound showed normal liver architecture with few well-defined 3-5 cm clear cystic collections in both the left and right lobes. The kidneys, gallbladder, and spleen were normal. The uterus was enlarged (50mm X 52mm X 88mm). The endometrium was 36mm thick and echogenic. There were no adnexal masses.

She was worked up for surgery; staging laparotomy and total abdominal hysterectomy and bilateral salpingo-oophorectomy. Surgery was done on 10/2/2012 and was uneventful. Histology of the specimen confirmed endometrial carcinoma of the endometroid type.

She was thereafter referred back to the radiotherapy unit for further management. She was seen in the radiotherapy clinic and was examined. The chest wall was free and there was no evidence of loco-regional recurrence. Investigations including full blood count, electrolyte, urea and creatinine, chest x-ray were all within normal limits. She received adjuvant Paclitaxel and Cisplatin which she completed and has been stable since then. She has been regular on her follow up visit.

Discussion

Carcinoma of the breast is the most common cancer affecting women worldwide accounting for 18% of all female cancers [2]. It is also the commonest female cancer seen at the University College Hospital (UCH) Ibadan according to the figures from our hospital cancer registry.

High incidence are found in North America and Northern Europe where the lifetime risk of developing breast cancer is put at 8%, while lower rates are found in Asian and African countries[3].The peak age of incidence of breast cancer is between 50 and 70 years and the average age at diagnosis is about 60 years in developed nations [4]. Among Nigerians, the peak age of incidence is between 30-50 years and it is rare below 20 years [5, 6].

Breast cancer survivors are at elevated risk for cancers of the ovary, endometrium, colon and the rectum independent of the treatment administered for the breast cancer [7, 8], suggesting that these organs share some risk factors with cancer of the breast. These shared factors include obesity, diet and reproductive and hormonal status. New discoveries in breast cancer genetics also implicate mutations in *BRCA1* and *BRCA2* as risk factors for ovarian as well as breast cancer. Kemijoki *et al* found out that the incidence rate of all second cancers associated with initial treatment for breast cancer was lower than that associated with no treatment. Only second corpus uteri cancer may be related to hormone therapy [9].

Endometrial cancer is one of the possible complications of breast cancer treatment in patients treated with tamoxifen. More aggressive non-endometroid malignancies are seen in greater proportion than in patients who have not been exposed to tamoxifen. These unfavourable aggressive tumour types include carcinosarcomas, clear cell adenocarcinoma and sarcomas [10].

Tayade and Kumar previously reported that breast cancer patients who used tamoxifen are at increased risk of having endometrial cancers especially Malignant Mixed Mullerian Tumours (MMMT)or carcinosarcomas with abnormal uterine bleeding or vaginal discharge being the most important symptoms indicative of lesion development[11].

Tamoxifen is used both in the treatment and the chemoprevention of Breast cancer. The National Surgical Adjuvant Breast and Bowel Project P1 (NSABP-P1) study 1 showed that tamoxifen can prevent 49% of invasive breast cancer in patients who have a 5-year risk of 1.67% or more. As a result the American Food and Drug Administration (FDA) approved tamoxifen as a preventive agent for breast cancer. However, this is not without risk as increased incidence of endometrial carcinoma has been noted in women who took tamoxifen either in the course of treatment for breast cancer or its prevention. This is in addition to other known side effects of tamoxifen which include pulmonary embolism and ischemic stroke. This is possibly why the use of tamoxifen for breast cancer prevention is much lower than expected as both the physicians and the potential beneficiary are weary of these side effects, some of which are life threatening [12].

Endometrial cancer remains a major side effect of prolonged use of tamoxifen. The risk of developing the malignancy increases with the duration of use. In a study by Bergman *et al* in Lancet, it was shown that women who used tamoxifen for between 2-5 years have a relative risks of 2 compared to non-users and 6·9 for women who had taken tamoxifen for at least 5 years [13]. In addition it was also shown that tamoxifen-related endometrial cancer tend to be of poorer prognosis as a result of advanced stage at presentation and preponderance of tumour with unfavourable histological types compared to non-users.

Endometrial cancer is the most common type of uterine cancer. Increased levels of oestrogen appear to play a role in its aetiology. Studies have shown that high levels of oestrogen in animals result in excessive endometrial growth and cancer. Other risk factors for endometrial cancer include diabetes mellitus, oestrogen replacement therapy without the use of progesterone, nulliparity, obesity and prolonged use of tamoxifen for breast cancer as previously shown. Symptoms usually include abnormal uterine bleeding, lower abdominal pain or pelvic cramping. Treatment options involve surgery, radiation therapy, and chemotherapy [14].

Most cases of endometrial cancer occur between the ages of 60 and 70 years, but a few cases may occur before age 40. Endometrial carcinoma for patients on tamoxifen are seen about five years and above after the exposure. [15, 16]. However, in the case presented here, endometrial carcinoma developed in the patient only 4 years after the beginning of exposure.

Although an immunohistochemistry was not done in our patient because it is not routinely available, she was however placed on tamoxifen as the reduced recurrence rates and overall survival benefits of tamoxifen treatment have made this drug the adjuvant treatment of choice for postmenopausal patients with breast cancer.

The potential oncogenic effect of tamoxifen on the endometrium has been widely studied in recent years although the exact modalities of treatment of endometrial lesions induced by the drug are still controversial.

Endometrial carcinoma following breast cancer had previously been reported in Nigeria by Abudu *et al* who reported the case of endometrial carcinoma following tamoxifen treatment for breast carcinoma in a 52-year old Nigerian female [17].

Semiglazov *et al* in a review of 1,969 breast cancer patients (stage I-III) (tamoxifen- 947; control-1, 022) showed that there was a double rise in endometrial carcinoma risk in cases receiving hormone therapy. Endometrial carcinoma incidence in tamoxifen-treated patients was 3% while in the untreated ones it was 1.6%. According to the endometrial tissue study in 439 breast cancer patients, proliferative effect of tamoxifen in the form of endometrial hyperplasia was 5-6 times commoner in tamoxifen users [18]. It has been reported that while tamoxifen acts as an antiestrogen with regard to breast cancer and significantly reduces the occurrence of contralateral breast cancer, it acts as a proestrogenic agent elsewhere, raising the risk for endometrial cancer.Thus, patients who have received long-term adjuvant hormonal therapy should have regular endometrial screening by a gynaecologist [19].

The age of our patient and the use of tamoxifen probably led to the development of the second malignancy in this patient, though we will never know for sure. The fact that the patient used tamoxifen for only a short period of 2.4 years indicate the need to rigorously follow up patients on tamoxifen from the beginning of exposure.

Conclusions and recommendations

The increased risk of endometrial cancer associated with tamoxifen treatment should be considered clinically for women during treatment and for at least 5 years after the last treatment.

Patients on hormonal therapy especially tamoxifen should be seen regularly on follow up and monitored, these patients require annual gynaecological examination with vaginal ultrasound and, if necessary, hysteroscopy. This follow-up must be performed even in the absence of symptoms.

After the treatment of cancers, while on follow up, physicians should not only focus on the primary neoplasm, they should also do routine surveillance for second cancers.

Counselling of survivors should include instructions for primary and secondary prevention of new malignancies.

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