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BREAST CANCER WITH METACHRONOUS ENDOMETRIAL CANCER: A CASE REPORT

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Abstract

Background: Breast cancer is the most commonly diagnosed cancer among women and the leading cause of cancer deaths globally. Some studies have reported an association between breast cancer management and subsequent development of endometrial cancer.

Case presentation: A 61-year-old female patient presented to the Kenyatta National Hospital (KNH) with postmenopausal per vaginal bleeding. She gave a history of diagnosis and management for breast cancer managed in 2016 at the same facility. She was started on tamoxifen therapy for two years and was subsequently diagnosed with metachronous endometrial cancer in 2020.

Conclusion: Tamoxifen therapy is beneficial in the treatment of breast cancer in women. However, clear protocols on follow up of these patients are required, especially in postmenopausal women with endometrial biopsy offered before or during tamoxifen therapy. This will increase the suspicion index and allow early diagnosis and management of endometrial cancer.

Keywords: breast cancer, tamoxifen, endometrial cancer

INTRODUCTION

Breast cancer is the leading cause of cancer deaths in women globally, particularly in ages 40 - 49 (1). In Kenya, breast cancer is one of the leading cancers in incidence, accounting for 12.5% of all new cancer cases and represents 20.9% of all female cancers (2). Treatment modalities for breast cancer require a multidisciplinary approach, including surgical therapy, medical therapy, and radiotherapy (3). Tamoxifen therapy is associated with increased survival rates in breast cancer patients. However, an increased risk of endometrial cancer has been reported in tamoxifen therapy (4). Tamoxifen is a Selective Estrogen Receptor Modulator (SERM) indicated for metastatic breast cancer treatment, reducing breast cancer incidence in high-risk women, and adjuvant treatment of breast cancer. Its primary therapeutic effect is antiestrogenic, but it has modest estrogenic activity (4). This is a case report of a 61-year-old female with a history of breast diagnosis and tamoxifen management. A diagnosis of endometrial cancer was made.

CASE PRESENTATION

A 61-year-old, para 1+1, presented to the Kenyatta National Hospital (KNH) with postmenopausal per vaginal bleeding. She gave a history of breast cancer diagnosed in 2016 when she initially presented with a painless right-sided breast mass, progressively enlarging and located in the lower outer quadrant. She gave no family history of cancer or contraceptive use. A right breast ultrasound confirmed the presence of a lesion. A mammogram did then was suspicious with a Breast Imaging Reporting and Database System (BI-RADS) score of 4. Subsequent core biopsy revealed a grade 3 ductal carcinoma negative for Estrogen, Progesterone, and Human Epidermal growth factor Receptor 2 (ER/PR/HER 2) receptors. She was scheduled for a right-sided modified radical mastectomy with axillary lymph node dissection. She was managed with 16 sessions and eight cycles

of radiotherapy and chemotherapy, respectively. She was started on tamoxifen therapy for two years. However, cervical screening or endometrial sampling were not done since her initial breast cancer diagnosis.

In February 2020, she presented with postmenopausal per vaginal spotting, minimal in amount with occasional suprapubic pain. Pap smear revealed a high grade squamous intraepithelial lesion and atypical glandular cells. Colposcopy and endocervical curettage revealed a papillary adenocarcinoma of the endometrium. Other investigations included a chest X-ray, abdominal ultrasound, and Positron Emission Tomography (PET) scan, which were normal. She was scheduled for surgery, but her operation was delayed due to the Covid-19 pandemic. A class 2 radical hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, and omental biopsy were done in July 2020. The fallopian tubes, ovaries, and nodes were not involved. A diagnosis of an endometrioid adenocarcinoma (FIGO grade 2) with >50% myometrial invasion was made on histology. She was started on cisplatin/paclitaxel. She has received three cycles at the writing of this case and was stable, continuing with her chemotherapy and follow-up.

DISCUSSION

Breast cancer is the most commonly diagnosed cancer globally, while endometrial cancer is the sixth most common malignancy globally (5). Endometrial cancer has multiple risk factors and is subdivided into type I and type II (6). Tamoxifen, a selective estrogen receptor modulator, is approved for adjuvant treatment of breast cancer and reduces its incidence in high-risk women (7). In the endometrial tissue, tamoxifen acts as an estrogen agonist in postmenopausal patients leading to sub-endometrial gland enlargement (8). Therefore, it increases the risk of endometrial cancer, particularly in postmenopausal patients. The level of risk is dose and time-dependent (9). The susceptibility of developing high-grade endometrial cancer is high following tamoxifen therapy (10). An overview analysis of patient data from 20 trials reported that tamoxifen use was associated with a 2.4-fold increased risk of developing uterine cancer compared to the placebo (11). This increase was almost exclusively in women above 50 years (12). The increased risk of endometrial cancer continues as long as the patient receives tamoxifen and decreases after treatment discontinuation. In contrast, other studies reported that breast cancer in itself is a risk factor for secondary endometrial cancer in patients not receiving tamoxifen, irrespective of their hormone receptor status (13).

The American College of Obstetricians and Gynecologists (ACOG) recommends postmenopausal women on tamoxifen to undergo routine screening for cervical cancer. However, routine endometrial biopsy and uterine ultrasounds are not indicated (14). If a patient were to develop postmenopausal bleeding, they would be evaluated with transvaginal ultrasonography and endometrial sampling (15). Some studies on routine surveillance of patients managed with tamoxifen reported increased side effects resulting from overtreatment of asymptomatic endometrial hyperplasia found on transvaginal ultrasonography (8,16). Many guidelines do not recommend routine transvaginal scans for asymptomatic women on tamoxifen, and it is only indicated for abnormal gynecological symptoms, such as abnormal uterine bleeding (16). Besides, there are no recommendations for uterine cancer screening in breast cancer patients receiving tamoxifen therapy in developing countries. Endometrial protection from the effects of tamoxifen with a local application of a levonorgestrel-releasing device has been found to have a significant reduction in the incidence of endometrial polyps (OR 0.14), hyperplasia (OR 0.3), and fibroids (OR 0.37) (17). Other modalities investigated to prevent tamoxifen-associated endometrial cancer include concurrent use of tamoxifen with intermittent medroxyprogesterone acetate or metformin, which have shown limited evidence of reduced incidence in endometrial proliferation and hyperplasia (18-19).

The patient in the presented case failed to undergo adequate evaluation, including any cervical cancer screening while receiving tamoxifen. This may be due to the lack of clear protocols guiding follow-up of breast cancer patients and the lack of a high index of suspicion of endometrial cancer development. Besides, she did not receive any protective therapies

while on tamoxifen. The failure to receive an endometrial biopsy before or during tamoxifen therapy made it difficult to definitively determine if endometrial cancer, in this case, was synchronous or metasynchronous. Therefore, the addition of an endometrial biopsy before tamoxifen therapy in breast cancer patients may detect any endometrial abnormalities early, providing a baseline for further follow-up.

Breast Cancer susceptibility gene (BRCA) 1 and 2 have been associated with the development of several cancers, including some evidence pointing toward an increased risk of endometrial cancer carriers, which can be attributed mainly to tamoxifen (20). Other gene mutations associated with endometrial cancer include tumor Protein (p53), Phosphatase, and Tensin homolog (PTEN), and DNA mismatch repair family genes (21). Risk reductive Bilateral Salpingo-Oophorectomy (rrBSO), recommended in women between 35 and 40 years who have completed childbearing, decreases the risk and mortality of ovarian cancer in BRCA 1 and 2 carriers (22). Some studies found no increased risk of endometrial cancer after rrBSO, the results of which were not affected by tamoxifen. However, hysterectomy is not recommended for prevention only (23). Testing for BRCA 1 and 2 is often not done due to genetic testing's unavailability in most developing countries and its high cost. Screening for these genes in high-risk patients would greatly benefit their follow-up, management, and survival.

CONCLUSION

Tamoxifen therapy is beneficial in treating breast cancer patients and those at high risk of developing breast cancer. However, clear protocols on follow up of these patients are required, especially in postmenopausal women with endometrial biopsy offered before or during tamoxifen therapy. This will increase the suspicion index and allow early diagnosis and management of endometrial cancer.

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