JOGECA Journal of Obstetrics and Gynaecology of Eastern and Central Africa

CASE REPORT

Gynecologic Oncology

Phyllodes tumor, cardiovascular and chronic renal disease in a young lady on hormone replacement therapy: A case report

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Received: 06 February 2024; Revised: 24 August 2024; Accepted: September 2024; Available online: December 2024
DOI: https://doi.org/10.59692/jogeca.v36i3.270

Abstract

Background: Hormonal replacement therapy (HRT) has been associated with an increased risk of developing breast cancer. The level of risk varies with different types of HRT and the duration of use. Phyllodes tumor accounts for less than 1% of all breast neoplasms and is associated with Li-Fraumeni syndrome.

Case presentation: A 37-year-old nulliparous woman presented with a left breast lump. Histological examination revealed a spindle cell neoplasm consistent with a malignant phyllodes tumor. She was diagnosed at age of 12 with ovarian dysgerminoma, had subtotal hysterectomy and right oophorectomy, radiotherapy and chemotherapy. She has been on HRT with conjugated equine estrogens for 13 years and tibolone for the last 5 years. Following the diagnosis of phyllodes tumor, a mastectomy was performed, and HRT was changed to vaginal estrogen gel.

Conclusion: Hormonal replacement therapy may pose a risk for certain types of breast cancer, especially with prolonged use of combined therapy. Patients who develop cancers early in life, as well as those on HRT, require close follow-up and adequate patient education with an emphasis on self-breast examination. Sensitization of healthcare providers and patients on the value of genetic screening would facilitate early identification of such patients and follow-up at high-risk clinics.

Keywords: breast cancer, dysgerminoma, hormonal replacement therapy, Li Fraumeni syndrome, phyllodes tumor

Introduction

The impact of hormonal replacement therapy (HRT) on the risk of developing breast cancer has been a contentious, with some studies associating the use of HRT with an increased risk of breast cancer (1-3). Higher risks have been noted with the use of combined hormonal treatment compared to estrogen-only therapy (1) and longer duration of use with the combined types peak in incidence after approximately 5 years of use (2, 3). The use of HRT in women with an intact uterus requires a combination with progesterone to confer endometrial protection. In younger patients diagnosed with premature ovarian insufficiency (POI), there is prolonged use of HRT. Phyllodes tumor is a fibroepithelial neoplasm that accounts for less than 1% of all breast neoplasms with a median age of presentation in the fourth decade (4). It is commonly detected as a palpable breast mass and is more likely to occur spontaneously

though there have been reports of progression from fibroadenomas. An estrogen dependency has been suggested with the estrogen receptor (ER) beta expression demonstrated in the stroma of fibroadenomas and phyllodes tumors (5). This may indicate that increased estrogen activity stimulates tumor growth (6) alongside multiple factors associated with the growth of phyllodes tumors (5). Phyllodes tumors are thought to have a genetic predisposition. They have been associated with Li-Fraumeni syndrome, a rare autosomal dominant condition characterized by the development of multiple tumors including osteosarcoma, soft tissue sarcoma, acute leukaemia, breast cancer, brain cancer, and adrenal cortical tumors (6). Women with Li Fraumeni syndrome have an increased risk of phyllodes tumor (7).

Case presentation

A 37-year-old nulliparous woman presented to Kenyatta National Hospital with a left breast lump detected on self-examination. She has been on follow-up for POI following a subtotal hysterectomy and right oophorectomy performed at the age of 12 years due to a diagnosis of ovarian dysgerminoma. This initial surgery was followed by radiotherapy and 10 courses of chemotherapy with vincristine, actinomycin and cyclophosphamide (VAC). Her father died of multiple myeloma, but both her mother and sisters have no history of cancer. She was initiated on HRT with conjugated equine estrogens (CEE) (cyclical Premarin 0.625 mg every 21 days followed by 7-day breaks). She then reported intermittent cyclical spotting, heavy per vaginal bleeding, and postcoital bleeding after about 13 years of use. An abdominopelvic ultrasound visualised the left ovary and a normal vaginal stump. There were features of obstructive uropathy (hydronephrosis with a distended bladder) and a small right kidney, but this was not evaluated further. The HRT was then changed to combined therapy with Premak-c which she used for 7 years and then combined oral contraceptives due to financial constraints. She has been on tibolone 2.5 mg orally once daily for the past 5 years. The HRT care included drug holidays with regular check-ups and emphasis on self-breast examination. Routine Pap smears were all normal.

During follow-up, she was also diagnosed with dilated cardiomyopathy with moderate left ventricular systolic dysfunction (LVEF) 40%, hypertension and chronic kidney disease. She was started on a loop diuretic, angiotensin II receptor blocker, beta blocker and statin. She later presented with a left breast lump, which was noted on self-examination. An oval-shaped, mobile, hypoechoic soft tissue mass was palpated in the inner quadrant (11 o'clock) measuring 2x3 cm with normal nipples, axilla and skin. A mammogram showed a partially circumscribed left-sided isodense mass (BIRADS 0), measuring 3 x 3.2 x 2.4 cm with no suspicious calcifications. This was followed by an ultrasound showing a heterogenous complex mass in the left peri areolar region, 3 x 2.6 x 2.1 cm, macrolobulated, with partially obscured margins, marked central vascularity and increased echogenicity of the surrounding tissues (BIRADS-4). The right breast was BIRADS-1. An ultrasound-guided core biopsy revealed a spindle cell neoplasm consistent with a malignant phyllodes tumor.

Hormone replacement therapy was stopped, and a mastectomy was performed. The breast mastectomy report indicated a malignant phyllodes tumor (TNM staging, pathologic primary tumor size <2cm, no lymph node metastasis and no signs of cancer metastasis noted). Histology report revealed malignant phyllodes with negative margins. Estrogen and progesterone receptor-positive, HER2 negative, p63 negative, Ki-67 percentage of stained cells 60-79%. The sample showed marked stromal cellularity and moderate atypia with stromal overgrowth. All margins were negative for phyllodes tumor with the distance from the closest margin as 4mm. A multi-disciplinary team meeting advised on radiotherapy, the use of vaginal or topical estrogens for HRT and a prophylactic mastectomy for the contralateral breast.

Discussion

Phyllodes tumors are fibroepithelial tumors with epithelial and stromal invasion. Mutations of the TP53 gene have been implicated in their development with significantly higher frequencies of mutations among malignant (3 of 13; 23%) compared to benign tumors (5 of 128; 3.4%) (8). The TP53 pathway has also been shown to play a role in the pathogenesis of dilated cardiomyopathy and Li-Fraumeni syndrome (9). Our patient's history suggests the possibility of an underlying genetic mutation that may explain her predisposition to tumors from a young age with a diagnosis of ovarian dysgerminoma at 12 years, development of dilated cardiomyopathy and later phyllodes tumor at age 37.

She was on long-term HRT which has been shown to increase the risk of breast cancer (2). While there is no clear evidence of an HRT association with phyllodes tumor, some cases of phyllodes tumors

in patients on long-term HRT have been reported in both men and women (10). Some studies suggest that estrogen may play a role in fibroadenomas, a common precursor lesion for phyllodes (5). The expression of estrogen beta receptors in the stroma of phyllodes tumors may indicate that increased estrogen activity stimulates tumor growth (5). This is thought to occur in combination with multiple factors and not be solely linked to estrogen. Our patient is likely to have had contributions from both genetic predisposition with the possibility of mutations of the TP53 gene as well as long-term exposure to estrogen from the HRT. However, due to financial constraints, genetic screening was not performed to confirm genetic mutations.

Conclusion

Hormone replacement therapy may pose a risk for certain types of breast cancer, especially with prolonged use of combined therapy. Malignant phyllodes tumors have not been specifically associated with HRT and are more commonly associated with preexisting lesions such as fibroadenomas and genetic predisposition in conditions such as Li-Fraumeni. Patients who develop cancers early in life, as well as those on HRT, require close follow-up and adequate patient education with an emphasis on self-breast examination. Sensitization of healthcare providers and patients regarding the value of genetic screening would facilitate early identification of such patients and follow-up at high-risk clinics.

Consent for publication

Informed consent for publication was obtained from the patient.

Declaration

Funding

None.

Conflicts of interest

The authors declare no conflict of interest.

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