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A Rare Case of Bilateral Synchronous Phyllodes Tumor and Triple Negative Breast Cancer

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ABSTRACT

Synchronous breast cancer is a rare event. The majority of cases of synchronous breast cancer will have minor differences in receptor status, but rarely different origins of the tumors. Various breast tumors can have either epithelial or mesenchymal origin and have different treatment strategies and outcomes. In the literature, there is a paucity of information regarding the synchronous presentation and treatment of a triple negative invasive ductal carcinoma (TN IDC) and a malignant phyllodes tumor (mPT). This case presentation discusses a 64-year-old woman who presented with a left breast TN IDC and a right breast malignant phyllodes tumor.

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INTRODUCTION

The incidence of breast cancer in the general population is between 8-12%, and a small number of patients can present with synchronous breast cancers.[1] The incidence of synchronous bilateral breast cancers is 0.6% of all cases.[2] The treatment of these cancers can be difficult due to the varying histology and hormone receptor status. The majority of cases presented in the literature discuss synchronous cancers with differing receptor profiles or differing types of true epithelial breast cancers (ductal carcinoma vs. lobular carcinoma).[2,3,4] There is very little information regarding synchronous breast cancers of differing histologic origins. An example of this is invasive ductal carcinoma which is of epithelial origin compared to a phyllodes tumor which is a fibroepithelial lesion with mesenchymal stem cell characteristics.[5]

Phyllodes tumors (PT) are rare and constitute only 0.3-0.5% of female breast cancers.[6] The majority of PT are seen in women in their late forties to early fifties and can present as part of a genetic syndrome such as Li-Fraumeni. PT can be described histologically as benign, borderline, or malignant. There is difficulty in differentiating between borderline and malignant histopathology on needle biopsy of the tumors. The cells microscopically form leaf and frond-like architecture. While all PT tend to grow aggressively locally, there is the potential for metastatic spread with mPT. The occurrence of metastatic disease can occur from months to years after diagnosis. The tumors spread hematogenously, bypassing the usual lymph node basins seen in true epithelial breast cancers. The most common sites of metastasis include the liver, lung, and skeletal system. PT do not express the hormone receptors seen in epithelial type of breast cancers. The main treatment of phyllodes tumors is aggressive surgical resection. If the tumors recur, they tend to recur as a more aggressive subtype.[7] Other forms of treatment are less effective, and PT typically do not respond well to chemotherapy or radiation therapy.[6]

Triple-negative breast cancers (TNBC) are more commonly found in premenopausal women under 50 years old, of African American descent, and with BRCA1 mutations. TNBC is an aggressive cancer and typically has a high recurrence rate (as high as 25%

after surgical removal) and increased metastatic potential.[8] The histology of the tumor is epithelial in origin and be either ductal or lobular types. The tumor does not express receptor targets for estrogen (ER), progesterone (PR), or Her2, making it more difficult to treat. The majority of TNBC are treated with neoadjuvant chemotherapy before surgical resection and the addition of adjuvant radiation therapy.[9] There is no role for endocrine therapy due to the lack of ER or PR on the tumor to target with these therapies.

The presence of synchronous tumors can present a dilemma with the treatment of breast cancer, especially when standard guidelines differ drastically between the 2 types of cancers involved. The multidisciplinary approach to breast cancer treatment becomes especially important in these cases.

CASE PRESENTATION

The patient is a Gravida 3 Para 3 (G3P3) post-menopausal 64-year-old woman who presented with enlargement of her left breast over 6 months. On physical examination, she was found to have asymmetric breasts. Her left breast was enlarged and erythematous with a 15 cm mass encompassing the entire central area with significant nipple retraction and a nonhealing area at the superior portion of the breast where an open biopsy had been performed. On the right breast, there was a 5 x 4 cm palpable mass at the 8:00 position with retraction of the skin. She had no family history of breast or ovarian cancer and she had never had a mammogram before.

A mammogram demonstrated a 14.9 x 11.5 cm solid and cystic mass in the left breast (Figure 1) and a 4.3 x 3.4 cm mass with spiculated margins at the 9:00 position in the right breast (Figure 2), both of which were BIRADS 5 (highly suggestive of malignancy). A subsequent ultrasound was performed and showed additional satellite nodules in the right breast. In addition, the right axilla was found to have an abnormal-appearing lymph node with a 6 mm cortex.

At an outside institution, the left breast mass underwent fine needle aspiration, and 450 cc of bloody fluid was collected. Cytology demonstrated atypical cells suspicious for malignancy. Both the left and right breast masses also had a core needle biopsy performed. The right breast mass came back as invasive ductal carcinoma (Estrogen Receptor negative, Progesterone Receptor negative, and Human Epidermal Growth Factor Receptor 2 negative). An incisional biopsy was performed on the left breast, which showed a borderline phyllodes tumor (positive for Vimentin, BCL2, and p53; Figure 3). A metastatic workup of the patient was performed

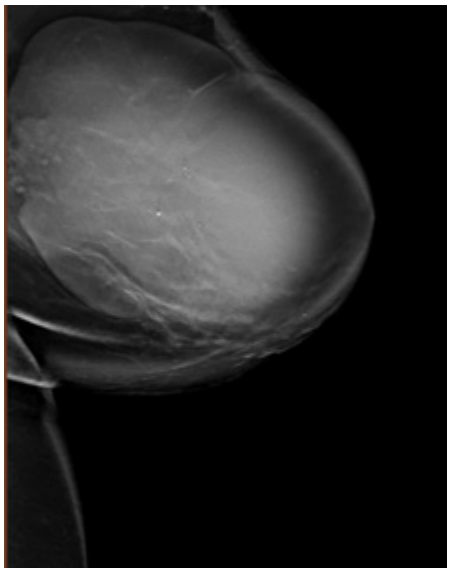

FIGURE 1. Left Breast Mammogram medial/lateral oblique (MLO)

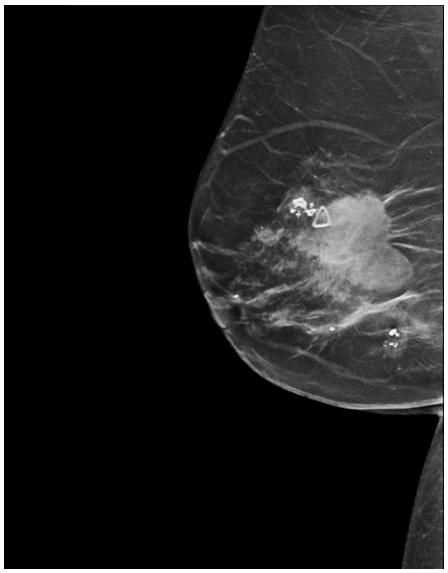

FIGURE 2. Right Breast Mammogram medial/lateral oblique (MLO)

with CT scan of the chest, abdomen, and pelvis, demonstrating a 9 mm left lung nodule which was indeterminate. A positron emission tomography (PET) scan showed a 1.6 cm soft tissue mass concerning for a primary parotid neoplasm. The patient denied any systemic symptoms of metastatic disease.

The case was presented at the Multidisciplinary Tumor Board to discuss options for the treatment plan. The decision was made to move forward with primary surgical therapy due to skin compromise on the left breast, along with the concern the PT would not respond to systemic therapies. She underwent a bilateral simple mastectomy with a complex skin flap closure on the left (Figure 4) and a right axillary sentinel node biopsy. The pathology report showed stage IIB triple-negative right breast invasive ductal carcinoma with apocrine differentiation measuring 40mm with an extensive background of DCIS. The margins were negative, and 2 out of 7 lymph nodes were positive for micro-metastatic carcinoma. The left breast pathology showed a malignant phyllodes tumor measuring 15 cm in the greatest dimension. All surgical margins were negative, and 3 intramammary lymph nodes were negative for carcinoma.

The patient had minor difficulties with the left mastectomy flap from surgery but was healed 5 weeks after surgery with local wound care. She was then scheduled to start adjuvant chemotherapy for the TN IDC, when she began to complain of shortness of breath and cough. She was placed on a course of Doxycycline by her primary care physician. She underwent fine needle aspiration (FNA) of the parotid gland and was found to have an oncocytic tumor (likely a Warthin's tumor) and a CT-guided biopsy of the pleural nodule. On repeat imaging for the biopsy, she was found to have a new 2.9 cm mass in the left lower lobe which was consistent with adenocarcinoma and suggested a new lung primary tumor. She started her adjuvant chemotherapy with Adriamycin and Cytoxan (ddAC). She underwent a second CT-guided biopsy of a right subpleural nodule which was found to be metastatic spindle cell malignancy. She finished her adjuvant ddAC, but PET CT continued to show progression of all metastatic lesions. She continued to worsen over the next 4 weeks. She began having trouble sleeping and difficulty walking. Chemotherapy was changed to Gemcitabine and Taxotere. Unfortunately, she worsened, and CT scan of the brain revealed multiple

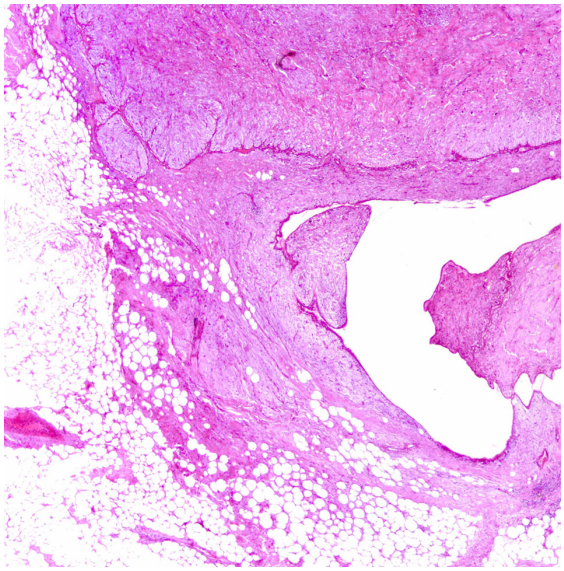

FIGURE 3. Malignant phyllodes with infiltrative borders (low power)

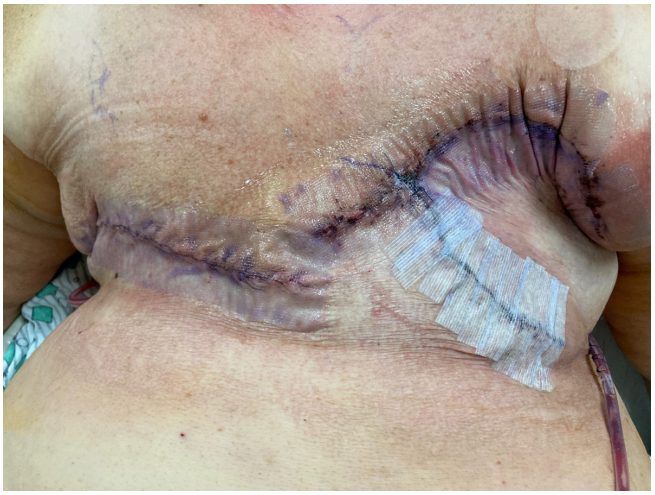

FIGURE 4. Post-mastectomy

metastatic lesions. She was referred to palliative care and succumbed to her disease shortly after.

DISCUSSION

Synchronous bilateral breast cancer consisting of a phyllodes tumor and a Triple Negative IDC is extremely rare in the literature. Most reported cases of a coexistent phyllodes tumor and an IDC are multifocal cancers in which 2 or more tumors are in the same breast quadrant, no more than 5 cm apart.[9] Synchronous bilateral breast cancer appears in contralateral breasts, both of which must be diagnosed less than a year apart. The incidence of synchronous breast cancer is 0.6% of all cases.[2]

Many risk factors have been identified in the pathogenesis of female breast cancer. Age of menarche, number of pregnancies, age at first pregnancy, breastfeeding, and age at menopause have all been shown to correlate with the risk of breast cancer.[10] A female's risk of breast cancer can increase with early menarche, late menopause, late age of first pregnancy, low parity, and hormonal therapies. For each 1 year later onset of menopause, a woman's risk of breast cancer increases by 3% for hormonally-influenced cancers.[11] Other negative prognostic factors include cigarette smoking, alcohol consumption, and excess estrogen, including obesity, whereas an increased number of births and later onset of menarche decreases the risk of breast cancer.

Numerous genetic mutations have been recognized to play a role in the development of breast cancer. A few of the most prevalent markers associated with breast cancer include BRCA 1, BRCA 2, TP53, CHEK2, and ATM. BRCA 1 and 2 mutations cause 5-10% of all breast cancers. TP53 has been shown to have increased protein expression in phyllodes tumors. Germline genetic mutations in TP53 have been exhibited in approximately 10% of mPT.[7] Moreover, a correlation between TP53 expression and negative prognostic outcomes have been noted in cases of PT.[12] Other germline mutations that have been associated with PT include BRCA 1 and RB1.[13] At this time, there is no recommendation from the National Comprehensive Cancer Network (NCCN) on genetic testing in patients with PT, and the incidence of genetic mutations may be higher in this population than previously thought.

Our patient underwent genetic testing of 91 genes associated with breast, colon, ovarian, uterine, pancreatic, and renal cancers. She was not found to have any of the aforementioned genetic mutations. However, she was found to have a SPINK1 genetic mutation. SPINK1 is associated with pancreatic and colon cancer. SPINK1 protein transcripts have been studied as a prognostic factor in breast cancer. A study by Soon et al. determined an increase in distant metastasis was seen in estrogen receptor positive (ER+) patients with patients expressing high levels of the SPINK1 protein transcripts. The same correlation was not seen in patients that had estrogen receptor-negative breast cancers.[14] Additional research should be conducted to determine SPINK1's potential as a therapeutic target in breast cancers as well as its role in estrogen receptor negative (ER–) breast cancers.

The mainstay of treatment for phyllodes tumors includes excision with wide margins (> 1 cm) or mastectomy.[6] There is a minimal role for axillary staging in PT and should only be performed if an abnormal lymph node is strongly suspected. Chemotherapy and adjuvant radiotherapy can serve a limited role in the treatment of PT and remains controversial.[15] Radiation therapy has shown to be beneficial in some cases. NCCN guidelines suggest consideration of RT in specific cases where recurrence would cause significant morbidity.[6] Chemotherapy for PT has shown no survival benefit.[16] For metastatic PT, utilization of soft tissue sarcoma regimens can be initiated.[17]

The treatment of TNBC is complex and differs from that of PT. The treatment options for TNBC include a combination of surgery, chemotherapy, and radiation. A total mastectomy or breast-conserving therapy is appropriate depending on the specifics of the case and patient preference. Surgical margins should be negative for appropriate surgical therapy. The addition of chemotherapy can be given in the neoadjuvant or adjuvant setting. TNBC may respond better to chemotherapy than estrogen receptor-positive breast cancer but has a lower 5-year survival when compared by stage to hormone receptor-positive breast cancer.[3,18] There is no role for adjuvant endocrine therapy in these patients due to the lack of estrogen receptors on the tumor. When metastasis

is present, systemic therapy is primary with a limited role in palliative surgery.[8] Surgery in the setting of triple-negative metastatic disease was shown to worsen distant disease-free progression.[19]

The treatment decisions for synchronous breast cancer of varying histology are complex and require the collaborative efforts of a multidisciplinary tumor board to weigh the benefits of different treatment strategies. The primary goal should be curative unless metastatic disease is found. Consideration of patient factors, genetics, and biology of the tumors all are important aspects of an individualized treatment plan.

CONCLUSION

Synchronous bilateral breast cancers, such as the one discussed, have a low incidence. A phyllodes tumor presenting concurrently with a triple negative IDC is an extremely rare finding. Treating a triple negative IDC is complex but can be done so with surgery, chemotherapy, and/or radiotherapy. Surgical removal with wide margins is the mainstay treatment for phyllodes tumors. Treatment decisions for synchronous breast cancer of varying histology are complex and must be individualized to each patient. This requires the collaborative efforts of a multidisciplinary tumor board. Furthermore, additional research should be done to explore the SPINK1 correlation to ER– breast cancer. SPINK1 could play a role in future treatment options as a therapeutic target in different types of breast cancers. Future efforts should be made to better understand and individualize treatment options to improve outcomes for breast cancers.

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