Gynecomastia and Malignancy: A Case of Male Invasive Ductal Breast Carcinoma Treated with Neoadjuvant Chemotherapy

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Patient: Male, 61-year-old
Final Diagnosis: Invasive ductal carcinoma
Symptoms: Areolar lesion • breast lesion discharge • breast mass • gynecomastia
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine • Oncology

Objective: Rare disease
Background: Male breast cancer represents a rare malignancy with identifiable risk factors, including genetics, radiation exposure, liver dysfunction, and concomitant diagnosis of Klinefelter syndrome. Gynecomastia can commonly present in these patients, and despite increased estrogen levels in adipose breast tissue, gynecomastia has not been proven to be a significant risk factor for carcinoma development. Male patients with new-onset breast masses are recommended to undergo diagnostic mammograms and breast ultrasound for further evaluation. Those diagnosed with breast cancer most commonly have invasive ductal carcinoma of the breast, and over half of these patients are found to have estrogen and progesterone receptor (ER/PR) positivity.

Case Report: In this case report, we present a Black man with gynecomastia and an areolar lesion for a 6-month duration following a traumatic event. He was initially referred to the surgical team for further evaluation, and subsequent imaging and biopsy data revealed ER/PR-positive invasive ductal carcinoma. Multidisciplinary discussions were held, and the patient was arranged to begin neoadjuvant treatment with doxorubicin hydrochloride and cyclophosphamide, followed by treatment with paclitaxel (AC-T) chemotherapy, followed by bilateral mastectomy and adjuvant hormonal therapy.

Conclusions: The treatment of male breast cancer has remained relatively like that of female breast cancer, which may be due to the limited data in the treatment of male breast cancer. Thus far, studies involving neoadjuvant chemotherapy of female patients have demonstrated promising responses to expand surgical options for patients and possibly decrease the rates of recurrence. Additional studies are warranted to discern optimal therapy for the male patient population.

Keywords: Breast Neoplasms, Male • Carcinoma • Gynecomastia • Neoadjuvant Therapy
Background

Female breast cancer has been widely discussed and researched. Conversely, male breast cancer remains a rare phenomenon, with a recently demonstrated increase in incidence from 1.0 to 1.2 per 100 000 [1]. Breast cancer represents 0.17% of malignancies in men and is less common in Black men, with age representing the greatest risk factor [1,2]. Additional risk factors include genetic predisposition, with BRCA1 or BRCA2 genomic alterations, positive family history of breast cancer, radiation exposure, testicular manifestations, such as cryptorchidism or injury, and hepatic dysfunction [3]. Although it has been proposed that an increase in estrogen in adipose tissue can predispose patients with gynecomastia to breast cancer, most recent data concluded that patients with gynecomastia for causes other than Klinefelter’s syndrome have not demonstrated an increased risk [4]. While gynecomastia is a benign condition, there are specific alarming signs that, if found, warrant further investigations [5]. Here, we present a rare case of a 61-year-old man with bilateral gynecomastia who was diagnosed with invasive ductal carcinoma.

Case Report

A 61-year-old Black man with a past medical history significant for bilateral gynecomastia presented to the Hematology-Oncology clinic following surgical referral. He initially presented with a right non-healing areolar lesion 6 months after a traumatic event. In the interim since the initial development of the lesion, the patient exhibited purulent discharge from the lesion that was treated with antibiotics via Emergency Department (ED) visits. The physical examination was notable for bilateral gynecomastia and an ulcerated peri-alveolar mass, with 3 palpable masses in the right breast. He underwent a bilateral diagnostic mammogram and breast ultrasound, which showed an unremarkable left breast. The right breast showed extensive skin thickening, with a fungating and lobulated mass measuring 3.7 cm, extending anteriorly to the nipple area, with subsequent nipple necrosis, and 2 additional masses. The second and third masses were located at the 12 and 9 o’clock positions, measuring 0.8 cm and 0.7 cm, respectively. Both masses were associated with skin dimpling and retraction. A spiculated mass was identified in the areolar region of the right breast, with associated skin thickening that measured 1.8×1.3×1.7 cm. The ultrasound findings were consistent with 3 malignant masses in the right breast.

The patient underwent an ultrasound-guided core needle biopsy of the right dominant breast mass, which showed histopathologic grade 3 invasive ductal carcinoma that was estrogen receptor (ER)-positive 100%/progesterone receptor (PR)-positive 50%, and HER2/neu +2 (HER2 subsequently was confirmed negative by fluorescent in situ hybridization [FISH] analysis), with a Ki-67 of 70%. Biopsy of the right breast mass at the 9 o’clock position demonstrated a grade 3 invasive ductal carcinoma with similar tumor biology as the dominant mass (Figures 1, 2). Both biopsies had negative lymphovascular invasions. Computed tomography scans of the chest, abdomen, and pelvis were negative for metastatic disease. The clinical prognostic stage was T4 pNx cM0, which was consistent with stage 3b disease.

In terms of the patient’s family history, his mother was diagnosed with colon cancer in her early 50s and died at age 58 with metastasis to multiple organs. The patient’s paternal female first cousin was diagnosed with breast cancer at age 59 and was still living 2 years later.
The patient was initiated on neoadjuvant doxorubicin hydrochloride and cyclophosphamide, followed by treatment with paclitaxel (AC-T) chemotherapy, with tbo-filgrastim administration during the AC phase, and plans for radiation therapy and hormonal therapy following mastectomy.

Discussion

Gynecomastia is defined as benign breast enlargement. It is more common during certain stages of life, such as early puberty and late adulthood [6]. The most common cause is obesity, but other risk factors include chronic illicit drug or alcohol consumption, medication adverse effects, medical problems that predispose patients to gynecomastia, and the use of hormones [7]. Although gynecomastia can present in a unilateral fashion, breast cancer can be distinguished, as the mass is typically painless, associated with older patients, and presented unilaterally [7]. Several case control studies have shown a strong relationship between male breast cancer and excess estrogen, which also contributes to gynecomastia [8]. However, an actual relationship could not be proven owing to the increased likelihood of this identified risk factor, recall bias, and the effect of chance [8]. Additionally, there are no recent prospective studies that report a relationship between gynecomastia and male breast cancer. Nevertheless, it has been concluded that patients with unilateral or rapid development gynecomastia, the presence of irregular or asymmetrical enlargement of the breasts, nipple discharge, or lesions fixed to the skin should undergo a biopsy for malignancy consideration [5]. Our patient presented with gynecomastia, and this was likely in the setting of excess adipose tissue and was unlikely a causative factor for his development of breast cancer. However, the presence of the alarming signs warranted further evaluation for breast cancer and confirmation of the diagnosis.

Given the rarity of male breast cancer, the mean age at diagnosis is older than that of women and usually in the seventh decade, as in our patient’s case [9]. Because they are closely related, the relationship between gynecomastia and male carcinoma affects the disease prognosis. Men with breast cancer can have a misdiagnosis of benign gynecomastia, which can lead to unnecessary delay in treatment and thus a worsened prognosis [10]. Regarding our patient, his lesion was initially diagnosed as an infection after trauma to his gynecomastia and was treated with antibiotics multiple times prior to referral to the Surgery or Oncology Departments.

Guidelines for diagnostic imaging of male breast cancer remain unclear; however, data suggest completing standard mammography as one would complete in a female patient, with additional mediolateral oblique and craniocaudal views, as well as pectoralis-displaced views if the patient has significant muscle that can compromise the image [3]. Mammography has demonstrated 90% sensitivity and specificity in terms of diagnosing male breast cancer [11]. Additionally, targeted ultrasound imaging of the specific mass or masses can be useful to further help with the diagnosis [3]. Similar to that of female breast cancer patients, the histologic presentation in male patients can be notable for irregular or spiculated lesions that can have pleomorphic calcifications; however, male breast cancer patients have also demonstrated hypoechoic or sometimes partially cystic masses on ultrasound imaging [3]. Our patient underwent a bilateral diagnostic mammogram as well as a subsequent breast ultrasound and was found to have a spiculated mass with irregular margins, consistent with common female breast cancer ultrasound findings.

Per the current National Comprehensive Cancer Network (NCCN) guidelines, male patients with breast cancer should undergo genetic testing for further evaluation. In terms of hormone testing, ER positivity and PR positivity have both been found in 69% of males patients with breast cancer, which is slightly higher than the percentage of hormone positivity found in female patients with this malignancy [12]. This increase in hormone sensitivity is attributed to lower blood estrogen levels, which allow for more receptor availability for binding [12]. Although the percentages of hormone sensitivity remain high in male breast cancer, the significance of this in terms of prognostic factors and response to hormone reduction therapy remains limited [12]. In a retrospective study of approximately 70 male breast cancer patients, infiltrating ductal carcinoma represented the most common histology (75%), and most of the tumors biopsied (91%) were ER positive, with 25% of patients exhibiting overexpression of HER2 [13]. In relation to current data, our patient’s masses were consistent with most male breast cancer tumors, as he was diagnosed with invasive ductal carcinoma with ER and PR positivity.

Although outcomes have demonstrated similar efficacy, most male patients with breast cancer have undergone mastectomy rather than breast conservation surgery [14]. Although unilateral mastectomy was recommended, our patient planned to proceed with bilateral mastectomy for cosmetic reasons. The administration of neoadjuvant chemotherapy has demonstrated an increase in options for breast conservation treatment as well as an improvement in recurrence rates in select patient populations (those without advanced lymph node involvement, tumors exceeding 2 cm, lymphovascular invasion, and residual disease that is multifocal in nature) [15]. The benefits of neoadjuvant therapy include early treatment of potentially distant micrometastatic disease, assessment of chemotherapy response prior to surgical intervention, and possible tumor burden reduction prior to surgery [15]. In a retrospective study investigating male patients with lymph node-positive breast cancer, it was found that male patients were less
frequently treated with neoadjuvant chemotherapy; however, among those who were, greater than 84% of patients demonstrated partial response [16]. Additionally, 13% of the male breast cancer patients with ER/PR positivity and HER2-negative status who underwent neoadjuvant therapy demonstrated a complete response [16]. According to this study, it is evident male patients do not receive neoadjuvant therapy as frequently; however, there may be benefits, such as decreased in tumor burden and improved outcomes, based on this preliminary data. Despite limited yet promising data for neoadjuvant chemotherapy treatment for male breast cancer patients, in our patient's case, neoadjuvant therapy was considered, given his multi-tumor presentation and diagnosis of stage 3 cancer, in the hopes of reducing the tumor burden and improving his overall prognosis.

According to current NCCN guidelines, male breast cancer patients are recommended to undergo adjuvant chemotherapy with or without HER2-targeted therapy (similar to female patients), and tamoxifen has demonstrated superior outcomes when compared with single adjuvant aromatase inhibitor therapy [14]. Given our patient's hormone susceptibility, he was recommended for adjuvant hormonal therapy following his mastectomy.

Conclusions

Although rare, male breast cancer incidence has increased, and research is limited regarding its management. Male breast cancer must be differentiated from gynecomastia, as patients have similar clinical presentations. Male patients more frequently have hormone positivity than do female patients; yet, current treatment guidelines for male patients with breast cancer remain similar to those of female patients. Promising studies have demonstrated benefits in attempting neoadjuvant therapy, especially with HER2-positive patients and trastuzumab. However, these studies have not involved male breast cancer patients due to the rarity of this disease. Our patient underwent neoadjuvant chemotherapy, given the advanced stage of disease, which may lead to benefits in expanding his surgical options and a possible decreased recurrence rate. Additional trials involving optimal treatment of hormone-sensitive male breast cancer are warranted to determine optimal management.

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