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Case Report

Breast cancer in a transgender woman undergoing gender-affirming exogenous hormone therapy ☆

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ABSTRACT

Gender-affirming hormone therapy may be utilized by transgender women hoping to induce feminizing changes and suppress the effects of endogenous testosterone. It is well established that exogenous hormone use increases risk of breast cancer in cisgender women; however, a link in the transgender population is less clear. Our case presents a transgender woman undergoing gender-affirming exogenous hormone therapy who subsequently developed breast cancer. We review the available literature regarding risks of exogenous hormone therapy with regards to breast cancer development. Additionally, we present current societal guidelines and recommendations for screening in this population.

Case report

A 39-year-old transgender woman underwent gender-affirming hormone therapy for 3 years with oral estradiol and spironolactone. Shortly after initiating hormone therapy, she was evaluated for a palpable mass in the left breast that was found to be benign with spontaneous resolution. There was otherwise no reported past medical or surgical history, including no personal or family history of breast cancer. She recently detected a new palpable mass in the right breast but did not seek further evaluation noting similar symptoms and onset as the prior benign palpable lesion in the left breast. The right breast mass continued to enlarge, and the patient discontinued hormone use, ultimately presenting with a large palpable right breast mass 6 months later.

Imaging and diagnosis

Diagnostic mammography (Fig. 1) and targeted ultrasound (Fig. 2) were performed, confirming the presence of a 7 cm irregular mass in the retroareolar right breast, with associated nipple retraction. Ultrasound-guided biopsy of the right breast mass was performed with pathology showing grade 2 invasive

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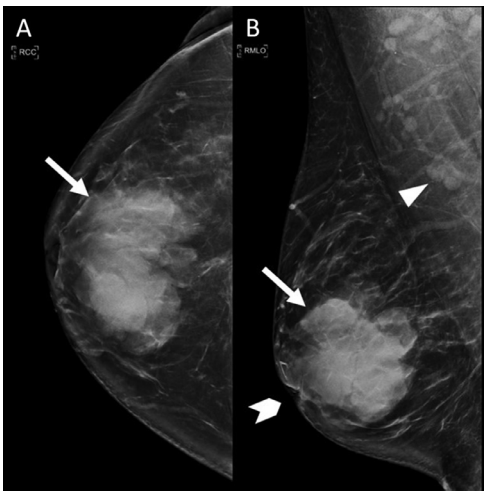

Fig. 1 – (A) Craniocaudal and (B) mediolateral oblique mammograms demonstrating an irregular high-density mass (arrow) in the retroareolar region with associated nipple retraction (chevron), as well as a suspicious axillary lymph node (arrowhead).

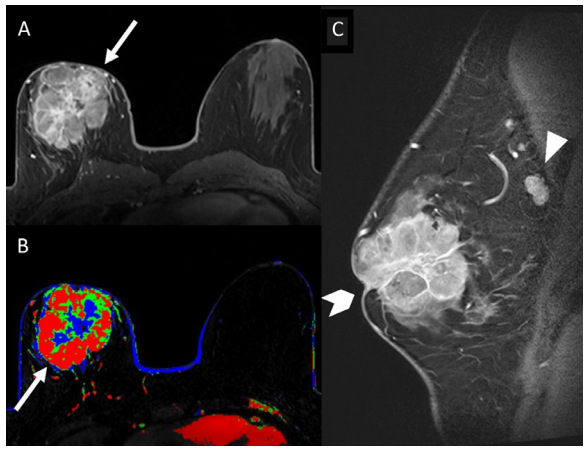

Fig. 3 – (A) Axial T1 contrast-enhanced fat-suppressed MRI image demonstrating an irregular rim-enhancing mass in the retroareolar right breast (arrow) with (B) washout kinetics (red) on computer-aided detection overlay. (C) Sagittal image from the same study showing nipple invasion/retraction (chevron) as well as an enlarged, enhancing level I axillary lymph node (arrowhead).

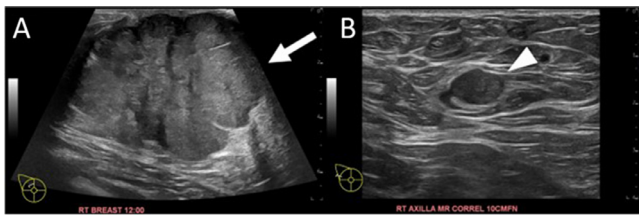

Fig. 2 – (A) Targeted right breast ultrasound in the transverse plane shows a large irregular hypoechoic mass (arrow), subsequently biopsied revealing invasive ductal carcinoma. (B) MRI-directed ultrasound in the transverse plane demonstrates a morphologically abnormal right axillary lymph node with eccentric cortical thickening (arrowhead) which was also biopsied, demonstrating metastatic breast carcinoma.

ductal carcinoma (strongly estrogen-receptor positive [96%], weakly progesterone-receptor positive [4%], and human epidermal growth factor receptor 2 negative).

Contrast-enhanced breast MRI (Fig. 3) was performed to evaluate disease extent, revealing an irregular rim-enhancing mass in the right breast with washout enhancement kinetics and nipple invasion, consistent with the biopsy-proven invasive ductal carcinoma. Additionally, a 1.4 cm level I right axillary lymph node demonstrated cortical thickening and increased enhancement compared to adjacent lymph nodes (Figs. 2 and 3). Ultrasound-guided right axillary lymph node biopsy was performed, confirming the presence of metastatic disease. Genetic testing revealed a pathogenic *PALB2* mutation.

Discussion

The link between exogenous hormone therapy and increased breast cancer risk is well-established in cisgender postmenopausal women. There is growing evidence to support a similar association in transgender women undergoing gender-affirming hormone therapy with exogenous hormone supplementation; however, this association remains less clear [1]. The strongest supporting evidence comes from a 2019 study from the Netherlands that evaluated the incidence and characteristics of 2260 adult transgender women undergoing exogenous hormone therapy compared to the general Dutch population [1]. This study demonstrated a 46-fold increased risk of developing breast cancer in transgender women when compared with cisgender men, although this risk was still less than that of cisgender women. However, the major limitation of this and similar prior studies was largely due to their retrospective designs that did not allow for precise patient selection and adequate follow-up.

Gender-affirming exogenous hormone therapy in transgender women most commonly involves the use of exogenous estrogen with adjunctive antiandrogen medications (typically spironolactone) with the goal of inducing feminizing changes and repressing the unwanted secondary sex characteristic effects of testosterone [2,3]. Breast tissue changes that occur following initiation of exogenous hormones include the formation of breast ducts, lobules, and acini resulting in a histologic pattern similar to that of cisgender women [2]. This is in contrast to the changes that occur in men with gynecomastia, which is typically limited to stromal hyperplasia without lobule and acini formation [2,4].

Breast cancers in the transgender population undergoing exogenous hormone therapy are predominantly of the luminal subtypes [1]. de Blok et al. [1] reviewed the hormone

receptor status of tumors found in transgender women and found that 83% of tumors were estrogen receptor positive, 67% were progesterone receptor positive, and only 8% were HER2 positive, further supporting the potential stimulatory effect of exogenous hormones to result in breast cancer development in this population.

As seen in our patient, studies have demonstrated a younger age at diagnosis in transgender women undergoing exogenous hormone therapy when compared to cisgender women, as well as a relatively short duration of exposure to exogenous hormones [1,2]. In addition to hormonal stimulation, another proposed mechanism to explain a rapid onset of breast cancer in a subset of this population may be related to underlying genetic susceptibility. Genetic testing in our patient revealed a pathogenic *PALB2* mutation which predisposes cisgender women to developing breast cancer (33%-58% risk of breast cancer development by age 70 years) [5]. This further highlights the importance of reviewing the family history with patients prior to initiation of gender-affirming exogenous hormone therapy, as risk thresholds for breast cancer will vary.

Breast cancer screening recommendations in this population are somewhat variable and continue to evolve. Important patient considerations regarding the initiation of screening include the length of time a patient has undergone exogenous hormone therapy, breast development, and known risk factors for breast cancer [2,6]. General recommendations from transgender health experts and professional societies include screening mammography beginning 5 years after initiation of exogenous hormone therapy. University of California San Francisco and Fenway Health recommend annual or biennial screening examinations to begin at age 50 years [2], while the Endocrine Society recommends screening at the same frequency as cisgender women beginning at age 40 years [1]. The Society of Breast Imaging (SBI) and American College of Radiology (ACR) agree with recommendations to begin annual screening at age 40 years in transgender women who have used hormones for at least 5 years. Additionally, the SBI and the ACR recommend all women undergo risk assessment by age 30 years to identify those at higher risk who may benefit from earlier screening [6,7].

Conclusion

There is growing evidence to support a link between gender-affirming exogenous hormone therapy in transgender women and a subsequent increased risk of breast cancer development. However, additional studies are needed to further elucidate breast cancer risk in this population and to help guide future screening recommendations. Our case presents one such instance in which a patient may have benefitted from risk assessment and earlier screening examinations as well as closer clinical surveillance. Clinicians caring for these patients play a critical role in assessing underlying risk factors and discussing the potential risks and expectations associated with gender-affirming exogenous hormone therapy. Radiologists should be aware of possible imaging presentations, providing reassurance for benign findings and expedited workups and diagnoses for malignant lesions.

Patient consent

Written informed consent was obtained from the patient for publication of this case report.

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