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Case Report

Invasive Ductal Carcinoma of the Breast in a Transgender Man: A Case Report

Yujing J. Heng[a] Kevin J. Zhang[b] Monica G. Valero[c] Gabrielle M. Baker[a]
Valerie J. Fein-Zachary[d] Michael S. Irwig[b] Gerburg M. Wulf[b]

[a]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [b]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [c]Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [d]Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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Gender dysphoria · Testosterone · Transmasculine · Breast cancer

Abstract
There is limited literature about breast cancer in the transgender population. Very little is known about how gender-affirming hormone therapy affects their breast cancer risk. On the other end, for those diagnosed with breast cancer, there are no clinical guidelines to manage their breast cancer, specifically, how to manage their gender-affirming hormone therapy during breast cancer treatment. Here, we report a 52-year-old transman diagnosed with a grade 2 invasive ductal carcinoma (ER+/PR+/HER2−), and ductal carcinoma in situ (DCIS) of intermediate grade. We discussed his risk factors as well as treatment options.

Introduction

Most transgender men (~65%) [1], assigned female at birth, pursue gender-affirming testosterone therapy (TT) to treat their gender dysphoria and for masculinization. Some may opt to pursue chest-contouring surgery, hysterectomy, and/or oophorectomy; receiving TT is not a prerequisite for any of those gender-affirming surgeries. There is limited research on the effects of testosterone on reproductive cancers in transmen. Specifically, very little is known about the extent to which TT modulates breast cancer risk.

Correspondence to:
Yujing J. Heng, yheng@bidmc.harvard.edu

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There are only three epidemiological studies about breast cancer risk in transgender men [2–4]. The studies by Gooren et al. [2] and Brown and Jones [4] concluded that TT did not increase breast cancer risk. de Blok et al. [3] estimated that the breast cancer risk for transmen who received TT and underwent both chest-contouring and oophorectomy surgeries was ≈3.8%, which was lower than cisgender women (≈12%) but remained higher than cisgender men (<0.12%). The breast cancer incidences, in Gooren et al. [2] (1 in 795), Brown and Jones (7 in 1,579) [4], and de Blok et al. (4 in 1,229) [3], were simply too small to draw a definitive conclusion about breast cancer risk in transmen. Meanwhile, studies in pre- and postmenopausal women demonstrated that high levels of circulating testosterone increase breast cancer risk [5–10]. Therefore, the association of TT and breast cancer risk remains to be elucidated.

To date, there are >30 published transmen breast cancer cases - in transmen and nonbinary individuals (assigned female at birth) [11–20]. The number of transmen breast cancer cases is likely underreported as transgender people traditionally have limited healthcare access due to discrimination, lack of insurance, or reside in medically underserved areas [21]. There is a paucity of literature pertaining to transgender health, as well as clinical guidelines on how to manage TT during breast cancer treatment [11]. It is unclear if and how TT affects breast cancer treatment outcomes, recurrence, or survivorship. In this case report, we present a 52-year-old transman diagnosed with invasive ductal carcinoma and discuss his treatment options as he transitions from premenopausal status to menopause.

Case Report

The patient is a 52-year-old transman who had been receiving testosterone cypionate 50 mg/week IM intermittently for the last 2 years. Figure 1 displays a timeline summarizing the main clinical events. The patient initially presented with a self-palpated right breast mass in October 2020. Diagnostic bilateral breast imaging in February 2021 revealed a simple cyst in the right breast – at the site of the patient's complaint – and a 0.6 cm group of coarse heterogeneous calcifications in the left breast. The left breast calcifications were recommended for a core needle biopsy, which reported atypical ductal hyperplasia (ADH; Fig. 2). Subsequently, 7 months later, the patient underwent left breast excisional biopsy of the ADH. Pathology of the excisional biopsy was upgraded to invasive cancer - a single focus of a 4 mm invasive ductal carcinoma (grade 2, ER+, PR+, and HER2−), and ductal carcinoma in situ (DCIS; intermediate nuclear grade) were identified (Fig. 3).

Given the upgrade to invasive breast cancer and a positive superior margin, margin re-excision and sentinel lymph node biopsy (SLNB) were performed. Margin re-excision reported DCIS of intermediate nuclear grade, ADH, and flat epithelial atypia. Three sentinel lymph nodes were negative for carcinoma. His Oncotype Dx score was 14; therefore, chemotherapy was not recommended. He completed adjuvant radiation to the left breast in January 2022 and started tamoxifen shortly after.

Of note, the patient had a strong family history of lung cancer (father diagnosed at 68 and maternal uncle diagnosed at 35) and breast cancer (sister diagnosed at 36). The patient underwent genetic testing using the Invitae Breast Cancer STAT Panel consisting of nine well-established breast cancer susceptibility genes - *ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11*, and *TP53* - and was negative. At the time of his invasive cancer diagnosis, the patient was premenopausal (estradiol 398 pg/mL), had been a smoker for over 20 years (up to three cigarettes a day), occasional alcohol drinker, and led a healthy lifestyle (exercised ×5 a week). As for his reproductive risk factors, his age of menarche was between 12 and 13 years old and he had never been pregnant.

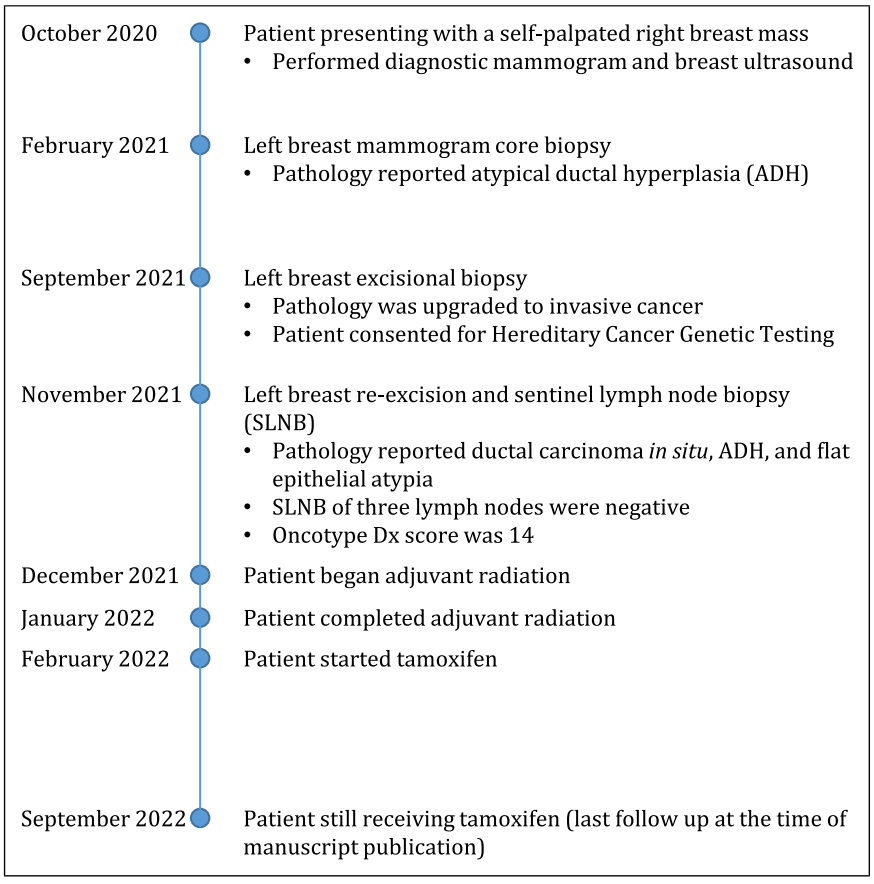

Fig. 1. Timeline that summarizing the main clinical events.

The patient provided written informed consent to take part in the study. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary (for all online suppl. material, see https://doi.org/10.1159/000529859).

Discussion

The patient had a small tumor with no lymph node involvement, placing him in the lowest stage, Stage IA. Thus, his overall prognosis was considered favorable. The patient was a candidate for breast-conserving surgery and underwent complete resection of the invasive carcinoma and DCIS. The patient also reported symptoms of menopause. The patient had expressed an interest in continuing with his TT.

There is no systematic investigation regarding the use of gender-affirming hormone therapies on breast cancer risk, treatment outcome, and risk of recurrence. Given the patient's strong family history of cancer [22], smoking habit [23, 24], and the fact that he is nulliparous, he can be considered at risk of developing breast cancer. It is uncertain if TT played a major role in modulating this patient's breast cancer risk. The patient was premenopausal at the time of diagnosis whereby his main source of estradiol was ovarian, and he only received TT 2 years prior; therefore, there is a low likelihood of exogenous testosterone aromatizing to estradiol in nongonadal tissues [25]. Even if aromatization occurred, the contribution of this nongonadal, testosterone-derived to systemic estradiol levels would be minimal in a premenopausal person.

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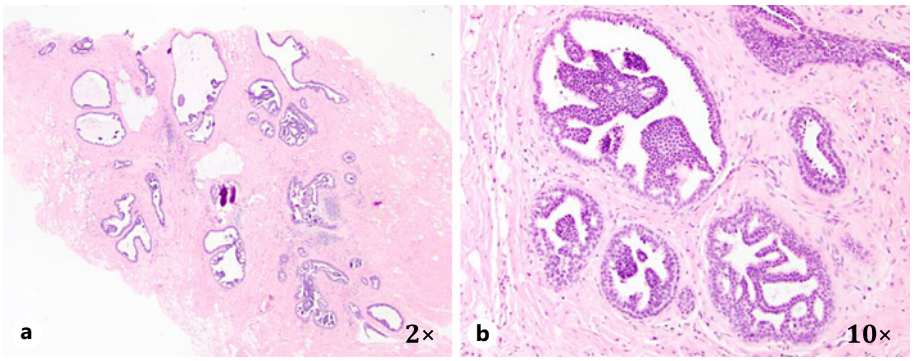

Fig. 2. Histology of the core needle biopsy. **a** Low power (×2) demonstrates intraductal proliferations with scattered associated calcifications. **b** Higher power (×10) shows that the intraductal proliferations consist of a monomorphic population of cohesive cells forming bridges and micropapillary structures, consistent with a diagnosis of atypical ductal hyperplasia.

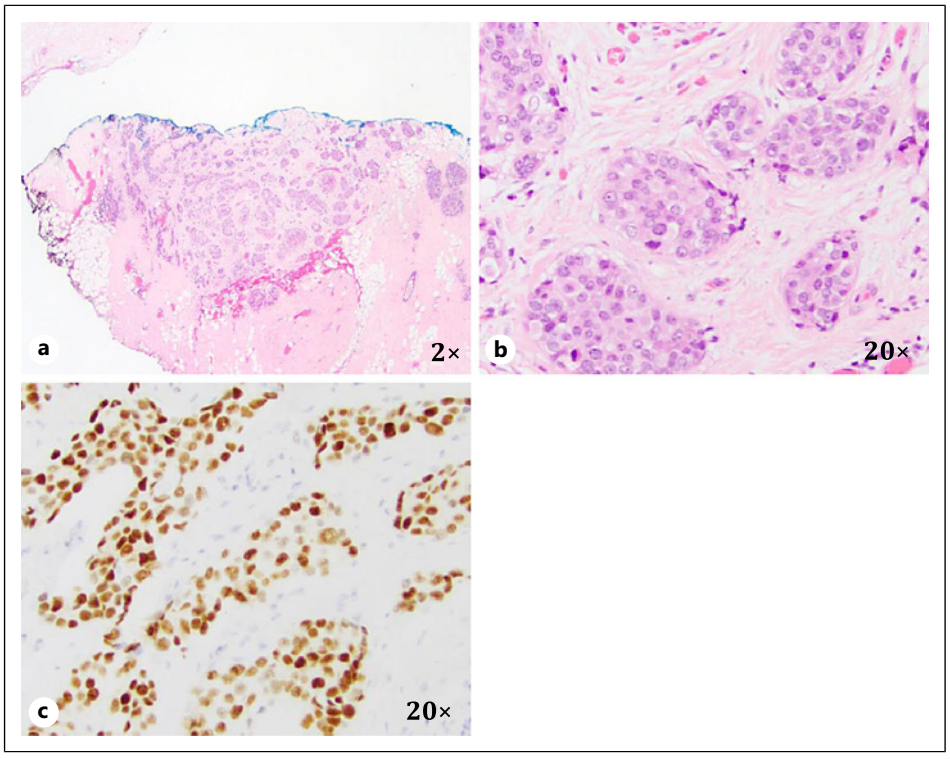

Fig. 3. Histology of the breast excision. **a** A focus of invasive ductal carcinoma, grade 2, was identified (×2). **b** A higher power view at ×20 of the invasive ductal carcinoma. **c** Immunostaining for estrogen receptor shows diffuse expression by the carcinoma cells (×20). Ductal carcinoma in situ of intermediate nuclear grade was also present (not shown). Refer to text for additional details regarding histologic findings.

The patient reported menopausal symptoms upon completion of his radiation therapy. In postmenopausal individuals, the aromatization of testosterone in nongonadal tissues takes over as the primary source of estradiol [25]. This aromatization pathway is clinically targeted by aromatase inhibitors, such as letrozole, to treat and prevent breast cancer in postmenopausal cisgender women [26, 27]. While it remains unclear whether continuing TT may

affect the patient's risk of recurrence - either by way of testosterone aromatizing to estradiol [6, 7, 10] or the activation of androgen receptors in the breast [28–32] - it may be beneficial for him to replace tamoxifen with an aromatase inhibitor after transitioning from a peri-menopausal state to menopause to limit the stimulatory effect of aromatized estrogen.

The current standard of care in the adjuvant setting is to offer premenopausal women secondary prevention with oral agents that interfere with estrogen receptor signaling. These can be either tamoxifen [33], which competes with estrogen for binding at the estrogen receptor, but does not lower estradiol levels, or ovarian ablation combined with an aromatase inhibitor such as letrozole, anastrozole, or exemestane, medications that block the inter-conversion of androgens into estrogens in nongonadal tissues [34]. Theoretically, this latter strategy might be particularly useful for the secondary prevention of breast cancer in transmasculine individuals as it would prevent any aromatization of exogenous testosterone. For estrogen receptor-negative breast cancers, we would use the same criteria for consid-eration of adjuvant chemotherapy that we use in cisgender women with estrogen receptor-negative breast cancer.

The US transgender population, previously estimated at 1.4 million adults and 150,000 youths in 2016 [35], has increased to two million in a 2021 report [36]. The transgender community is the fastest growing LGBTQ subgroup - 23% of transgender individuals in the USA are between 13 and 24 years old [35]. This actively expanding transgender population will increase the demand for more specialized healthcare. More large scale and long-term studies in the transgender population are needed to better understand gender-affirming hormone use and cancer, particularly in breast cancer [37–39]. This will be crucial to establish clinical guidelines for cancer screening, treatment, and follow-up care to support the medically underserved transgender population as they age.

Acknowledgments

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Statement of Ethics

Ethics approval was not required in accordance with institutional policy as this case report consisted of less than three subjects, is a medical/educational activity, and did not meet the Federal Policy for the Protection of Human Subjects definition of "Research." Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yujing J. Heng and Kevin J. Zhang wrote the original draft of the manuscript. Monica Valero, Gabrielle Baker, Valerie J. Fein-Zachary, and Michael S. Irwig reviewed and edited the manuscript. Gerburg M. Wulf supervised, reviewed, and edited the manuscript. All authors approved the final manuscript version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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