Breast Cancer in Female-to-Male Transsexuals: Two Cases With a Review of Physiology and Management

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Clinical Practice Points

- Testosterone is important for the development of secondary sexual characteristics in female-to-male (FtM) transsexuals, but it may increase breast cancer risk. To date, only one breast cancer case has been reported in the literature in a FtM transsexual after 10 years of testosterone therapy.
- We describe 2 cases of breast cancers diagnosed in FtM transsexuals who have been treated with supraphysiological doses of testosterone.
- Our 2 cases demonstrate the unique issues that concern the management of FtM transsexuals with breast cancer and examine possible roles of testosterone in the development of breast cancer.

Clinical Breast Cancer, Vol. 11, No. 6, 417-9 © 2011 Elsevier Inc. Open access under CC BY-NC-ND license.
Keywords: Androgen receptor, Breast cancer, Female-to-male transsexuals, Testosterone

Introduction

Testosterone is the crucial hormone in female-to-male (FtM) transsexuals for the development of secondary sexual characteristics of the desired gender. However, a major safety concern is whether testosterones have a stimulatory affect on the breast that can increase the risk of developing breast cancer. The first report of hormone treatments of transsexuals started in the 1970s. To date, only one breast cancer case in a FtM person has been reported in the medical literature.[1] Here we report 2 cases of breast cancers diagnosed in FtM transsexuals.

Case 1

JK is a FtM transsexual who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) at age 46 years to control severe endometriosis. At age 48 years, he began testosterone injections to induce masculinization. At the same time, he began letrozole, an aromatase inhibitor (AI), to control his residual symptomatic endometriosis. He discontinued letrozole 4 years later secondary to severe joint symptoms. At age 53 years, a year after discontinuing letrozole, he noted a palpable mass in his left breast. He underwent bilateral mastectomies with a left sentinel lymph node biopsy. Histologic examination revealed invasive ductal carcinoma, poorly differentiated, that measured 0.9 cm, grade II. All 3 nodes were negative. The estrogen receptor (ER) expression was positive, at 90%; progesterone receptor (PR), 0%; human epidermal growth factor receptor 2 (HER2), 3+; and Ki-67, 30%. The right breast was densely fibrotic. He had a strong family history of breast and ovarian cancer, with a maternal aunt diagnosed with breast cancer at age 32 years and a maternal grandmother diagnosed with ovarian cancer at age 60 years. He tested negative for BRCA mutations.

Clinical examination at the time of the initial oncology clinic visit revealed masculinization, with facial and body hair. A hormone profile was consistent with a menopausal state with high follicle-stimulating hormone and luteinizing hormone, and a low estradiol level because he had discontinued testosterone therapy before surgery. He received 6 cycles of TCH (docetaxel [Taxotere]/carboplatin/trastuzumab), followed by 1 year of trastuzumab therapy. He initially received adjuvant tamoxifen therapy but was not able to tolerate it due to severe adverse effects. His therapy was changed to exemestane, which he continues with tolerable joint symptoms. He restarted low-dose testosterone cream to maintain his masculinity and is currently free of recurrence after 2 years of follow-up.

Case 2

NO is a FtM transsexual who began supplemental testosterone at age 21 years to induce masculinization. At age 27 years, he noted a mass in his left breast. He subsequently underwent bilateral mastec-

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Submitted: Feb 5, 2011; Accepted: Jun 15, 2011

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doi: 10.1016/j.clbc.2011.06.006

tomies, with a left axillary lymph node dissection. Pathology results revealed a 2.5-cm, poorly differentiate, invasive ductal carcinoma in the left breast, and 1 positive lymph node of 14 examined. ER expression was 90%, PR was 10%, HER2 was 3+, and Ki-67 was 90%. The right breast demonstrated nonproliferative fibrocystic changes. He has no other significant medical history. His family history was notable for a maternal grandmother with breast cancer. He tested negative for BRCA mutations.

He discontinued testosterone 3 days before his initial oncology clinic visit, and, therefore, his hormone profile demonstrated follicle-stimulating hormone, luteinizing hormone, and estradiol levels consistent with a mid-cycle range, with a total testosterone of 104 ng/dL. Staging positron emission tomography showed no evidence of metastatic disease. He began treatment with TCH. Adjuvant hormonal therapy with BSO with or without tamoxifen or AI was discussed with the patient and was to begin after the completion of chemotherapy. Due to severe depression with suicidal ideations, he resumed testosterone therapy.

Discussion

Testosterone is an androgen found in low levels in the female body. It is produced in the ovaries and the adrenal gland, and via conversion of other steroid hormones. Circulating testosterone can be converted to dihydrotestosterone (DHT) by 5α-reductase or to estradiol by the aromatase enzyme. Testosterone levels typically decline as women age, due to declining ovarian and adrenal function. Although the mechanism by which estrogens promote breast cancer is described in the literature,[2] the role of testosterone on breast tissue is not certain. One proposed mechanism for a stimulatory effect on the breast (or on breast cancers) is that testosterone can be aromatized into estrogens. Higher circulating testosterones may increase estrogen generation within peripheral tissues, particularly the mammary glands.

Another mechanism of testosterone's stimulatory effect is through the direct activation of the androgen receptors (ARs). Ligand-activated AR can regulate gene expression through binding to androgen response elements located in a gene's enhancer or promoter region. ARs are abundant in normal mammary tissue and in the majority of breast cancer cell lines.[3,4] In addition, a significant number of tumors that are negative for ER and PR are positive for AR, which suggests the independent expression of AR in human breast cancer. The presence of AR in breast cancer tumors has been associated with distinct clinical and pathological prognostic factors.[5] Several studies have examined the effects of androgens on the growth of AR-positive breast cancer cell lines, and results have shown stimulatory effects in cells, regardless of their ER status.[6-9] Bicalutamide, an inhibitor of ARs, is currently in a phase II clinical trial for patients with metastatic breast cancer that are ER and PR negative but express AR. It is very plausible that both testosterones and dihydrotestosterone, through binding to ARs, can modulate breast cancer carcinogenesis, but the precise mechanisms involved remain unknown.[10]

Breast cancer has been linked to elevations in endogenous testosterone levels in many epidemiologic studies. A pooled analysis of 9 prospective studies in postmenopausal women found a strong association of breast cancer risk with serum concentration of testosterone, the relative risk for breast cancer was 2.22 (95% confidence interval, 1.59-3.10) when comparing testosterone levels from the highest to lowest quintile.[11] The Nurses' Health Study[12] and the large European Prospective Study into Cancer and Nutrition[13] reached similar conclusions. Whether this association reflects a role of testosterone in promotion of breast cancers or, alternatively, indicates that testosterone may serve as a growth factor for an already established tumor cannot be determined based on present data.

FtM transsexuals serve as an ideal model to examine the effects of testosterone on breast tissue because they are treated with supraphysiological doses of testosterone that result in serum levels in the mid-normal male range. In FtM transsexuals receiving androgen treatment, substantial amounts of circulating levels of 17ß-estradiol (E2) are generated from peripheral aromatization of testosterone. In a study of testosterone-treated FtM transsexuals, peak plasma E2 levels reached >300 pmol/L, and never fell below 85 pmol/L.[14]

Interestingly, on clinical examination, systemic testosterone therapy in FtM transsexuals usually leads to a reduction of breast size mediated by connective tissue shrinking and local fibrosis.[15-17] Histologic examinations of breast tissues in FtM individuals after testosterone therapy also showed marked reduction of glandular mammary gland tissues and increased fibrous connective tissue.[18,19] Only one breast cancer case has been reported in the literature, in a FtM transsexual after 10 years of testosterone therapy.[1] Similarly, our 2 patients were treated with >5 years of testosterone before the development of breast cancers. It is likely that most studies of FtM transsexuals were too short to observe any hormone-related tumors.[16,20] In addition, transsexualism is rare, which may lead to underestimation of tumors because most clinicians will only encounter single cases, which are less likely to be reported in the literature.

In addition, in a recent study that examined gene expression signatures in breast tissues of 5 FtM transsexuals before and after 2 years of intramuscular testosterone therapy, testosterone led to upregulation of 243 genes that were associated with breast cancer–specific gene expression signatures.[21] The researchers concluded that testosterone has widespread genetic effects on breast tissue, which can lead to the development of breast cancer.[21] FtM transsexuals who request testosterone supplements, therefore, must be made aware of the increased risk arising from such treatment.

Both cases of breast cancer in our study are ER^+ and $HER2^+$, with low to no PR expression. In a few studies that have looked at testosterone and breast cancer hormone receptor status, 2 have shown high testosterone levels to be associated with increased risk of ER^+ breast cancer irrespective of PR status.[12,22] Could these 2 patients illustrate the association of testosterone supplementation with ER^+ breast cancer? A purported mechanism is that testosterone is likely converted to estrogen by aromatization within tumor cells, which would directly stimulate tumor cell proliferation.

Data on HER2 expression in relation to testosterone exposure are limited. One study showed that the increased breast cancer risk associated with high testosterone was independent of the HER2 status of the cancer.[22] The overexpression of HER2 seen in both of our cases suggests that testosterone can affect breast cancer by mechanismsm, in addition to its conversion to estrogen, possibly through differential interactions between estrogen and AR signaling.

Both individuals also have family histories of breast cancer but did not have prophylactic mastectomy while receiving hormonal manip-

ulation. The first patient had a BSO, which did not prevent the development of breast cancer. In FtM transsexuals who have not undergone mastectomy, clinicians should be aware of the potential for development of breast cancer.

There are several challenges regarding the management of our patients. First, both patients chose to remain on testosterone. Testosterone use is contraindicated in women with a history of breast cancer, therefore, little is known about its use in this setting. Treatment of women with physiological testosterone to remedy sexual dysfunction has been an area of great interest. Most of the studies used testosterone in addition to estrogen, thereby confounding the assessment of breast cancer risk. In 1 large study, 814 postmenopausal women with sexual dysfunction and who were not receiving estrogen were randomized to receive a testosterone patch of either 150 or 300 μg/day or placebo.[23] At 24 weeks, there were only 4 cases of breast cancer in the group, but all happened in patients who received testosterone.[23] However, the short time on testosterone therapy implies that all of these cases of breast cancer were established before testosterone therapy was started.

The only case of breast cancer in an FtM transsexual reported in the literature continued on low-dose testosterone, with no disease recurrence after 5 years of follow-up.[1] Although adequate androgen replacement is necessary to preserve both patients reassigned gender and masculinity, these benefits must be balanced against the theoretical risk that androgen therapy may promote recurrence of their breast cancers. The use of an AI may mitigate the deleterious effects of exogenous testosterone by inhibiting aromatization. An ongoing pilot study is evaluating the safety of 1% testosterone cream as treatment for vaginal dryness and decreased libido in postmenopausal women with early-stage breast cancer and who are receiving an AI.

The optimal hormonal management in breast cancer patients who continue testosterone is of debate. Prophylactic oophorectomy was suggested to patient NO because it leads to induction of artificial menopause. Adjuvant tamoxifen is recommended for most men after mastectomy, but there are no data regarding the role of AIs in male breast cancer. Although the administration of AIs to patients who continue testosterone is theoretically attractive, the efficacy of AI in the presence of exogenous testosterones has not been studied, and it is unclear if FtM on exogenous testosterone will have as complete estrogen suppression with AI as do postmenopausal women.

As a compromise, Patient JK has been maintained on a low-dose testosterone cream that provides acceptable features of masculinity. He could not tolerate tamoxifen because of increased lower extremity edema, vaginal discharge, and joint pain, and is currently receiving exemestane. He has been followed-up closely with estradiol levels remaining in the menopausal range, with no evidence of recurrent cancer 2 years after his initial diagnosis. Patient NO likely will undergo BSO and start adjuvant tamoxifen. He also will be monitored closely, with the goal of maintaining his well-being with the lowest possible dose of testosterone supplement.

Conclusion

Our 2 cases demonstrate the unique issues concerning the management of FtM transsexuals with breast cancer, and address possible roles of testosterone in the development of breast cancer. Although high doses of testosterone might increase the risk of breast cancer, it is evident that testosterone is not a single contributing hormonal factor. To date, testosterone's role in female physiology is not yet fully defined, and further research is needed to determine the molecular defects involved in the androgenic pathways in breast cancer.

Disclosure

All authors have no conflicts of interest.

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