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Case Report

Complexities in Adjuvant Endocrine Therapy for Breast Cancer in Female-to-Male Transgender Patients

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Female-to-male transgender · Breast cancer · Endocrine therapy

Abstract
Introduction: Managing breast cancer in female-to-male (FtM) transgender patients is complicated and challenging. Androgens play a crucial role in the development of secondary sexual identity in FtM transgender patients, but their effectiveness in breast cancer remains unclear. Furthermore, the considerations for adjuvant endocrine therapy in this population are highly intricate and warrant thorough discussion. ***Case Presentation:*** We describe the case of a 44-year-old FtM transgender diagnosed with breast cancer 3 years after initiating androgen receptor agonist therapy as part of his gender identity transition. After mastectomy, adjuvant endocrine therapy was initiated, consisting of a combination of an aromatase inhibitor and a gonadotropin-releasing hormone agonist, along with a cross-sex hormone. ***Conclusion:*** Estradiol levels were significantly reduced, and male-typical levels of sex hormones were attained.

Introduction

Gender dysphoria is defined as a "significant incongruity between one's assigned sex at birth and their gender identity, leading to both physical and emotional distress [1]," and its prevalence has notably increased in recent decades. The self-reported prevalence

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of transgender identity ranges from 0.5% to 1.3%, which is significantly higher than the prevalence rates based on adults referred to clinics [2].

The comprehensive management of gender dysphoria involves psychological counseling, endocrinologic therapy, and surgical interventions. In particular, hormonal therapy aims to substitute naturally occurring hormones with cross-sex hormones [3]. Thus, certain diseases in the transgender population may necessitate a distinct approach from that applied to the general population, specifically hormone-dependent conditions such as breast cancer. In such cases, practitioners must balance the patient's objectives for gender-affirming hormone therapy with the necessity for breast cancer-specific treatment to optimize the patient's health outcomes.

Medical oncologists are often tasked with making decisions regarding hormonal cancer treatments for these patients in the absence of randomized trial data. We present a rare case of breast cancer in a female-to-male (FtM) transgender individual undergoing testosterone therapy.

Case Report

A 44-year-old FtM transgender man who was taking an androgen receptor (AR) agonist presented with a right breast mass discovered on self-examination. The patient had never sought consult for gender dysphoria, and he purchased the AR agonist on a website himself for 3 years prior to consult. Gynecological history was unremarkable; his menses had stopped since gender-affirming hormone therapy was started.

Breast examination revealed a palpable right lower breast lump with a skin dell; axillary lymphadenopathy was absent. Laboratory findings 11 days after stopping the AR agonist were consistent with the hormone levels of a premenopausal woman: testosterone of 0.24 ng/mL (reference range for women: 0.11–0.47), estradiol of 151 pg/mL (reference range for premenopausal women: 28.8–525.9), luteinizing hormone (LH) of 5.07 mIU/mL (reference range for women: 1.13–88.33), and follicle-stimulating hormone (FSH) of 2.42 mIU/mL (reference range for premenopausal women: 1.47–16.60). Diagnostic mammography revealed a spiculated mass with a tubular shadow. Breast ultrasound revealed a 2.2 × 2.0 × 1.7-cm hypoechoic right lower breast mass with indistinct margins, which was suspicious for malignancy. Contrast-enhanced magnetic resonance imaging revealed a 21-mm round, centrally necrotic mass with rim enhancement and invasion, suggesting enhancement into the overlying skin in the right breast. No distant organ and axillary lymph node metastases were detected on thoracic and abdominal computed tomography, classifying this patient as stage IIA T2N0M0 (Fig. 1). Histologic examination after core needle revealed histological grade 2, estrogen receptor (ER)/progesterone receptor-negative, human epidermal growth factor receptor 2 (HER-2)-positive, and invasive ductal carcinoma of the right breast (Fig. 2). Genetic testing was negative for breast cancer type 1 and 2 (BRCA-1 and BRCA-2) mutations.

Mastectomy and sentinel lymph node biopsy were performed. Surgical pathology of the specimen revealed invasive ductal carcinoma without skin invasion or lymph node involvement. On immunohistochemistry, the tumor was negative for HER2, 95% positive for ER, 95% positive for progesterone receptor, 25% positive for Ki-67, and 90% positive for AR.

The patient stopped using the AR agonist and was instead started on testosterone for gender-affirming hormone therapy. Anastrozole and a gonadotropin-releasing hormone agonist were administered as adjuvant endocrine therapy. After 1 year, there was no recurrence, and laboratory workup revealed extremely low levels of estradiol and sex hormone levels consistent with male values: testosterone of 7.82 ng/mL (reference range for men:

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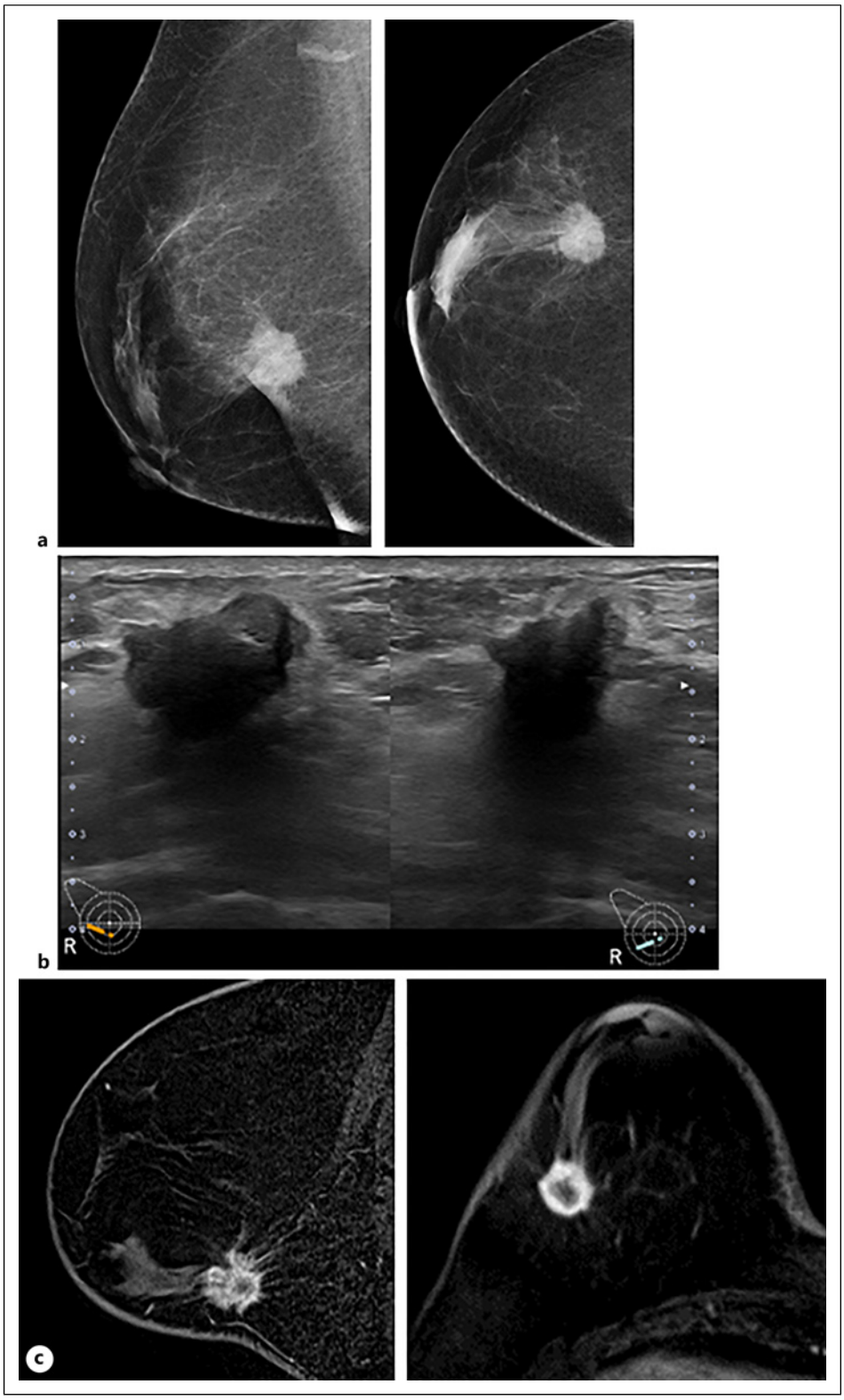

Fig. 1. Preoperative examinations. **a** Mammography showed a high-density mass with spiculation. **b** Ultrasonography revealed a hypoechoic nodular lesion of 2.2 × 2.0 × 1.7 cm. **c** Contrast-enhanced magnetic resonance imaging revealed a 21-mm round mass with central necrosis, exhibiting rim enhancement.

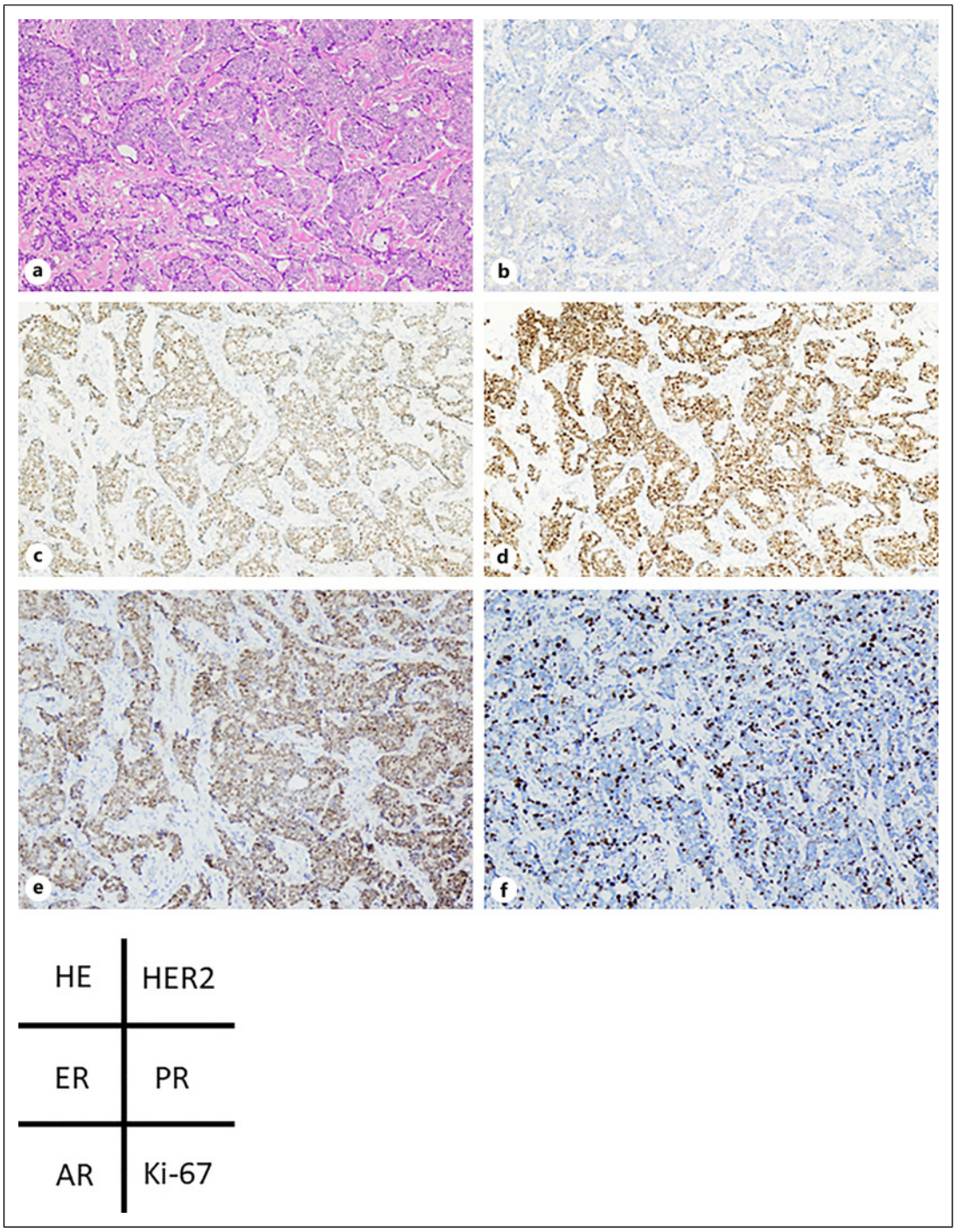

Fig. 2. Histological findings of invasive ductal carcinoma. **a** Hematoxylin and eosin staining showing invasive ductal carcinoma. Immunohistochemistry images showing expression of HER2 (**b**), ER (**c**), PR (**d**), AR (**e**), and Ki-67 (**f**). PR, progesterone receptor.

1.31–8.71), estradiol less than 5.0 pg/mL (reference range for postmenopausal women and men: 0–47.0), LH of 0.1 mIU/mL (reference range for men: 0.79–5.72), and FSH of 6.28 mIU/mL (reference range for men: 2–8.3) (Fig. 3).

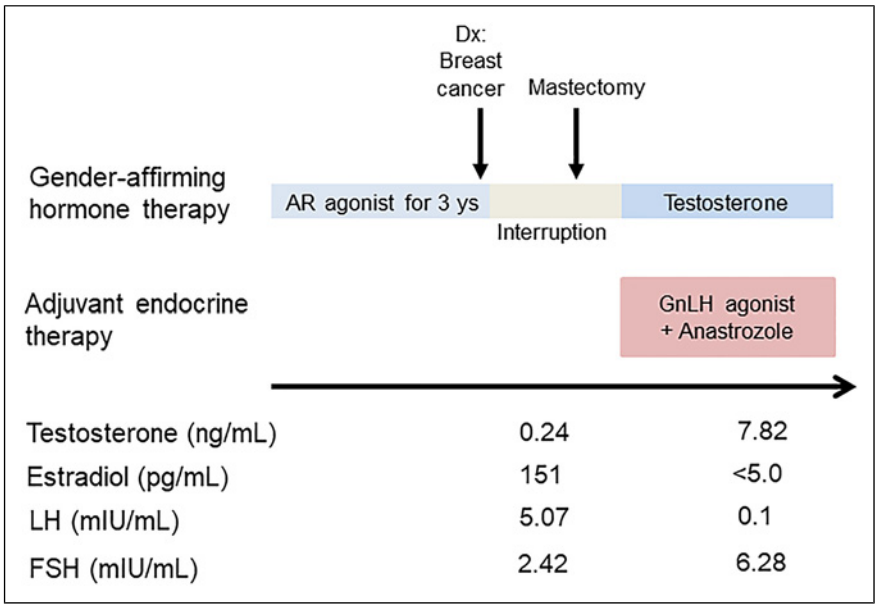

Fig. 3. Overview of the clinical course.

Discussion

This case of breast cancer in an FtM transgender patient exposed to external androgens is rare in the existing literature. This situation warrants discussion regarding the potential causative influence of androgen replacement in breast malignancy, along with an exploration of the benefits, risks, and safety associated with such treatment in individuals with breast cancer. In addition, there is also a need to determine the optimal hormonal management for this specific case. Currently, there are only 25 discretely reported cases of breast cancer in FtM transgender individuals, including our case (Table 1) [3–14].

Transgender men typically undergo masculinization through gender-affirming therapy involving testosterone. While there is robust evidence linking higher estrogen levels to breast cancer development, there is emerging yet inconclusive evidence of a connection between elevated androgen levels and breast cancer in individuals assigned female at birth, and the exact role of AR in the pathophysiology of breast cancer in general is unclear [15]. Previous studies primarily involved cisgender females, with only around 20 reported cases of breast cancer associated with testosterone therapy in transgender men. There are two suggested mechanisms for breast cancer due to elevated androgen levels: (1) the conversion of testosterone to estrogen in peripheral tissues and (2) the activation of ARs, leading to cellular growth and proliferation, particularly in mammary tissues. Another study in a mouse model demonstrated that dihydrotestosterone induces epithelial-to-mesenchymal transition in breast cancer cells in an AR-dependent manner, resulting in a more metastatic phenotype of breast cancer [16]. On the other hand, there is another suggested mechanism for the direct stimulation of ARs. Normal mammary cells and most breast cancer cells both express a significant number of ARs [15]. A meta-analysis of female breast cancers found that the presence of the AR receptor is generally considered a positive prognostic factor, particularly in ER-positive breast cancers [17].

When managing breast cancer in FtM transgender patients, it is important to carefully consider the need for androgen supplements. While adequate androgen supplementation is necessary to maintain a masculine phenotype and identity, individuals should be reminded of the theoretically increased risk of breast cancer recurrence due to androgen use. Determining

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Table 1. Summary of FtM transgender breast cancer cases

Paper	Age, years	Prior testosterone/ androgen	ER	PR	HER2	AR	BRCA	Treatment	BSO	Testosterone after Dx
Burcombe et al. [4] (2003)	33	Yes	+	+	NR[g]	NR	–	TAM[a]	Yes	Yes
Shao et al. [5] (2011)	53	Yes	+	–	+	NR	–	TCH[b] Exemestane	Yes	Yes
Shao et al. [5] (2011)	27	Yes	+	+	+	NR	–	TCH[b]	NR	Yes
Nikolic et al. [3] (2012)	42	Yes	–	–	+	+	NR	FAC[c] Paclitaxel, trastuzumab	NR	NR
Gooren et al. [6] (2015)	48	Yes	–	–	–	NR	NR	DDC[d]	NR	NR
Gooren et al. [6] (2015)	41	No	+	+	–	+	–	FEC-D[e] TAM[a]	NR	No
Gooren et al. [6] (2015)	41	Yes	+	+	–	NR	NR	NR	NR	Yes
Brown et al. [7] (2015)	77	Yes	+	–	NR	NR	NR	NR	NR	NR
Brown et al. [7] (2015)	47	NR	+	+	NR	NR	NR	NR	NR	NR
Brown et al. [7] (2015)	48	No	+	+	NR	NR	NR	NR	NR	Yes
Brown et al. [7] (2015)	52	No	+	+	NR	NR	NR	NR	NR	Yes
Brown et al. [7] (2015)	47	No	NR	NR	NR	NR	NR	NR	NR	NR
Brown et al. [7] (2015)	42	No	NR	NR	NR	NR	NR	NR	NR	Yes
Brown et al. [7] (2015)	52	No	+	+	NR	NR	NR	NR	NR	NR
Katayama et al. [8] (2016)	41	Yes	+	+	–	+	NR	Aromatase inhibitor	Yes	No
Eismann et al. [9] (2019)	29	Yes	+	–	–	NR	–	No	NR	NR
Fundytus et al. [10] (2020)	48	Yes	+	+	–	+	NR	Anastrozole	Yes	No

(Continued on following page)

Table 1 (continued)

Paper	Age, years	Prior testosterone/ androgen	ER	PR	HER2	AR	BRCA	Treatment	BSO	Testosterone after Dx
De Blok et al. [11] (2019)	35–59 (median 47)	Yes	+	+	−	−	NR	NR	NR	NR
De Blok et al. [11] (2019)		Yes	+	+	−	−	NR	NR	NR	NR
De Blok et al. [11] (2019)		Yes	−	−	+	−	NR	NR	NR	NR
De Blok et al. [11] (2019)		Yes	−	−	−	+	NR	NR	NR	NR
Gooren et al. [12] (2013)	27	Yes	+	+	−	NR	NR	NR	NR	NR
Chotai et al. [13] (2019)	58	Yes	+	+	±	NR	NR	Letrozole	No	No
Kopetti et al. [14] (2020)	28	Yes	+	−	+	+	−	Trastuzumab, pertuzumab, paclitaxel→EC[f] TAM[a]	Yes	Yes
Present case	44	Yes	+	+	−	+	−	Anastrozole+GnRH analog	No	Yes

PR, progesterone receptor. [a]Tamoxifen. [b]Docetaxel/carboplatin/trastuzumab. [c]5-Fu/anthracycline/cyclophosphamide. [d]Docetaxel, doxorubicin, and cyclophosphamide. [e]5-FU/epirubicin/cyclophosphamide followed by docetaxel. [f]Epirubicin/cyclophosphamide. [g]NR indicates that the value was not reported or commented on and as such is unknown at this time.

the AR status of the tumor may provide valuable information for making informed decisions. However, in a review of previous similar cases, 9 out of 25 (36%) patients received exogenous testosterone therapy after treatment of primary breast cancer, but AR status was documented in only two cases (Table 1).

The ideal adjuvant endocrine therapy in a patient who wishes to continue testosterone therapy is controversial. In postmenopausal natal females, aromatase inhibitors have shown efficacy in large trials and meta-analyses, but their efficacy in the presence of exogenous testosterone is not well known [18]. We considered the possibility that some portion of exogenous testosterone might be aromatized to estradiol in our patient; therefore, we deemed the continuation of testosterone therapy potentially unsafe. However, using an aromatase inhibitor would address this concern, provided that it could efficiently and completely halt aromatization, especially in ER-positive breast cancer.

The potent binding of GnRH agonists to receptors, in contrast to endogenous GnRH, leads to the continuous stimulation of GnRH receptors. This persistent stimulation results in the downregulation of these receptors, subsequently inhibiting LH and FSH production

by the anterior pituitary gland. Consequently, this downregulation suppresses the synthesis of testosterone from the testes and estrogen from the ovaries. Among previous reports, out of 5 breast cancer patients who were using aromatase inhibitors, 3 had undergone bilateral salpingo-oophorectomy (BSO). In the remaining two cases, one with metastatic breast cancer may present challenges for the indication of BSO, whereas in the other case (the present case), a postmenopausal state was achieved using a GnRH agonist rather than through BSO (Table 1). In short, adjuvant endocrine therapy for this patient using testosterone was performed through combination therapy using an aromatase inhibitor plus a GnRH agonist, resulting in markedly reduced estradiol levels and hormonal values consistent with males.

The intersection of hormone therapy and breast cancer treatment in FtM transgender patients introduces complex ethical considerations that demand careful examination. A significant ethical dilemma arises in balancing the pursuit of gender affirmation through hormone therapy with the imperative of effective breast cancer treatment. Therefore, it is crucial to thoroughly evaluate the risks and benefits associated with combining hormone therapy and adjuvant endocrine therapy for breast cancer, considering potential impacts on the patient's mental health, quality of life, and overall treatment success. Incorporating this ethical consideration into the discussion is paramount to fostering understanding and sensitivity toward the complex interplay of these factors. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536212).

In conclusion, adjuvant endocrine therapy for breast cancer in FtM transgender patients undergoing testosterone replacement therapy is complex. The precise role of testosterone supplementation and optimal selection of adjuvant endocrine therapy remains uncertain. It is crucial to emphasize the need for systematic data collection within this special population to improve our understanding of the influence of hormone therapy on breast cancer.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.M. and S.S. wrote the main manuscript. S.I., R.H., K.A., R.K., and M.T. contributed to the interpretation of data and critically revised the manuscript.

Data Availability Statement

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

References

1 Frey JD, Poudrier G, Chiodo MV, Hazen A. An update on Genital reconstruction options for the female-to-male transgender patient: a review of the literature. Plast Reconstr Surg. 2017;139(3):728–37.
2 Zucker KJ. Epidemiology of gender dysphoria and transgender identity. Sex Health. 2017;14(5):404–11.
3 Nikolic DV, Djordjevic ML, Granic M, Nikolic AT, Stanimirovic VV, Zdravkovic D, et al. Importance of revealing a rare case of breast cancer in a female to male transsexual after bilateral mastectomy. World J Surg Oncol. 2012;10:280.
4 Burcombe RJ, Makris A, Pittam M, Finer N. Breast cancer after bilateral subcutaneous mastectomy in a female-to-male trans-sexual. Breast. 2003;12(4):290–3.
5 Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. Clin Breast Cancer. 2011;11(6):417–9.
6 Gooren L, Bowers M, Lips P, Konings IR. Five new cases of breast cancer in transsexual persons. Andrologia. 2015;47(10):1202–5.
7 Brown GR, Jones KT. Incidence of breast cancer in a cohort of 5,135 transgender veterans. Breast Cancer Res Treat. 2015;149(1):191–8.
8 Katayama Y, Motoki T, Watanabe S, Miho S, Kimata Y, Matsuoka J, et al. A very rare case of breast cancer in a female-to-male transsexual. Breast Cancer. 2016;23(6):939–44.
9 Eismann J, Heng YJ, Fleischmann-Rose K, Tobias AM, Phillips J, Wulf GM, et al. Interdisciplinary management of transgender individuals at risk for breast cancer: case reports and review of the literature. Clin Breast Cancer. 2019;19(1):e12–9.
10 Fundytus A, Saad N, Logie N, Roldan Urgoiti G. Breast cancer in transgender female-to-male individuals: a case report of androgen receptor-positive breast cancer. Breast J. 2020;26(5):1007–12.
11 de Blok CJM, Wiepjes CM, Nota NM, van Engelen K, Adank MA, Dreijerink KMA, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in The Netherlands. BMJ. 2019;365:l1652.
12 Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. J Sex Med. 2013;10(12):3129–34.
13 Chotai N, Tang S, Lim H, Lu S. Breast cancer in a female to male transgender patient 20 years post-mastectomy: issues to consider. Breast J. 2019;25(6):1066–70.
14 Kopetti C, Schaffer C, Zaman K, Liapi A, di Summa PG, Bauquis O. Invasive breast cancer in a trans man after bilateral mastectomy: case report and literature review. Clin Breast Cancer. 2021;21(3):e154–7.
15 Giovannelli P, Di Donato M, Galasso G, Di Zazzo E, Bilancio A, Migliaccio A. The androgen receptor in breast cancer. Front Endocrinol. 2018;9:492.
16 Feng J, Li L, Zhang N, Liu J, Zhang L, Gao H, et al. Androgen and AR contribute to breast cancer development and metastasis: an insight of mechanisms. Oncogene. 2017;36(20):2775–90.
17 Vera-Badillo FE, Templeton AJ, de Gouveia P, Diaz-Padilla I, Bedard PL, Al-Mubarak M, et al. Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(1):djt319.
18 Early Breast Cancer Trialists' Collaborative Group EBCTCG. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341–52.