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Breast Cancer in Female to Male Transsexuals Before and After Mastectomy Surgery; A Case Report and Literature Review

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ABSTRACT

The role of post-mastectomy screening in female to male transsexual patients remains uncertain; however, breast cancers may appear more invasively after sex reassignment surgery. Female-to-male transsexuals should undergo regular breast screening examinations, and any mastectomy specimen should be sent for full histopathological examination.

1 | Introduction

Female-to-male (FtM) transsexuals, although genotypically female, exhibit a male gender identity, often opting for androgenic therapies during their gender transition. Notably, a significant proportion of these individuals choose to undergo sex reassignment surgeries (SRS), such as mastectomy and bilateral salpingo-oophorectomy to preclude menopausal cycles and eliminate potential iatrogenic endometrial carcinoma risks [1, 2].

Research has shown that FtM transsexual individuals often experience a poorer quality of life and mental health outcomes compared to the general population [3, 4]. On the other hand, FtM transsexual individuals may face an increased likelihood of developing breast cancer as a result of the testosterone treatments they might undergo for masculinization. However, two opposing theories suggest a link between testosterone therapy and the development of breast cancer. The first paradigm posits that testosterone initiates breast cancer due to its aromatization into estradiol, a hormone linked to breast tumor proliferation [5]. Conversely, the second hypothesis suggests that testosterone has a protective effect on breast cancer, potentially reducing the risk of breast tumor formation [6]. Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related mortality among natal women; however, the effects of prior testosterone exposure on breast cancer risk in FtM transsexuals remain unresolved, creating ambiguity about their susceptibility to this condition [7–12]; this situation underscores the need for a thorough reassessment of screening protocols specifically designed for these individuals. Noteworthy, anecdotal reports of breast cancer incidence in FtM transgender individuals have been documented [2, 13, 14]. Therefore, this study aims to conduct a literature review of case reports to document instances of breast cancer among FtM female-to-male transsexual individuals. Furthermore, we report a case of breast cancer in an FtM transsexual diagnosed after mastectomy.

2 | Case History/Examination

A 36-year-old FtM transsexual individual underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy 2 years ago. About one year later, he was also a candidate for bilateral subareolar mastectomy without lymphadenectomy, as

part of a sex reassignment surgical procedure. He complained of a non-tender palpable mass situated in the right breast region one year after the breast surgery. There was a 2×2 cm mass in the 7 o'clock peri-areolar soft tissue fixed mass with a lymph node in the same side axillary region, in the physical examination. Notably, he had been receiving testosterone replacement therapy for 15 months and lacked a personal or family history of cancer.

3 | Methods (Differential Diagnosis, Investigations and Treatment)

In this case, the sonography revealed a 10×6 mm heterogeneous mass with malignant features, accentuated by axillary lymphadenopathy (T1N1). We performed a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral subareolar mastectomy without lymphadenectomy, who presented with a palpable mass in the right breast. Moreover, histopathological examination via core needle biopsy together with immunohistochemistry (IHC) confirmed the presence of invasive ductal carcinoma and then the patient was deemed a candidate for adjuvant chemo-radiotherapy (Doxorubicin + cyclophosphamide for 4 courses in 3 months and Paclitaxel for 4 courses in 3 months).

4 | Conclusion and Results (Outcome and Follow-Up)

In consequence, the patient underwent an additional breast surgical procedure, involving the excision of the mass and residual breast tissue, as well as axillary lymph node dissection (ALND). Permanent pathology revealed a 10×8 mm invasive ductal carcinoma mass with lymph node involvement in 2 of 13 examined nodes. The glandular/tubular differentiation score was 3, nuclear pleomorphism score was 2, overall score was 7 of 9 (grade 2), and the mitotic rate score was 2 using Nottingham histologic score. Additionally, estrogen receptor (ER+) and progesterone receptor (PR+) expression were observed (ER+ [90%], PR+ [10%]), with a Ki 67 index of 20%. IHC marker of HER-2 was equivocal. So, HER-2 was evaluated using chromogenic in situ hybridization (CISH) and found to be negative. In consideration of these findings, the patient followed up twice and continues using sonography every 6 months and underwent tamoxifen therapy as maintenance, and the results showed normal findings. The adjuvant tamoxifen therapy continues for at least 5 years. Figure 1A,B shows the tumor site before and after surgery, respectively. Figure 1A shows the palpable peri-areolar mass 2×2 cm, and Figure 1B shows the surgical site one week after the excision of the mass with ALND.

5 | Discussion

From an initial 42 articles, 23 were selected, and ultimately 15 articles focusing on FTM patients with breast cancer (both pre- and post-SRS) were included in the study. Table 1 presents a compilation of breast cancer cases in FtM transsexual individuals, with the majority of cases featuring a documented history of hormone therapy, as reported in case studies (Table 1).

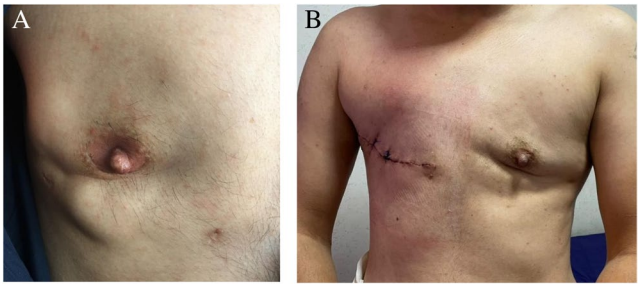

FIGURE 1 | (A) The peri-areolar palpable mass at the 7 o'clock position. (B) One week after the excision of the mass and nipple-areolar complex with axillary lymph node dissection.

Breast cancer in female-to-male transsexuals is rare. However, this disease needs more attention because it may be underestimated, especially after SRS mastectomy. Mastectomy is often the first step of gender reassignment surgery for FtM transsexuals. It has been reported that the probability of breast carcinogenesis after prophylactic mastectomy is remarkably low, approximating a frequency of less than 2%. The lifetime risk of breast cancer in this population is challenging due to the young age of study participants, high mastectomy rates in some groups, and difficulties in tracking patients' outcomes [25–27].

Only a minute proportion of patients subsequently manifested breast cancer [28]. Nevertheless, the intractable threat of breast carcinogenesis persisting after nipple-sparing mastectomy employed as a prophylaxis remains a pressing concern.

FtM transsexuals often receive androgens to acquire muscularity and subsequently undergo numerous surgeries to undergo a comprehensive physical transformation into a male form. During this process, mastectomies are frequently conducted without lymphadenectomy, whereas the breast tissue is not radically excised [29]. Many surgeons opt for subcutaneous mastectomy for SRS, which may lead to the remaining breast tissue potentially developing into neoplasms. The incidence of breast cancer in FtM transsexual individuals is remarkably low, and the risk of developing breast cancer is significantly reduced by approximately 90% after mastectomy with nipple reimplantation [30, 31]. Notably, the majority of breast cancer diagnoses in FtM transsexuals are classified as ductal carcinoma (Table 1).

The cancer may be diagnosed before and after mastectomy for SRS. However, the cancers represent many years after surgery, have more invasive features, especially in lymph node involvement (N+). It may be justified by the effect of androgens on normal breast tissue. Also, neglecting regular screening for breast cancer and inadequate radiologic examinations in previously operated breasts may result in delayed diagnoses at advanced stages.

Many case reports and studies have documented FtM patients who developed breast cancer before and following SRS mastectomy, subsequently requiring additional investigations such as mammography or sonography before SRS incidentally. During the SRS process, patients may be stunned, which is frequently characterized by tumors of relatively early pathological stage, lacking lymphatic invasion, and thus presenting a more benign profile.

TABLE 1 | Cases of FtM transsexuals developing breast cancer.

Study	Age	Surgery	Tumor type	Lymph	Immunohistochemistry (IHC)				HRT[a]	Sur[b]	FH[c]
					ER	PR	Ki	HER2		(Years)	
Before sex reassignment surgery (mastectomy) cancer occurred											
Shao et al. [15]	53	Bilateral mastectomies with left SLNB	Invasive ductal carcinoma	−	+	−	+	+	5	0	+
Shao et al. [15]	27	Bilateral mastectomies with left SLNB	Invasive ductal carcinoma	+(1/14)	+	+	+	+	6	0	+
Gooren et al. [1]	27	Mastectomy	N/S	−	+	+	N/S	−	3	0	N/S
Gooren et al. [1]	41	Mastectomy	Tubular adenocarcinoma	−	+	+	N/S	−	1	0	N/S
Eismann et al. [16]	29	Mastectomy	High grade ductal carcinoma	−	N/S	N/S	N/S	N/S	4	0	−
Fledderus et al. [4]	50	Bilateral subcutaneous mastectomy	DCIS	N/S	N/S	N/S	N/S	N/S	3	0	−
Harris et al. [17]	28	Bilateral mastectomies with left SLNB	Persistent DCIS	−	−	−	+	+	1.1	0	N/S
After sex reassignment surgery (mastectomy) cancer occurs											
Burcombe et al. [18]	20	Completion left mastectomy and level 2 ALND	Ductal carcinoma	−	+	+	N/S	N/S	13	N/S	N/S
Nikolic et al. [2]	43	Radical Mastectomy with ALND	Invasive ductal carcinoma	+(12/13)	N/S	N/S	+	+	N/S	1	−
Gooren et al. [19]	48	Residual tissue excised	Infiltrating ductal carcinoma	−	−	−	N/S	−	9	7	N/S
Katayama et al. [20]	41	Residual tissue excised	Invasive ductal carcinoma	−	+	+	N/S	+	15	12	N/S
Chotai et al. [21]	58	Bilateral mastectomy	Ductal carcinoma	−	+	+	N/S	N/S	10	20	+
Fundytus et al. [22]	28	Full left mastectomy with SLND	Invasive ductal carcinoma	+(2/6)	+	+	N/S	+	19	15	+
Kopetti C et al. [23]	28	Residual tissue excised with ALND	Invasive carcinoma	N/S	+	−	+	+	2.5	2	−
Nishida M et al. [24]	44	Residual tissue excised	Invasive carcinoma	N/S	+	−	+	+	N/S	N/S	N/S
Current Study	36	Mass and residual breast tissue excised with ALND	Invasive ductal carcinoma	+(2/13)	+	+	+	−	1.25	1	−

Abbreviations: ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; Ki 67, antigen Kiel 67; N/S, not specified in the literatures; PR, progesterone receptor; SLN, sentinel lymph node dissection; SLNB, sentinel lymph node biopsy; SLND, sentinel lymph node dissection.

[a]The tumor was diagnosed years after hormone replacement therapy (HRT).

[b]The tumor diagnosed years after sex reassignment surgery (SRS Surgery).

[c]Family history.

Thereby implying the necessity of routine breast cancer screening preceding every mastectomy as well as histological examination after mastectomy [4, 32, 33]. In cases where the histopathological examination reveals a ductal carcinoma in situ (DCIS) with a non-invasive phenotype, namely, failure to breach the basement membrane, a comprehensive excisional strategy may signify a sufficient treatment approach, with subsequent radiation therapy potentially serving as a viable adjunctive modality for these patients.

A review of case reports indicated that breast cancer can develop before or many years after SRS, with occurrences any time after mastectomy for SRS [2, 21, 34]. Moreover, the permanent pathology of most cases was characterized by advanced or locally advanced invasive ductal carcinoma. Following a diagnosis of breast cancer, these individuals may require adjunctive surgical procedures, encompassing the removal of residual breast tissue coupled with ALND to achieve optimal oncological.

The overwhelming majority of cases exhibited estrogen receptor (ER) and progesterone receptor (PR) positivity (Table 1). It has been reported that androgens may potentially mitigate the risk of hormone-negative breast cancer [6], while elevated levels of androgens in blood plasma have been linked to an increased risk of hormone-receptor-positive breast cancer [35, 36]. In our study, there is a 36-year-old patient with invasive ductal carcinoma and lymph node involvement, and ER and PR were positive.

This finding suggests a complex interplay between androgens and breast cancer, warranting further investigation into the relationship between these hormonal factors and breast cancer development.

Given that mastectomy in sex reassignment surgery typically does not involve a complete removal of breast tissue, leaving residual tissue that can potentially transform into a cancerous lesion, evidence suggests excising as much breast tissue as possible during mastectomy in non-compliant patients, thereby reducing the likelihood of breast cancer development in the remaining tissue. Also, breast cancers may appear more invasively after SRS. So, continuing the follow-ups even after mastectomy for SRS is recommended.

Author Contributions

Maryam Rezaee: conceptualization, investigation, validation, writing – original draft, writing – review and editing. **Shahriar Najafizadeh-Sari:** conceptualization, data curation, investigation, validation, writing – original draft. **Mohammad Javanbakht:** conceptualization, investigation, validation, writing – original draft.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

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

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study is included in this published article.

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