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REVIEW ARTICLE

Difficulties of gender affirming treatment in trans women with BRCA1+ mutation: A case report

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Abstract Gender affirming treatment in transgender women is based on a combination of antiandrogens and estrogens, with the latter maintained over the long term. When prescribing these treatments, we must consider the possibility of developing estrogen-dependent breast cancer. In transgender women, a breast cancer incidence of 4.1 per 100,000 has been estimated, which would increase the risk by 46% in relation to cisgender men but decrease it by 70% in relation to cisgender women. It is known that certain gene mutations such as BRCA1 imply an increased risk of breast cancer, but at present the risk in transgender women with BRCA1 treated with estrogens is not well established. We present the case of a transgender woman with a family history of breast cancer and BRCA1 mutation and the therapeutic decisions made in a multidisciplinary team. Following this case, we review and discuss the published literature.

PALABRAS CLAVE
Mujer transgénero;
Cáncer de mama;
BRCA1;
Terapia estrogénica;
LGBT

Dificultades del tratamiento de afirmación de género en mujeres trans con mutación BRCA1+: a propósito de un caso

Resumen El tratamiento de afirmación del género en las mujeres transgénero se basa en una combinación de antiandrógenos y estrógenos, manteniéndose estos últimos a largo plazo. A la hora de prescribir estos tratamientos hay que tener en cuenta la posibilidad de desarrollar un cáncer de mama estrógeno-dependiente. En las mujeres transgénero se ha estimado una incidencia de cáncer de mama de 4,1 por 100.000, lo que aumentaría el riesgo en un 46% en relación con los hombres cisgénero, pero lo disminuiría en un 70% en relación con las mujeres

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cisgénero. Se sabe que ciertas mutaciones genéticas como BRCA1 implican un mayor riesgo de cáncer de mama, pero en la actualidad no está bien establecido el riesgo en mujeres transgénero con mutación en BRCA1 tratadas con estrógenos. Presentamos el caso de una mujer transgénero con antecedentes familiares de cáncer de mama y mutación BRCA1 y las decisiones terapéuticas tomadas en un equipo multidisciplinar. Tras este caso, revisamos y discutimos la literatura publicada.

Introduction

Gender affirming treatment in transgender women is based on a combination of antiandrogens and estrogens, with the latter maintained over the long term, allowing the persistence of female secondary sexual characteristics. However, we must consider the possibility of developing estrogen-dependent breast cancer in transgender women undergoing such treatment.

The incidence of breast cancer in cisgender women and men is 12% and 0.1% respectively.[1] In transgender women an incidence of 4.1 per 100,000 has been estimated,[2] which would increase the risk by 46% in relation to cisgender men but decrease it by 70% in relation to cisgender women.

It is known that certain gene mutations such as BRCA1 imply an increased risk of breast cancer, but at present the risk in transgender women with BRCA1 treated with estrogens is not established.[3]

We present the case of a transgender woman with a family history of breast cancer and BRCA1 mutation and we will review and discuss the published literature.

Case description

We present the case of a 23-year-old assigned male at birth patient, who came to our Transgender Care Unit (TCU) showing intense anxiety for gender incongruity and manifesting dysphoria toward certain male secondary sexual characteristics and especially toward her genitalia. She presented preferences for female gender roles since childhood, making the social transition at the age of 17, with good family and social acceptance.

She came to our medical office requesting hormonal and surgical treatment for gender reaffirmation. The patient was previously assessed by Mental Health at her own request for psychological support, discarding psychopathological or psychiatric alterations susceptible of further intervention.

Among her family history, her mother was diagnosed with breast cancer at 46 years of age, her maternal grandmother at 70 years of age, and her maternal grandfather with prostate cancer at 78 years of age.

Case management

Given this history, a genetic study of hereditary-familial breast cancer syndromes was performed, with a positive result for the c.70_73dupTGTC (p.Pro25Leufs) mutation of the *BRCA1* gene, of pathological significance, in heterozygosis.

Due to the need to establish the risk-benefit ratio of hormone therapy with estradiol in carriers of this mutation, the patient was referred to the Hereditary Oncogynecologic Pathology Unit and in a multidisciplinary committee (with the participation of endocrinologists, gynecologists and surgeons), and given the scarcity of published data, a decision was reached to perform a prophylactic bilateral mastectomy prior to the initiation of hormonal treatment with estrogens, with subsequent reconstruction surgery.

Few days after, a mutual agreement was reached to start hormone therapy with estradiol, once the patient was included in the surgical intervention list, due to a significant increase in the state of anxiety and suicidal ideation in the patient. This decision was made despite knowing that hormone therapy would be related to an unknown increase in the risk of developing tumors associated with this mutation. With this measure, the emotional stress was attenuated in a very important way, achieving the disappearance of suicidal ideation.

At present, a breast ultrasound has been performed in which no nodular pathology is seen, the patient is awaiting bilateral mastectomy and is feeling much better with the treatment started (cyproterone acetate 25 mg/day and estradiol valerate 2 mg/day).

Areas of uncertainty

Breast cancer in men is very rare and accounts for less than 1% of breast cancers in developed countries. It represents only 1% of all male cancers[4] although its incidence has increased in recent years.[5] Patients with Klinefelter's syndrome, testicular atrophy, those who have received thoracic radiation and those with a family history of breast cancer associated with BRCA gene mutations are at higher risk.[4]

BRCA1 is a tumor suppressor gene located on chromosome 17. Mutations in this gene are inherited in an autosomal dominant pattern and usually have a high penetrance. Carriers of the mutation have an increased risk of cancer, especially breast, ovarian and prostate cancer.[6] On the other hand, *BRCA2* is also a tumor suppressor gene located on chromosome 13 and is the main genetic predisposing factor implicated in cis-male breast cancer. In addition, it is associated with prostate, pancreatic, stomach and melanoma cancer.[7]

It is estimated that the frequency of breast cancer in cisgender women reaches 12% while it only affect 0.1% of men.[1] In cis women carrying BRCA1 the incidence is higher, with a cumulative breast cancer risk of 72% up to the age of 80 years.[8] Cis women carrying BRCA2 have a 50% higher risk of developing breast cancer, while trans women have 80 times the risk of the cis male population.[9]

Ford et al., in 1994[10] did not find a clear association between the presence of the BRCA1 mutation and the development of breast cancer in cis-males, but subsequently several studies have been published in which BRCA1 male patients and breast cancer were detected with very low frequency.[11–14] In 2002, Brose et al.[15] estimated that the lifetime risk of developing breast cancer in male carriers of pathologic BRCA1 mutations was 5.8%. In 2008, Tai et al.[16] estimated that in the United States the cumulative risk of breast cancer in men with mutations in this gene was 1.2% at 70 years of age [CI 95%, 0.22–2.8%], higher than the risk in the general population (0.1%). There are currently no data on the risk of breast cancer in male patients carrying the mutation and undergoing estrogen hormone therapy.

In the general population (without BRCA1 mutation) there is more evidence regarding the risk of breast cancer with estrogen therapy. In cisgender men, both the use of estrogen therapy (formerly used as part of the treatment of some cases of prostate cancer) and gynecomastia have been described as risk factors for breast cancer.[17]

The long-term risk of cancer related to hormone therapy in transgender women is not well known.[18] Estrogen use in transgender women is often at higher doses than those prescribed for hormone replacement therapy in cis women and is also maintained until beyond the age of menopause. There are three retrospective studies evaluating this risk. Two have shown no difference in breast cancer risk when comparing transgender women on hormone therapy with population data in cisgender men: the first showed a breast cancer incidence of 4.1 cases per 100,000 person-years in transgender women; the second showed 2 observed cases vs. 3.55 expected cases per 100,000 person-years in transgender women on estrogen therapy.[2,19] The third[1] included 2260 transgender women and identified 15 cases of invasive breast cancer after a median duration of hormone treatment of 18 years. The risk in these women was 46 times higher than that of cisgender males in the same country, and although the risk with respect to cisgender women was lower (incidence ratio of 0.3), an earlier age of diagnosis was objectified with respect to the latter (52 vs 61 years).[1] Furthermore, in 2018 Hartley et al.[20] conducted a systematic review in which they included 26 studies reporting 22 cases of breast cancer in transgender women, of which one had BRCA2 mutation. The median age at diagnosis was 51.5 years and 81.8–90.1% were undergoing hormonal treatment.

Most of the tumors described were luminal ductal carcinomas. These are similar to those suffered by cisgender men and generally present worse prognosis and higher positivity for estrogen and progesterone receptors.[23] This suggests a possible stimulating effect of estrogens and cyproterone acetate, a progesterone derivatives used as an anti-androgens.[1] On the other hand, these tumors are inhibited by androgens, with androgen receptors being found in 78% of BRCA2-associated tumors and in 30% of BRCA1-associated tumors. The use of cyproterone acetate could therefore favor tumorigenesis also by this pathway.[9]

In the literature reviewed, in 2016 Corman et al.[9] published the case of a 53-year-old transgender woman who, after undergoing treatment for 7 years with estradiol gel, was diagnosed with high-grade ductal breast carcinoma in situ, simple mastectomy was performed, gender affirming therapy was discontinued and the patient refused Tamoxifen. Subsequently, hormonal therapy was not reinitiated since the carcinoma was 100% positive for estrogen receptors. Breast reconstruction was also not performed. She presented a local recurrence at 30 months which required treatment with radiochemotherapy. Given her age and her father's history of prostate cancer, a genetic study was performed and the result was positive for the c.9117G>A mutation in the BRCA2 gene. Although it is not the same gene, this case is interesting since mutations in the BRCA2 gene behave similarly to those in the BRCA1 gene.

Currently, two cases similar to ours have been described, in which the initiation of estrogen treatment is a conflicting decision, knowing the increased risk of developing hereditary-familial breast cancer. In 2014, Colebunders et al.[21] published the first case of a transgender woman with BRCA1 mutation. The mutation was detected after two years of treatment with topical estrogens and oral cyproterone acetate. The patient refused to undergo prophylactic mastectomy, with only breast cancer screening being performed according to existing guidelines for cisgender women. In 2014, she hadn't developed cancer. In 2018, Wolf-Gould et al.[22] published the case of a 14-year-old transgender girl with BRCA1 mutation and on treatment with GnRH analogs who was finally, after weighing the risks, also treated with estrogens. In 2019, Eismann et al.[3] also published the case of a transgender woman on hormone therapy with BRCA2 mutation. She underwent bilateral orchiectomy and prophylactic mastectomy and subsequently continued treatment with estradiol.

Guidelines

In our case, after assessing the risk of breast cancer and the benefits of initiating hormone therapy, it was decided to perform a prophylactic bilateral mastectomy and subsequent reconstruction and then initiate hormone treatment. This decision was based on studies of cis women carrying the BRCA mutation showing a reduction in risk after surgery.[23] The final decision taken, to initiate hormonal treatment for reaffirmation once the presence of neoplasms associated with the mutation had been ruled out and before prophylactic mastectomy was performed, involved a compromise between the risk of developing breast cancer and respect for the patient's wish to initiate hormonal treatment with estrogens as soon as possible. Given that the effective surgical waiting list inclusion for the prophylactic bilateral mastectomy procedure in BCRA1 carriers is less than 6 months in our hospital, the benefit of hormonal reassurance treatment in this patient clearly outweighs the risks, especially considering that she had not previously undergone any hormonal treatment and that close follow-up would always be performed.

Finally, regarding breast cancer screening in transgender women, in 2014 Phillips et al.[24] recommended annual mammography in those over 50 years of age with risk factors: BMI > 35 kg/m^2, family history of breast cancer or use of hormonal therapy with estrogens and progestins for >5 years. However, the evidence for this recommendation is questionable and did not take into account that in some cases patients have breast prostheses that make follow-up by mammography difficult. Subsequently, in 2017 both Imborek et al.,[25] Deutchs et al.[26] and in 2018 the Canadian Society Guidelines for MtF[27] recommended biannual mammography for those transgender women on hormone therapy for >5 years. Smilow Cancer Hospital[28] has developed its own recommendations for transgender women with BRCA1/BRCA2 mutations; they recommend that in cases without breast tissue and without hormone therapy or breast implants, mammography is not recommended but annual clinical breast examination and monthly self-examination starting at age 35 years should be performed; in cases that have used hormone therapy, the screening should be individualized considering the duration and type of hormone therapy, the presence of breast tissue, and the use of implants.

Another relevant issue in these cases is the risk of prostate cancer. Specifically, our patient had a family history of this pathology. The germline BRCA1 mutations increase the risk of HPCa by 3.8-fold (relative risk of 1.82) in cisgender men aged < 65 years.[29,30] However, they receive antiandrogen treatment that can be used as part of prostate cancer treatment and undergo gender-affirming surgery, which reduces prostate cancer risk.[31] There are generally few data on transgender women and prostate cancer. Nor are there any specific guidelines in this regard.

Although many authors recommend starting PSA screening at the same age as cisgender men, other authors recommend individualization based on, for example, genetic risk. As for the reference value, it has been published that it could be set at 1 ng/mL, lower than that established in cisgender men, since the PSA value depends on testosterone, which is inhibited in transgender women. It could also be interesting to have a baseline PSA value before starting hormone therapy as a later reference. As for imaging tests, transvaginal ultrasound to evaluate the prostate would be more acceptable to patients than transrectal. As for MRI, there are no studies evaluating the difficulty of interpretation in these cases. Finally, if a prostate biopsy is necessary, the transvaginal route should also be considered before the transrectal route.[32]

Conclusions and recommendations

In conclusion, the importance of communicating this case lies in helping to make decisions in similar situations, and in emphasizing the absence of protocols or guidelines for these cases. Given the current increase in the demand for gender affirming treatment in transgender people as well as for genetic diagnosis of inherited-familial cancer mutations, cases similar to ours will most likely increase in the coming years. Because of the difficulty in medical or surgical management, these patients should be attended by highly specialized physicians, always individualizing the risk, both physical and mental of our actions; and making available to them, all the necessary information on the options that could be considered in order to take the best decision.

Authors' contributions

A.P.-G., S.D.-D., and M.A.M.-C. conceptualized the study. A.P.-G., I.D.L.-R. drafted the article; S.D.-D., C.G.-C., J.T.-D. and M.A.M.-C. critically revised the article regarding important intellectual content. All authors read and approved the final article.

Ethics approval and consent to participate

The protocols of the Ethics Committee of the hospital were followed regarding informed consent of the patient. Written informed consent to publish this case report was obtained.

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Conflict of interest

No competing financial interests exist.

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