Breast cancer is rare in male patients. Certain predisposing factors, be they genetic (e.g., BRCA2 gene mutations) or hormonal (imbalance between estrogen and androgen levels), have been implicated in male breast cancer pathophysiology. Male-to-female (MtF) transsexualism is a condition that generally involves cross-sex hormone therapy. Anti-androgens and estrogens are used to mimic the female hormonal environment and induce the cross-sex secondary characteristics. In certain situations, the change in the hormonal milieu can be disadvantageous and favor the development of hormone-dependent pathologies, such as cancer. We report a case of a MtF transgender patient who developed breast cancer after 7 years of cross-sex hormonal therapy. The patient was found to be BRCA2 positive, and suffered recurrent disease. The patient was unaware of being a member of an established BRCA2 mutation-positive kindred. This represents the first case of a BRCA2 mutation predisposing to breast cancer in a MtF transgender patient.
Breast cancer in a male-to-female transsexual patient

A 46-year-old biologically male patient who was seeking MtF transition was referred to a specialized endocrinologist. He had been diagnosed with sexual identity dysphoria and transsexualism 8 years previously. Before starting hormone therapy, the patient weighed 92 kg, had a height of 1.82 m, and had a normal physical examination. His medical history was unremarkable except for statin-treated hypercholesterolemia and he smoked five cigarettes daily. His family history revealed type 2 diabetes and prostate cancer in his father. The patient had fathered two children, both without significant health problems. General hematology and biochemistry results (glucose, liver, and renal function tests, blood count, lipids) were normal and eventually he was started on a hormonal regimen of cyproterone acetate 25 mg twice daily, increasing to 50 mg twice daily after a month and estradiol gel, two puffs daily.

One year later, follow-up hormonal testing revealed suppressed gonadotropins (LH 0.14 IU/mL, FSH 0.11 IU/mL) and hyperprolactinemia at 35.97 ng/mL. Estrogen and testosterone were at normal female levels. The hyperprolactinemia was considered secondary to estrogen therapy, as frequently observed in MtF TG patients. (a pituitary MRI was negative for prolactinoma). Over the following years, the MtF transition progressed to the patient's satisfaction with a decrease in male-pattern pilosity and an increase in breast size. Biological tests and mammography were performed annually and bone densitometry was done every 2 years. As the patient was satisfied with the results of hormone therapy, no request for gender reassignment surgery was made.

After 7 years of hormone therapy, a routine mammogram revealed retro-areolar micro-calculcations in the right breast, which measured 16 mm in diameter. The lesion was judged suspicious and micro-biopsies were performed. The histological analysis of the region with micro-calculcations revealed a high-grade ductal in situ carcinoma (DIN 3) without obvious signs of infiltration. The histology of a region without micro-calculcations found an intermediate grade ductal carcinoma in situ (DIN 2) without signs of infiltration. Immunohistochemically, 80% of cells expressed the estrogen receptor (ER), whereas 10% expressed the progesterone receptor (PR). HER2 expression was absent. Hormone therapy was stopped immediately after the discovery of the carcinoma. A breast MRI was performed to assess the extent of disease. It revealed multiple foci of enhancement on the right side and a 6 mm focus of enhancement in the left retro-areolar region. Second-look ultrasound of the left breast revealed an echogenic structure without architectural distortion, or cystic/solid lesions. As the 6 mm focus of enhancement found on MRI had no corresponding lesion on ultrasound and the patient had stopped hormonal therapy, a follow-up MRI was recommended with complementary biopsy if required. It has remained unchanged to date on long-term follow-up.

A right simple mastectomy with sentinel lymph node biopsy was performed. The histopathology showed locally undifferentiated invasive ductal carcinoma (Fig. 1A), without invasion of sentinel nodes or the nipple. The margins of resection were clear. Analysis of the lesion revealed 100% ER positivity, 10% PR positivity, a Ki67 index of 50%, and negative HER2. Androgen receptor staining showed positivity in 80% of cells (Fig. 1B). These results represented a formal contraindication to reintroducing hormone therapy. Tamoxifen treatment was recommended, but was declined by the patient. MRI follow-up of the left breast lesion found no progression, therefore the initial MRI focus of enhancement was considered to be the result of prolonged hormone therapy. Follow-up post-mastectomy was unremarkable until 30 months after surgery, when local recurrence was diagnosed at the site...
Radiation therapy and adjuvant chemotherapy (epirubicin plus cyclophosphamide, with paclitaxel) were instituted.

Genetic analysis of the \textit{BRCA1} and \textit{BRCA2} genes was performed and the presence of the heterozygous mutation c.9117G>A in \textit{BRCA2} was found. The same mutation had already been noted in a family with the same surname from the same region; however, the patient had made no reference to them previously. Further questioning demonstrated that the patient was indeed related to the family in which the mutation was previously identified (Fig. 1C). Several cases of breast and prostate cancers were present in the kindred, expanding over four generations.

\textbf{Discussion}

We present the first report of a \textit{BRCA2} mutation in a MtF transsexual patient with breast cancer. The patient was diagnosed with breast cancer at the age of 53, after 7 years of hormonal treatment. A heterozygous c.9117G>A mutation of the \textit{BRCA2} gene was found and previously unsuspected links to an extensive kindred with multiple cases of hormone-related tumors were revealed on follow up.

Breast cancer is a rare neoplasm in men. Predisposing factors include genetic predisposition, obesity, estrogen–testosterone imbalance (such as those seen in Kleinfelter syndrome) (Brinton \textit{et al}. 2008). Also potentially implicated are radiation exposure, smoking, and alcohol consumption (Johansen Taber \textit{et al}. 2010). \textit{BRCA2} gene mutations are the main genetic predisposing factor, responsible for around 5–20% of male breast cancer cases; fewer cases are attributed to \textit{BRCA1} mutations (Liede \textit{et al}. 2004).

MtF TG patients receive hormonal treatment based on their transition needs. Anti-androgens are administered until removal of the gonads, while estrogens are prescribed for longer periods of time, with the dual purpose of promoting feminization and avoiding bone density loss. Often, the doses administered in this setting are higher than those used in the treatment of genetic females for hypogonadism, although the aim is to target normal values of testosterone and estradiol for genetic females. Breast development is a key element in transitioning to a female body form and identity. Historically, various breast augmentation techniques have been attempted, but the current regimens of hormonal treatment often induce the desired changes. Prolonged estrogen treatment combined with anti-androgens lead to the development of lobules and acini and even pseudolactational acinar changes (Kanhai \textit{et al}. 2000).

Breast cancer occurring in males is typically ductal carcinoma and is more frequently ER and PR positive than in females (Fentiman \textit{et al}. 2006). Approximately 80% of male breast cancer patients have a positive status for both
hormone receptors, as occurred in the current patient (Chavez-Macgregor et al. 2013). In a large breast cancer series in women, BRCA2 mutations were more often found to be ER and PR positive than BRCA1 mutations (Atchley et al. 2008). Triple negative (ER, PR, HER2) cancers were found in 57.1% of BRCA1 positive cases as compared with only 23.3% of BRCA2 carriers and 13.8% of BRCA1-negative patients (Atchley et al. 2008). In the current case, the prolonged use of high doses of sex steroids (7 years) against the background of a BRCA2 mutation may have contributed to cancer formation.

Recent research has focused on the role of the androgen receptor in breast cancer. In a series of 135 breast cancer patients, androgen receptors were found in 78% in BRCA2-positive cases compared with 30% of BRCA1-positive tumors, whereas BRCA-negative tumors expressed AR in 76% of cases (Pristauz et al. 2010). Androgens were shown to inhibit the proliferation of AR-positive breast cancer cell lines in vitro (Hackenberg et al. 1991). BRCA2 seems to be a coactivator of the AR (Shin & Verma 2003), which suggests that mutations of the BRCA2 could promote breast tumorigenesis by reducing the antiproliferative effect of androgens. In our patient, AR status was positive in 80% of cells. Hence, the anti-androgen therapy and BRCA2 mutation positivity could have favored tumorigenesis.

The impact of hormonal treatment on breast cancer risks in MtF patients is controversial. Considering treatment with estrogen, the total lifetime period of exposure is shorter than that for genetic females. However, this could be counterbalanced by the higher doses, different route of administration, and use of more potent compounds. In a large series of transsexual patients treated with cross-sex hormones for a period of 5 to >30 years, breast cancer was not more frequent in 2307 MtF patients compared with the expected frequency for genetically male patients (Gooren et al. 2013). Although this is the first report of a BRCA gene mutation in a MtF TG person with breast cancer, to date 12 other cases of breast cancer in MtF TG patients have been reported (Table 1). Most were treated with variable doses and formulations of estrogens for >10 years. The most frequent type of cancer in this series was invasive ductal carcinoma, which corresponds to the type most frequently diagnosed in males (Johansen Tabet et al. 2010). Among the cases that have reported receptor status, only 50% were hormone receptor positive, which is less than that usually found in male breast cancer (Johansen Tabet et al. 2010). HER2 status was reported in five cases, of which four were found to be negative. In the most recent reports, genetic alterations in the BRCA genes were sought and no anomaly was found. However, older reports mentioned familial cases of breast or unknown types of cancer that could have had a genetic background.

The c.9117G>A BRCA2 mutation seen in this case has already been described in the literature (according to the previous nomenclature, c.9345G>A). Codon 9117 is the last nucleotide in exon 23 and the G-to-A substitution does not alter the amino acid sequence of the protein (p.Pro3039Pro). Although it was previously considered a variant of unknown significance, Acedo et al. (2012) demonstrated that the c.9117G>A change modifies a splice site, resulting in either skipping of exon 23 alone, skipping of exons 23 and 24 or deletion of 51 nucleotides from exon 23. The mutation was inherited from the patient’s paternal branch, and several members of the family had prostate and breast cancers. Unfortunately, as the family was large, our patient was unaware of the BRCA2 mutation detected in second-degree cousins.

A thorough family history is important in the evaluation of MtF persons seeking hormonal treatment. As in the current case, the awareness of familial risk by the patients may not be sufficient. As part of the MtF transition process, specific questioning regarding familial occurrence of breast and other cancers could be beneficial. Apart from breast cancer, BRCA2 carriers also have higher risks of developing pancreatic and prostate cancers. Pancreatic cancer in male BRCA2 mutation carriers is 82.5 times more frequent than in the general population (Mersch et al. 2015). The risk of prostate cancer is considered to be five times that of the general population (Mersch et al. 2015), but in male patients under 65 years, it was found to be 7.3 times increased (Breast Cancer Linkage Consortium 1999), whereas in men under 56 years, it was 23 times higher (Edwards et al. 2003). Moreover, prostate cancer in BRCA2 mutation carriers seems to be diagnosed at a younger age and has a more aggressive presentation and a worse prognosis (Tryggyadottir et al. 2007). Other types of cancer may be associated with BRCA2 mutations, such as malignant melanoma and various gastrointestinal neoplasias (Breast Cancer Linkage Consortium 1999, Liede et al. 2004, Mohamad & Apffelstaedt 2008, Ginsburg et al. 2010), but these associations were not confirmed by other studies and still remain controversial.

A BRCA2 mutation complicates management and follow-up in MtF TG persons. In those who have a BRCA2 mutation diagnosed before initiation of hormonal therapy, cancer risks and alternatives to hormonal therapy (e.g., prosthetic breast augmentation)
Table 1: Cases of breast cancer in male-to-female transgender patients reported in the literature

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Type of breast cancer</th>
<th>Estrogen treatment and duration</th>
<th>IHC</th>
<th>Genetics</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Poorly differentiated primary mammary adenocarcinoma</td>
<td>Estrogen orally and implants of estrogen pellets, contraceptive pills for over 6 years and transcutaneous mammary estrogen for an undetermined period</td>
<td>NR</td>
<td>NR</td>
<td>Symmers (1968)</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>Infiltrating adenocarcinoma, partly scirrhous and partly papillary, unequivocal evidence of its origin as an intraduct carcinoma</td>
<td>Estrogens orally and subcutaneous pellets for around 5 years, probably estrogen-containing cream applied on breasts for over 2 years</td>
<td>NR</td>
<td>NR</td>
<td>Symmers (1968)</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>High-grade infiltrating ductal carcinoma</td>
<td>1.25 mg/day oral conjugated estrogen for 11 years</td>
<td>ER− (but false negative possible), PR+, ER−, PR not reported</td>
<td>Metastatic breast cancer in mother</td>
<td>Pritchard et al. (1988)</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Infiltrating adenocarcinoma</td>
<td>0.625 mg/day oral conjugated estrogen for 14 years</td>
<td>NR</td>
<td>NR</td>
<td>Ganly &amp; Taylor (1995)</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>Secretory carcinoma</td>
<td>Long-term cross-hormone treatment</td>
<td>ER−, PR−, HER2−</td>
<td>NR, grandmother died of cancer (unknown)</td>
<td>Grabellus et al. (2005)</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>Adenocarcinoma</td>
<td>Estrogen treatment for &gt;11 years</td>
<td>ER+, PR+</td>
<td>NR; mother with cancer</td>
<td>Dhand &amp; Dhaliwal (2010)</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Invasive ductal carcinoma</td>
<td>Oral conjugated estrogen and cyproterone acetate for 7 years, then intermittent use for 3 years, then estradiol valerate 4 mg/day and cyproterone acetate 50 mg/day for 5 years</td>
<td>ER−, PR−, HER2−</td>
<td>Negative family history for breast or ovarian cancer</td>
<td>Pattison &amp; McLaren (2013)</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>Ductal carcinoma</td>
<td>Various estrogen preparations for 36 years</td>
<td>ER+, PR−, HER2−</td>
<td>NR</td>
<td>Gooren et al. (2013)</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
<td>Initial histology of breast tumor benign; 10 years later generalized poorly differentiated carcinoma with a probable, but unconfirmed breast origin</td>
<td>Estrogens for 17 years</td>
<td>Not reported</td>
<td>NR</td>
<td>Gooren et al. (2013)</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>Poorly differentiated invasive ductal carcinoma</td>
<td>Oral conjugated estrogens for unknown period and estradiol valerate 20 μg/month for 30 years</td>
<td>ER−, PR−, HER2+</td>
<td>NR</td>
<td>Maglione et al. (2014)</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>Ductal carcinoma in situ</td>
<td>Oral conjugated estrogens 2.5 mg/day for 13 years</td>
<td>ER+, PR+</td>
<td>Family history of breast cancer in father, maternal aunt and ovarian cancer in mother, BRCA negative BRCA1 and 2 negative, no family history of breast or ovarian cancer</td>
<td>Maglione et al. (2014)</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>Infiltrating ductal carcinoma</td>
<td>Unspecified hormone therapy for 8 years</td>
<td>ER+, PR+, HER2−</td>
<td>Breast cancer in four female and one male 2nd degree and other cousins; prostate cancer in father, cousin, great grandfather; BRCA2 mutation</td>
<td>Sattari (2015)</td>
</tr>
<tr>
<td>13</td>
<td>53</td>
<td>Focally undifferentiated ductal carcinoma</td>
<td>Estradiol gel 2 pumps/day and cyproterone acetate 100 mg/day for 7 years</td>
<td>ER+, PR+, HER2−</td>
<td>This study</td>
<td></td>
</tr>
</tbody>
</table>
should be discussed. Male BRCA2 mutation carriers should undergo surveillance that includes regular self and clinical breast examination, but in men, imaging studies and prophylactic mastectomy are not part of guideline recommendations (National Comprehensive Cancer Network 2016). In BRCA2-positive MtF cases that have hormone-induced breast formation, it would seem prudent to adopt yearly screening mammography and/or MRI, as would be the case in adult genetic females (Balmaña et al. 2011, National Comprehensive Cancer Network 2016). BRCA2-positive patients have higher risks for prostate cancer. As complications of prostatectomy can be significant, removal of the prostate is generally not part of the sex reassignment surgery of MtF patients (Hembree et al. 2009). Prostate examinations should be performed at least once a year along with prostate-specific antigen measurement. During follow-up, the risk of other potential BRCA2-associated cancers should be kept in mind.

Nearly 1/11,000 males have gender identity dysphoria that leads to MtF transsexualism. The past few decades have seen a better acceptance of transsexualism and increased understanding of the particular healthcare needs of MtF persons. In parallel, there has been a greater public awareness of the role of genetic mutations of BRCA genes in the risk of endocrine-related cancers. As MtF TG persons attain their desired gender through hormonal treatment, they develop a new physical and personal identity. In parallel they also undergo an important transition in their cancer risks due to hormonal therapy. This case highlights the convergence of two topical endocrine-related issues: MtF TG and BRCA2 mutation-related cancer risk. It raises an infrequent but crucial aspect in the comprehensive endocrine care of MtF TG individuals.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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