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Gynecologic Oncology Tumor Board Presentation

Implications for management of ovarian cancer in a transgender man: Impact of androgens and androgen receptor status

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ABSTRACT

A 36-year-old transgender man (assigned female at birth) on exogenous testosterone therapy was found to have stage IIA ovarian endometrioid carcinoma, and underwent adjuvant chemotherapy. Diffuse androgen receptor expression in the tumor initiated a multidisciplinary discussion regarding the safety of continuing exogenous testosterone as gender-affirming hormone therapy.

1. Presentation of the case

A 36-year-old transmasculine individual (assigned female at birth), and identifying as genderqueer toward masculinity (pronouns: he/him) presented to a community hospital with acute onset pelvic pain. At that time, he was on exogenous testosterone therapy with a transdermal formulation (1% testosterone gel) for the purpose of medical gender affirmation, following a course of injectable testosterone until a year before presentation.

He endorsed symptoms of nausea, and associated bloating and incomplete voiding for several weeks prior to presentation. Physical examination revealed mild tenderness to palpation the right lower quadrant. A pelvic ultrasound showed an isoechoic heterogenous right adnexal mass with cystic internal components and vascularity, measuring 10.7 × 7.3 × 9.8 cm. Beta HGC was negative, and tumor markers (AFP, LDH, CA 125, CA 15–3, CA 19–9) were within normal limits, with the exception of an elevated CEA (6.0 μg/L). The following day, he subsequently underwent an urgent laparoscopic right salpingo-oophorectomy for increased abdominal pain and suspected ovarian torsion. Intraoperatively, a 15 cm ovarian tumor, twisted several times on the fallopian tube and ovarian artery and vein leading to partial necrosis was found. With manipulation, there was with intraoperative capsular rupture. The specimen was removed contained in a bag, and due to the limited availability and minimal concern for malignancy- a frozen section was not sent. Final pathology showed a FIGO grade 2 ovarian endometrioid carcinoma of the right ovary.

He was referred to Gynecologic Oncology and underwent completion staging six weeks later, which included a total abdominal hysterectomy, left salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, and omentectomy. There was no macroscopic disease evident at the time of the operation, however final pathology showed a FIGO grade 2 metastatic ovarian endometrioid adenocarcinoma in the left ovary, measuring 1.1 cm in size. The uterine serosa was positive for metastatic ovarian endometrioid carcinoma. The endometrium was proliferative but negative for malignancy. The omentum, pelvic, and paraaortic lymph node specimens, and cytology were also negative for malignancy. The final diagnosis was a stage IIA grade 2 endometrioid ovarian carcinoma. The endometrioid carcinoma was of no specific molecular subtype [1] (mismatch repair protein expression retained, not tested for *TP53* mutation but low-grade nuclear features). Prognostic biomarker testing yielded a favorable profile, with diffuse estrogen and progesterone receptor expression [2,3], and normal CKDN2A status [4].

He subsequently received six cycles of adjuvant carboplatin and paclitaxel chemotherapy. In light of emerging data suggesting the possible role of androgen receptor (AR) signaling in ovarian cancer outgrowth [5–7], AR expression status was requested and revealed diffuse expression in 70% of tumor cell nuclei with moderate intensity. Given these results, shared decision making led to the discontinuation of testosterone therapy as a trial to evaluate his physical and psychological responses. The case was then brought forward for Gynecologic Oncology Tumor Board discussion regarding the risks and benefits of resumption of

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long-term continuous exogenous testosterone therapy in the context of this transgender man.

2. Androgens and androgen receptors (AR) in ovarian carcinoma

The impact of testosterone therapy on ovarian tissue is not fully elucidated. Androgens are known to promote proliferation of theca and granulosa cells, increase cortical thickness, luteinization and inhibit apoptosis [8]. In a pathologic analysis of 112 transgender men who had at least six months of testosterone therapy prior to oophorectomy it was shown that the mean ovarian volume increased, and there was a histologic appearance of polycystic ovaries (>12 antral follicles per ovary) in 80% of patients, and no evidence of ovarian neoplasia [9]. However, the findings of polycystic ovaries in transgender men has been inconsistent across studies [10].

2.1. Androgens and ovarian cancer risk

It has been proposed that circulating androgens may lead to increased estradiol and estrone concentrations through aromatase conversion within endometriotic implants [11], and therefore theoretically the use of testosterone therapy in an individual with endometriosis may increase the risk of malignant transformation. Additionally, AR is expressed in endometriotic tissue and ovarian cancer cells but not in normal mesothelial cells [12]. Ovarian stromal tissue surrounding ovarian tumors (including endometriosis-related tumors) is activated to produce androgens that can stimulate tumorigenesis providing further evidence of the role of androgens in cancer growth [13].

Excess androgens have been therefore suggested to be associated with an increase in ovarian cancer risk [14]. In a large case-control study, both androgenic and nonandrogenic oral contraceptives had a protective impact on risk of ovarian carcinoma; however, in women with endometriosis, the use of an androgenic oral contraceptive was shown to have less protective benefit [15]. In a small subset of patients with endometriosis receiving hormonal suppression treatment, a 3.2-fold increased risk of ovarian cancer was found in danazol users compared to those using leuprolide, further implicating the role of androgens in malignant transformation of endometriosis [16]. However, all of these women had endometriosis, and there was no comparison group in this study. In a large cohort of Australian women that had signs of increased circulating androgen levels (such as hirsutism, acne or polycystic ovarian syndrome), there was no increased risk of ovarian cancer. Interestingly, despite the lack of increased cancer risk with danazol, there was an association between use of exogenous testosterone and increased risk of ovarian carcinoma (OR 3.7, 95% CI 1.1–12.0), although the numbers were small with only 11 cases and 4 controls [17].

The hormonal impact of circulating levels of androgens and sex hormone binding globulin was investigated in a pooled analysis of seven nested case-control studies, and testosterone was associated with an increased risk of ovarian cancer (OR 1.12, 95% CI 1.02–1.24). The effect was most pronounced between the highest versus lowest quintile of testosterone levels, with a 25% increased risk of ovarian cancer with higher testosterone levels [18]. This effect was only seen in endometrioid and mucinous tumors (OR 1.40, 95% CI 1.03–1.91) [18]. Based on current evidence, testosterone therapy may be linked to an increased risk of ovarian carcinoma, particularly when associated with endometriosis, although higher quality evidence is needed [19–21].

2.2. Androgens and the impact on ovarian cancer prognosis

AR signaling has been shown to promote proliferation of tumor cells in-vivo, where androgens appear to stimulate ovarian carcinogenesis through upregulation of telomerase [6]. Ex-vivo, six out of eight samples of ovarian cancer cells with AR expression showed stimulated growth in response to androgens, compared to none of three samples without AR expression [5]. AR expression is present in 17–32% of ovarian endometrioid carcinomas compared to 37% of high-grade serous carcinomas [22]. Ovarian endometrioid carcinoma has a much more favorable prognosis compared to high-grade serous carcinoma, in the low or high stage setting [23]. Overall survival for stage II endometrioid carcinoma has been estimated to be 97.5% at 1 year, and 83.9% at 5 years [23]. Our case falls into the uncommon category of AR expression positivity in ovarian endometrioid carcinoma. The significance of this finding is unclear, specifically for ovarian endometrioid carcinoma, since association of AR expression with survival has not been reported [22,24].

The prevalence of reproductive cancers, including ovarian carcinoma, in the transgender population is difficult to estimate due to low quality of evidence and inconsistency of inclusive gender terminology in cancer reporting. There have only been five cases of ovarian cancer reported in transgender men, and only one where AR has been tested in the tumor [19].

Similar to our case, Dizon et al. [19] reported a case of a 47-year-old transgender male who had been on exogenous testosterone therapy for five years prior to presentation with a low-grade ovarian endometrioid carcinoma, stage IIA. He similarly had tumor AR testing in anticipation of resumption of exogenous testosterone therapy after adjuvant carboplatin and paclitaxel chemotherapy. AR expression was present, and he was advised to discontinue testosterone therapy; he remained in remission at one-year post adjuvant therapy. It was postulated in this report that if the androgen receptors played a functional role in the development of the ovarian endometrioid carcinoma in the setting of exogenous testosterone therapy, the implications of resuming this therapy on disease prognosis was unclear [19].

3. Endocrinology: testosterone therapy in transgender men

3.1. Impact and timeline of testosterone therapy

The general goal of masculinizing hormone therapy in transgender men is virilization with the development of masculine secondary sexual characteristics that match their masculine gender identity, and to improve psychological well-being through gender affirmation [25]. This is accomplished by using exogenous testosterone therapy in order to raise testosterone levels into the male physiological range by using either injectable or transdermal testosterone formulations [26]. Generally, the expected time of onset for masculine changes is within 1–12 months and the expected timeframe for maximum effect can be up to 5 years [27]. Typically, desired masculine changes induced by testosterone therapy in this setting include the reversible changes of body fat redistribution, increase in muscle mass and strength and menstrual suppression which would lessen and reverse over time if testosterone therapy was stopped. These changes are influenced by individual patient factors such as age, body habitus, and genetics [28]. Further, there are also desired masculine changes that are irreversible which include voice deepening, facial and body hair growth and clitoral enlargement [29].

4. Oncologic implications of androgens

Oncologic risks in transgender men are difficult to identify due to the lack of large studies and long-term data. When compared to the general population, in a case-control study of 365 transgender men taking testosterone therapy, similar mortality rates to the general population were observed, and overall cancer mortality was equivalent [30]. Overall, an increased risk of endometrial cancer and hyperplasia has not been identified. Increased prevalence of HPV-associated risk factors, nondiagnostic Pap test due to testosterone-induced cervical atrophy, and reduced screening as a result of non-inclusive environments and outreach all contribute to an increased risk of cervical dysplasia [31–33]. Breast cancer risk is reduced in transgender men compared to cisgender women, but there remains a risk even after mastectomy (also termed “top surgery”)

as the reconstructive chest surgery does leave some breast tissue [34]. The recommendation is for periodical self-chest exams, but the evidence for efficacy is poor [33].

4.1. The impact of androgens in AR positive cancer

Although the risk of exogenous androgens in those with ovarian cancer is not clear, extrapolation from other cancers may be helpful. As an example, 72% of all female breast cancers routinely express AR and although the role of AR in the development of breast cancer and breast cancer recurrence risk is not clear [35], it is important to evaluate and discuss the cessation or continuation of exogenous testosterone therapy in transgender men with breast cancer on this gender-affirming hormone therapy. In case reports of transgender men with breast cancer, individual decisions regarding the cessation or continuation of exogenous testosterone therapy have occurred [35,36]. However, it has been proposed that AR testing should become standard of care for these patients on testosterone who subsequently develop breast cancer, due to the considerations for minimizing risk of recurrent breast cancer [35]. This same argument for AR testing of the tumor could be made for those on testosterone who present with ovarian cancer (particularly endometrioid ovarian carcinoma), given the possible increased risk in those on testosterone therapy.

4.2. The impact of androgens and androgen-deprivation on ovarian cancer

Androgen-deprivation therapy refers to blocking either the production, or the action of androgens, and is commonly used in other androgen-receptive cancers, such as prostate cancer. This can be achieved through the use of flutamide or bicalutamide, which are selective antagonists of the AR, blocking androgen action but not lowering androgen levels, or through GnRH agonists, which leads the suppression of pituitary gonadotropins, and thereby decreasing androgen production and secretion levels.

In reviewing the impact of androgen deprivation therapy for women with recurrent ovarian carcinoma, it has been shown that only a small subset of women will respond with disease improvement or stability [7]. Additionally, inconsistency has been seen in studies looking at risk of recurrence of ovarian cancer and androgen levels [7], although as detailed above, stimulation of cancer growth has been shown in those with androgen receptivity [5]. Therefore, continued testosterone use in the context of known androgen receptor positivity is theoretically not advisable, although there is no evidence to suggest how this may impact risk of recurrence or overall survival.

5. Psychosocial impact of Gender-Affirming Hormonal Therapy (GAHT)

The psychosocial impact of cessation of exogenous testosterone as gender-affirming hormone therapy (GAHT) will be individual, just as is the experience of the transition process itself, which is any action used by a gender diverse individual to better align themselves with their gender identity. As per each individual's gender-affirming goals, some transgender individuals may only proceed with a social transition whereas others may undergo a medical transition consisting of GAHT and/or gender-affirming surgeries [27]. For those who desire, GAHT has been shown to significantly improve psychological well-being in transgender individuals [37]. Specifically, in a cross-sectional study of 446 transgender men, those who received testosterone therapy reported significantly higher quality-of-life scores, specifically in social functioning, mental health, vitality, and emotional domains [38]. Therefore, the decision to discontinue GAHT in light of theoretical oncologic risk must be balanced with overall quality of life on an individual basis, which is consistent with shared decision-making model of care [39]. It is paramount to evaluate this on an individual basis and understand the patient's individual concerns around this analysis along with their baseline mental health and supports. A detailed discussion is required to explain the option of staying on or coming off exogenous testosterone therapy. Given the limited data regarding the role of exogenous testosterone therapy and ovarian cancer recurrence in the setting of positive AR expression, this risk needs to be weighed against the continued physical and psychological benefits of GAHT.

6. Gender-affirming gynecological care

The estimated prevalence of transgender individuals worldwide is 0.3–0.5%, and is under-reported [26]. In a cross-sectional study of 280 transgender individuals (234 transgender women, and 46 transgender men), 58% of transgender men and 63% transgender men had ever taken hormone therapy. In this study, treatment costs and access to qualified healthcare professionals were identified as barriers [40]. In a retrospective chart review of 99 transgender individuals, transgender men were more likely to have undergone surgery than transgender women, and overall, 35% had undergone at least one gender-affirming surgery [41]. In both studies, the most common surgery for transgender men was chest surgery, whereas a minority had undergone genital gender-affirming surgery—consistent with our case. Despite the prevalence, there is a paucity in preparedness for the nuances of care within this unique patient population [42].

Caring adequately for transgender men in gynecologic oncology may pose additional challenges due to the incongruence between care for reproductive organs and gender identity, gendered terminology of "women's cancer", and being cared for by teams who have exclusively cared for cisgender women [33]. Ensuring a transgender-inclusive practice is paramount to providing patient-centered care and improving psychological outcomes. It is critical to create a safe and welcoming clinic space for transgender patients and provide culturally competent care [43]. Care environment improvements such as signage (gender-neutral terminology, and symbols, inclusive artwork and pamphlets, and magazines), gender-neutral restrooms, appropriate use of terminology, pronouns, and charting consistencies will promote inclusivity and reduce the risk of individuals being misgendered, or "dead-named" (use of a former name of a transgender person) [44]. Additionally, use of gender-neutral gynecologic language when referring to anatomic and reproductive organs, and attention to the independence of gender identity and sexual orientation during clinical history-taking will foster inclusion [42]. For example, instead of referring to the vulva, labia, vagina, or uterus/ovaries, one could refer to external pelvic area, outer fold, genital opening, or internal organs, respectively [42]. This is all important in the acknowledgement and respect of gender identities in order to foster trust in the patient-physician rapport. Additionally, provider and support staff training and education is essential, as transgender persons may have had negative experiences with healthcare professionals, and providers have been consistently shown to feel ill-prepared for these interactions [33] (Fig. 1).

7. Back to the case

The recommendations from the Gynecologic Oncology Tumor Board discussion were brought back and presented to the patient. The option of continuation of exogenous testosterone therapy in the context of possible increased ovarian cancer recurrence risk, versus the physical and psychological impact of discontinuation of GAHT was discussed in detail. Ultimately the patient's overriding concern was the risk of ovarian cancer recurrence. Additionally, due to psychosocial stressors and lack of regular health care, he had experienced a period of time off exogenous testosterone therapy in the past, and he was confident that overall psychosocially he would not be at risk of mental health deterioration. The recommendation was ideally a trial off of testosterone therapy for a duration of two years, as this would represent the highest risk period for cancer recurrence, and thereafter further discussion regarding the risks and benefits of resumption of testosterone therapy. In a follow-up visit three months off of testosterone, he reported that he had an

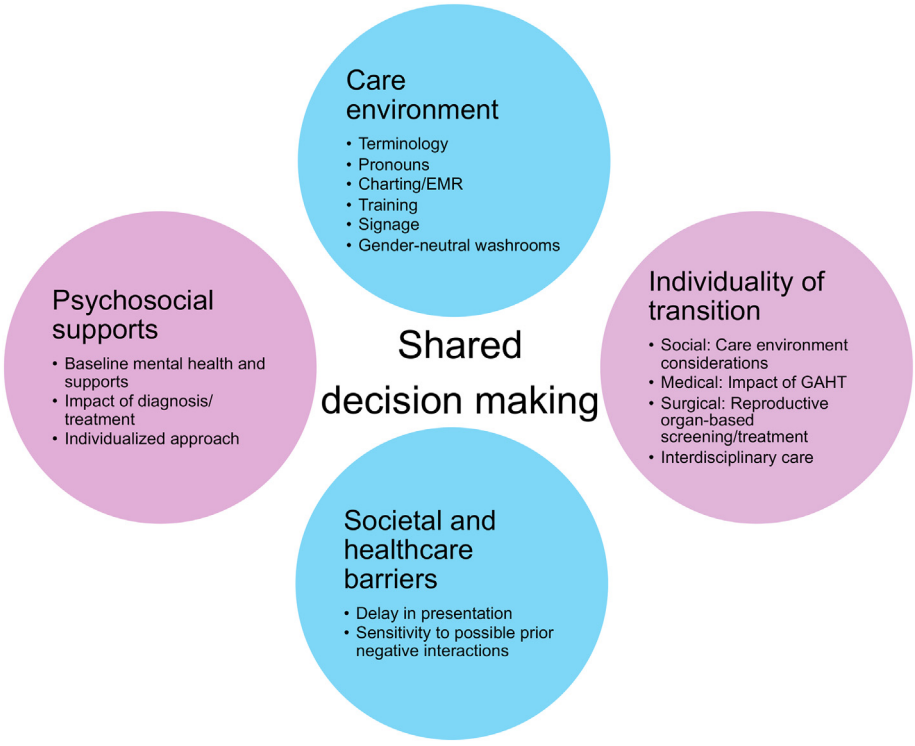

Fig. 1. Framework for providing care to transgender men in gynecologic oncology. Shared decision making with the patient is essential to providing adequate care for transgender men in gynecologic oncology. Special attention to care environments, individuality of the person and how their transition impacts aspects of the disease process and risk profile, recognition of societal and healthcare barriers that transgender individuals face, as well as psychosocial supports at baseline and throughout their care trajectory, acknowledging that traditional cancer support systems may not be appropriate, and therefore requires an individualized approach. The color of this graphic is inspired by the transgender pride flag, developed by Monica Helms. The colors blue and pink representing men and women, with the central white for those transitioning, or non-binary.

initial reduction in energy but this had since improved, and otherwise had not noticed any other significant effects of GAHT discontinuation to date. Through a continued multidisciplinary approach, the patient's team will continue to monitor closely his physical, biochemical, bone and psychosocial health alongside ongoing gynecological surveillance with review of history and physical examination every four months, or sooner if needed.

8. Summary

Transgender men have unique needs in the gynecologic oncology population. In addition to the demographic and socioeconomic risk factors for cancer-related risk, transgender men have additional barriers accessing care due to discrimination, patient and provider discomfort/unfamiliarity. This case demonstrates a further challenge from the perspective of patient-centered care where risk of cancer recurrence intersects with use of exogenous testosterone as gender-affirming hormone therapy. It is imperative that a collaborative approach between gynecologic oncology, endocrinology, pathology, primary care, and patient be considered, balancing oncologic risk alongside the psychosocial impact on the individual patient.

Author contribution

All authors listed have contributed in accordance with the ICMJE Authorship recommendations. The manuscript was drafted by C. Aubrey. Figures and Pathology expertise were provided by M. Köbel. Endocrinology expertise was provided by N. Saad. Primary gynecologic care expertise in transgender persons was provided by F. Mattatall, and N. Saad. G. Nelson and S. Glaze provided Gynecologic Oncology expertise. S. Glaze is the main supervising author. All authors were involved in the process of review and editing the manuscript.

Declaration of Competing Interest

The authors C. Aubrey, F. Mattatall, N. Saad, M. Köbel, S. Glaze have no conflicts of interest to declare. G. Nelson reports personal fees from Abbott and Medtronic, outside the submitted work.

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