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Androgen receptor expression in recurrent granulosa cell tumor of the ovary: Clinical considerations of treatment and surveillance in a transgender male

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ABSTRACT

Granulosa cell tumors (GCT) represent a rare subtype of ovarian cancers. A majority of these tumors express androgen receptor (AR), making them hormonally sensitive. AR positivity not only suggests a potential role of anti-androgen therapy in treating these tumors but also poses a cause for concern: female to male (FTM) transgender patients undergoing exogenous testosterone therapy may be at risk for recurrence, progression, or even incidence of this type of cancer. Although treatment of GCT in transgender individuals has not been well-described, the impact of exogenous hormone use on cancer physiology and treatment should be considered, while also addressing gender dysphoria throughout treatment and in surveillance. Here, we describe a FTM transgender patient with recurrent AR-positive adult granulosa cell tumor after starting testosterone supplementation, along with a literature review to explore the current knowledge of ovarian changes observed following FTM gender transition and subsequent risk of ovarian cancer.

1. Introduction

Sex cord stromal tumors comprise a rare group of ovarian cancers. The most common subtype, granulosa cell tumors (GCTs), represent only ~3% of all ovarian cancers. (Schumer and Cannistra, 2003) While most granulosa cell tumors are diagnosed early at stage I disease, recurrence often happens several years later, usually at least 5 years after treatment completion. (Chen et al., 2012) In general, GCTs are hormonally sensitive tumors with variable estrogen receptor (ER) and progesterone receptor (PR) expression, as detected by immunohistochemical (IHC) studies. Recent biomarker studies have revealed up to almost 60% of granulosa cell tumors express androgen receptor (AR). (Mills, 2018) AR expression testing is not routinely performed, though it may be clinically relevant. AR positivity not only suggests a potential role of anti-androgen therapy in treating this tumor type but also poses a cause for concern: female to male (FTM) transgender patients undergoing exogenous testosterone therapy may potentially be at increased risk of recurrence, progression, or even incidence of this type of tumor. (Mills, 2018) Given the rarity of GCTs, this data is difficult to quantify. Systemic androgen levels can be elevated in patients taking exogenous testosterone for gender affirmation, which may also complicate the use of serum testosterone levels in monitoring for tumor recurrence.

Treatment of GCT in transgender individuals has not been well described, with only two other case reports published. However, in counseling transgender patients with GCT, the impact of exogenous hormone use on cancer physiology and treatment should be considered, while also addressing gender dysphoria throughout treatment and in surveillance. Here, we describe a FTM transgender patient with recurrent AR-positive adult granulosa cell tumor after starting testosterone supplementation, along with a literature review to explore the current knowledge of ovarian changes observed following FTM gender transition and subsequent risk of ovarian cancer.

2. Case Report

A 33-year-old G0 patient, assigned female at birth, with past medical history of class III obesity (body mass index (BMI) 41), anxiety, depression, venous thromboembolism and stroke (secondary to blood

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clot while undergoing cancer workup with no residual effect) presented to our clinic with recurrent GCT while on testosterone supplementation therapy.

The patient initially presented to the emergency department at an outside hospital in 2017 at age 26, prior to gender transition, with pleuritic chest pain after a 10-hour drive. Ultimately, a left subsegmental pulmonary embolism was identified, for which anticoagulation was started. Upon further work-up, a computed tomography (CT) scan incidentally revealed a 14 cm complex adnexal mass and ascites.

The patient then underwent an exploratory laparotomy, total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and pericolic and diaphragmatic biopsies. Final pathology was consistent with adult-type granulosa cell tumor, FIGO stage IC. Initial tumor markers were notable for an elevated CA-125 level of 532 U/mL and inhibin B level of 8,484 pg/mL. Adjuvant treatment with cisplatin, etoposide, and bleomycin for three cycles resulted in a complete response.

In 2021, while surveillance bloodwork, imaging, and physical exam confirmed no evidence of disease, the patient underwent gender-affirming mastectomy and desired to start testosterone injections. The patient's gynecologic oncologist at the time advised against testosterone use, suggesting a possible increased recurrence risk of the granulosa cell tumor. However, the patient felt strongly about pursuing this intervention, and understanding the risks and benefits, began testosterone therapy with 100 mg intramuscular (IM) injections every two weeks. In August 2022, a routine surveillance pelvic CT scan was concerning for vaginal cuff recurrence, along with an elevated inhibin B level (20.1 pg/mL; previously undetectable). The patient transferred medical practices, and a follow-up scan in March 2023 displayed similar findings along with a concurrent rise in inhibin B (45.6 pg/mL). The patient had been asymptomatic, without any abdominal/pelvic pain or vaginal bleeding.

In June 2023, the patient underwent an exploratory laparotomy with resection of the mass, complicated by severe adhesive disease and a postoperative hematoma. The pathology was consistent with recurrent granulosa cell tumor from the ovarian primary. IHC staining revealed the tumor was PR positive with 80%, 1 + expression and ER negative with 30%, 1 + expression. Pathology slides from this tumor are shown in Fig. 1. In July 2023, after healing from the surgical resection, the patient was planned to start second-line carboplatin and paclitaxel; however, further tumor testing revealed AR positivity of 90%, 2 + expression. IHC also demonstrated positive PD-L1 status. Mismatch repair proteins were intact (MMR proficient) with microsatellite stability (MSS). Tumor mutation burden (TMB) and loss of heterozygosity (LOH) were low. DNA tumor sequencing revealed a pathologic variant of FOXL2. Other biomarkers were negative. At this point, following multidisciplinary discussion, the patient was advised to stop testosterone and undergo hormone suppression with letrozole in lieu of chemotherapy. The recommendation to start a medication that would reverse his physical gender transformation caused him a significant amount of psychological distress, for which the patient continued counseling and intervention with psychiatry. He was counseled that the decision was ultimately his, and he chose to discontinue the testosterone. Changes to his body physique and the fluctuating hormone levels added to his emotional lability, necessitating an increase in the dosing of his psychiatric treatment regimen.

An interval positron emission tomography (PET) CT scan performed in December 2023 revealed findings suggestive of metastasis, including an FDG avid right-sided vaginal focus with curvilinear uptake just above/within the midline vaginal cuff, an associated fluid collection with probable associated abscess, and an FDG avid left pelvic lymph node (see Fig. 2).

As testosterone levels remained elevated on letrozole, spironolactone was added. The patient's medical oncologist had attempted to start degarelix, a GnRH-antagonist; however, the insurance company denied this request for an ovarian cancer indication. Leuprolide acetate with bicalutamide was subsequently ordered, which also did not get insurance approval for a non-prostate cancer indication.

The patient was referred for consultations with radiation oncology and with gynecology oncology. Neither radiation nor surgical resection were recommended given the complex surgical history and location of the disease; rather, systemic, or hormonal therapy was favored. In January 2024, a repeat attempt to initiate leuprolide acetate 7.5 mg IM injection was successful and approved by insurance. This was started with bicalutamide 50 mg PO daily in addition to letrozole 2.5 mg PO daily; spironolactone was discontinued. For convenience, leuprolide acetate injection was changed to 22.5 mg IM for 3-month dosing after the first monthly dose. Tumor markers thereafter were low/stable, and testosterone levels stabilized (see Fig. 3 for full trend of testosterone levels). A repeat PET CT in March 2024 showed improvement in all areas noted on the previous study. Further improvement was noted on the most recent PET CT scan in June 2024, with diminished intensity of focal uptake in/abutting the midline vaginal cuff and resolved hypermetabolism along with diminished size of the left pelvic lymph node. Upon physical examination, the patient remained asymptomatic and was tolerating the hormonal regimen well. He continued to follow with medical oncology, gynecologic oncology, endocrinology, and psychiatry thereafter.

2.1. Epidemiology and Pathogenesis of GCT

Ovarian cancer arises from three cellular origins: surface epithelial cells, germ cells, and in the case of granulosa cell tumors, stromal cells. GCTs make up about 2–5% of ovarian neoplasms; they can be divided into two subtypes based on clinical symptoms and histological characteristics: adult-type GCT and juvenile GCT (JGCT). JGCTs are rarer than the adult type, consisting of only 5% of all GCTs. (Ing et al., 2023) JGCT typically present before puberty and produce estradiol, progesterone, or androgens, often manifesting as pseudoprecocious puberty. (Ing et al., 2023) An association exists with JGCT and Ollier's Disease (OD), a rare bone disease characterized by skeletal dysplasia and development of enchondromas, noncancerous cartilaginous growths within bones. (Zhang, 2023) Both conditions share a common pathogenesis, likely involving the same mutation in the IDH1 gene. (Zhang, 2023).

Studies suggest an inherent deficiency of aromatase production occurs within virilizing GCT, preventing the conversion of androgens to estrogens. (Morrison et al., 2023) Aromatase deficiency in adult-type GCT may be caused by *FOXL2* mutations, which impairs steroidogenesis; specifically, FOXL2C402G mutation is thought to disrupt CYP19 (aromatase) and CYP17 gene transcription. (Summey, 2022).

In GCT, ER is the most abundant steroid receptor, followed by AR and PR; all three can be overexpressed in ovarian cancer. AR expression has been found to promote tumorigenesis and metastasis in several cancer types, including epithelial ovarian cancer and sex cord stromal tumors. (Chung, 2021) While activating and inactivating mutations of the AR are known features of hormonally sensitive cancers like prostate and breast cancer, respectively, mutations in the AR have not been systemically evaluated in GCT. (Alexiadis, 2011).

2.2. Case Reports in Literature

There have been two other cases reported in the literature of granulosa cell tumors in transgender men (see Table 1). One was published in 2023, describing a 34 year-old with OD. (Ing et al., 2023) Prior to starting testosterone treatments in 2016, medical history was significant for mood changes and acne with regular monthly menstrual cycles with no signs of hyperandrogenism; anxiety and depression on buspirone and escitalopram; and obesity with BMI 48. (Ing et al., 2023) Surgical history included orthopedic right lower extremity surgeries, as well as an appendectomy. (Ing et al., 2023) The patient had a 6-year use of testosterone prior to diagnosis of stage IA JGCT. In this case, the tumor demonstrated ER 40% (weakly to moderately positive), PR 90% (moderately to strongly positive), AR >90% (strongly positive). Lab

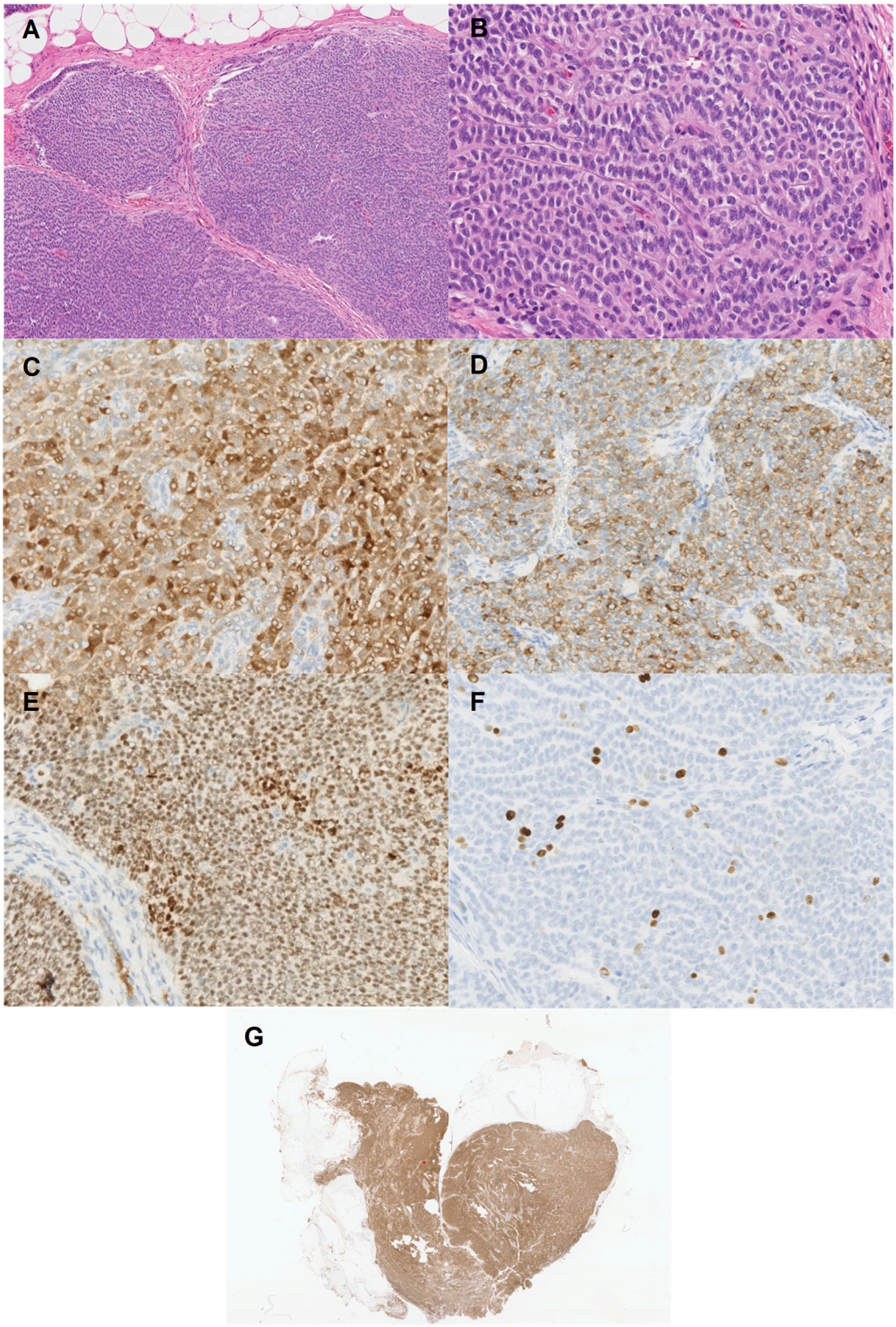

Fig. 1. Histology Slides of the Patient's Recurrent Granulosa Cell Tumor with Special Stains. A. Nodular growth of classic diffuse-pattern granulosa cell tumor, the most common pattern seen in this disease. (H&E, 10x). B. GCT showing uniform small cuboidal cells with scant pale cytoplasm, round to oval nuclei, and occasional "coffee bean" nuclei with grooves (H&E, 20x). C. IHC stain demonstrating diffuse positivity for calretinin in tumor cells (calretinin IHC, 20x). Calretinin, a calcium-binding protein, is typically positive in sex cord stromal tumors of the ovary and testis, though it may also be positive in other tumors. D. IHC stain showing diffuse positivity for inhibin in tumor cells (inhibin IHC, 20x). Inhibin, a glycoprotein primarily produced in the gonads to regulate follicle stimulating hormone (FSH) secretion, is highly expressed in GCTs and Sertoli-Leydig cell tumors, helping to distinguish these from other malignant ovarian neoplasms. E. IHC stain showing nuclear expression of steroidogenic factor 1 (SF-1) in tumor cells (SF-1 IHC, 20x). SF-1 is a transcription factor that regulates gonadotroph cell differentiation and is positive in granulosa cells. F. The proliferation index (Ki-67), a marker of tumor cell proliferation, is approximately 15% in this case (Ki-67 IHC, 20x). G. Androgen receptor stain showing diffuse AR positivity. (Clone AR441 antibody, 0.6X; this image was provided by Caris Life Sciences®).

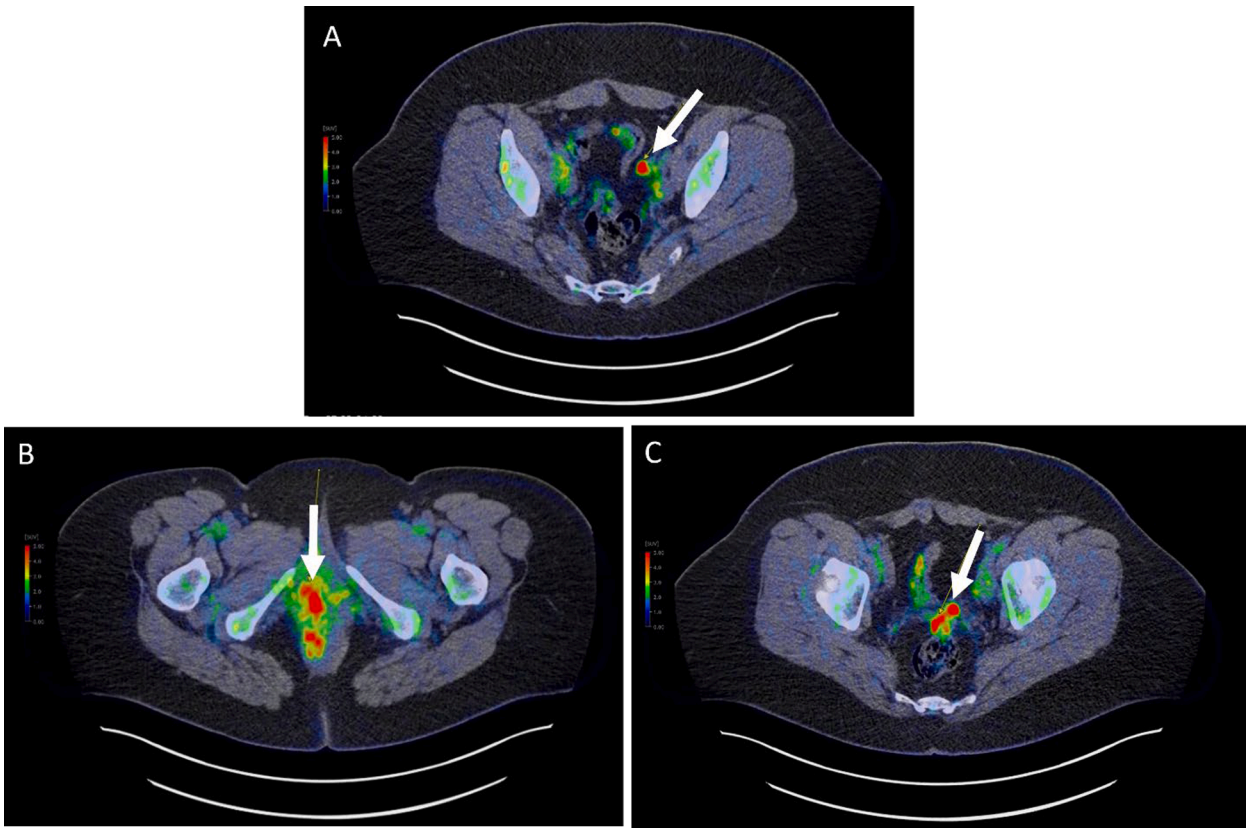

Fig. 2. PET CT Demonstrating Areas Suspicious of Recurrent Disease. This is an interval PET CT performed six months after the patient's first recurrence of GCT. At this time, the patient was treated with surgical resection and letrozole, as efforts to obtain additional hormonal medications were delayed due to insurance denials. The selected images demonstrate: an FDG avid left pelvic lymph node suspicious for metastasis (A), curvilinear uptake just above/within the midline vaginal cuff, with associated fluid collection, suspicious for malignancy, with probable associated tiny abscess (B), and an FDG avid right-sided vaginal focus suspicious for malignancy (C).

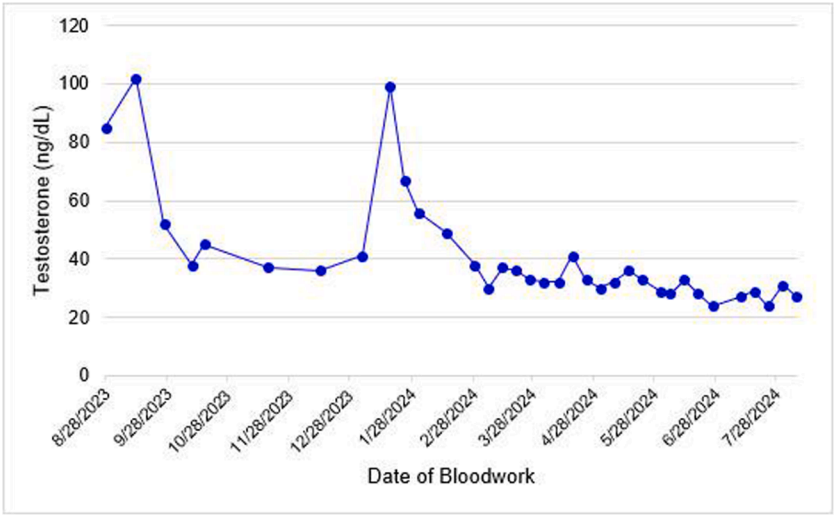

Fig. 3. Testosterone Levels Since Recurrence of AR-Positive Granulosa Cell Tumor in Our Patient on Hormonal Therapy. The testosterone level trend as shown in the line plot above begins when tumor testing revealed the recurrent granulosa cell tumor was androgen receptor positive. In correlation with the findings above, recall the patient was started on letrozole in 7/2023 after surgery for the vaginal recurrence; spironolactone was added in 11/2023; and finally, leuprolide acetate and bicalutamide were added to letrozole, with spironolactone discontinuation, in 1/2024. After that time, testosterone levels stabilized to the low/normal range. For reference, the expected testosterone range for this institution for males is 241–827 ng/dL and normal range for females is 14–76 ng/dL.

Table 1
Summary of Published GCT Case Reports in Transgender Males

Author (Year Published)	Diagnosis	Age at Initial Diagnosis	Patient History	Testosterone Use Duration Prior to Diagnosis	Time to First Recurrence	Disease Characteristics	Treatment
Kwiatkowska *et al.* (2020)	Recurrent juvenile GCT (initial diagnosis stage IA folliculoma)	16	Hyperthyroidism, insulin resistance, psoriasis, hirsutism	N/A	9 months	Elevated testosterone and insulin No IHC available	Laparoscopic enucleation of tumor (initial), USO (recurrence)
Ing *et al.* (2023)	Stage IA juvenile GCT	34	Ollier's Disease, low-grade chondrosarcoma, anxiety/depression, obesity, endometrial hyperplasia	6 years	N/A as of 4 weeks post-operatively	Elevated CA-125, LDH, inhibin A, inhibin B ER 40%, PR 90%, AR>90%	TAH-BSO, omentectomy
Tumas and Berman (2024)	Recurrent adult GCT (initial stage IC2)	26	Obesity, anxiety/depression, stroke, venous thromboembolism	None initially; 1 year prior to recurrence	5 years	Elevated testosterone (concurrent exogenous testosterone use) ER 30%, PR 80%, AR 90%	TAH-BSO, complete cytoreductive surgery (initial),triple hormone therapy with letrozole, bicalutamide, and leuprolide acetate (recurrence)

*Abbreviations: GCT=granulosa cell tumor; USO=Unilateral salpingo-oophorectomy, TAH-BSO=total abdominal hysterectomy, bilateral salpingo-oophorectomy; IHC=immunohistochemistry; LDH=lactate dehydrogenase; ER=estrogen receptor; PR=progesterone receptor; AR=androgen receptor.

findings were significant for an elevated CA-125 of 198 U/mL, LDH 426 U/L, inhibin A 473 pg/mL and inhibin B 23,419 pg/mL. Treatment consisted of primary surgical debulking with exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and radical optimal tumor reductive surgery to no gross residual disease. No adjuvant treatment was administered post-surgery. His testosterone levels naturally declined to 31 ng/dL, and his estradiol level to 8 pg/mL. He reported feeling more "delicate" than he had been in many years, with heightened emotional lability and being more prone to crying. He still desired gender-affirming bilateral mastectomy and to be restarted on testosterone therapy soon thereafter. The ongoing plan was for surveillance with inhibin A and B monitoring every 3 months for the first year, every 4 months second year, every 6 months the third year, and then annually.

The authors posited that prior exogenous testosterone therapy may have contributed to the growth of the tumor and questioned the need to stop gender-affirming testosterone therapy due to increased risk of recurrence. (Ing et al., 2023).

The other case reported in the literature describes a 17-year-old adolescent patient assigned female at birth with gender dysphoria who was diagnosed with a recurrent JGCT in the setting of multiple endocrinopathies. (Kwiatkowska et al., 2020) During the surgery qualification process, the patient expressed identifying as male, reporting discomfort with body habitus and with the expected roles of the gender assigned at birth. These sentiments led the patient to request a total hysterectomy with a bilateral salpingo-oophorectomy, but parental permission was required, as the patient was a minor. The parents denied permission, considering the patient's young age and irreversible reproductive consequences of the procedure. Subsequently, the patient underwent unilateral removal of the affected ovary with additional ongoing hormonal, psychological, and psychiatric evaluation.

This case of concurrent JGCT with gender dysphoria spectrum disorder in an adolescent assigned female at birth highlights the therapeutic and ethical challenges in this patient population. Multidisciplinary coordination of care involving developmental psychology, psychotherapy, family dynamics, and hormonal treatment, in addition to surgery, should be considered, especially given the potential therapeutic implications for gender dysphoria and patient wellbeing.

2.3. Transgender Care Considerations

Gender dysphoria, a dissociation between the sex assigned at birth and an inner conviction of belonging to another gender, affects approximately 0.6% of people worldwide. (Scheim, 2024) In the United States, about 1 in 250 individuals or about 1 million people self-identify as transgender or gender non-conforming. (Meerwijk and Sevelius, 2017) Gender-affirming modalities, such as gender-affirming hormone therapy (GAHT) and gender-affirming surgery, are often employed by individuals desiring a gender transition.

Overall, GAHT has been shown to be safe and have predictable effects on hormone levels in transgender individuals. The effective GAHT dose, however, can vary widely amongst patients, with some having higher serum levels of hormones or their metabolites. This may theoretically increase risk of diseases in organ systems with sex hormone receptors, as well as risk for hormone-sensitive cancers. (Sterling and Garcia, 2020) While androgens are necessary for normal ovulatory function and follicle health, testosterone exposure to the ovaries has been associated with reduced follicle growth activation, poor follicle health, and increased DNA damage, (Bailie, 2023) which may promote ovarian tumorigenesis. Consideration of potential risks should be included in discussions with patients initiating GAHT, particularly in cases with a history of or risk for hormone-sensitive malignancy, such as ovarian cancer. Equal consideration in these discussions should be placed on the benefits of GAHT for these individuals.

2.4. Guidelines Regarding Risk of Ovarian Cancer

Myriad organizations have published guidelines on primary and gynecologic care for transgender men. However, these guidelines are inconsistent in recommending oophorectomy to reduce the risk of ovarian cancer. The World Professional Association for Transgender Health (WPATH) was one of the first organizations to publish clinical guidelines on healthcare for transgender individuals.

WPATH's *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People* cautions, "Analogous to persons born with female genitalia with elevated androgen levels, testosterone therapy in female-to-male (FTM) patients may increase the risk of ovarian cancer, although evidence is limited." (Sterling and Garcia, 2020).

Similarly, The Endocrine Society's clinical practice guideline recognizes a possible increased risk for ovarian cancer in individuals undergoing long-term testosterone therapy and recommends health care providers determine the medical necessity of a laparoscopic total hysterectomy and bilateral salpingo-oophorectomy as part of a gender-affirming surgery to prevent reproductive tract cancer. (Hembree,

2017).

Despite a perceived increased risk for ovarian cancer in transgender individuals on long-term testosterone therapy, few transgender-specific cancer screening recommendations exist. In Gooren's manuscript in the *New England Journal of Medicine*, monitoring for estrogen-sensitive cancers of the breast, endometrium, and ovaries is recommended for FTM transgender individuals who have not undergone mastectomy and oophorectomy. (Gooren, 2011) However, just how often to monitor these patients and by which modalities is not specified.

A contrasting perspective is offered by the United States Preventive Services Task Force (USPSTF), which currently recommends against the use of routine screening for ovarian cancer in (cisgender [cis]) women. (The Guide to Clinical Preventive Services, 2014) In reviewing the literature, no strong evidence was found to suggest transmasculine patients have a higher risk of ovarian cancer. (Harris et al., 2017) Therefore, it is recommended transgender males follow the guidelines for cis-females: routine cancer screening is not recommended and prophylactic oophorectomy without other risk factors is unnecessary. (Harris et al., 2017) The USPSTF states more research is needed to make specific evidence-based recommendations. (Caughey, 2021).

Ultimately, the need exists for comprehensive cancer screening and prevention initiatives centered on relevant anatomy and high-risk behaviors specific to the transgender population. In the meantime, established guidelines focusing on cisgender patients may be applied to the transgender community based on the organs remaining *in situ*. As the USPSTF advocates, an inclusive, respectful approach should be taken recommending preventive services so not to further marginalize the transgender population. (Caughey, 2021).

2.5. Exogenous Androgen Effects on Ovarian Tissue

During the reproductive years, the ovaries produce, on average, 0.7 mg of testosterone per day. (Pirtea et al., 2021) While this is higher than estradiol production (up to 0.5 mg per day, depending on menstrual cycle phase), it is 10 times less than the production of testosterone observed in adult cisgender men. (Pirtea et al., 2021) Androgens play a vital role in the ovary, stimulating the growth and development of follicles. (Gervásio et al., 2014) Based on data from animal studies, androgens may influence folliculogenesis by exerting pro-atretic effects on growing follicles and antiapoptotic action on granulosa cells. (Gervásio et al., 2014).

In patients taking long-term exogenous testosterone, induced ovarian effects become apparent after approximately 6 months of therapy. (Pirtea et al., 2021) Specifically, investigations into the impact of high testosterone doses administered as part of GAHT in transgender men report histological changes in the ovaries. (Pirtea et al., 2021) These changes consist of both macroscopic and microscopic alterations of ovarian morphology, mimicking the typical ovarian morphology encountered in women with polycystic ovarian syndrome (PCOS) but without an effect on antral follicle count. PCOS-like features in androgen-exposed ovaries of transmen include: thickened ovarian cortex with marked collagenization, greater numbers of cystic and cystic atretic follicles in the ovarian stroma, diffuse ovarian stromal hyperplasia, and luteinization of stromal cells. (Ikeda, 2013) Although studies suggest that excessive androgen is closely related to the development of PCOS, high-dose androgens administered to FTM patients does not induce PCOS. Interestingly, though, several studies of transgender men have found an increased incidence of PCOS, even in those who have *not* taken testosterone. One source estimates that PCOS may affect up to 58% of FTM individuals, compared to 5–15% of cis-females, on average, who may be affected by PCOS. (Gezer, 2022)The relationship between PCOS and androgens is complex. Current evidence of a link between PCOS and ovarian cancer is limited and contradictory.

2.6. Treatment of GCT: Hormonal Interventions in the Recurrent Setting

For malignant sex cord-stromal tumors, including GCTs, complete surgical staging is recommended, and for tumors other than low-risk stage I, platinum-based chemotherapy is recommended. The National Comprehensive Cancer Network (NCCN) preferred recommendation is carboplatin and paclitaxel, or alternatively, etoposide and cisplatin (EP) or bleomycin, etoposide, and cisplatin (BEP). (NCCN, 2024) Localized radiation therapy can be considered to palliate symptoms or to treat oligometastatic disease.

Given the aberrant steroid pathways involved in pathogenesis, hormonal invention might appear as a reasonable treatment option. However, due to limited phase III clinical trial data, current NCCN guidelines only recommend hormonal therapy for sex cord stromal tumors in the recurrent setting. (NCCN, 2024) It is unknown if hormonal treatment after initial surgery may affect recurrence rates.

Hormonal therapy options for GCTs per NCCN include aromatase inhibitors (anastrozole, exemestane, or letrozole), gonadotropin-releasing hormone (GnRH) agonists (leuprolide acetate or goserelin acetate), or a selective estrogen receptor modulator (tamoxifen). (NCCN, 2024).

Data to support leuprolide in this setting stem from mostly small case studies and series. Recently, however, a retrospective cohort study evaluated 62 patients enrolled in the Rare Gynecologic Malignancy Registry with recurrent adult GCTs treated with leuprolide acetate. (Foster, 2023) These patients had similar outcomes to a comparison group treated with chemotherapy in the recurrent setting with minimal toxicity. Challenges in interpreting the study include that the patients received varying dosages and frequency of leuprolide, as there is no standardized dosing schedule, and hormone receptor expression of the tumors was not reported. (Foster, 2023) Currently, the only FDA-approved indication for Lupron (leuprolide acetate) is for the treatment of prostate cancer. (Stenzel et al., 2020) Attempts to use Lupron off-label for an ovarian cancer indication may be denied by insurance, resulting in treatment delays, as was the case with our patient.

Novel triple hormonal therapy using an androgen receptor antagonist, aromatase inhibitor, and GnRH agonist was recently evaluated in a case series of AR-positive recurrent adult GCT. (Summey, 2022) Seven patients with recurrent GCT were treated with bicalutamide 50 mg orally once daily, leuprolide acetate 7.5 mg intramuscular (IM) injection every 4 weeks, and a daily oral aromatase inhibitor. (Summey, 2022) Six of seven patients derived clinical benefit from this regimen. (Summey, 2022) Of the two patients with partial response (versus four with stable disease), strong expression of AR was reported on tumor IHC. (Summey, 2022) Of note, this was the regimen selected to treat our patient with GCT, given the high AR expression of his tumor, and to which he continues to derive clinical benefit after several months of treatment.

Although most data to support hormonal therapies come from retrospective trials, one prospective trial, PARAGON (ANZGOG-0903), investigated treatment with anastrozole in ER/PR-positive recurrent and metastatic granulosa cell tumors. (Banerjee, 2021) Despite a high clinical benefit rate of almost 79% in 38 evaluable patients at 12 weeks, the objective response rate was only 10.5%, which is lower than reported in the literature. (Banerjee, 2021) More prospective trials like PARAGON are needed to evaluate the role of hormonal agents in GCT.

Additionally, the GREKO (GRanulosa Et KetOconazole) trial investigated ketoconazole in recurrent GCT in patients with a particular mutation in the *FOXL2* gene (402C>G): a mutation leading to overactivation of steroidogenesis. (Garcia-Donas, 2023) Ketoconazole inhibits CYP17, a key enzyme in the process of steroidogenesis. (Garcia-Donas, 2023) Six evaluable patients were recruited for this study; five achieved stable disease longer than 12 months on this regimen, suggesting activity of ketoconazole in this tumor and the potential for synergism with other hormone therapies. (Garcia-Donas, 2023).

Spironolactone has not been mentioned in the literature in the context of treating GCTs. Its main mechanism of action is to compete

with aldosterone for receptor sites in the distal renal tubules, increasing sodium chloride and water excretion while sparing potassium and hydrogen ions. Clinical indications for use include hirsutism and acne vulgaris. However, the FDA-approved indication only extends to primary hyperaldosteronism, managing edema and sodium retention in congestive heart failure, managing edema and sodium retention in cirrhosis, nephrotic syndrome, essential hypertension, and hypokalemia. (Aldactone (Spironolactone), 2024).

Finally, after treatment is completed, patients will be followed by their providers with active surveillance, which includes regular examinations with a gynecologic oncologist and monitoring tumor markers if previously elevated. Monitoring serum inhibin levels may be utilized in long-term follow-up in cases of GCT with initially elevated levels.

3. Discussion and Future Directions for GCT Management in Transgender Patients

Transgender men remain an underserved population at risk for gynecologic malignancies. At present, patients transitioning to gender-affirming identities have no documented increased risk of developing gynecologic malignancies secondary to hormone use, but this may be due, in part, to the limited available data. (Chung, 2021).

A particular challenge in studying ovarian GCTs, in the transgender population or otherwise, is the tendency for decades-long progression free survival. (Pectasides et al., 2008) Prior studies are mainly limited to case studies and series, which lack the necessary extended follow-up periods. Randomized controlled trials on these rare and slow-growing tumors would be the gold standard, however, inherent challenges include patient accrual and duration of follow-up.

Medical monitoring of hormone levels for patients on GAHT could help prevent an excess of testosterone and estrogen. An added challenge exists if hormones are acquired through means other than through licensed physicians and no primary care provider is involved to monitor the patient. Even with proper initial gynecologic care, due to a constellation of provider and patient factors, including discrimination, insurance issues, personal discomfort, or misconceptions, transgender men may be less likely to pursue follow-up with their providers, forgoing necessary evaluation to detect gynecologic pathologies, including ovarian cancer.

Despite limited data and still emerging knowledge of AR-positive tumors, it may not be recommended for a patient to start or continue exogenous testosterone after diagnosis of an AR-positive granulosa cell tumor, given the propensity of androgens to stimulate growth of this rare tumor. This in turn calls for consideration of how anti-androgenic treatment may physically, psychologically, and emotionally affect a patient who has begun or desires a transition.

Reviewing hormonally sensitive cancers in transgender individuals, such as this case of ovarian GCT in a transgender male, highlights the need for more evidenced-based recommendations in this underserved population. Prospective, randomized, controlled trials in both the preventive and treatment space are needed in the transgender community, to address those at risk of developing cancer or recurrent disease and those already afflicted with cancer. Ultimately, evidence-informed discussions can help guide challenging decisions surrounding gender affirming care and implication for disease progression or recurrence.

Author Contributions

The manuscript was researched and written by, Jordyn Tumas, MD and Tara Berman, MD, who contributed equally to writing this manuscript. Dr. Berman was the patient's primary medical oncologist. Ruben D. Alberto Hiraldo, MD, was one of the pathologists who reviewed the original slides and provided the images and explanations for Fig. 1.

Credit authorship contribution statement

Jordyn Tumas: Writing – review & editing, Writing – original draft, Formal analysis. **Ruben D. Alberto Hiraldo:** Data curation. **Tara Berman:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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