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Case report

Endometrial cancer in a transgender male: A rare case and review of the literature

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ABSTRACT

Objective: Endometrial cancer is the most common gynecological malignancy in the United States. Despite the high prevalence amongst cisgender females the prevalence of this gynecological malignancy in transgender men has not been clearly identified. To date, only four reported cases have been described in the literature.
Case: A 36-year-old nulliparous assigned female at birth, transgender premenopausal male underwent a laparoscopic total hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node mapping and omental biopsy after having an endometrial biopsy that demonstrated well differential endometroid adenocarcinoma. He had been on testosterone therapy for at least five years prior to presenting to his gynecologist with the chief complaint of vaginal bleeding. Final pathology showed FIGO Stage 1A endometroid endometrial carcinoma.
Conclusion: This case report adds to the body of literature demonstrating that transgender men can develop endometrial carcinoma while on exogenous testosterone therapy. In addition, this report illustrates the importance of routine gynecological care in the transgender patient population.

1. Introduction

Endometrial cancer is the most common gynecological malignancy in the United States with over 63,000 new cases reported annually. Each year, 1 in 342 persons under age 49 and 1 in 166 between the ages of 50–59 are diagnosed(StatPearls., 2022). Despite the high prevalence amongst cisgender females, the prevalence of this gynecological malignancy in transgender men has not been clearly identified.

Transgender men may choose to undergo gender affirming hormone therapy with testosterone to aid in the development of masculine physical features. These features include changes in facial/body hair, genital appearance, vocal changes, and menstrual suppression(Stenzel et al., 2020). However, the long-term effect of testosterone on the uterus is have not been extensively studied.

Historically exogenous testosterone was thought to increase the risk of endometrial hyperplasia and carcinoma due to aromatization of testosterone to estrogen. However, retrospective studies on the use of testosterone have revealed varying uterine pathology findings. In premenopausal transgender men, a large percentage will have active endometrium while on testosterone(Grynberg et al., 2010; Perrone et al., 2009; Cao et al., 2021; Grimstad et al., 2019). A retrospective review of 94 patients revealed that nearly 65% of patients on gender-affirming therapy continue to have proliferative endometrium while 24.5% showed atrophic morphology. Of note, only one patient had endometrial hyperplasia without atypia and there were no reported cases of endometrial carcinoma(Grimstad et al., 2019). Another retrospective review of 112 patients found 8 patients with endometrial hyperplasia without atypia and one patient with atypical hyperplasia with adenocarcinoma(Grynberg et al., 2010).

To date, only 4 reports case reports of endometrial carcinoma in transgender men have been reported in the literature. The first case was in a 51-year-old diagnosed with stage IIIC grade 2 endometroid adenocarcinoma after undergoing gender-affirming hormonal treatment for 7 years(Urban et al., 2011). A second case was reported in a 41 year old who was diagnosed with stage IIIA endometroid adenocarcinoma after he presented with vaginal bleeding while on exogenous testosterone for five years(Jeevananthan and Iyengar, 2021). The third case described a transgender man with Lynch Syndrome diagnosed with endometrial and

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Table 1
Literature Review.

Case	Age, presenting symptom	BMI	Medical Conditions	Duration of Testosterone Use	FIGO Stage	Surgery	Adjuvant Therapy
Case	36; AUB	43	T2DM; previous smoker	5+	IA, G1	H; BSO; SLND; OB	Not recommended
Urban, 2011	51, AUB	31	NR	7 years	IIIC, G2	H; BSO; LD	Systemic chemotherapy; declined radiation therapy
Jeevanantha, 2021	41, AUB	NR	NR	5 + years	IIIA, G1	H; BSO; PLND; PALD	Neoadjuvant chemotherapy; Pelvic radiation therapy; Systemic chemotherapy
Bobola, 2021	31, AUB	NR	Lynch syndrome; NF1	10 + years	IIIA	H; BSO; PLND	Pelvic radiation therapy; Systemic chemotherapy
Yoshiba, 2023	30, AUB, AP	42	HTN; current smoker	2 years	Metastatic disease; G3	H; BSO; LD; OB	Systemic chemotherapy

AP: abdominal pain; AUB: abdominal uterine bleeding; BSO: bilateral salpingo-oophorectomy; HTN; hypertension; H: hysterectomy; NF1: von Recklinghausen's disease; NR: not reported; lymphadenectomy; PLND: pelvic lymph node dissection; PALD: *para*-aortic lymphadenectomy; OB: omental biopsy; T2DM; Type 2 diabetes mellitus.

colon cancer(Bobola et al., 2021). The final case report described a 30 year old obese man who presented with abdominal pain and vaginal bleeding (Yoshida et al., 2023). (Table 1). We present a rare case of endometroid adenocarcinoma in a transgender male and describe the pathology.

2. Case

A 36-year-old nulliparous assigned female at birth, transgender premenopausal male was referred to gynecologic oncology for an endometrial biopsy that showed focal well differentiated FIGO grade 1 endometroid adenocarcinoma. The patient had presented to his primary gynecologist to discuss a hysterectomy as he was having dysphoria due to a recent episode of vaginal spotting while on testosterone. He reported that he had been on exogenous testosterone for over 5 years and denied a history of abnormal Papanicolaou smears or sexually transmitted diseases. He was found on transvaginal ultrasound to have a uterus measuring 10.2x4.3x 6.2 cm and an endometrial stripe of 17 mm. His history was notable for Type 2 diabetes, class III obesity (BMI 43), and was a previous smoker. No significant family history of cancer.

He underwent a laparoscopic total hysterectomy, bilateral salpingo-oophorectomy, omental biopsy, and sentinel lymph node mapping with excision of an enlarged right pelvic sentinel lymph node in February 2022. Operative findings were notable for a plaque of implants emanating from the left fallopian tube that were present on the surface of the left ovary as well as the peritoneum of the posterior cul-de-sac, predominately on the left uterosacral ligament. Frozen section of the uterus revealed endometroid adenocarcinoma with less than 50% invasion. The peritoneal implants were found to have a desmoplastic reaction with squamous components. Final pathology confirmed endometrioid endometrial adenocarcinoma FIGO grade 1, with squamous differentiation with less than 50% myometrial invasion, FIGO stage 1A. Background endometrium showed focal complex atypical hyperplasia. Interestingly, the pelvic implants demonstrated a foreign body giant cell reaction around a possible gland as indicated by immunohistochemical staining positive for MOC31, BerEp4, ER and PAX-8. The staining for the DNA mismatch repair (MMR) proteins was intact.

The patient's postoperative course was uncomplicated and after discussion with a multi-disciplinary tumor board, the decision was made for routine surveillance. The patient restarted exogenous testosterone postoperatively.

3. Discussion

According to a 2015 United States Transgender Survey, 1.4 million individuals identify as transgender in the United States. The gender affirmation process for these individuals is variable, with many opting for gender affirming surgery or hormone therapy. In that same survey, results showed that approximately 49% had received gender-affirming hormone therapy(Lane et al., 2018). With increasing numbers of individuals receiving gender confirmation therapy in the United States, research is needed to understand the effects of these therapies.

Amongst transgender men not on exogenous therapy, the risk of endometrial cancer is comparable to their cisgender counterparts(Sterling and Garcia, 2020). Exogenous testosterone has traditionally been the mainstay for gender-affirming hormone therapy in female to male individuals. However, data on long-term effects of testosterone on biologic female pelvic organs are largely confined to retrospective case series. A theoretical risk of endometrial cancer and hyperplasia has been proposed due to the aromatization of testosterone to estrogen, particularly in postmenopausal women. Additionally, the physiologic role of androgens is not entirely understood as androgen receptors are detected in the epithelium and in the stroma of the uterus.

Interestingly, gene expression of post hysterectomy samples of transgender men receiving testosterone therapy showed that neither Ki-67(a nuclear protein that is associated with cellular proliferation), or ZIC2 (a marker of cellular proliferation in endometrial cancer), was upregulated(Perrone et al., 2009). However, retrospective studies have shown a more variable effect of testosterone on the endometrium and uterus. Grimstad et al. concluded that about half of patients on exogenous testosterone will continue to have active endometrium, with the predominate histology proliferative endometrium(Grimstad et al., 2019). In addition, persons on testosterone will continue to have typical uterine pathology such as adenomyosis, leiomyomata, and polyps. Of the four retrospective analyses reported in the literature pertaining to this topic, the duration of testosterone therapy, BMI, and history of bleeding did not correlate with the presence of endometrial hyperplasia or endometrial proliferation(Grynberg et al., 2010; Perrone et al., 2009; Cao et al., 2021; Grimstad et al., 2019; Hawkins et al., 2021).

Based on the limited data available, testosterone does not appear to increase endometrial hyperplasia or carcinoma and is relatively safe in transgender men. To date, only four reported cases of endometrial carcinoma and ten cases of endometrial hyperplasia are reported in the literature(Grynberg et al., 2010; Perrone et al., 2009; Cao et al., 2021; Grimstad et al., 2019; Urban et al., 2011; Jeevananthan and Iyengar, 2021; Bobola et al., 2021; Hawkins et al., 2021; O'Connor et al., 2022). All cases of endometrial carcinoma were diagnosed with late stage endometroid type disease after first presenting with vaginal bleeding. Treatment was adjuvant carboplatin and taxol chemotherapy with pelvic radiation or consideration on consolidation ration therapy. In the case of a 41-year-old patient the decision was made to restart hormonal therapy following completion of chemotherapy due to gender dysphoria that they were experiencing. The delay to re-initiate hormone treatment was due to the risk of cancer recurrence from an increase in circulating estrogen from aromatized testosterone. In contrast to the cases reported in the literature, our patient was diagnosed at an earlier age and stage of disease. Of note, our patient re-initiated hormone therapy

approximately two weeks after surgery.

In summary, we described a rare case of FIGO Stage 1A Grade 1 endometroid endometrial carcinoma in a transgender male. This case also described a rare histological feature, peritoneal implants with a desmoplastic reaction, yet to be reported in the literature in this patient population. Our case highlights the need for transgender men to continue appropriate gynecological care despite the administration of exogenous testosterone due to the risk of endometrial carcinoma. This care includes age-related cervical screening if a cervix is present and breast cancer screening if breast tissue is present. In addition, yearly annual exams are recommended for transgender men who have not undergone surgical removal of pelvic organs (Sterling and Garcia, 2020). Future research is needed to address barriers in providing adequate care for this population.

CRediT authorship contribution statement

Kieran Seay: Visualization, Writing – original draft. **Karin Shih:** Supervision, Writing – review & editing. **Ariel Kredentser:** Writing – review & editing. **Dongling Wu:** Resources, Writing – review & editing. **Elizabeth Schmidt:** Project administration, Supervision, Writing – review & editing.

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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