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Case report

A case of endometrial intraepithelial neoplasia in a transgender man on testosterone therapy

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ABSTRACT

Testosterone is commonly used as gender-affirming therapy to induce masculinization in transmasculine individuals. The effects of testosterone therapy on endometrial tissue are complex, and while some patients experience endometrial atrophy while taking testosterone, others do not. Reports of gynecologic malignancies, and endometrial cancer in particular, in transmasculine patients taking testosterone are extremely rare (Urban et al., May 2011; Jeevananthan and Iyengar, 2021; Agnieszka Bobola, 2021). Here we report a case of endometrial intraepithelial neoplasia in a transgender man taking testosterone.

1. Introduction

Interventions aimed at gender affirmation in transgender patients include changes in social gender expression, psychotherapy to explore and enhance understanding of one's own gender identity, hormone therapy to achieve masculinization or feminization, and surgical removal or reconstruction of sex-related tissues including the genitalia and reproductive organs (Braun et al., Jan. 2017). Many transgender patients use a combination of these approaches to live in their gender identity.

Transgender patients face significant health disparities globally across all income levels, and discrimination and lack of understanding from providers represent a significant barrier to care for this population (Reisner, Jul. 2016; Safer et al., 2016). Transgender men may face additional barriers to accessing gynecologic care given the gendered nature of the specialty. These disparities extend to gynecologic oncology care, and while the available data is lacking, transgender men are thought to experience numerous barriers to appropriate oncologic screening, diagnosis, and treatment (Labanca et al., 2020; Stenzel et al., Dec. 2020).

Data on the risk of gynecologic malignancy in transmasculine individuals is sparse, largely due to the relatively low incidence of these cancers with a lack of large-scale studies in this population. The interaction between sex hormone therapy and carcinogenesis in reproductive tissues remains an open area of investigation. Here we report the case of a transgender man on testosterone therapy who was incidentally found to have endometrial intraepithelial neoplasia at the time of gender-affirming hysterectomy.

2. Case report

A 32-year-old transgender man with gender dysphoria presented for consultation for gender-affirming hysterectomy. He had been taking testosterone for four years and had undergone bilateral mastectomy and male chest reconstruction. He initially became amenorrheic after 6 weeks of testosterone therapy. He later reported significant dysphoria regarding vaginal bleeding which he had experienced prior to adjusting his dose of testosterone. At the time of his initial consultation, he did not complain of any vaginal bleeding or discharge, pelvic pain, hematuria, dysuria, or other symptoms.

He had no significant medical history. His surgical history was notable only for removal of a congenital cataract in childhood and his gender-affirming bilateral mastectomy and chest reconstruction. He had never been pregnant, had no history of gynecologic conditions, and denied use of tobacco, alcohol, or drugs. He had never taken combined oral contraceptive pills. He had no known family history of breast, ovarian, uterine, or colon cancer. His BMI was 22 kg/m^2 and his physical exam was unremarkable; in-office pelvic exam was deferred to the OR for patient comfort. Preoperative complete blood count and basic metabolic panel were within normal limits.

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After discussion of the risks, benefits, and alternatives to surgery, he elected to proceed with a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. He underwent the procedure without major complications and recovered well postoperatively. Pathology was notable for scattered foci of endometrial intraepithelial neoplasia in a background of inactive endometrium (Fig. 1). Immunohistochemistry studies demonstrated intact nuclear expression of mismatch repair proteins, decreasing the likelihood of Lynch syndrome.

3. Discussion

In transmasculine individuals receiving hormone therapy for gender affirmation, androgens like testosterone are used to induce masculinization. The effects of androgen therapy on the endometrium remain unclear. The high prevalence of amenorrhea in transmasculine patients taking testosterone has led to the inference that testosterone, and its highly potent product dihydrotestosterone (DHT, formed by the reduction of testosterone by 5α-reductase), induce endometrial atrophy (Defreyne et al., 2020; Ito et al., Jul. 2016). One study of 267 transgender men in Europe reported amenorrhea in 100% of patients after 18 months of testosterone therapy (Defreyne et al., 2020).

However, several studies have refuted the idea that testosterone therapy uniformly induces endometrial atrophy (Grimstad et al., 2019; Hawkins, May 2021; Cao et al., Jul. 2021). One retrospective study of 94 transgender men who had taken testosterone prior to hysterectomy noted active endometrium in 69.1% of subjects, complex hyperplasia without atypia in one case, and no cases of endometrial cancer (Grimstad et al., 2019). Another study reported similar findings, with 40% of their 81 cases demonstrating proliferative endometrium, as compared with 50% with atrophic endometrium (Hawkins, May 2021). Of note, 74% of patients in the second study were amenorrheic prior to hysterectomy. Taken together, these results suggest that testosterone fails to induce endometrial atrophy in a substantial proportion of patients, and that hyperplasia can develop in the setting of testosterone therapy in rare cases.

The androgenic effects of testosterone therapy on the endometrium are complicated by the interaction of testosterone with epidermal growth factor receptor, activity of which promotes endometrial proliferation. This effect, in combination with increased estradiol levels driven by aromatization of testosterone, is thought to underly the increased risk of endometrial cancer seen in cisgender women with polycystic ovarian syndrome, another hyperandrogenic state (Ito et al., Jul. 2016; Shen et al., Jan. 2015). One study demonstrated increased risk of endometrial cancer in postmenopausal women with high blood concentrations of free testosterone (Allen et al., 2008). It remains unclear whether this increased risk is attributable to the direct action of testosterone itself, to secondary increases in estradiol, or to some other effect related or unrelated to testosterone therapy.

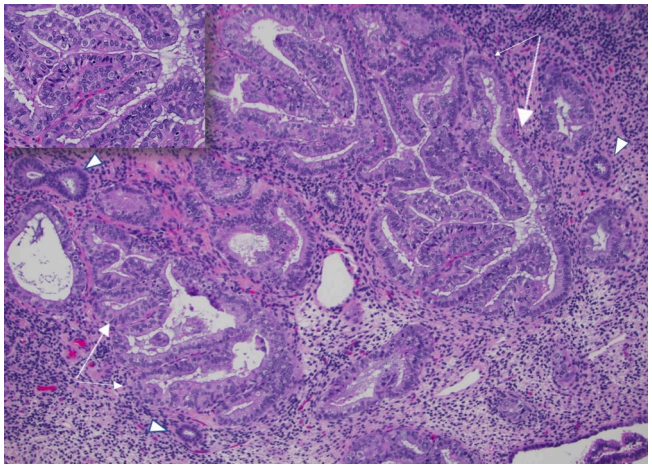

Fig. 1. Endometrial Intraepithelial Neoplasia (EIN)/Atypical Hyperplasia. A 1.5 mm focus of crowded glands with complex architecture and little intervening stroma (Arrows), 10x. Notice the glands are lined by atypical epithelium with round nuclei displaying loss of polarity and prominent nucleoli (insert, top left, 40x), cytologically distinct from background uninvolved glands (arrow heads).

While both of these proposed mechanisms suggest a causal role for testosterone therapy in endometrial carcinogenesis, cases of endometrial cancer in transmasculine individuals on testosterone are exceptionally rare, with only three prior case reports published in the literature. Until 2021, only one such case had ever been reported, and that was in a 51 year old trans man who experienced vaginal bleeding after 7 years of amenorrhea on testosterone therapy (Urban et al., May 2011). He was found to have Stage IIIC grade 2 endometrioid adenocarcinoma and was treated with radical hysterectomy; bilateral salpingo-oophorectomy, lymphadenectomy, and adjuvant carboplatin/paclitaxel. In another case, a 41 year old trans man was found to have stage IIIA low grade endometrioid adenocarcinoma after presenting with vaginal bleeding (Jeevananthan and Iyengar, 2021). The case report does not give the duration of testosterone exposure prior to cancer diagnosis. Interestingly; he had also received anastrazole, an aromatase inhibitor, in addition to testosterone for his gender-affirming hormone therapy prior to diagnosis. Co-administration of anastrazole presumably would have blunted the increased production of estradiol in the setting of exogenous testosterone administration. The final case report describes the diagnosis of endometrial and colon cancer in a trans man with Lynch syndrome (Agnieszka Bobola, 2021).

The case described here represents only the third reported case of non-syndromic endometrial cancer in transgender men taking testosterone therapy. This is the only reported case where the patient was asymptomatic and the diagnosis was incidental, however the other two cases were noted in older patients with considerably more advanced malignancies. Given that our patient lacked risk factors for the development of endometrial cancer, this could suggest that testosterone exposure increased his endometrial cancer risk. However, the currently available data is insufficient to establish a definitive link between testosterone therapy and the development of endometrial cancer. The extremely low incidence of gynecologic cancers in patients receiving testosterone suggests that testosterone is safe for gender affirming therapy. Moreover, if testosterone does exert carcinogenic effects on the endometrium, the duration of testosterone exposure prior to hysterectomy may be too short in most cases to be clinically significant. More work is needed to understand the risk of gynecologic cancer in transgender men, and appropriate cancer screening and surveillance should not be withheld in patients receiving hormone therapy. Vaginal bleeding can be expected for 1–6 months after initiation of testosterone therapy. If bleeding persists after 6 months, further workup should be pursued to identify the cause of the vaginal bleeding and to exclude malignancy.

4. Conclusion

Transgender men taking testosterone therapy are at risk for the development of endometrial cancer and EIN. Abnormal vaginal bleeding should prompt a workup that includes neoplasia in the differential. The risk of malignant endometrial pathology is poorly defined, and larger studies are needed to improve delivery of oncologic care in this population.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contributions

The manuscript was prepared by R.M.O., M.E.S., and B.J.R. Pathology slide and description were contributed by R.B.

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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