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Case report

Androgen receptor expression in low grade serous ovarian cancer; clinical considerations in the diagnosis, treatment and surveillance of disease in a transgender male

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1. Introduction

Low grade serous ovarian cancer is an uncommon subtype of ovarian cancer. It accounts for less than 5% of all cases of ovarian cancer. (Slomovitz et al., 2020) It is a separate entity from high grade serous (HGS) cancer of the ovary. Similar to HGS, patients with low grade serous (LGS) ovarian cancer often present at an advanced stage. Unlike HGS, LGS tumors are slow growing and indolent. They often test positive for mutations in BRAF and/or KRAS genes. (Jordan et al., 2020) LGS tumors are often diffusely positive for PAX-8, ER and WT-1, with variable expression of PR, patchy expression of p16 and wild-type (non-mutated) expression of p53. (Jordan et al., 2020; Fader et al., 2017) AR receptor expression is not routinely performed or reported in the literature, though it may be clinically relevant.

Systemic androgen levels can be elevated in patients with polycystic ovary syndrome (PCOS) and those taking exogenous testosterone for gender affirmation, making AR expression a potentially important biomarker for this population of patients. The treatment of LGS in transgender individuals has not been well described, but consideration should be made for the impact of exogenous hormone use on cancer physiology and treatment, as well as gender dysphoria throughout care and in survivorship. The present case discusses the clinical relevance of androgen receptor expression in a transgender male who was recently diagnosed with low grade serous ovarian cancer.

2. Case report

This is a case of a 19-year-old transgender male who presented to the local emergency department with abdominal pain and bloating, along with anorexia and worsening indigestion for one week.

His past medical history included gastroesophageal reflux disease, anxiety, depression and gender dysphoria. The patient was on weekly IM testosterone injections for one year after undergoing ovarian stimulation and egg retrieval with oocyte cryopreservation. His surgical history was not pertinent. Family history is without report of cancer of the breast, uterus, ovary or colon in three successive generations.

Emergency department CT scan (Fig. 1) revealed a bulky partially cystic and calcified mass within the pelvis. This mass completely enveloped the proximal rectum and distal sigmoid colon. There were multiple peritoneal implants, an umbilical mass, and a dense omental cake. Tumor markers revealed an elevated CA-125 at 720 U/mL, with normal levels of inhibin B, AFP, LDH, CEA and CA19-9.

He underwent a diagnostic and therapeutic paracentesis that demonstrated neoplastic epithelial cells of possible Mullerian origin. Core biopsy of the umbilical soft tissue nodule resulted as LGS carcinoma with immunohistochemistry stains that were positive for CK7, WT-1, PAX8, ER and p16, and wild-type expression of p53. As he identified as a transgender male and with exogenous testosterone exposure, androgen receptor status was assessed by immunohistochemistry and

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was strongly/diffusely positive (Fig. 2). He was recommended to discontinue weekly IM testosterone injections and underwent a primary debulking surgery.

Widespread metastatic disease was identified during surgery. He underwent an uncomplicated *en bloc* resection of the uterus, cervix, bilateral fallopian tubes, ovaries, appendix and total colon, splenectomy, ileocecal resection with an end ileostomy and resection of the umbilical nodule. There was unresectable, residual disease at the porta hepatis that measured greater than one centimeter. This was ablated with the argon beam. His case was reviewed at the gynecologic oncology tumor board with a recommendation for systemic chemotherapy followed by maintenance endocrine therapy, and a referral to radiation oncology was made for stereotactic body radiation (SBRT). He completed three fractions of SBRT at a dose of 2400 cGy to the liver hilum and site of residual disease and six cycles of adjuvant platinum based chemotherapy. He is currently on maintenance endocrine therapy with letrozole 2.5 mg PO daily and is doing well.

3. Discussion

LGS carcinoma of the ovary, fallopian tube and peritoneum are uncommon with limited options for treatment. This case was unique in the fact that the patient presented at a young age and identifies as a transgender male on gender affirming hormone therapy. These unique factors create challenges in the diagnosis, treatment and surveillance of this disease.

LGS tumors are diagnosed in young patients of reproductive age. The average age of diagnosis is the fourth decade, and the treatment of the disease can impact fertility. Fertility desires should be elicited before treatment is initiated and a referral to a fertility expert should be recommended. In this case, our patient had been seen by REI one year prior to the diagnosis and had completed treatment with ovarian stimulation and oocyte retrieval. Imaging at the time of his retrieval was normal. Fertility treatment is thought to be safe as there is insufficient evidence to suggest an increased risk of ovarian cancer. Therefore, it is unlikely that this contributed to the development of disease in this patient. (Kroener et al., 2017; Yin et al., 2019).

At a young age, the treatment of advanced stage low grade tumors with surgery often results in premature menopause. The patient was well counseled on the risks of menopause before treatment initiation. The specific risks include vasomotor symptoms that may affect quality of life, as well as the long term risks of dementia, cardiovascular disease, osteopenia and osteoporosis. Baseline bone mineral density (BMD) testing with central/axial dual-energy x-ray absorptiometry (DXA) will be recommended and this will be repeated every two years while on endocrine therapy. (Shapiro et al., 2019) This recommendation is extrapolated from ASCO guidelines for patients with breast cancer. Further, optimizing bone health with nutrition, exercise and lifestyle will be a focus area following treatment.

Finally the age at the time of diagnosis has prognostic significance. Slomovitz et al reported patients less than 35 years of age at the time of diagnosis, with an elevated body mass index (BMI) (>35 kg/m2) and active tobacco use portend a worse prognosis. However, the single most important variable that impacts outcomes is whether or not an optimal resection can be completed. (Slomovitz et al., 2020) In this case, the patient had a suboptimal resection. While radiation therapy is not typically part of ovarian cancer treatment, it was recommended in this case to reduce the risk associated with residual disease measuring > 1 cm at the porta hepatis and the dysfunction of upstream organs.

While age is a complicating factor in this case, the fact that the patient was undergoing testosterone replacement at the time of diagnosis further complicated management. Testosterone activity is mediated through the androgen receptor. The prevalence of androgen receptor expression in LGS ovarian cancer is unknown. However, it has been shown that androgen receptor gene expression is present on normal human ovaries in the surface epithelium, as well as in some ovarian carcinomas including serous, endometrioid, and mucinous carcinomas, as well as granulosa cell tumors. (Mizushima and Miyamoto, 2019) There is early evidence to suggest that androgen levels and receptor expression may lead to ovarian cancer carcinogenesis and possibly cancer growth in primary cell cultures, but there is limited *in vivo* research as to the functional role of AR and testosterone in tumor progression and effectiveness of antiandrogen therapies (Mizushima and Miyamoto, 2019; Tumolo et al., 1994).

With the expression of AR in normal ovaries and ovarian cancers, there is concern that transgender patients receiving testosterone supplementation could be at risk of ovarian carcinogenesis or tumor progression, though only a few cases of ovarian cancers have been documented in female-to-male transgender patients. Hage *et al* reported two transgender patients: a 45 year old who developed HGS carcinoma after 18 years of hormonal therapy, and a second 38 year old with a serous papillary borderline tumor after one year of hormonal therapy.

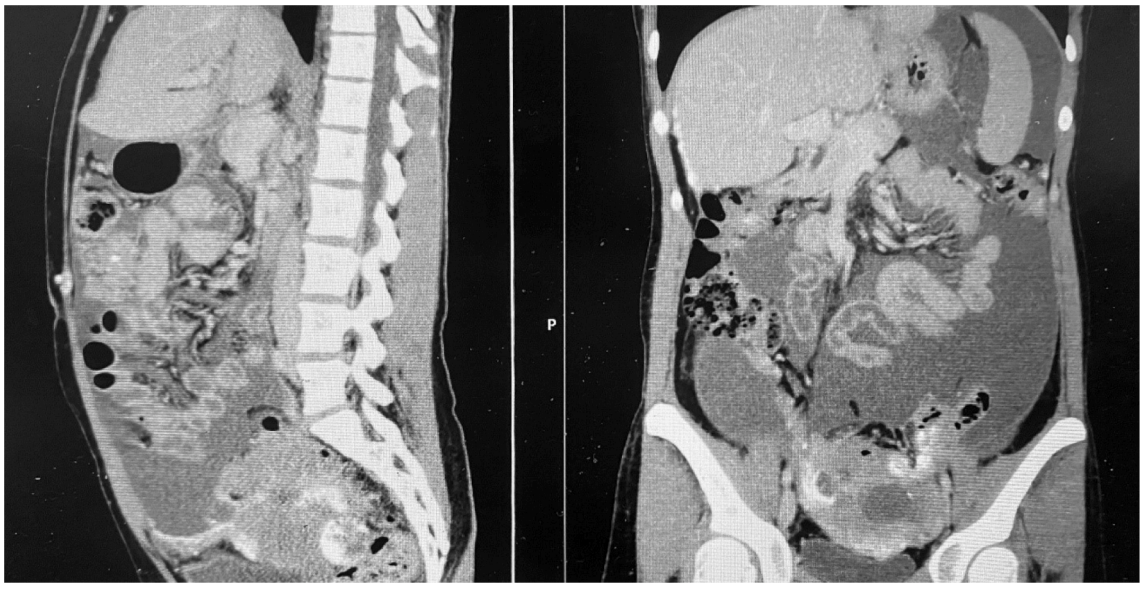

Fig. 1. CT abdomen/pelvis with contrast at the time of diagnosis with calcified pelvic mass and metastatic disease involving portions of the colon, small bowel, peritoneum, omentum and anterior abdominal wall.

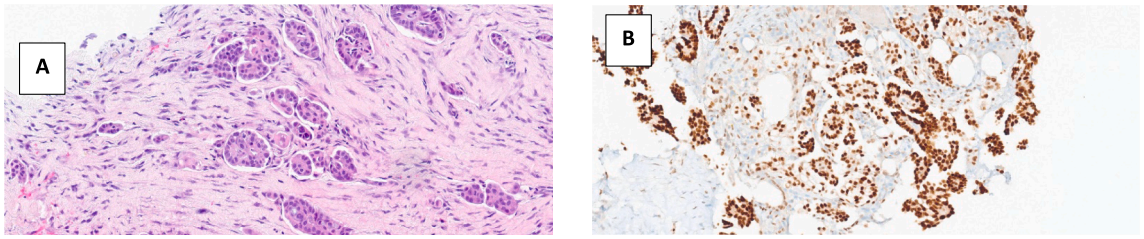

Fig. 2. A) H&E of low grade serous carcinoma of the ovary with uniform populations of small cells with scant cytoplasm and mild to moderate nuclear atypia and B) Diffuse/strong AR immunostain.

(Hage et al., 2000) Dizon *et al* reported a 46 year old patient with a well-differentiated endometroid ovarian carcinoma occurring five years after starting testosterone supplementation. (Dizon et al., 2006).

The role of testosterone and androgen receptors in LGS carcinoma is largely unstudied. Buttarelli *et al* reported "negligible" AR expression in their study of 25 untreated primary LGSOC and 6 micropapillary serous borderline tumors, though the exact percentage of tumors expressing AR was not reported. (Buttarelli et al., 2017) While AR immunoreactive receptor scores were lower than ER and PR, it was not absent in their cases. Additional studies in the expression and functionality of AR in patients with LGS carcinomas are warranted. The effects of increased testosterone levels in transgender patients taking exogenous androgen therapy or even patients with elevated testosterone levels, such as those with obesity or PCOS on carcinogenesis and tumor progression in LGS carcinoma are unknown and further studies are needed.

While this patient's tumor did show strong/diffuse expression of AR by immunohistochemistry, the functionality of the androgen receptor in his disease remains unknown. We do not have a way to test *in vivo* whether the patient's testosterone exposure and strong AR expression are actually driving his tumor progression. However, the patient was counseled on the theoretical risk of testosterone and it was recommended to discontinue its use. Monitoring the impact of discontinuation of hormonal therapy on potential gender dysphoria, anxiety, depression and quality of life has been and will continue to be a focus of his care.

Adjuvant treatment with platinum based chemotherapy followed by endocrine therapy was recommended. A clinical pharmacologist was consulted to determine optimal medication dosing. Gender affirming hormonal therapy can alter physiology and drug metabolism. It is our institutional practice to dose chemotherapy based on the sex assigned at birth if a patient has been on hormonal therapy for less than six months, but to dose based on the affirmed gender if they have been on hormonal therapy for greater than six months. (Webb et al., 2020) For this patient, we dosed based on the affirmed gender.

Surveillance after treatment completion may present an additional challenge in a transgender population related to pelvic exams. An estimated 26–50% of recurrences occur in the pelvis. (Salani et al., 2017) These recurrences are detected in 49% of cases by symptoms alone and in 60% of cases with exams alone. However, physical examination is unlikely to detect extra pelvic disease. (Salani et al., 2011) Current NCCN guidelines recommend a physical exam and CA-125 every 3–6 months. Frequent pelvic exams may not only be uncomfortable, but unacceptable in a patient with gender dysphoria. Shared decision making was used to develop an individualized plan for surveillance with symptom awareness and serial physical exams at his discretion. This plan was implemented in an effort to reduce anxiety, ensure compliance with visits, and maintain his quality of life without compromising oncologic outcomes.

Patient verbal and written consent was obtained for publication.

4. Conclusion

LGS ovarian cancer is an uncommon cancer and one that presents unique challenges in the diagnosis and treatment for the general population. AR expression is not routinely assessed, but it may impact tumor biology and treatment in a select population of patients including transgender males on gender affirming hormonal therapy.

Author contributions

Each author contributed to the review of the case, writing and preparation of the article, and approved the final submission.

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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