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Juvenile granulosa cell tumor in a transgender male with Ollier disease: A case report

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1. Introduction

Sex-cord stromal tumors (SCSTs) account for about 5 % of all ovarian tumors (Beffa et al., 2022). Granulosa cell tumors comprise most of these tumors and include adult and juvenile subtypes. Juvenile granulosa cell tumors (JGCT) are much rarer, consisting of only 5 % of all granulosa cell tumors (Beffa et al., 2022). They typically present before age 30 and produce estradiol, progesterone or androgens, often manifesting clinically as a pseudoprecocious puberty. Given these clinical signs and symptoms, greater than 90 % of JGCTs are Stage 1 at presentation and unilateral (Beffa et al., 2022). Ollier's disease (OD) is a rare benign skeletal disorder that involves the abnormal growth of cartilaginous bone tissue (enchondromas) that can lead to skeletal deformities and fractures (NIH GARD). Certain mutations in IDH1, IDH2 and PTHR1 genes are found in the enchondromas, but the underlying cause of OD is not known (NORD). There have been multiple reports of enchondromas presenting simultaneously with granulosa cell tumors (Zhang et al., 2023). Here, we discuss the rare case of a transgender male on long-term testosterone therapy with OD who develops a JGCT.

2. Case report

A 34 year-old G0 transgender male with OD presented in April 2024 with one month of left lower quadrant pain. He first noticed the pain after falling out of bed, with the pain gradually worsening with intermittent spikes, moderately controlled with acetaminophen and ibuprofen. He denied any fever or chills, vaginal bleeding or vaginal discharge, but did report early satiety and bloating. He otherwise reported being amenorrheic, other than having two cycles within the year following a change in his testosterone formulation, and when he is late with his testosterone injections. Normal pap smear and normal mammogram were reported 1.5 years prior to presentation.

The patient was originally diagnosed with OD at 1 year of age at an outside institution which was originally managed with an ankle–foot orthosis brace, followed by a Lizeroff rod placement due to leg shortening, subsequently followed by a right below-the-knee amputation after a spontaneous femoral fracture due to an enchondroma. He was then referred to orthopedic oncology at our institution in 2004 at age 16 due to concern for malignant transformation of a right-sided distal femur enchondroma. His presenting enchondroma was deemed benign and he was initially managed conservatively and then underwent a right distal femur and proximal tibia resection with an endoprosthetic reconstruction in December 2011 with pathology demonstrating a low-grade chondrosarcoma. Subsequent imaging demonstrated overall stable enchondromatosis, with most recent PET CT in 2016. He was last seen by orthopedic oncology in November 2019 due to a fracture at his right tibia stump which was managed conservatively with return of weight-bearing status on his prosthesis, with no further evidence of malignant transformation at that time.

Regarding his gender dysphoria, the patient began transitioning to male phenotype in February 2016. He was started on 200 mg intramuscular testosterone injections every 2 weeks for nearly 5 years, then

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decreased his dosing to 160 mg every 2 weeks on subcutaneous injections. Then in 2022, he trialed testosterone transdermal 1.62 % gel 40.5 mg daily in appliance to his upper arms and shoulders due to anxiety over the injections. He used the gel for six months but he was not consistent with daily application and he did not think it was as effective as the injections so he restarted the 160 mg subcutaneous injections every 2 weeks from January to March 2023. His latest testosterone level in 5/2022 was elevated at 567 NG/dL. Prior to starting testosterone treatments in 2016, he reported having mood changes and acne with regular monthly menstrual cycles and no signs of hyperandrogenism. Other significant medical history includes anxiety and depression on buspirone and escitalopram, and obesity with BMI 48. Surgical history includes the above orthopedic right lower extremity surgeries as well as an appendectomy.

Upon presentation in April 2023, physical exam findings were consistent with abdominal distension and tenderness but no guarding or rebound tenderness. Lab findings were significant for an elevated CA-125 at 198 U/mL, LDH at 426 U/L, inhibin A of 473 pg/mL and inhibin B of 23,419 pg/mL. A CT of the chest, abdomen and pelvis was significant for a 15 cm cystic and solid right ovarian mass, 4.9 cm uterine fundal fibroid, and endometrial thickness of 1.4 cm (Fig. 1). Heterogeneous stranding was also seen within the omentum with a trace right pleural effusion, and a right 1.5 cm pleural nodule seen at the lung base. Pelvic ultrasound confirmed a 20 cm cystic and solid right adnexal mass with a 1.7 cm endometrial stripe with cystic changes observed in the endometrium. His pain was controlled with oral medications, and he was discharged from the hospital in stable condition with outpatient follow-up. Physical exam findings at the one-week follow-up were still significant for abdominal distension and tenderness. Pelvic exam confirmed the abdominal mass but the cervix appeared normal and the mass was not fixed in the pelvis. Pap smear was obtained with findings of atypical endometrial cells and HPV 16 positive. Endometrial biopsy was also obtained with final pathology of fragmented endometrium with foci of non-atypical hyperplasia.

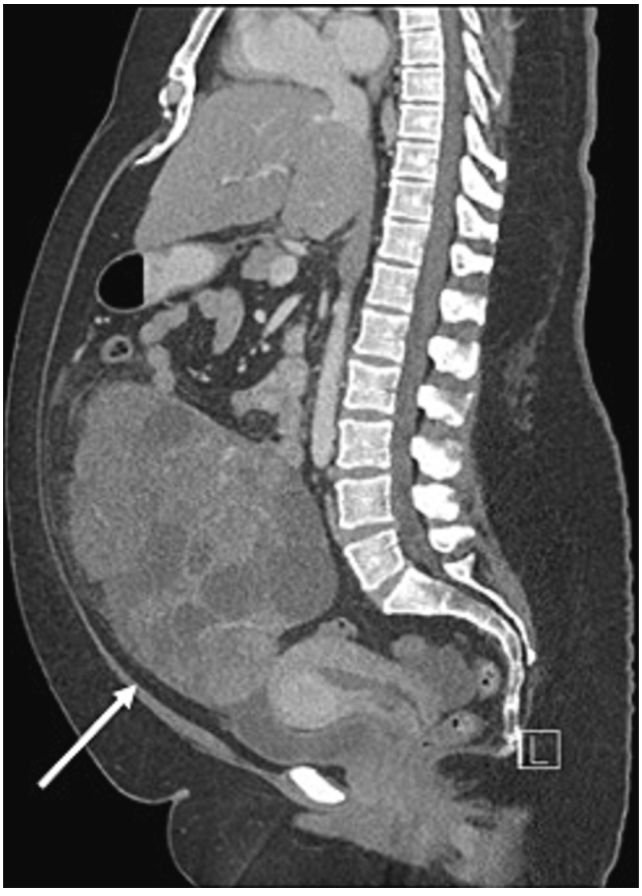

Fig. 1. Sagittal CT view of original tumor prior to resection: 15 cm cystic and solid right ovarian mass.

A multidisciplinary conference was held and given high suspicion for a granulosa cell tumor, the recommendation was to proceed with primary surgical debulking. In May 2023, the patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and radical optimal tumor reductive surgery to no gross residual disease. Bilateral ureteral stents were placed preoperatively to aid in ureteral identification and removed at the conclusion of the surgery. Operative findings included a large right ovarian mass weighing 3340 g, normal left ovary, normal bilateral fallopian tubes, a small uterine fibroid with otherwise normal uterus, omental adhesions to the right ovarian mass, and otherwise no visible disease seen in the abdomen or pelvis, including no diaphragmatic disease. His immediate postoperative course was overall unremarkable with a mild ileus that resolved with conservative management, and an incidental leukocytosis without evidence of systemic infection. He was discharged on postoperative day 4 with prophylaxis enoxaparin sodium for 28 days.

The final pathology demonstrated a Stage IA Juvenile granulosa cell tumor with tumor confined to the right ovary (supportive H&E stains are shown in Figs. 2 and 3). The uterus and cervix returned with small focus of atypical endometrial hyperplasia in a background of disordered proliferative endometrium, uterine leiomyoma with degenerative and apoplectic changes, and uterine cervix with Nabothian cysts. Omentum was negative for malignancy. Immunohistochemistry stains on the ovarian tumor were weakly to moderately positive for estrogen receptor (40 %), moderately to strongly positive for progesterone receptor (90 %), and strongly positive for androgen receptor (>90 %).

At the time of his postoperative visit 4 weeks after surgery, the patient was overall doing well. Our institutional tumor board recommended IR biopsy of his previously seen pleural nodule, which spontaneously regressed at time of the planned procedure, and he has no other evidence of metastatic disease. Now four months post-surgery, his testosterone levels are significantly reduced at 31 NG/dL, and his estradiol level is at 8 pg/mL. He reports feeling more “delicate” than he has been in many years, more sensitive to crying and mood fluctuations. He still desires top surgery and to be restarted on testosterone therapy soon. Ongoing plan is 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.

3. Discussion

Here, we present the case of a transgender male on long-term testosterone therapy, with a history of OD, who developed a JGCT. The association of OD and JGCT dates back to the 1980s (Tamimi and Bolen, 1984; Velasco-Oses et al., 1988). While the pathogenesis is not clearly known, the leading thought is that both OD and JGCT arise from generalized mesodermal dysplasia (Tamimi and Bolen, 1984; Velasco-Oses et al., 1988). This is supported embryologically given that the lateral plate mesoderm forms the long bones, and the adjacent intermediate mesoderm forms the gonads. Several studies have also identified the same mutation in Isocitrate dehydrogenase 1 (IDH1) detected in both the enchondroma and JGCT (Littrell et al., 2023; Zhang et al., 2023). A single point mutation in the IDH1 protein is likely involved in the pathogenesis of cartilage tumors, where a high association is observed with the hypermethylation and downregulation of certain genes (Pansuriya et al., 2011).

JGCTs typically produce an over-abundance of estrogens but on rare occasions produce androgens. This patient was already taking exogenous testosterone at the time of diagnosis and no hormonal labs were obtained at the time of presentation. His latest testosterone levels were obtained nearly one year prior to presentation, and they were likely

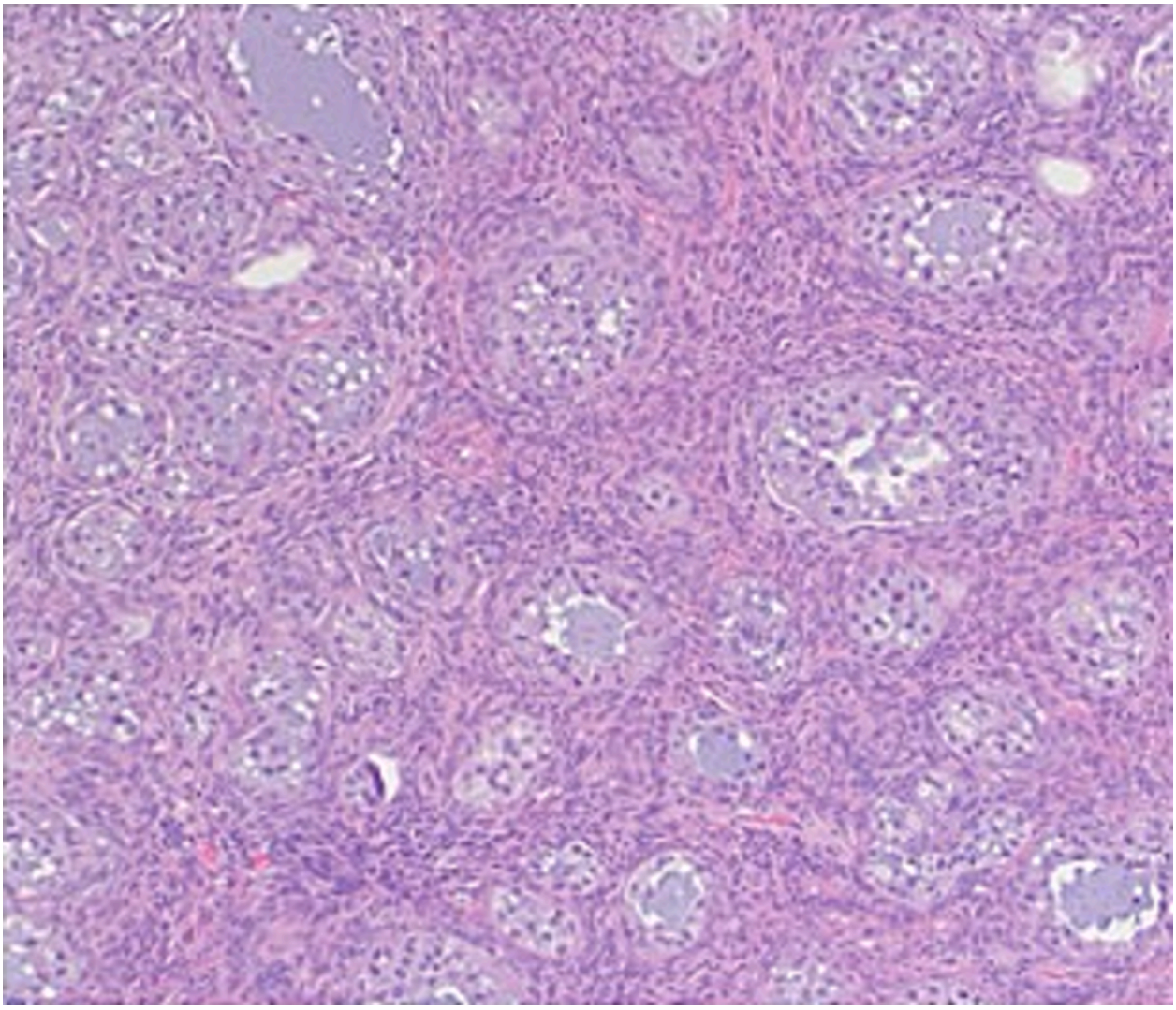

Fig. 2. Juvenile Granulosa cell Tumor with typical follicle-like spaces and basophilic secretions.

elevated for iatrogenic reasons.

To date, there has been one other reported case of gender dysphoria in a patient with JGCT (Kwiatkowska et al., 2020). This patient was diagnosed at the age of 17 with an androgen-producing JGCT. The patient was initially treated with removal of the folliculoma in the left ovary but 9 months later there was a recurrence of a 7 cm mass in the same ovary. During this interval growth, the patient had developing thoughts of gender dysphoria and requested for a gender-affirming total hysterectomy and bilateral salpingo-oophorectomy but the patient's parents declined the surgery and instead, a unilateral salpingo-oophrectomy was performed. Given that two days after the surgery the patient's testosterone levels significantly decreased, the authors suggest that the tumor may have played a role in his gender dysphoria. The patient in our case, however, did not have signs of androgen upregulation until he started taking testosterone injections 7 years prior to presentation of his JGCT and abdominal imaging performed that year further confirmed no intra-abdominal masses. Thus, it is unlikely that the tumor was present at the time of his gender-affirming care, and therefore, not contributory to his gender dysphoria.

There is in vitro evidence to suggest that ovarian cancers are fueled by estrogens and androgens, especially in sex-cord stromal tumors (Modugno et al., 2012). In our patient's case, his tumor staining was strongly positive for both progesterone receptor and androgen receptor. Given these findings, the question remains if his exogenous testosterone therapy contributed to the growth of the JGCT, and as such, if his testosterone therapy should be continued as part of his gender-affirming care or if this may contribute to a higher risk of recurrence. Given the unusual nature of his presentation and the paucity of evidence regarding best practice in this case, we have recommended that he discontinue testosterone therapy for now.

4. Conclusion

To our knowledge, this is the first case of a patient with JGCT and Ollier disease who was simultaneously undergoing testosterone treatments as part of his gender-affirming care. Providers should consider prescreening for hormonally responsive medical conditions.

CRediT authorship contribution statement

Brandon I. Ing: Conceptualization, Investigation, Writing – original draft, Visualization. **Sarah P. Huepenbecker:** Conceptualization, Investigation, Writing – review & editing, Resources. **Nadia Hameed:** Resources, Visualization. **Karen H. Lu:** Investigation, Writing – review & editing, Supervision, Funding acquisition.

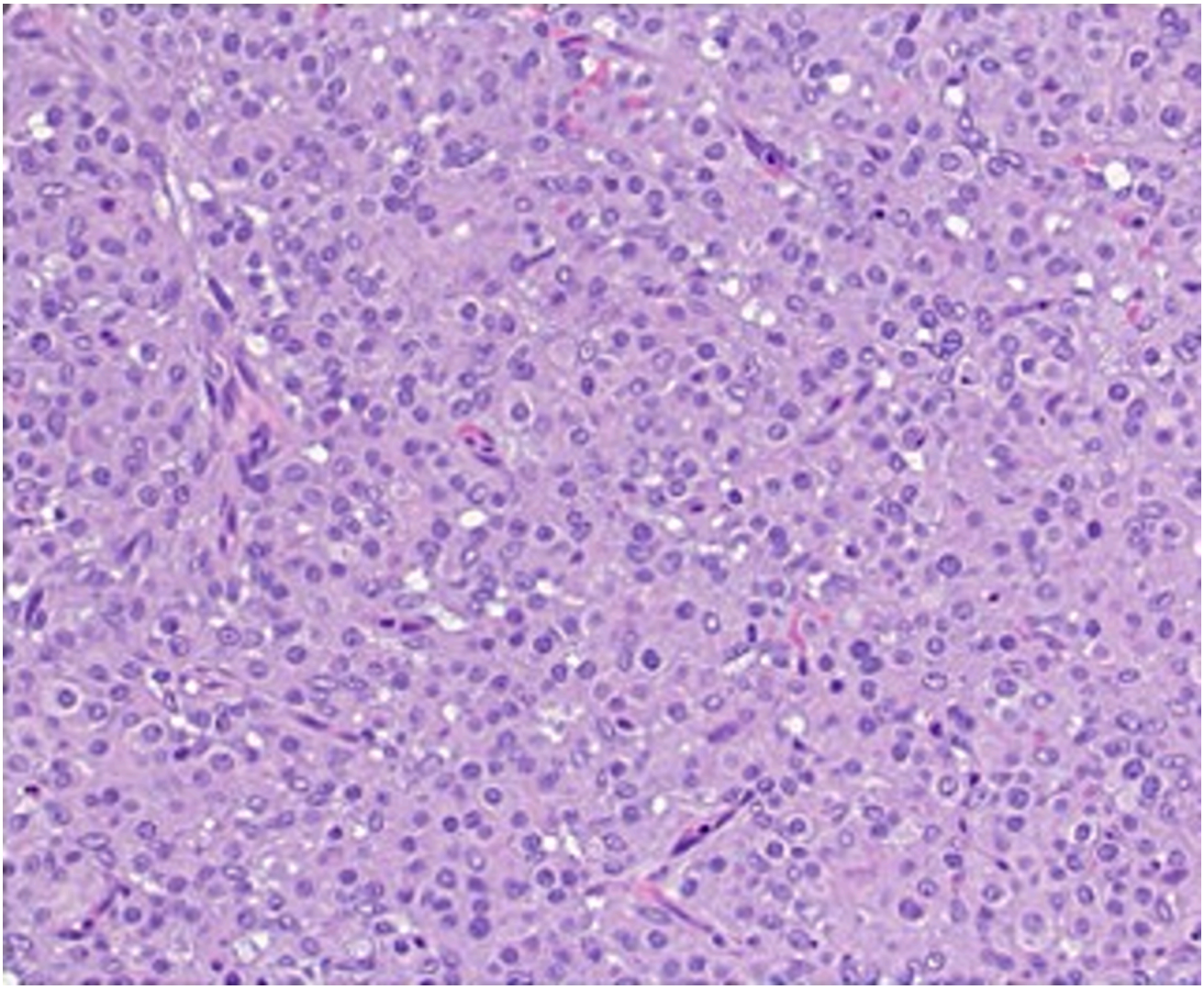

Fig. 3. Juvenile Granulosa cell tumor composed of luteinized tumor cells arranged in solid/nodular pattern.

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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