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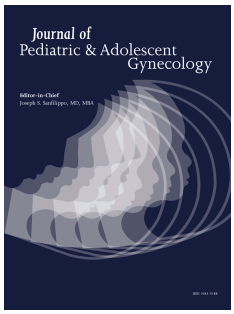

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PII: S1083-3188(20)30295-3

DOI: https://doi.org/10.1016/j.jpag.2020.08.001

Reference: PEDADO 2532

To appear in: *Journal of Pediatric and Adolescent Gynecology*

Received Date: 24 April 2020

Revised Date: 10 July 2020

Accepted Date: 2 August 2020

Please cite this article as: Schnuckle E, Williamson A, Carpentieri D, Taylor S, Ovarian sex cord stromal tumor, steroid cell, NOS in an adolescent: a case report, *Journal of Pediatric and Adolescent Gynecology* (2020), doi: https://doi.org/10.1016/j.jpag.2020.08.001.

Ovarian sex cord stromal tumor, steroid cell, NOS in an adolescent: a case report

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Presented at:
NASPAG Annual Clinical and Research Meeting
Toronto, Canada
April 7-9, 2016

Word Counts:
Abstract: 130 words
Main Text: 1,692 words

Abstract

Background

Ovarian steroid cell tumor, NOS is a rare type of sex cord stromal tumor, which often presents with androgenic symptoms and has a high frequency of malignancy.

Case

This is a case of a 14-year-old Native American girl who presented with acne, amenorrhea, and virilization was found to have a 2.9 cm solid ovarian mass. Initial pathology revealed steroid appearing cells with round nuclei, clear/vacuolated cytoplasm and a low mitotic index. Final diagnosis was ovarian steroid cell tumor, NOS Stage IA and a subsequent laparoscopic left salpingo-oophorectomy was performed. No tumor recurrence was noted 2 years after her initial diagnosis.

Summary and Conclusion

Long-term data on these tumors is limited; however, malignancy, recurrence, and death have been reported. This suggests that close follow-up is essential for appropriate management.

Keywords: sex cord stromal tumor, steroid cell tumor, virilization, androgen, adolescent, salpingo-oophorectomy, case report

Introduction

Ovarian steroid cell tumors are a rare type of sex cord stromal tumor and the majority are classified as not otherwise specified (NOS). Sex cord stromal tumors makeup less than 0.1% of all ovarian tumors.[1] Steroid cell tumors can be classified into three major categories: stromal luteoma that arise from ovarian stromal tissue, Leydig cell tumors that arise from hilar Leydig cells, and steroid cell tumors, not otherwise specified (NOS) that arise from an unknown location.[1,2] Leydig cell tumors are identified by the presence Reinke crystals and may be present within the ovarian hilus (hilus cell tumor) or the ovarian stroma (non-hilus cell type).[3] Tumors of the steroid cell type with an unidentifiable origin that do not contain Reinke crystals are designated as sex cord stromal tumor, steroid cell, NOS.[2] These tumors can present at any age, often with androgenic symptoms, and have a high incidence of malignancy. Appropriate pathological evaluation, staging, and treatment of these tumors is critical.

Case

A 14-year-old Native American female presented to the adolescent gynecology clinic with 1 year of amenorrhea, worsening facial acne, and a husky voice. Menarche occurred at age 11 and she reported regular monthly cycles for 1.5 years. Her periods subsequently became irregular and ultimately resulted in amenorrhea of 1-year duration. Her facial acne had been worsening over the last year and her pediatrician had noticed a deepening in her voice over the past 6 months. She denied abnormal hair growth, chest or back acne, and abdominal symptoms. She did not shave or wax. She had never been sexually active. She denied any significant past medical or surgical history. Her family history was significant for a paternal family history of acne and a maternal aunt who died of an unknown type of ovarian cancer at age 25.

Physical exam showed an obese female with BMI 35.5 kg/m^2 (99%tile). Blood pressure was 118/85. Significant exam findings included a deep voice, severe cystic facial acne, and acanthosis nigricans of the neck, axilla, and groin. No abnormal facial hair or body hair was noted. No moon face, buffalo hump, or skin striae were noted. Abdominal exam demonstrated no palpable masses. Breast exam demonstrated Tanner stage 4 breast development and no nipple discharge and her external genitalia demonstrated Tanner stage 4 pubic hair with mild clitoromegaly noted. Polycystic ovarian syndrome (PCOS) was considered in the differential diagnosis due to obesity, acne, and acanthosis nigricans. However, the deep voice and clitoromegaly were worrisome for an androgen producing tumor and additional imaging and labs were performed. Late onset congenital adrenal hyperplasia and Cushing syndrome was also considered in the differential diagnosis.

Laboratory data was obtained by her primary care physician and endocrinologist prior to her visit with gynecology and she was noted to have an elevated testosterone at 177 ng/dl and an elevated androstenedione at 451 ng/dl. Additional tumor markers were negative (Table 1).

A pelvic ultrasound showed a normal uterus and ovaries bilaterally. A CT scan of the abdomen and pelvis revealed a 2.9 cm solid mass in the left ovary. The right ovary appeared normal and there was no free fluid, or lymphadenopathy noted.

An exam under anesthesia revealed clitoromegaly with a clitoral gans width of 8 mm and a total clitoral length of 25 mm. Laparoscopy revealed a suspicious, solid, spongy, yellow-orange mass

in the left ovary (Figure 1). A portion of the mass was sent for intraoperative pathology consultation and a diagnosis of, “ovarian tumor; rule out sex cord-stromal tumor,” was delivered. Due to the unclear nature of the mass, only the mass was removed, and the left ovary was preserved. Pathology received a 6.0g, 3.2 cm x2.1 cm x1.8 cm aggregate of golden orange to hemorrhagic, disrupted, rubbery tissue with similar variegated cut surfaces. Permanent histology revealed ovarian tissue involved by a proliferation of steroid-appearing cells with round nuclei and clear/vacuolated cytoplasm in a nested pattern. Necrosis was absent and lesional cells revealed low mitotic activity (<1 per high power field). Immunohistochemical investigation of the aberrant cells demonstrated reactivity with calretinin and inhibin; the cells were negative for epithelial membrane antigen, broad-spectrum cytokeratin, chromogranin and Melan-A (Figure 2). Given the clinical and pathological features, a final diagnosis of sex cord-stromal tumor, steroid cell, NOS, was rendered. Pelvic washings were negative for malignancy.

She was referred to pediatric oncology and a CT scan of the chest, abdomen, and pelvis was performed. Pertinent findings included fatty liver and no residual ovarian masses. The tumor was designated Stage IA and subsequent laparoscopic left salpingo-oophorectomy was performed two months after the initial operation when the final pathologic diagnosis was confirmed. No residual tumor was identified in the ovary, the fallopian tube, or the pelvic washings.

At her 6-week follow-up appointment, she reported improvement in her voice and acne and she had had a spontaneous menses. Her postoperative testosterone level was 28 ng/dl. Since the initial tumor was not visible on ultrasound, oncology recommended CT surveillance every 3 months for the first year, every 6 months for the following year, then annually for 5 years.

Unfortunately, follow-up was limited as the patient lives in a remote area with limited access to medical care. At her 2-year follow-up appointment, she reported no symptoms and regular menses. CT scan 2 years post-surgery showed no evidence of recurrence and she remained asymptomatic. Testosterone levels were normal. The patient has been lost to further follow-up.

Summary and Conclusions

The largest study of these tumors to date, by Hayes and Scully, described 63 cases and found that the not otherwise specified (NOS) type made up 56% of the steroid cell tumor cases. In this series, steroid cell tumor, NOS presented with androgen excess in 56% of cases and 43% were found to be malignant.[1]

Histologically, these tumors demonstrate monomorphic, round to polygonal cells arranged in nests. The tumor cells have clear to vacuolated to eosinophilic cytoplasm with clearly defined cell borders. The nuclei are round with a fine chromatin pattern and inconspicuous mitotic figures. The appearance of these cells allows for a differential diagnosis that includes other steroid secreting cells such as lutein cells, Leydig cells, and adrenal cortical cells.[1] In a study by Deavers, the two most useful immunohistochemical markers for histological diagnosis of steroid cell tumors are calretinin and inhibin, with calretinin showing greater sensitivity than inhibin.[4] Calretinin stained 60% to 90% of the tumor cells studied whereas inhibin stained <5% to >90% of the cells in the same tumors.[4] The tumor in this case report stained positively for both markers. It is important to remember that inhibin has been reported in renal cell carcinoma, adrenal cortical carcinoma, and ovarian clear cell carcinoma.[4] Calretinin may also be positive in renal cell carcinoma, and adrenal cortical neoplasms as well.[4]

Hayes and Scully report several features that correlate strongly with malignant behavior. These include 2 or more mitotic figures per 10 high-power fields (92% malignant), diameter of 7 cm or more (78% malignant), hemorrhage (77% malignant), and grade 2 or 3 nuclear atypia (64% malignant)[1]. This case did not exhibit any of these features and, thus, had a low probability of malignancy. Hayes and Scully have the largest series of cases and follow up data was available for 50 patients. Twenty-four patients had tumors designated "probably benign, defined as no evidence of spread beyond the ovary within 3 years or more postoperatively." Eighteen patients had a tumor that was clinically malignant and 14 of these patients died of their disease. Of note, 4 of these patients had recurrences five years after the first operation. Two were as far removed as 15 and 19 years after their initial diagnosis. Therefore, due to the limited knowledge of these tumor's long term behavior, the literature still suggests a need for close monitoring over several years to ensure that no recurrence or malignant transformation occurs.

An interesting aspect of this case is the non-visualization of the tumor on ultrasound. National radiology organizations typically recommend radiation exposure that follow the As Low As Reasonably Achievable (ALARA) approach.[5] Of note, this tumor did not contain any cystic components which would normally be easily identified on pelvic ultrasound. Successful ultrasound imaging is dependent on tissue density and compressibility. If the compressibility differences (how hard the sonographer has to push on the mass) cancels out the density differences, the tumor will not be visible on ultrasound imaging. In contrast, CT depends on the tissue density and the atomic number. In this case, the ovary and the tumor had similar atomic numbers, but the density differences between the tumor and surrounding ovary were different

which allowed for visualization of the mass. Fat measures -130 to -70 HU on CT scan, while fluids measure 0-30 HU, and muscle and soft tissue measures 40-60 HU.[6] It is this difference in density that allowed the tumor to be visualized on CT scan. Several factors were considered in determining the mode of follow-up imaging. Future fertility risks were evaluated and the necessary dose of radiation to cause infertility in the youngest most sensitive populations is approximately 6 Gy. The dose to the ovaries from a CT scan was calculated by the radiologist to be less than 0.01 mGy and serial CT scans was deemed not to be a factor in her future fertility. The possibility of follow-up MRIs was also considered, however, the patient lives in a remote area where MRI is not readily available. When the risks and benefits of different imaging modalities were evaluated, the ultimate decision was to proceed with serial CT scans.

The case reported here serves as an important example of a very rare ovarian tumor in an adolescent girl. A key strength of this report is the discussion of a unique tumor presentation and the pathology description. Limitations include a lack of medical knowledge of this tumor and this patient's loss to follow-up. Symptoms of androgen excess in an adolescent, particularly in cases of virilization, should not be overlooked. Androgen producing tumors should be included in the differential diagnosis and appropriate imaging and evaluation should be performed to ensure the correct diagnosis and treatment.

Disclosure

The authors of this report have no conflicts of interest to disclose, financial or otherwise.

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Figure 1: Intraoperative laparoscopic images of left ovary (1A) and the yellow-orange tumor dissected from the ovarian stroma (1B-C).

Figure 2: Scanning microscopy (2A) revealed fragmented tissue with focal, recognizable ovarian follicles (arrows) adjacent to disrupted tumor (star – hematoxylin and eosin [H&E] x 20). Higher magnification (2B) of the tumor cells showed monomorphic, round to polygonal

cells arranged in nests. The tumor cells have clear to vacuolated to eosinophilic cytoplasm with distinct cell borders. Lesional nuclei were round with a fine chromatin pattern with inconspicuous mitotic figures (<1 per 10 high powered fields – H&E x 100). When subjected to immunohistochemical staining, the tumor cells revealed diffuse reactivity with calretinin (2C) and inhibin (2D) supporting the clinical and pathological findings (each x 100).

Table 1: Laboratory results and tumor markers.

Hormone and Tumor Marker Levels			
Hormone/Marker	**Pre-operative**	**Post-operative**	**Normal Values**
Glucose	98 mg/dl		65-105 mg/dl
HbA1c	7%		4.8-5.6%
TSH	3.000 µIU/ml		0.450-4.500 µIU/ml
Prolactin	11.1 ng/ml		4.8 -23.3 ng/ml
DHEA	173 ng/dl		0-318 ng/dl
FSH	2.9 IU/L	6.0 IU/L	0.7-12.8 IU/L Tanner 4
LH	2.0 IU/L	6.8 IU/L	0.5- 26.3 IU/L Tanner 4
Estradiol	42 pg/ml		12.5-166 pg/ml follicular
Total Testosterone	177 ng/dl	28 ng/dl	<3-27 ng/dl Tanner 4
Free Testosterone	43.6 pg/ml	8.2 pg/ml	0.5-3.9 pg/ml 14-17.9yrs
Androstenedione	451 ng/dl		77-225 ng/dl Tanner 4
17-hydroxyprogesterone	78 mIU/ml		36-200 mIU/ml Tanner 4
LDH	216 IU/L	244 IU/L	81-234 U/L
hCG	<1 mIU/ml	<1 mIU/ml	<4 mIU/ml
AFP	1.7 ng/ml	1.6 ng/ml	≤8.7 ng/ml
CA-125	6 U/ml		≤35 U/ml
CA-19-9	7 U/ml		≤35 U/ml
Inhibin A	5 pg/ml	3.2 pg/ml	<98 pg/ml
Inhibin B	24 pg/ml	36 pg/ml	<123 pg/ml 14-17.9yrs