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Ovarian steroid cell tumor "not otherwise specified" in a reproductive-aged female presenting with abnormal uterine bleeding and virilization: A case report

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Abstract:

Steroid cell tumors occur in <0.1% of all ovarian tumors, and steroid cell tumors, not otherwise specified occur in 80% of those steroid cell tumor cases. In the Philippines, there is only one published case of a steroid cell tumor, not otherwise specified. This is a case of a 25-year-old nulligravid, who manifested with heavy menstrual bleeding accompanied by hirsutism, and deepening of the voice. Ultrasound revealed the left ovary with a well-circumscribed, hypoechoic solid mass, measuring 36.8 mm × 34 mm × 32.1 mm with benign features on the International Ovarian Tumor Analysis. The patient underwent a left salpingo-oophorectomy with frozen section. Final histopathology showed a steroid cell tumor, not otherwise specified. Prompt surveillance and increasing awareness of steroid cell tumors, especially those that manifest with abnormal uterine bleeding and virilization, may initiate prompt and proper management that can have an impact on the quality of life of the patient.

Keywords:

Abnormal uterine bleeding, heavy menstrual bleeding, hirsutism, salpingo-oophorectomy, sex cord-gonadal stromal tumor

Introduction

According to the more recent 2020 World Health Organization (WHO) Classification of Female Genital Tumours, what used to be termed Ovarian Steroid Cell Tumor Not Otherwise Specified (SCT-NOS) is now designated as an Ovarian Steroid Cell Tumors (SCT), and it is under the general category of Sex Cord Stromal Tumors – Pure Stromal Tumors.[1] There are three main categories of Sex Cord Stromal Tumors: Pure Stromal Tumors, Pure Sex Cord Stromal Tumors, and Mixed Sex Cord Stromal Tumors. Steroid cell tumors occur in <0.1% of all ovarian tumors.[1,2] About 50% of patients present with androgenic symptoms.[1]

To date, the first and so far only published case of an ovarian steroid cell tumor not otherwise specified occurring in a Filipino female was reported by Andres *et al.* in 2014.[3] It was a case of a 46-year-old nulligravid presenting with problematic defeminization and virilizing symptoms. We present a case of an ovarian steroid cell tumor not otherwise specified in a 25-year-old, Filipino nulligravid who sought consult at our institution because of abnormal uterine bleeding rather than the usual androgenic symptoms.

Case Report

We present a case of a 25-year-old Filipino nulligravid who has been diagnosed

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with polycystic ovarian syndrome since 2018 and type II diabetes mellitus since 2019. She was started on metformin 500 mg/tab, taking one tab once a day, but the patient eventually lost to follow-up. Two years before the consultation, she experienced an irregular menstrual cycle with an interval of 60 days. A transrectal ultrasound revealed bilateral polycystic ovaries. The patient was then prescribed drospirenone + ethinyl estradiol 3 mg/0.03 mg, with instructions to take one tab orally once a day, to which she adhered for one year and achieved a regular menstrual cycle. However, one year before the consultation, the patient discontinued this medication and subsequently experienced a recurrence of irregular menstrual cycles. Five months prior to the consultation, she did not have menstruation for 3 months. Two months before the consultation, she noted heavy menstrual bleeding, amounting to four fully soaked diapers, accompanied by persistent dysmenorrhea graded 10/10, breast tenderness, and bloating. The patient denies urinary and bowel symptoms, weakness, easy fatigability, palpitations, and significant weight loss. The heavy menstrual bleeding prompted a consultation at the hospital. Review of systems was generally unremarkable.

She has a family history of breast cancer from her paternal grandmother and cousin, and ovarian cancer from her paternal grandmother. She is a 1.4-pack-year smoker, and nonalcoholic beverage drinker, with no illicit drug use.

Physical examination showed low pitched female voice, stable vital signs, body mass index of 34.9 (Obese Class I), pink palpebral conjunctivae, hirsutism with a Ferriman-Gallwey hirsutism score of 15, no moon facies, no cervical lymphadenopathy, no buffalo hump, adynamic precordium with regular rate and rhythm. Breast exam showed symmetric breast, no discoloration and dimpling, no nipple discharge, no tenderness, and no palpable mass. The abdomen was flabby with no striae, soft with direct tenderness at the left lower quadrant, tympanitic on all quadrants, and no palpable mass. There were no palpable inguinal lymph nodes.

Transrectal and transabdominal ultrasound revealed an anteverted-sized uterus, thin and intact endometrium, normal right ovary, ovarian new growth, left with benign features by International Ovarian Tumor Analysis (IOTA) [Figure 1]. Magnetic Resonance Imaging revealed a well-defined heterogeneous mass arising from the left ovary with mild heterogeneous enhancement. The mass measured 33.0 mm × 37.0 mm × 38.0 mm (anteroposterior, transverse, and craniocaudal dimensions) with no enlarged lymph nodes and no ascites [Figure 2]. The remaining visualized organs were normal. The patient was advised exploratory laparotomy with frozen section, hence admission.

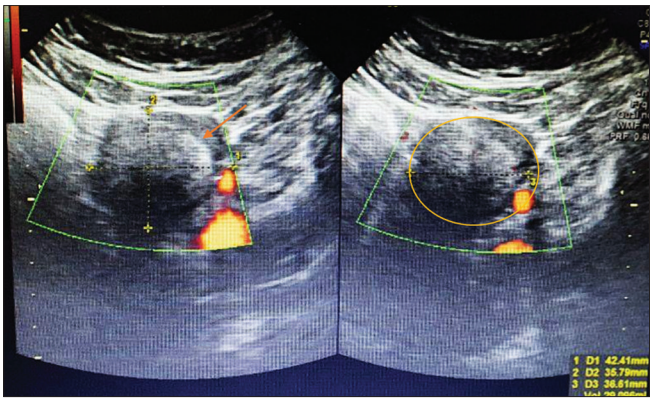

Figure 1: Transvaginal ultrasound showing the left ovary (arrow) measuring 42.4 x 35.1 x 36.6mm (Volume = 29.0 cc) with few small follicles and a well-circumscribed, hypoechoic solid mass that has no color flow (B5) measuring 36.8 x 34.0 x 32.1mm (Volume = 21.0 cc)

During exploratory laparotomy, the left ovary measured approximately 4.0 cm × 3.0 cm × 3.0 cm, and no ascitic fluid was observed. The other organs were found to be normal. A left salpingo-oophorectomy was performed. Grossly, the left ovary was characterized as cream tan and glistening, with intact mucosa measuring 4.5 cm × 3.5 cm × 3.0 cm. Upon sectioning, it revealed a yellow, soft to firm, lobulated mass that occupied the entire ovary and was abutting the serosal surface, measuring 3.5 cm × 3.0 cm × 2.0 cm. The specimen was sent for a frozen section, which indicated a "sex cord-stromal tumor to consider thecoma." Microscopy showed solid aggregates of cells with occasional nests. Tumor cells were polygonal, with granular eosinophilic cytoplasm and clear intracytoplasmic vacuoles. No Reinke crystals, nuclear atypia, hemorrhage, or mitosis were detected. The final histopathologic diagnosis was "steroid cell tumor, not otherwise specified" [Figure 3]. Postoperatively, the patient had an unremarkable hospital stay and was subsequently discharged on the 4th postoperative day.

Four months postoperation, she claims resolution of symptoms such as irregularity in the menstrual cycle, bloatedness, and hypogastric pain. She also noted improvement on her hirsutism described as a decrease in hair and a deepening of voice described as being higher in pitch. The current Ferriman-Gallwey score has now decreased to 6.

Discussion

The term "Steroid cell tumors" was first introduced by Hayes and Scully in 1987 to replace the terms "lipid cell tumor" and "lipoid cell tumor", which were previously referred to as "morphologically similar ovarian neoplasms of diverse cellular origin", "composed exclusively of cells resembling typical steroid hormone-secreting cells." These tumors were associated

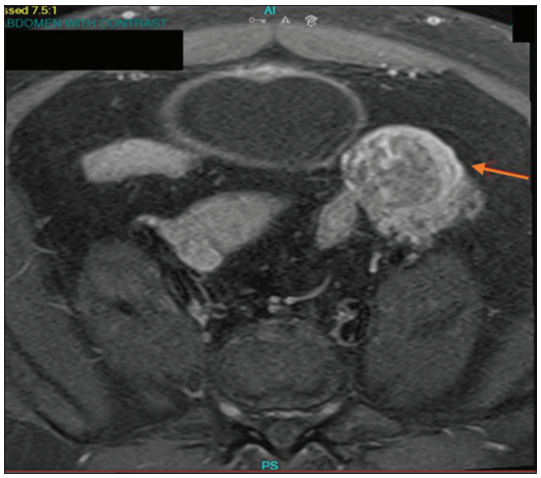

Figure 2: Magnetic Resonance Imaging of the left ovary (arrow)

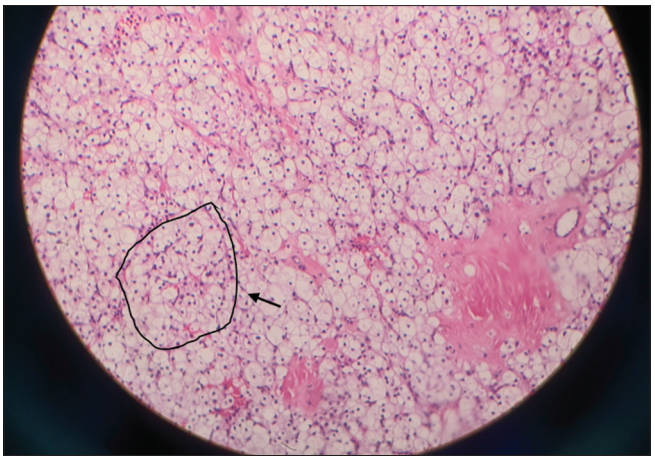

Figure 3: Histopathology of the left ovary: On microscopy, solid aggregates of cells with occasional nests were seen. Tumour cells were polygonal with cytoplasm that is granular and eosinophilic with clear intracytoplasmic vacuoles. No Reinke crystals, no nuclear atypia, hemorrhage and mitosis were seen

with characteristic virilizing clinical syndromes.[2] All of them contained steroid hormone-secreting cells such as lutein cells, Leydig cells, and adrenal cortical cells. Hence, the Hayes-Scully proposal to use the term steroid cell tumors for this unique group of ovarian neoplasms. The proposal further subclassified steroid cell tumors as (1) Stromal luteoma arising from the ovarian stroma, (2) Leydig cell tumor – Hilus and non-Hilus type arising from Leydig cells, and (3) Not otherwise specified if the lineage of the tumor is unknown.[2,4]

An update by the World Health Organization International Agency for Research on Cancer (IARC) revealed a new classification system for sex cord-stromal tumors. Steroid cell tumors and Leydig cell tumors are now two separate subtypes under the category of *Sex Cord Stromal Tumors-Pure Stromal Tumors*. However, a Leydig cell tumor was still defined as a "steroid cell tumor composed of Leydig cells" which could be misleading. In addition, the formerly known stromal luteoma and steroid cell tumors not otherwise specified have all been classified as steroid cell tumors.[1]

Steroid cell tumors occur in <0.1% of all ovarian tumors, and the subtype steroid cell tumors, not otherwise specified occur in 80% of those steroid cell tumor cases.[1] To date, there are only two published cases of ovarian steroid cell tumors in the Philippines. The first case report was by Andres *et al*. in the Philippine Journal of Obstetrics and Gynecology (PJOG) in 2014 on a perimenopausal, Filipino nulligravid who presented with defeminization and virilizing symptoms.[3] The second case published is by Uyking-Naranjo and Mirasol in 2013, where they reported a case of a postmenopausal woman with virilization who was eventually diagnosed with an ovarian stromal luteoma.[5] However, we entertain the possibility that the latter case may be a Steroid Cell Tumor Not Otherwise Specified. Grossly, stromal luteomas are more commonly multifocal and bilateral in 1/3 of the cases.[6] Furthermore, the microscopic description in their study seems more consistent with a steroid cell tumor, not otherwise specified: "sheets of polygonal cells with eosinophilic to pale and granular cytoplasm, small round nuclei and prominent nucleoli."[5] Figure 4 shows the histopathology of steroid cell tumors not otherwise specified in comparison to the case report of Uyking-Naranjo and Mirasol. Nevertheless, this may no longer be debatable because, in the latest update of the World Health Organization in 2014, stromal luteomas are now labeled as Steroid Cell Tumors as well.[1] Data are still limited concerning young adult nulligravid patients with specifically a steroid cell tumor. In the case we presented, she is only a 25-year-old, Filipino nulligravid who initially sought consult for acute abnormal uterine bleeding rather than her virializing symptoms.

Clinically, steroid cell tumors present with androgenic changes such as hirsutism, clitoral enlargement, deepening of the voice, and alopecia in 56%-77% of patients. Estrogenic changes are in 6%–23%, i.e., menorrhagia, postmenopausal bleeding, or endometrial carcinoma. Around 6%–10% may be associated with Cushing's syndrome, and 25% may be nonfunctioning.[7] In our case report, the patient's more prominent symptom is abnormal uterine bleeding; In contrast to the two local studies where their patients initially presented with the typical symptoms such as deepening of the voice, breast atrophy, loss of female curves, hirsutism, male pattern baldness, and hirsutism.[3,5]

Steroid cell tumors, not otherwise specified-still have no unique radiological characteristics in literature. A study by Monteagudo *et al*.[8] showed that small steroid cell tumors had a different echogenicity compared to the surrounding ovarian tissue, and there are low

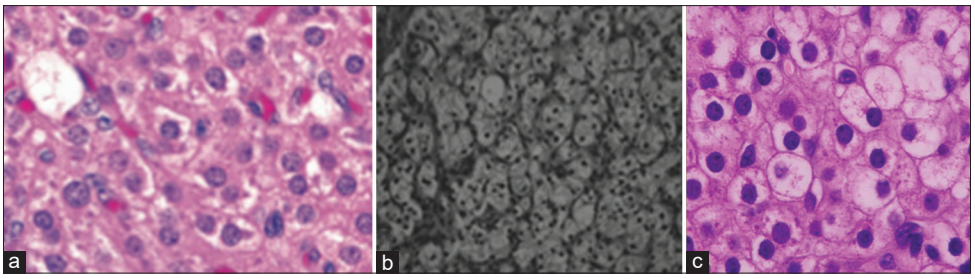

Figure 4: (a) Microscopy of Steroid Cell Tumor by World Health Organization Classification of Tumours of Female Reproductive Organs, 2014,[1] (b) Steroid cell tumor, not otherwise specified by Andres *et al*.,[3] (c) Stromal luteoma of the left ovary by Uyking-Naranjo and Mirasol[5]

impedance-to-flow values in 66.6% of the cases, but the sample size is too low for it to prove its significance.[9]

Grossly, the description of a steroid cell tumor is a solid, soft to firm, lobulated, and friable mass with or without hemorrhage and/or necrosis. On cut section, it is described as yellow, orange, red or brown which may have areas of necrosis or hemorrhage.[1,6] In this study, the left ovary on the cut section was described as a yellow, soft to firm lobulated mass abutting the serosal surface occupying the entire left ovary. This description supports the diagnosis of a steroid cell tumor not otherwise specified.

Steroid cell tumor not otherwise specified (NOS) on histopathology is described as solid aggregates of cells with some nests or trabeculae that is similar to columns or cords like in zona glomerulosa and zona fasciculata.[9] Cells are seen as round or polygonal with spongy to granular and eosinophilic cytoplasm, which includes intracytoplasmic vacuoles.[10]

To differentiate from a stromal luteoma, luteomas have stromal hyperthecosis, and degenerative pseudovascular spaces containing red blood cells, while Leydig tumors contain Reinke crystals.[6,11] In the case presented, there was none of the abovementioned descriptions of the different steroid cell tumors, hence a diagnosis of steroid cell tumor, not otherwise specified can be made.

Immunohistochemistry stains for these tumors include positivity to inhibin, calretinin, steroidogenic factor-1, and Melan-A, and negative for FOXL2.[1] However, in the case presented, no immunohistochemistry was done because histopathologic review already showed the pattern of steroid cell tumor not otherwise specified.

Most of these tumors are benign however the risk for malignancy occurs in 25%–40% of the cases. Fortunately, distant metastasis is rare for this type.[6] Steroid cell tumor not otherwise specified may have nuclear atypia and significant mitotic figures with areas of hemorrhage and necrosis.[12] In ruling out malignancy, Hayes and Scully identified 5 pathologic features that are associated with malignancy; tumor diameter of more than 7 cm (78%), mitotic figures per 10 high-power fields >2 (92%), necrosis (86%), hemorrhage (77%), and grade 2 or 3 nuclear atypia (64%).[2] The patient's histopathology presented with none of these features therefore, the case can be considered as a benign tumor.

The primary treatment for steroid cell tumor is surgical removal of the tumor.[6] Thus, for a young patient who needs to preserve fertility, a left salpingo-oophorectomy done sufficed as the main management.

Conclusion

This is a rare case of an ovarian steroid cell tumor not otherwise specified (NOS) that occurred in a 25-year-old nulligravid who underwent exploratory laparotomy with frozen section and left salpingo-oophorectomy. Increasing surveillance and awareness of steroid cell tumors, especially those who manifest with abnormal uterine bleeding and virilization, may initiate prompt and proper management that can have an impact on the quality of life of the patient.

Recommendation

Since there are only a few locally reported cases because of its rarity, there should be proper documentation and registry to be able to note the occurrence and progression of this disease in the Philippine population. In addition, a standardized nomenclature and classification of steroid cell tumors should be set in place in order to have effective communication between different medical fields.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Maria Mikaela V. Comendador - Involved in conceptualization, resources, writing draft, reviewing, editing, visualization, funding.

Jay Arnold Famador - Involved in conceptualization, reviewing, supervision.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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