Chapter 90

Rare steroid cell tumor found in region North Brazil: case report

ABSTRACT

Ovarian tumors occupy the seventh position in the ranking of the most common neoplasms among women, being the eighth cause of mortality in relation to gynecological neoplasms. The Steroid Tumor Without Other Specification (NOS) corresponds to 60% of all ovarian tumors of steroid cells and is associated with the development of hyperandrogenic syndromes. Given the rarity of steroid cell tumors, it is important to describe the diagnostic and therapeutic methods used in the clinical approach in order to contribute information to the medical-scientific community. Objective: To describe a case report of a patient diagnosed with a type rare of tumor of cells that induce steroid hormones present in the ovary. Case report: We report a case of a 52-year-old postmenopausal patient with a history of previous surgery, clinically with signs of virilization and hisuristics with diagnostic conclusion of Steroid Tumor Without Other Specification. Conclusion: NOS tumor are rare and can be difficult to diagnose due to the similarity with several other hormonal disorders, mainly affecting postmenopausal women and in these cases bilateral salpingo-oophorectomy surgery is the eligible therapy.

Keywords: Ovary, Neoplasms, Hyperandrogenism, Hormone, Virilization.

1 INTRODUCTION

Ovarian tumors occupy the seventh position in the ranking of the most common neoplasms among women, being the eighth cause of mortality among gynecological neoplasms. According to data from the Global Cancer Observatory (Globocan), in 2012 there were 239,000 cases of ovarian tumors, so, it is estimated that in 2035 there will be a worldwide increase in the incidence of (55%) and mortality (67%) of ovarian neoplasms (1). According to the National Cancer Institute (INCA), it is the second most frequent gynecological neoplasia in Brazil, it is estimated that for each year of the 2020/2022 triennium, 6,650 new cases of ovarian cancer will be diagnosed in Brazil, with a risk estimated 6.18 cases per 100 thousand women (2).

Ovarian tumors can originate from three distinct components: surface epithelium, germ cells and stroma of the ovary including the sexual cord (3). Androgen hormone inducing sexual cord tumors represent 5-6% of ovarian neoplasms (1,4), these tumors are composed of cells with morphological characteristics
that indicate secretion of steroid hormones (3). Within these, tumors of steroid cells represent about 0.1% of tumors of the sexual cord (5). According to the classification by the World Health Organization (WHO), cord tumors are classified into three subtypes: Stromal Luteoma, Leydig Cell Tumors and Not Otherwise Specified Steroid Cell Tumors (NOS).

Stromal Luteoma is a stromal origin steroid cells tumor, usually unilateral, benign, of small dimensions with approximately 3.0 cm in diameter, composed of luteinized cells of diffuse pattern with scarce lipid component and abundant lipofuscin pigment. The nuclei are normotrophic showing prominent nucleoli, rare mitotic figures, without the presence of Reinke crystals. They correspond to 20% of all steroid cell tumors and 80% occur in postmenopausal women (3). Tumors of Leydig cells are rare, consisting predominantly of Leydig cells, which are large, polyhedral cells, showing granular and eosinophilic cytoplasm, often vacuolized. The nuclei are round and monomorphic, nucleoli show usual appearance, rare figures of mitosis are seen and presence of mild atypias is often reported. Reinke Crystals are present in most cases, varying in number and size. These tumors are located predominantly in the hilum and correspond to 15% of tumors of steroid cells, usually occur in postmenopausal women and often with high levels of testosterone, leading to androgenic manifestations (3). Not Otherwise Specified Steroid Tumors represent 60% of all ovarian tumors of steroid cells of which 1/3 can evolve to malignancy, their histological classification is based on the absence of common characteristics of the other types of sex cord tumors (luteoma and cells Leydig's) (5,6). These tumors can appear at any age, frequently occurring in women with an mean age of 43 years (7), sometimes they are associated with the presence of hirsutism and virilization in approximately 50% of cases and about 10% to 15% of patients do not have symptoms of overproduction of steroid hormones (8).

NOS tumor is associated with the development of hyperandrogenic syndromes, in adult women a series of clinical manifestations can occur, such as: hirsutism, acne, androgenic alopecia, amenorrhea, metabolic syndromes and virilization signs, such as voice alteration and clitoromegaly (9). It is important to highlight that there is not always a correlation between the levels of circulating androgens and the intensity of clinical manifestations (9).

Thus, given the rarity of steroid cell tumors, it is important to describe the diagnostic and therapeutic methods used in the clinical approach in order to contribute to the dissemination of information to the medical-scientific community. So, we report the case of a 52-year-old patient with a history of previous surgery, showing signs of virilization diagnosed with Not Otherwise Specified Steroid Tumor.

2 CASE REPORT

Female 52 year-old patient, from the city of Tabatinga, in the interior of the state of Amazonas, with a surgical history of subtotal hysterectomy performed years ago due to a benign pathology, underwent an echographic examination at the health service that showed the presence of an adnexal complexmass in the
right ovary, with regular contours, measuring 6.3 x 4.5 x 4.4 cm (estimated volume of 67 cm³) and in the color-doppler ultrasound examination, a mass with hypervascularization was observed.

Figure 01: Transvaginal ultrasound: A - Projection of the right ovary containing complex mass of regular contour, measuring 6.3 x 4.4 x 4.5 cm; B - Color Doppler showing hypervascularized mass.

The patient underwent a computed tomography scan (CT) with contrast administration, which showed a hypodense lesion, 55UH (Hounsfield Unit) density in the right adnexal region, with a solid heterogeneous enhancement aspect, measuring 6.8 x 6.0 x 6.0 cm in topography of the right adnexal region without adequate cleavage plan.

Due to the imaging findings, the patient was referred to the oncology reference center in the state of Amazonas, where she underwent clinical evaluation, showing signs of virilization such as hirsutism (hair growth) and impaired vocal intonation. She underwent new imaging exams that confirmed the previous findings, no tests of hormonal origin were found. The patient underwent aspiration of ascitic fluid for cytological analysis where four (04) slides were made, being stained with Papanicolaou, Giemsa. Also, a cell block was performed. Optical microscopy showed mesothelial cells without evident atypias, erythrocytes, lymphocytes, granulocytes and typical histiocytes, with no cytological indications of malignancy (Fig. 02 A-B). The radiological changes found guided the surgical approach, so an exploratory laparotomy was performed, showing the presence of a tumor mass in the right adnexal region, with led to a bilateral salpingoophorectomy without complications in the surgical act, with the patient being discharged within same time day. On the fifth postoperative day, the patient presented abdominal pain, arterial hypotension, syncope, dyspnea, being diagnosed with acute hemorrhagic abdomen, leading to an urgent surgical re-approach that showed a moderate amount of hemorrhagic content in the abdominal cavity and a pelvic hematoma. After the second surgical procedure, the patient underwent a blood transfusion showing clinical improvement.
Figure 02: Cytological examination of ascitic aspirate: A (10x) - Smear consisting of mesothelial cells, red blood cells, lymphocytes and histiocytes; B (40x) - Cellular cell containing granulocytes, erythrocytes and amorphous protein material.

The surgical parts removed were sent to the pathological anatomy laboratory of the referred oncology hospital for histological analysis. On macroscopic examination, it was observed uterine tube attached to the right ovarian lesion, measuring 5.0 x 3.9 x 3.2 cm, weighing 55 grams, with a round surface presenting a dark brown color with whitish areas. On cuts in tumor mass, a compact yellow parenchyma was seen, covered by an intact capsule similar to a “giant yellow body” (fig.03-A).

Upon microscopic examination, polygonal cells with clear and abundant cytoplasm were observed, sometimes with a microvacuolar aspect, central and paracentral located nuclei, evident nucleolus, lack of atypia and necrosis, less than 02 mitosis / 10 high-power field (HPF 400x), areas of irrelevant erythrocyte leakage alongside fibrous septa and consistent vascular proliferation (fig. 03 BE). The findings were compatible with clear cell neoplasms with lipoid characteristics representing Not Otherwise Specified Steroid Cell Tumor.

As it is a tumor of steroid cells and in order to give greater meaning to the histopathological diagnosis, the immunohistochemical study was indicated, where some markers were performed and the following results were obtained: positive for Alpha-Inhibin (fig. 04- A) and Calretinin; negative for Cytokeratin, PAX8, FOXL2, Melan-A, SOX10 and Androgen Receptor. The immunohistochemical findings were compatible with the anatomopathological diagnosis confirming the presence of NOS tumor.

The patient is being followed up a year ago on an outpatient basis, undergoing treatment for systemic arterial hypertension, osteoarthritis and even after the surgery, still complains of hirsutism and altered voice intonation.
Figure 03: A - Tumoral mass with a round surface, covered by a fibrous capsule, composed by a solid, compact parenchyma, showing yellow-orange brown color, with dark punctual areas of wine-like color. B (4x) - The sections of tissue stained in H&E (hematoxylin and eosin) show mesenchymal neoplasm of the sexual cord composed of proliferation of clear cells; C (10x) - Scarse stroma, with proliferated vascular structures and fibrous sticks; D (40x) - Cells round to the polygonal edge of defined contours, varied sizes, granular-looking cytoplasmics containing vesicles; E (100x) - Central and paracentral nuclei, evident nucleolus, without evident atypias. Clear intracytoplasmic vacuoles.

Figure 04: Immunohistochemistry: A - Positive for the Alpha - Inhibin and Calretinin markers; B - Negative for the Cytokeratin marker; C - Negative for the PAX8 marker; D - Negative for the FOXL2 marker; E - Negative for the Melan - marker; F - Negative for the SOX10 marker; G - Negative for the Androgen Receptor marker.

3 DISCUSSION
Steroid cell ovarian tumors are a rare subset of sexual stromal tumors of the ovaries that account for less than 0.1% of all ovarian tumors. They can be secretors of hormones such as androstenedione, α-Hydroxyprogesterone and testosterone that cause androgenic manifestations (10). The neoplasms show morphological similarities, which were previously called lipid tumors. In 1979, Scully first used the term ovarian steroid cell to better describe the morphology of these tumors and the correlation with their clinical manifestations. They are classified into three subtypes: Stromal Luteoma, Leydig Cell Tumor and Not Otherwise Specified Steroid Tumor (NOS) (5,11), however, only in 1999 did WHO accept the term to classify this group of neoplasms (8).
Tumor NOS is the most common of all ovarian steroid cell tumors, representing approximately 60%. It receives this designation for having unknown cell origin and are identified based on the absence of characteristics observed in other secretory ovarian tumors androgens, such as Reinke Crystals, exner bodies and prominent nucleoli (6).

The NOS tumor develops in practically all ages, however, it is more common in postmenopausal women with mean age of 43 years. Clinical manifestations come in two forms: physically with abdominal pain, distension and edema; and associated with hormonal activity with high secretion of steroid hormones (testosterone in 50% of cases), about 8% to 10% of cases secrete estrogens. A minimum portion of 10% to 15% of patients with NOS has no symptoms due to the production of steroid hormones (8). Hirsutism and virilization are the symptoms most commonly found, in 56 - 77% of patients (5). Thus, this report describes the case of a 52-year-old woman who showed signs of virilization and hirsutism, which were noted as the main findings of hormonal overproduction, alteration of vocal intonation and increase in hair development, similar to the descriptions present in the medical literature.

The differential diagnosis of these tumors requires caution and attention, especially in the case of a non-palpable ovarian tumor, usually based on its clinical presentation, imaging exams or surgical findings (12). According to Mark (1999), CT can identify a minimum adrenal mass of about 1.5 cm, similarly, transabdominal and vaginal ultrasonography can be useful in most cases (12). NOS-type tumors can vary from less than 1.0 cm to more than 45 cm. The average size at diagnosis is 8.4 cm. These tumors are in most cases unilateral, but in 6% of cases they can be bilateral. They are usually solid, well defined in 89% of cases. They are usually yellow or red depending on the lipid content and in some cases, they present lobulated surface, areas of necrose and of hemorrhage areas can also be seen (8). According to a study by Hayes and Scully with 61 cases of NOS tumors, only 1 was described as almost totally cystic (8) The reported tumor presented with a solid heterogeneous enhancement aspect, measuring 5 cm, unilateral, well delimited with a round surface, showing a yellow surface color and covered by an intact capsule.

NOS tumors in most cases are benign, however, in 25-43% of these tumors show clinically malignant behaviors, in 20% of cases they have metastasis outside the ovary. Metastatic lesions generally occur in the peritoneal cavity region and rarely in distant sites (7). Hayes and Scully identified five characteristics associated with malignancy in steroid cell tumors, such as: presence of two or more mitosis figures per 10 (HPF) (92%), necrosis (86%), tumor size ≥7 cm (78 %), hemorrhage (77%), grade two or three of nuclear atypia (64%) (8,13). In our case, the anatomopathological examination of the tumor did not reveal patterns associated with malignancy, the size was 5 cm in its largest diameter, no more than two figures of mitosis by HPF were observed, no focus of necrosis, hemorrhage, signs of invasion and rare nuclear atypia was observed.

The immunohistochemistry method is an important aid in the diagnosis of ovarian tumors derived from the sexual cord and acts as a differential in other types of ovarian tumors. In this context, NOS tumors
are positive for alpha-inhibin and vimentin in 75% of cases, protein S-100 (7%), calretinin (8). and it can be positive for Melan-A, being negative for FOXL2 (14). Our case was positive for Alpha-inhibin and Calretinine and negative for Cytokeratin, PAX8, FOXL2, Melan-A, SOX10 and Androgen Receptor, thus confirming the diagnosis of NOS Steroid Cell Tumor.

Due to the rarity of this tumor, the efficacy of chemotherapy is unknown, so the therapy is based on the surgical approach in most cases, with the exception of those that present as a disseminated disease or the desire to maintain fertility in cases of young women.
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