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Case Report

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Non-Specific Steroid Cell Tumor of The Ovary: Case Report And Review of The Literature

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Abstract

Steroid cell tumors of the ovary are particularly rare, secreting sex hormones, characterized by steroid cell proliferation and represent only 0.1% of all ovarian tumors. They are classified into three subtypes according to their cell of origin: stromal luteoma, Leydig cell tumors and a third subtype of unknown lineage corresponds to a not specified steroid cell tumor (SCT-NOS). This third subtype accounts for 60% of steroid cell tumors. The clinical manifestations of SCT-NOS can take many forms, including pain, abdominal distension, but perhaps the most visible presentations are those related to hormonal activity and virilization of the tumor. We present a rare case of a 48-year-old woman with vaginal bleeding and a history of trunk obesity, hirsutism for 2 years and hypothyroidism with hormone replacement therapy. Clinical examination revealed a characteristic of obesity, virilization. Serum testosterone was 3.62 µg / L and CA-125 was 40.67. Magnetic resonance imaging identified a left ovarian solid mass and histopathology confirmed a steroid cell tumor not specific. The patient underwent exploratory laparotomy and left salpingoophorectomy. Macroscopically, the mass is well circumscribed, solid, homogeneous and yellowish. Microscopically, the tumor is mainly composed of eosinophilic or vacuolar granular cytoplasm. Immunohistochemistry showed that the tumor cells were strongly positive for inhibin. The postoperative period was uneventful. Through this rare observation, we will discuss the aspects that characterize this type of tumor and present some guidelines to be used in the differential diagnosis, as well as the difficulties encountered in the clinical, radiological and therapeutic fields.

Introduction

Steroid cell tumors of the ovary are particularly rare, accounting for 0.1% of all ovarian tumors. Steroid cell tumors a not otherwise specified

(SCT-NOS) are a rarely subtype stromal tumors of the ovarian sex cord, which have a difficult clinical and radiological presentation. A few cases of SCT-NOS have been described in the literature. Appropriate evaluation is recommended for patients with symptoms of virilization such as hirsutism, amenorrhea, and ovarian mass. The histological, clinical, and radiological features of SCT-NOS are briefly summarized. A discussion of the differential pathologic, radiologic diagnostic criteria, guidelines, and treatment options appropriate for this tumor are presented in this article along with a review of the literature.

Case Report

A 48-year-old premenopausal woman in her 48th year had hair growth on her face and back over the past 2 years, bleeding from her vagina for 3 weeks and lower abdominal pain for 1 week. She had a history of recent weight gain, voice changes and medication use. There was a history of hypertension and hypothyroidism with hormone replacement therapy. There was no history of gynecological or breast tumors in the family. The examination revealed a patient with no objective clinical signs. Her BMI was 34.81 kg/m2 with a weight of 91 kg and a height of 167 cm. Systemic examination was normal. The patient was evaluated for bleeding and androgen excess characteristics. Pelvic ultrasound showed a normal uterus and a left ovarian mass of 5 cm. The DHEAS was 117 µg / dL and serum testosterone were elevated to 6.3 ng / mL (normal 0.1 - 1.2 ng / mL). CA-125 was 40.67 IU/ mL, LH was 0.07 MIU/mL (normal 15.9-54 MIU/mL) and FSH was 0.37 MIU/mL (normal 23.0-116.3 MIU/mL). The dexamethasone suppression test suppressive cortisol by 19.29-0.81 µg/mL

Une IRM realized without and with contrast Gadolinium, in sequence T1,T2, DIFFUSION and confirmed one left masse ovarian

Figure 1, (A, B) Axial T1-Weighted image shows (6 cm) ovoid hypointense masse (arrows) in left adnexal region. Ill- defined area of high signal intensity is noted, indicating lipid content. On T2-weighted image, masse (arrows) is heterogeneously hyperintense(C). After gadolinium administration, T1-weighted image shows tumor (arrows) is very intensely enhanced (D,E,F). F, diffusion image

A stepwise laparotomy was performed, peritoneal fluid was sent for cytological analysis. There was a 4x4 cm friable yellow mass on the left ovary (Figure. 2). A left salpingo-oophorectomy was performed and sent for frozen section (Fig.ure 2), which revealed a steroid cell tumor of a benign nature characterized by polygonal cells with abundant clear to vacuolar cytoplasm with no evidence of necrosis, hemorrhage or increased mitosis (Figure 3) The oil-red stain showed abundant lipid content in the cells, confirming the diagnosis of non-specific steroid tumor and there were no malignant cells in the peritoneal fluid. The postoperative period was uneventful, and she was discharged on Day 6. (Figure 2)

Figure 2, Gross examination shows an ovary weighing 93 g, measuring 8.5 x 5.5 x 3.5 cm. The surface is smooth. On sectioning, a yellowish multinodular lesion measuring 8 x 5 x 3 cm is found, without necrosis. Lobulated mass of the ovary with yellow-orange cut surface.

Histology shows no necrosis or intra-tumor hemorrhage. Less than one mitosis for every 10 W.H.P.'s. Nuclear atypia is moderate.

Crystals of Reinke were not seen. The staining of Oil-red-O has revealed numerous intracellular lipid droplets. No mitotic figures were identified. No hemorrhagic or necrotic contents were noted.

Figure 3, On immunostaining, tumor cells are positive for SF1, Calretinin and Inhibin. On the other hand, they are negative for Melan-A. [2, 10].

Discussion

Ovarian steroid cell tumors are a rare tumor that secrete sex hormones and are characterized by a proliferation of steroid cells. They account for less than 0.1% of all ovarian tumors and are grouped into three subtypes according to their cells of origin: stromal luteoma, Leydig cell tumor (or hilus) and steroid cell tumor not otherwise specified (SCT-NOS) [2].

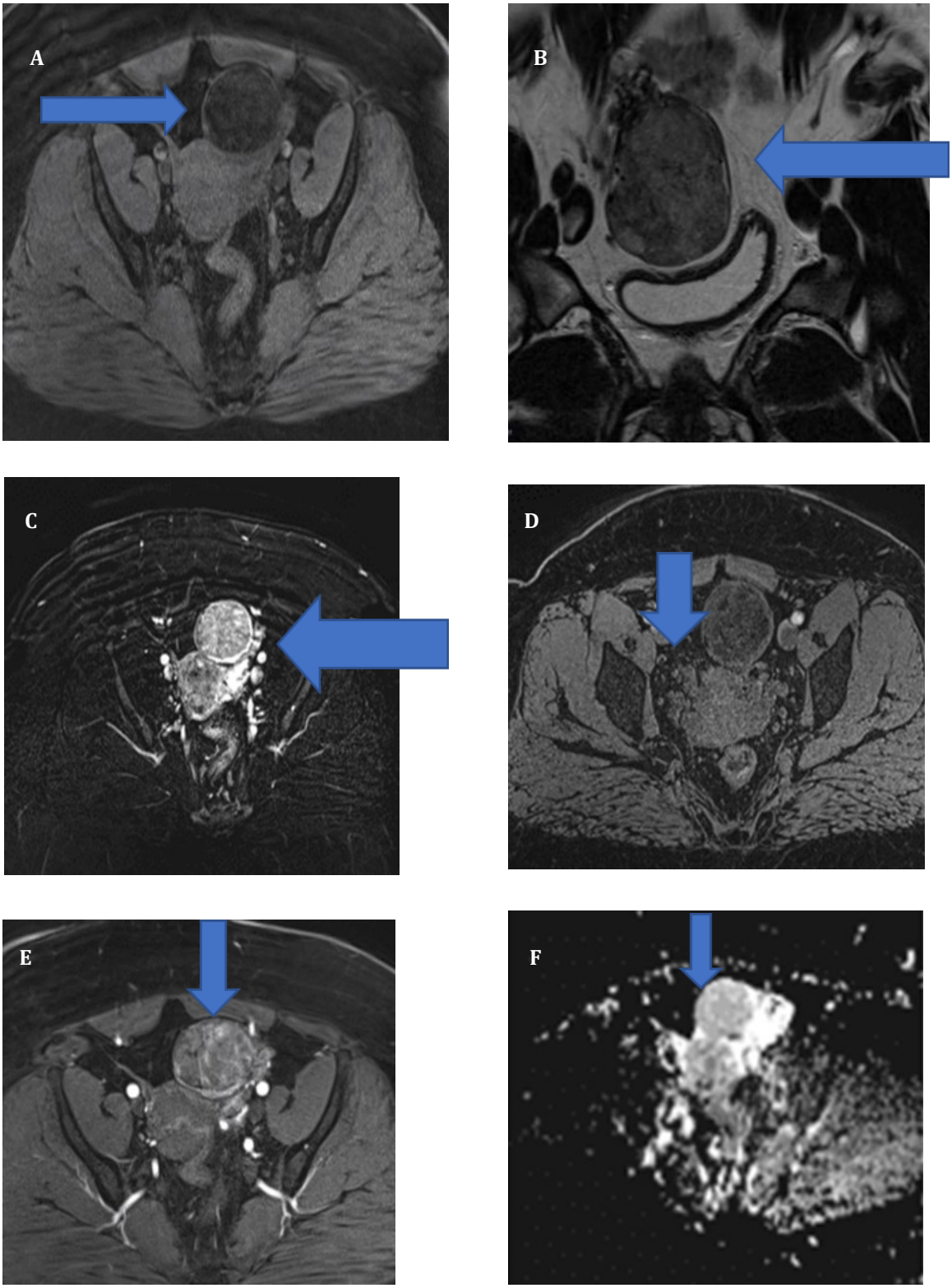

Figure 1. A) Sequence T1 without contrast B) Sequence T2 without contrast c) T2 with contrast GADO D) Sequence T1 with contrast GADO E) Sequence T1 with contrast GADO F) Sequence diffusion

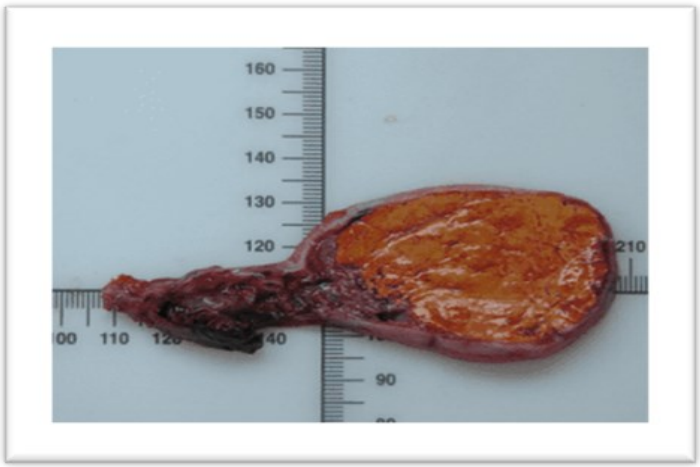

Figure 2. Anatomopathological and Immunohistochemistry

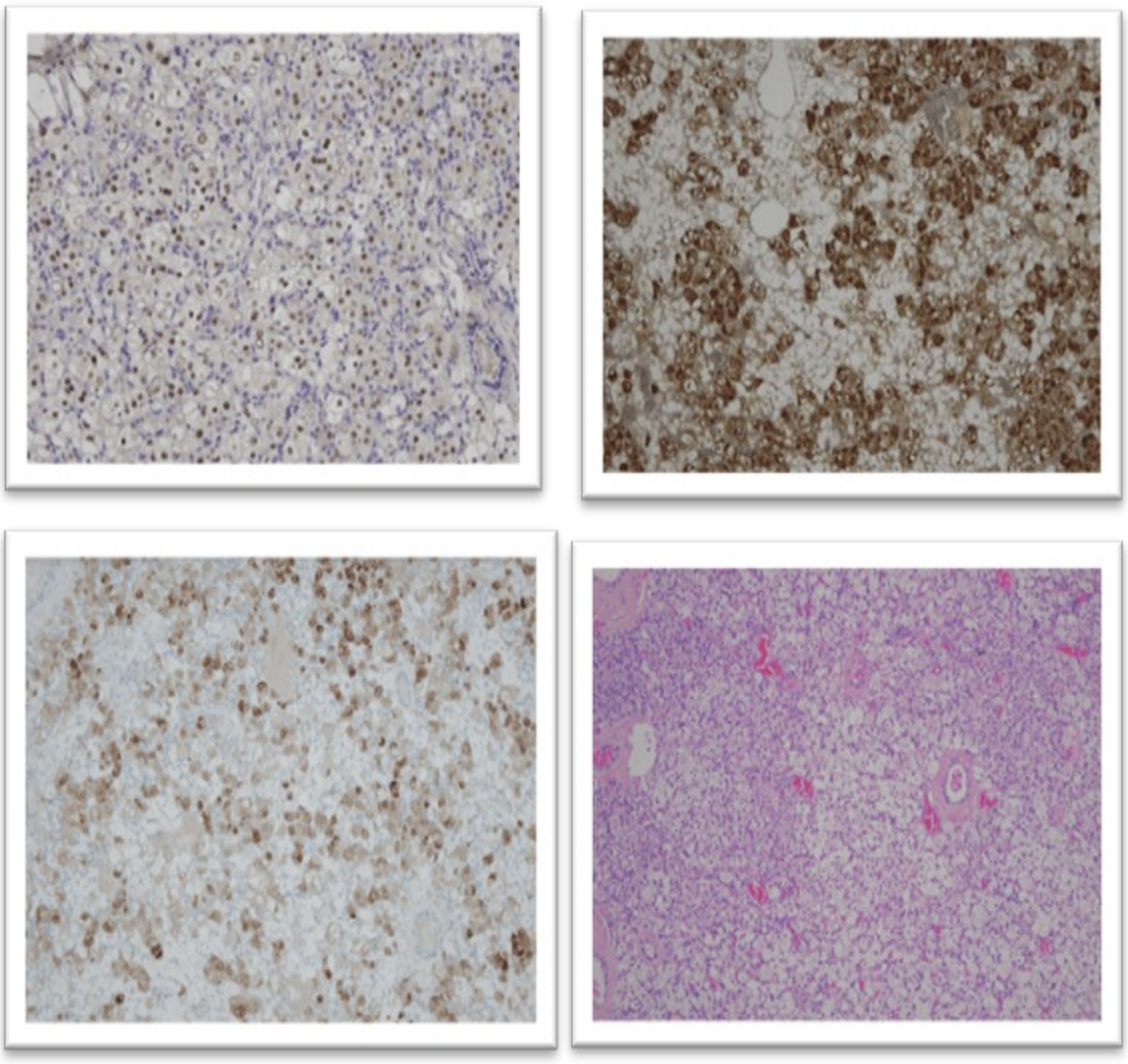

Figure 3. Photo HE et 4 IHC: 3 positives (inhibin, calretinin et SF1) et one negative (Melan A).

The first description and term of steroid cell tumor not otherwise specified was given in 1979 by Scully [1]. SCT-NOS have a 60% incidence of ovarian steroid cell tumors. The English literature mentions less than a hundred cases through the PubMed search [3]. It occurs at any age, with a high incidence between the third and fourth decade. To date, rare cases have been reported in the literature in children as young as 2 years of age and postmenopausal women [4].

They are mostly benign, diagnosed early at stage I at presentation with good prognosis, however malignant development with metastasis occurs in 25 to 40% of cases [5]. SCT-NOS tumors are often unilateral in 94% of cases, although rare bilateral cases have been described in the literature [6].

This tumor produces several steroids, particularly testosterone, and are associated with androgen changes in 55-75% of cases [7]. The main manifestation in 56-77% of patients is virilization with hirsutism, acne, voice changes, temporal baldness. Only 10% of patients suffer from amenorrhea [8]. Manifestations such as hypothyroidism, endometrial hyperplasia or menorrhagia are associated in 6 to 23% of cases [9]. Cushing's syndrome has been reported in 6-10% due to elevated plasma pro-renin and hypokalemia [10]. Occasionally, HAT, stretch marks, hyper pilosis, osteoporosis, and acne are seen objectively.

However, 25% of patients with SCT- NOS, are asymptomatic, non-functional tumor [11], and their diagnosis is made postoperatively by immunohistochemistry.

To make a definite diagnosis of an endocrine tumor of ovarian origin, hormonal tests will be required. Elevated testosterone levels with normal levels of DHEA, LH, FSH and 17-hydroxyprogesterone are indicative of a virilizing tumor of the ovary.

There are three main markers of ovarian cancer: CA 125, CA 19-9 and ACE [12]. Only CA 125 is of primary importance since its rate is increased regardless of histological type [13]. According to Malkasaian et al [14], a CA125 level greater than 65 µ/ml is predictive of malignancy in 98% of cases, while a low level is predictive of benignity in 72% of cases. However, CA125 levels may increase in other cancers (cervix, endometrium, digestive tract). In Hayes and Scully's studies, five pathological signs are linked to the malignancy of these tumors, namely more than two mitoses, necrosis, a diameter greater than 7 cm, hemorrhagic foci and nuclear atypia of two or three. [15].

MR imaging and color flow Doppler ultrasound are two excellent imaging modalities that may demonstrate characteristic radiologic features and characterization differential diagnosis for these tumors.

Sonography is generally used as the first-line imaging technique for the evaluation of ovarian pathologic abnormalities. It makes it possible to specify the tumor ovarian origin; its structure, dimensions, solid and/or cystic component, its vascularization, either unitary or bilateral, also show its extension to adjacent organs. The SCT-NOS ovarian tumor varies in size from 1.5 cm to 40 cm and is bilateral in 6% of cases [16]. Ultrasound remains effective in postmenopausal women with atrophied ovaries and less accurate in younger women.

MR imaging is useful for identifying these tumors in young and postmenopausal women [17]. The diagnosis of an ovarian tumor is made by clearly indicating its location, size, contour and the presence or absence of an adjacent or distant malignant abnormality. This technique allows optimal exploration in all 3 planes as well as the characteristics of the diffusion and perfusion of the lesion and the pattern of enhancement (homogeneous or heterogeneous) after gadolinium injection.

Laparoscopy is indicated when the ultrasound scan is not formal and when there is doubt about the organic nature of the lesion. It eliminates non-ovarian lesions, determines the ovarian tumor and makes an etiological diagnosis by cytological punctures of the mass.

Macroscopically, these tumors are typically very limited, well circumscribed and unilateral, yellow to orange, red or brown in color depending on the lipid content. It varies in size from 1 cm to 45 cm, with a generally solid consistency, but a combination of solid and cystic forms can be observed. In our case, the tumor was

entirely solid, with no cystic area. Its cross-sectional area was generally yellow and lobulated [18].

Histological examination allows the definitive diagnosis and is confirmed by immunohistochemistry. Cells with abundant granular or vacuolar eosinophilic cytoplasm, positive for fat spots and negative for Reinke's crystals and stromal hyperthecosis were found [19]. Immunohistochemical validation is necessary condition for the definitive diagnosis of SCT-NOS. Inhibin is positive in most steroid cell tumors and is very useful in the differential diagnosis between sex cord tumors and non-steroid cell tumors. These tumors are negative for CK and EMA, although a small subset of tumors may be positive for EMA. This presentation diagnosed SCT-NOS based on microscopic images and found that our case had positive immune reactivity: 3 positive (inhibin, calretinin and SF1) and negative (Melan A) [20].

SCT-NOS steroid cell tumors should be differentiated from other types of steroid cell tumors, in which the development of steroid hormone-producing cells occurs secondarily.

This includes granulosa cell tumors, fibroids and thecomas, stromal luteoma and Leydig cell tumor.

1) Granulosa cell tumors are the most common malignant stromal tumors and are often revealed at stage 1 at diagnosis. They constitute the main group of hormone-secreting ovarian tumors and are subdivided into two different clinicopathological subtypes: adult and juvenile, depending on age, and are distinguished by size and solid or cystic type [21]. The adult form occurs in women over 30 years of age and postmenopausal. As for the juvenile subtype, it appears mainly in children. These tumors are easier to diagnose because of their characteristics, since they have a differentiated radiological and histological behavior [22]. In terms of imaging, these tumors are very diverse, ranging from solid masses through hemorrhagic or fibrous tumors to multilocular or simply cystic lesions [23] (Table 1). An assessment of the underlying histopathological parameters of the tumor is essential for a definitive diagnosis. In adults, these tumors are characterized by pale nucleus tumor cells, often with regular mucin-depleted follicles, longitudinal grooves and an emergency corpus callosum [24]. Whereas in the juvenile type, dark nuclei with irregular follicles contain mucin and are only rarely striated or have the microfollicular pattern, with numerous rosette-like structures that simulate the Call-Exner bodies of the Graafian follicle [25]. Recently, a mutation of the FOXL2 gene has been detected in the majority of adult granulosa cell tumors

Table 1. Typical Appearances of More Common Sex Cord-Stromal Tumors

S. No	Tumor	Typical Tumor Morphology	Key Imaging Features
1	GCT		
	Juvenile	Multicyclic	Hemorrhage, pseudoprecocious puberty
	Adult (polyps, earcinoma)	Solid or multicystic and solid	Hemorrhage, spongelike cysts in tumor, endometrial abnormalities
2	The coma	Solid	Nonspecific
3	Fibroma	Solid	Sound attenuation at US, low signal at T2
4	Sertoli-Leydig tumor	Solid	Nonspecific
5	Steroid cell tumor	Solid	Nonspecific

(97%), and very rarely in juvenile tumors (10%) [26]. The distinction between AGT and undifferentiated carcinomas, the positive immunostaining test for α-inhibin, calretinin and vimentin, and the lack of staining for EMA all argue in favour of a diagnosis of AGT. A FOXL2 immune reaction is useful [27]. The prognosis varies according to the stage of diagnosis, tumor size and nuclear atypia. Survival at 10 years is greater than 90% with local recurrence and a 5-25% risk of malignancy at 20 years [28].

2) Fibroma, fibro-thecomas and thecomas are benign ovarian tumors, accounting for 4%-6% of all ovarian tumors and affect pre- and post-menopausal women. Thecomas are stromal tumors composed of theca-type lipids, as well as lutein cells and fibroblasts [29]. They occur in elderly patients with estrogenic activity and are associated with uterine bleeding, with 21% having endometrial carcinoma [30]. They are unilateral in 97% of cases and consist of round to spindle-shaped cell sheets with an ill-defined pale cytoplasm, usually vacuolated and lipid-rich, and alternating with collagen-producing fibroblasts. Thecomas are immunoreactive to vimentin, inhibin, calretinin and other sex cord markers [31]. Radiologically, they are usually solid masses with T2-weighted dark MRI signal intensity and a variable rate of calcification or degeneration [32]. Thecomas typically are usually benign and surgical excision is the best treatment [33].

Fibromas are composed of a non-functional stroma with no estrogenic activity, formed exclusively of collagen-producing spindle cells containing only small amounts of cytoplasmic lipids [34]. In CT Scanner, they appear as a homogeneous solid tumor, with delayed contrast on I.V. and MRI, a T1-weighted iso intense mass and a T2-weighted hypointense mass. Hypointense calcifications and hyperintense areas, occasionally scattered, were often observed, indicating edema or a cystic degeneration [35]. Lastly, fibroids containing ≥ 4 mitoses per 10 HPF are now known as "mitotically active cellular fibroids" and should be distinguished from fibrosarcoma's [36].

3) Sclerosing stromal tumors (SSTs) were first described by Chalvardijaian and Scully in 1973 [37]. They affect young women with menstrual disorders and lower abdominal mass. However, SSDs remain very limited and are devoid of Reinke's crystalloids [38]. They are characterized by cellular areas separated from each other by hypocellular areas composed of dense collagen, edematous or myxoid tissues and by significant vascularization, all forming a pseudo-lobular structure [39]. The cytoplasm is moderately abundant, eosinophilic and sometimes vacuolized [40]. On non-contrast CT, SST shows solid densities corresponding to cellularity, vascularity, and distribution of collagen or fibrous stroma, while foci of necrosis or cystic degeneration are low density [41]. In the arterial phase, after intravenous administration of contrast material, rapid improvement of the external region of the tumor is observed due to the cellular area with numerous vascular spaces. In the venous phase, an extension of the reinforcement zone is observed on the internal part of the lesions in association with a hypocellular collagen zone. The areas of the tumor that do not show obvious improvement correspond to the edematous regions. On MRI, they appear as a large mass with hyperintense or heterogeneous solid cystic components, iso to hyperintense in T2-weighted sequence. They are slow-growing tumors with a hypo-intense peripheral edge in T2 and a thin ovarian cortex [42]. Following injection of gadolinium, the intense and early contrast of the septum between internal and peripheral cysts with centripetal progression reveals hypercellularity with an abundant vascular network. The differential diagnosis of TSS should also include other thecoma-fibroma and malignancies [43], because of its rarity, since diagnosis by prospective imaging is not possible. Surgical resection of the tumor is curative and local or distant recurrence should be avoided.

4) Sertoli-Leydig cell tumors are very rare and benign and occur in young women with clinical androgenic symptoms and account for less than 0.5% of ovarian

tumors [44]. These tumors are almost always unilateral and are either solid and cystic or papillary. They appear as a well-defined solid mass with intra-tumoral cysts on CT scan and hypo-intense cysts with numerous cystic areas of varying size on MRI [45]. They are also known as androblastomas and are the most common virilizing tumors [46]. They secrete androgens with male characteristics such as amenorrhea, facial hair, low voice, chloritoid hypertrophy and hyper seborrhea [46]. Leydig cells are classified by Roth and Steinberg into two basic forms [47]:

- the dominant hilar form, consisting of a small benign unilateral nodule. Leydig cells are well limited with Reinke's crystalloids in 50% of cases [48].
- the non-hilar form consists of tumors of the ovarian stroma, located in the ovarian parenchyma and containing 100% Reinke's crystalloids.

Anatomopathological, they are small reddish-brown lesions with eosinophilic cells with low cytoplasmic lipid content, presenting mainly intracytoplasmic Reinke crystals. Their nuclei are hyperchromatic and have only one small nucleolus. Mitoses are rare and always benign [49]. On MRI, a small mass with hyper-intense areas can be seen on sequqncesT1-weighted images due to the abundance of intracellular lipids and the large increase in contrast medium after gadolinium injection due to rich vascularity [50].

Treatment

The basic therapy for steroid-induced ovarian tumors is total abdominal hysterectomy with bilateral salpingo-oophorectomy and complete surgical staging. However, for women who wish to maintain their fertility, conservative surgical treatment with unilateral oophorectomy may be accepted.

Surgical management of SCT-NOS should be prompt, imperative, based on two essential elements: histological type and patient desires.

In the first instance, satisfactory resection of the tumor must be carried out for any benign or malignant case with multiple variants [51]:

-Total hysterectomy with bilateral salpingectomy for elderly women who do not wish to preserve the uterus.

- For young women, before the age of 40, conservative treatment is applied in the case of benign tumors, with a conservative cystectomy to preserve ovarian function.
- Uni-lateral salpingo-ovarectomy in women of child-bearing age with a benign tumor.
- Unilateral salpingo-ovarectomy with malignant tumor and preservation of the uterus for future fertility, but close monitoring with staging is essential.
- Metastatic malignant tumour, requires post-operative adjuvant chemotherapy BEP, Bleomycin, Etoposide and Cisplatin. The best adjuvant chemotherapy is still unknown [52].

In our case, the patient is young and eager to have children, and has had a successful unilateral sapling-oophorectomy.

Prognosis

For this, it is important to establish a close correlation between various clinical, pathological parameters and the undesirable behavior of the tumor, such as the age of patients in the clinical stage, tumor size greater than 7, 0 cm or more (78% malignant tumors), pituitary field mitoses greater than 2 mitoses (92% malignant tumors), grade 2-3 nuclear atypia (64% malignant tumors), necrosis (86% malignant tumors) and hemorrhage (77% malignant tumors) [53].

Regular monitoring with measurement of serum testosterone levels is mandatory, and since little is known about the behavior of these tumors, it is not known for how long.

In our case, the prognosis is favorable since the size of the tumor is less than 7 cm, without mitosis, necrosis or hemorrhage. Clinically malignant tumours

occur in 25 to 43% of cases, whereas clinically malignant cases are histologically benign [53].

Conclusion

SCT-NOS are particularly rare stromal tumors of the ovarian sex cord, which are difficult and misleading to diagnose clinically and radiologically, as this observation demonstrates. For early diagnosis, careful physical examination, supplemented by laboratory values and imaging, is useful in patients with symptoms of virilization and amenorrhea. In most cases, typical histopathological analyses confirm the diagnosis. In case of difficulties, immunohistochemistry is an important diagnostic tool. Treatment depends on the histology, surgical stage and the desire to preserve fertility. The treatment of malignant tumors should combine surgery and chemotherapy.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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