

## Ovarian Sertoli cell tumours: practical points

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### Abstract

Rarity of Sertoli cell tumours contributes to a low index of suspicion and therefore a thorough knowledge of the clinicopathological and immunological characteristics of such tumours is essential to diagnosis and proper management of the treatment and follow-up. The current narrative review of literature was planned to focus on ovarian Sertoli cell tumours that arise from the sex cords cells, which are typically benign unilateral neoplasia incidentally detected, or associated with hormonal hyperactivity, in women of reproductive age. A priority unpublished case of a 35-year old female is also introduced as the base of discussion. Abdominal mass-related syndrome and vaginal bleeding anomalies have been reported. Genetic background, if presented, is mostly related to Peutz-Jeghers syndrome caused by *STK11/LKB1* mutation. The tumour displays a microscopic tubular pattern and rarely displays cords or trabecular, retiform, spindles, diffuse or areolar structures. Although immunohistochemistry can be helpful in establishing the diagnosis, the results are sometimes inconclusive and the current results require new research to establish a specific immunological panel.

**Keywords:** Sex cord tumour, Ovarian Sertoli cell tumour, Histology diagnosis, Immunohistochemistry.

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### Introduction

Ovarian Sertoli cell tumours (OSCTs) are rare neoplasia associating a relatively large number of morphological aspects in addition to heterogeneous endocrine behaviour. Typically benign, they are frequently seen in women of reproductive age with ranges between first years of life to the seventh decade.<sup>1</sup> Their detection may be either incidental in women seeking fertility or having

a routine gynaecological control, either due to associated hormonal hyperactivity which requires endocrine evaluation. Therefore, neoplasia is usually detected by a gynaecologist or an endocrinologist. The underlying histological reports include these tumours in the vast family of sex cord-stromal tumours,<sup>2,3</sup> and some have a genetic background, as seen in Peutz-Jeghers syndrome or DICER mutation (the gene encoding endoribonuclease Dicer), the latter more frequently associated with Sertoli-Leydig cell tumours.<sup>4-6</sup>

### Method

In the current narrative literature review, some examples are introduced based on a prior unpublished case diagnosed with unilateral OSCT and displayed as ovarian incidentaloma. The patient signed the informed written consent to anonymously use her medical data referring to the pathological report as well as medical history and hormonal profile. The research of literature is focussed on clinical and histological aspects of OSCT, as a topic of gynaecological endocrinology. Most studies were found while searching on PubMed.

### Results

#### Classification

According to the World Health Organisation (WHO) 2016 classification, OSCT, a subgroup of ovarian sex cord-stromal tumours, are rare sex cord tumours of the ovary. Distinctive feature of OSCT is the lack of Leydig cells and immature stroma which is in contrast with Sertoli-Leydig cell tumours.<sup>7,8</sup> The report of cases has low level of statistical evidence because most of these tumours have been described in literature as series of cases.

#### Main characteristics

The onset age is between 2 and 79 years, with an average of about 30 years. Classically, they are considered tumours of reproductive age and, therefore, the possibility of detection during periodical gynaecological control.<sup>9</sup> Their hormonal profile can be of several types: completely negative or associated with an excess of oestrogens, androgens (less than oestrogen excess) or even

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progesterone, secondary to hormone secretion by the tumour cells.<sup>7,8</sup> Recent studies suggested that a DICER1 mutation (or DICER mutation involving helicase with RNase motif) as back ground induces a higher risk of androgen production rather than oestrogens.<sup>10</sup> Two cases have been reported in association with rennin and aldosterone production.<sup>11</sup>

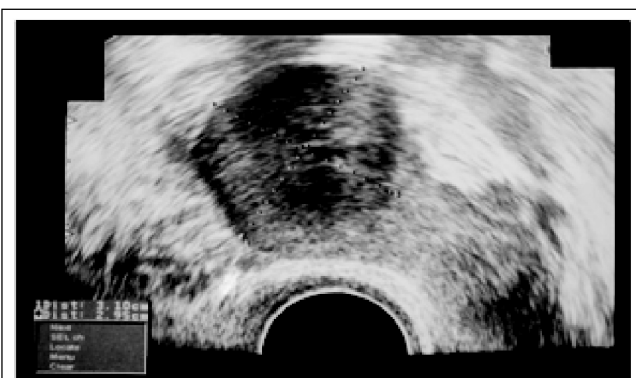
Virilisation potential is less seen than in tumours with Sertoli-Leydig cells (androblastoma) or Leydig cell profile.<sup>12</sup> Sometimes, local symptoms as pain and menstrual abnormalities lead to tumour detection. Postmenopausal vaginal bleeding in association with high cancer antigen 125 (CA125) levels mimicking an ovarian cancer has been described.<sup>13</sup> Cases completely asymptomatic display the scenario of ovarian incidentaloma, a term that is still incompletely defined when it comes to ovaries and it subscribes various pathological reports.<sup>14-16</sup> The case in question had a baseline ovarian ultrasound showing a solid tumour at the level of left ovary of 3.1 x 2.95 cm with penetrating vessels on a 35-year old non-smoking female with irrelevant family and personal clinical history who was detected with the mass during a routine endocrine and gynaecological exam, displaying the scenario of an ovarian incidentaloma. (Figure 1) Pelvic computed tomography (CT) confirmed a solid, well-shaped left ovarian tumour of 3.13 x 2.93 cm. (Figure 2) She had normal baseline hormones, including total and free testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (day 14 of menstrual cycle), thyroid stimulating hormone (TSH), free levothyroxine and prolactin, negative thyroid antibodies, and a level of progesterone of 11 ng/mL (day 21 of menstrual cycle), normal for ovulatory status (the level

required for proving ovulation is above 10 ng/mL).

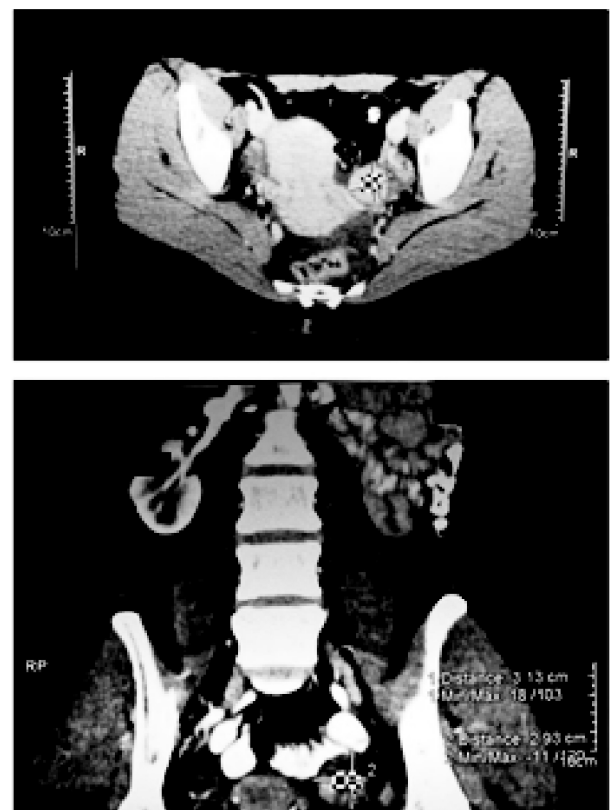
The most common clinical presentation when occurring in children is isosexual precocity.<sup>17</sup> Genetic syndromes, like Peutz-Jeghers, are associated especially with cases detected in young population, counting less than a fifth of subjects. Peutz-Jeghers syndrome is caused by STK11/LKB1 mutation which causes a higher risk of some digestive cancers as well as hamartomatous polyposis or hyperpigmentation of skin and mucosa.<sup>4,18</sup> New mutations as DICER or FOL2 (the gene encoding GTP cyclohydrolase I) are still incompletely described. DICER syndrome includes multinodular goitre (MNG) and it is linked in majority of cases with neoplasia displaying both Sertoli and Leydig cells.<sup>19-21</sup>

In addition to a complete physical examination, the patient should undergo imaging tests that may include ultrasonography (US), CT, and magnetic resonance imaging (MRI) of the pelvis to look for an ovarian tumour.

Fine needle aspiration (FNA) is cited as useful in one large series of cases in order to appreciate the malignant



**Figure-1:** Preoperative transvaginal ultrasound. A heterogeneous mass of 3.10cm x 2.95 cm, well-shaped in left adnexa.



**Figure-2:** Preoperative computed tomography of the abdomen and pelvis with intravenous contrast showing a 3.13x2.93 cm soft tissue lesion consistent with a left ovarian mass.

potential as alternative of surgery.<sup>22</sup>

Most OSCTs are stage I, following a non-aggressive clinical course. Therefore, the primary treatment is surgical (unilateral oophorectomy) and the prognosis is generally favourable.

Histological and immunohistochemistry feature

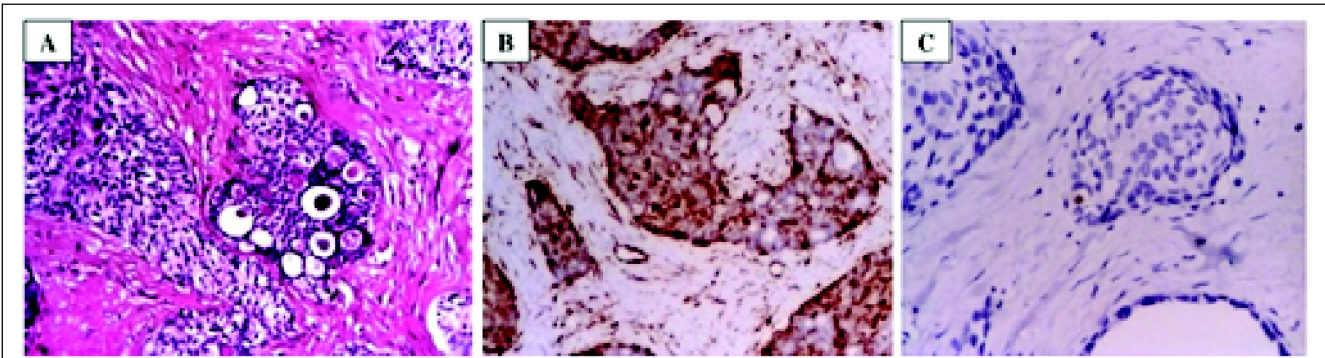
Pathology and immunocytochemistry are basic tools for the diagnosis of OSCT, having also a prognostic value. Macroscopically, the tumour is yellow or brown, usually solid, with potential mix structure (solid-cyst). The diameter varies from <1 cm to 30 cm, usually between 4 cm and 12 cm. Most reported cases are unilateral.<sup>7,8,23</sup> Their morphological spectrum are not clearly established. Many other neoplasms of diverse types can closely simulate Sertoli cell tumours.<sup>24</sup> OSCT shows a histological resemblance to developing or adult testes, with follicle trans-differentiation to structures resembling seminiferous tubules of the testis, with Sertoli-like cells. The neoplasia with Sertoli cells of gonads, ovary and testes, have common by the lobular aspect, but the lobulation is less evident in ovaries than the testis.<sup>25</sup> On microscopic exam, tubular pattern, a very distinctive profile rarely seen in other types of ovarian neoplasia, is most frequent but not exclusive. Other features have been identified in ovarian Sertoli cell tumours like cord or trabecular, retiform, spindles, diffuse or alveolar areas. Several pattern scan coexist in the same tumour. The stroma devoid of Leydig cells can be abundant with marked hyalinisation. It can be noticed round or elongated tubules, hollow or solid, lined by columnar or cuboidal Sertoli-like cells, with moderate to abundant amounts of slightly eosinophilic cytoplasm, occasionally vacuolated. The nuclei of the tumoural cells usually lack atypical features or mitotic activity. Ultrastructurally, abundant trough endoplasmic reticulum, some cystically dilated smooth endoplasmic reticulum profile and mitochondria with tubular crystals visible. These, together with lipid droplets, suggest a potential or steroid hormone synthesis which is not always expressed clinically. The free border of cell show occasional cilia or microvili, considered to be a manifestation of focal metaplasia of the neoplastic Sertoli cell. Laterally, the cells show tight junctions and desmosomes.<sup>26,27</sup> Long-term follow-up associates a good prognosis, but recurrences have rarely been found in cases with atypia or high mitotic index.<sup>17,23</sup>

The good behaviour is predictable through pathological report, and even some atypical aspects mimicking other tumours have been reported.<sup>17,23</sup>

Microscopic appearance requires a differential diagnosis, firstly with endometrioid carcinoma and carcinoid tumour.

The immunohistochemical (IHC) panel can be helpful in establishing the diagnosis. Many IHC markers have been studied for diagnosis, but currently available markers are not 100% sensitive or specific. Some reports revealed calretinin-positive reaction in more than half of the cases, as well as vimentin, and inhibin.<sup>28-30</sup> In one study on 26 cases of Sertoli cell tumours, nuclear expression of Wilms tumour protein (WT1) was present in 96%.<sup>31</sup> Negative staining for epithelial membrane antigen (EMA) was found to be most useful as discriminative element, while pan-cytokeratin (pan-CK) and Cluster of differentiation 99 (CD99) were not identified as being useful. In one series of 160 cases of ovarian tumours, including 40 of Sertoli cell type tumours, 7% had cytokeratin 7 (CK7) positive stain, 8%, were positive for oestrogen receptor, and 13% for progesterone receptor.<sup>32</sup> One study on 36 cases tried to find if a SOX9 (which is a key transcription factor during sex determination, and tumour growth) positive reaction may be highly suggestive in the IHC profile of ovarian Sertoli cells neoplasia since SOX9 is a transcription factor involved in Sertoli cell differentiation in the testes but its ovarian stain was irrelevant.<sup>33</sup> Overall, there is no specific combination of immunostain to sustain 100% diagnosis. IHC report seems to be more useful in cases where classical tubular pattern is not clearly identified. In our case, tumour cells were positive for vimentin and CK7, but negative for inhibin, with a low Ki67 index of proliferation which is usually correlated with tumour progression.

Pathological report after left laparoscopic ovariectomy on a 35-year-old asymptomatic female with ovarian incidentaloma showed a benign sex cord tumour with Sertoli cells (Figure 3A). IHC report revealed positive vimentin and CK7 (Figure 3B) and a low index of proliferation (3%) into the tumour cells (Figure 3C). The tumour was negative for chromogranin, carcinoembryonic antigen (CEA), cytokeratin20 (CK20), inhibin, and high molecular weight cytokeratins 1,5,10 and 14 (34βE12). Positive actin was found in stroma but not into the tumour cells. The patient was followed for the next 12 months assessing normal ovulation based



**Figure-3:** Microscopic images of resected tumours. (A) Ovarian Sertoli cell tumour: proliferation consisting of islands of sexual cords with tubular pattern and eosinophilic content or calcifications. The tubules are lined with cuboidal cells with slightly eosinophilic cytoplasm and round nuclei showing no mitotic activity. Hyalinised fibrous stroma (Hematoxylin and eosin (HE) stain x10) (B) Diffuse positive staining for vimentin (immunohistochemical [IHC], 20x). (C). Weak positive staining for Ki-67 (IHC, 20x).

**Table:** Main features of ovarian Sertoli cell tumours.

Ovarian Sertoli cell tumours - at glance	
Parameter	Feature
Frequency	rare, women of reproductive age
Age of onset	average 30 years; ranges: 2 - 79 years
Level of evidence	series of cases
Pathological report	mostly benign; 4 - 12 cms (ranges: 1 - 30 cms)
Cluster	sex cord tumours
Detection	incidental or due to active hormonal profile
Genetic background	(some) Peutz-Jeghers syndrome; DICER mutation
Prognosis	usually good
Approach	multidisciplinary

on progesterone levels of 16 ng/mL (day 21 of menstrual cycle).

**Limitations**

Rarity of Sertoli cell tumours cases reported to date contributes to a low index of suspicion and therefore at thorough knowledge of the clinicopathological and immunological characteristics of such tumours is essential for diagnosis and proper management right up to treatment and patient follow-up. As current limits of the concept related to OSCT, we consider five aspects: the insufficient description of risk factors and genetic predisposition, especially in non-Peutz Jeghers syndrome cases, and the exact role of identifying DICER1 mutations in selected cases; which is the driven force of endocrine activity in relationship to a particular histological expression; lack of high specificity markers regarding IHC features; the poor prognosis markers are still a matter of debate, an aspect that cannot be sustained based on small sample size studies; and, finally, which is the clear definition and multi-disciplinary protocol for ovarian

incidentaloma underlying various pathological reports, including OSCT.<sup>34,35</sup> The current level of evidence regarding OSC is essential for all concerned (Table).

**Conclusion**

Sertoli cell tumour of the ovary is a rare neoplasia of low malignancy risk that typically occurs in women of reproductive age, and it has a good prognosis in association with the usual tubular pattern. IHC may be useful but current results require new research to establish a specific immunological panel. The detection of the tumour and its follow-up after removal may be done either by a gynaecologist or an endocrinologist.

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**Conflict of Interest:** None.

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**Abbreviations**

cm = centimetre, FSH = Follicle Stimulating Hormone, LH = Luteinizing Hormone, TSH = Thyroid Stimulating Hormone, CK7 = cytokeratin7, CEA = Carcinoembryonic antigen, CK20 = cytokeratin 20, 34βE12 = high molecular weight cytokeratins 1,5,10 and 14, WT1 = Wilms tumour protein, EMA = epithelial membrane antigen, CD99 = Cluster of differentiation 99, pan-CK = pan-cytokeratin

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