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Adult Granulosa Tumor: Case Report

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ABSTRACT

Granulosa tumors account for approximately 2-3% of ovarian tumors. They are the most frequent malignant tumors in the group of sexual cord and stromal tumors. They are mostly localized forms with a good prognosis. The main prognostic factor is the stage, with a high risk of recurrence when the tumor is of stage IB or higher. Recurrences are sometimes very late (more than 20 years after the initial treatment) and surveillance must be prolonged.

We report a case of adult granulosa tumor in a 70-year-old patient, married nulligest, menopausal for 15 years, whose reason for consultation was spontaneous postmenopausal metrorrhagia associated with pelvic pain evolving for 1 year and whose pelvic imaging was in favor of a large suspicious solid-cystic formation measuring 20x12x9cm. A total hysterectomy with bilateral adnexectomy completed with multiple ascites fluid samples, epiploic and peritoneal biopsy was performed and found to be an adult granulosa tumor classified as IC1.

No adjuvant treatment was proposed and the immediate evolution was favorable. Through this case we will study the clinical presentation, the characteristics, the modalities of treatment as well as the prognosis of this rare entity.

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Introduction

Ovarian granulosa tumours (OGTTs) are rare tumours that arise from the granulosa cells that form the inner layer of the follicle wall. They belong to the group of stromal and sex cord tumours and account for 3 to 5% of malignant tumours of the ovary [1]. There are two subtypes, which differ epidemiologically, histologically and prognostically: the adult form, which is the most common (95% of cases), and the juvenile form (5% of cases), which is common in young patients and has a poor prognosis with an increased risk of recurrence [2]. The discrimination between these subtypes is not based on the age of the patient, but rather on the histological appearance of the tumour [3]. Most often, they are estrogen-secreting (70% of cases), causing clinical signs that vary according to age, leading to early puberty in juvenile forms and postmenopausal metrorrhagia, or amenorrhoea in adult forms. Management is essentially based on surgery, which must be radical in older patients. A conservative approach by adnexectomy can be envisaged in young women who wish to become pregnant. Chemotherapy is indicated for localisedtumours with a high risk of recurrence, and for advanced or recurrent tumours. Prolonged monitoring is recommended [4].

Observation

A 70 year old patient, married, null and void, menopausal for 15 years, asthmatic under treatment, operated for uterine myoma 20 years ago, admitted for spontaneous postmenopausal metrorrhagia associated with pelvic pain evolving for 1 year without accompanying signs. The clinical examination showed a sloping dullness of the flanks with the presence of a reddish cervix on examination under speculum, the site of a polyp that had been delivered, and a right latero-uterine mass measuring 10 cm in length, renitent and sensitive, on vaginal touch and abdominal palpation.

A pelvic ultrasound showed a large cystic formation with thick partitions in the right latero- and supra-uterine region, the largest of which was 12.5 mm thick, and at least 3 vegetations, the largest of which was 15, 9mm long axis, vascularised on Doppler, measuring 100.8x90.3mm with a normal sized uterus with regular endometrial thickening of 12.7mm and a calcified fundal myoma measuring 9.6x8.8mm (figure 1). The pelvic CT scan showed a solid cystic formation, mostly cystic, roughly rounded, with supravesical and intra-abdominal development, with multiple partitions delimiting pockets with hypodense fleshy buds enhanced after injection of PDC, measuring 20x12x9cm (figure 2).

The cervico-uterine smear and the anatomopathological examination of the polyp delivered through the cervix came back without any sign of malignancy and the CA125 was negative at 15U/ml. Surgical exploration revealed a small amount of ascites and an accidentally ruptured 20 cm polylobed mass of the right ovary with areas of necrosis. The left ovary, liver, diaphragm, parietocolic gutters were unremarkable. A total hysterectomy with

bilateral adnexectomy referred for extemporaneous examination returned in favour of a poorly differentiated tumour proliferation requiring extensive sampling and immunohistochemical study to label it.

Multiple samples were taken from the ascites fluid, epiploic and peritoneal biopsies and on definitive pathology an adult granulosa tumour (figure 4 and 5) with immunohistochemical study the tumour cells express WT1 (figure 6 and 7), calretinin (figure 8), Melan A (figure 9), and inhibin. They weakly express cytokeratin AE1AE3 (figure10), with no sign of malignancy on all the samples taken. No adjuvant treatment was proposed. The immediate evolution was favourable.

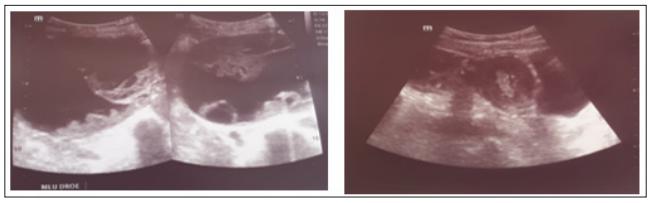

Figure 1: ultrasound appearance of a 20x12x9cm solidocystic right MLU of probable ovarian origin, suspicious looking with 13mm endometrial thickening

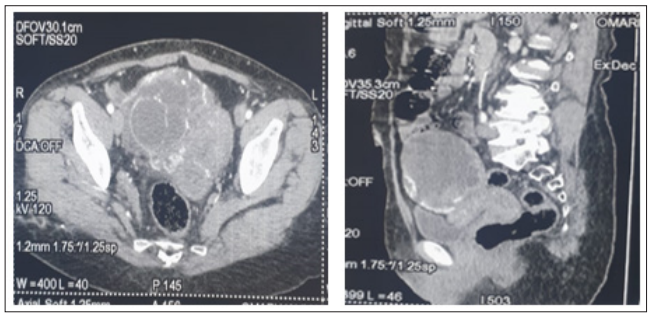

Figure 2: CT scan of a straight 20x12x9cm solidocystic MLU of probable ovarian origin, of suspicious appearance

Discussion

Granular cell tumour (GCT) of the ovary is a rare subtype of ovarian cancer arising from the stromal component of the sex cord of the ovary [5]. The incidence of GCTs is 0.6-0.8/100,000 and represents 3-5% of all ovarian malignancies [6]. GCTs have two clinically and molecularly distinct subtypes; the juvenile and adult type [5]. The adult type GCT (AGCT) is the most common, whereas the juvenile type accounts for only 5% of all GCTs. AGCT is usually diagnosed in perimenopausal women aged 50-54 years, although it can occur throughout the adult woman's life.

AGCTs are a unique subtype of ovarian cancer with distinct clinical and molecular features. They are characterised by their high hormonal activity and production of oestrogens and inhibins [5]. The most common symptoms are abnormal uterine bleeding (45%) and abdominal pain or bloating (10-20%) [7]. In premenopausal patients, AGCT usually causes irregular bleeding, amenorrhoea and more rarely infertility. In postmenopausal patients, abnormal uterine bleeding associated with a unilateral ovarian mass is the most common clinical presentation, as in our patient. Ascites is rarely present. In 8-15% of cases, the tumour ruptures spontaneously with acute abdominal pain and haemoperitoneum [7,8]. AGCT can sometimes be asymptomatic and diagnosed incidentally [2].

Radiological signs are non-specific to these tumours, and they cannot be easily distinguished from other ovarian neoplasia on imaging alone. On ultrasound and CT, their appearance varies widely, but they often present as large, solid, unilateral, encapsulated, cystic, multilobulated tumours with multiple, thin or thick, irregular septa [9]. Intratumoral haemorrhage, central areas of necrosis and fibrous degeneration may result in a heterogeneous solid appearance [9]. On magnetic resonance imaging (MRI), these tumours show a T1 hypersignal, related to the haemorrhagic changes. On T2, GISTs show an intermediate signal and have a spongy appearance, indicating alternating solid and cystic spaces [9]. Metastases are less frequent and are mainly located in the peritoneum and liver. These patients usually also have an abnormally thick endometrium, pathological examination may reveal endometrial hyperplasia in 26-38% and synchronous endometrial cancer is diagnosed in 6-7% of patients [7,10].

In the series of the study by Lee et al, endometrial pathology was evident in 26.4% of patients; 14% with simple hyperplasia without atypia, 1.4% simple hyperplasia with atypia, 2.9% complex hyperplasia without atypia, 4.4% complex hyperplasia with atypia and 2.9% endometrial cancer. In the study by Mangili, 17.5% had endometrial hyperplasia and 6.2% had evidence of endometrial carcinoma. Haupsy et al reported an even higher rate of endometrial carcinoma (17%) [11-13]. Therefore, biopsy of the endometrium as well as the cervix is essential to define the therapeutic strategy.

The CA 125 level was assessed by Lee in 76 patients with AGCT in whom only 13.1% had an elevated level (> 35 IU/mL) [11]. In the same study, in contrast to AGCT, CA 125 was elevated in 45.5% of patients with JGCT. In a case-control study of Yesilyurt including 34 patients, GCT patients had high mean CA 125 levels (64.5 ± 130.3 IU/mL) [14]. Others have reported the use of CA-125 in various risk calculators for the assessment of malignant ovarian neoplasms. The Malignancy Risk Index (MRI) first defined by Jacobs et al included the use of ultrasound findings, menopausal status and serum CA125 level. The RMI with a cut-off of 150 has been shown to have a sensitivity of 84% and specificity of 97% in detecting ovarian cancer [15,16].

As a result, patients with TCG have a higher IMR (mean 285.6 ± 677.6) than those with benign masses. A new diagnostic marker has recently been published (FOXL2) whose 402C→G (C134W) missense mutation was found in 97% of patients with adult granulosa tumours compared with only 21% with thecomas and 10% with juvenile granulosa tumours [17]. It could be used as a diagnostic marker, in addition to inhibin, which is mostly overexpressed, and whose interpretation is not always easy, but whose measurement seems interesting during surveillance to look for possible relapses [17].

Over the last decade, our understanding of the molecular pathogenesis of AGCT has improved considerably, while developments in chemotherapeutic regimens and in particular targeted therapies have remained modest. Thus, optimal primary surgery has always maintained its position as the most important factor in the treatment of primary and recurrent AGCT [18]. The standard treatment for JGCT or AGCT is primary surgery, which is usually curative due to the early stage of the disease and the unilateral involvement in most cases. Surgery should include hysterectomy and bilateral salpingo-oophorectomy, following endometrial biopsy to rule out endometrial pathology.

Node dissection is of limited value, particularly in early disease, and is not currently recommended. Patients with advanced disease (stages II-IV) should undergo maximal cytoreductive surgery. Ipsilateral salpingo-oophorectomy and staging can be proposed in

early stages [18]. AGCTs are known to express steroid hormone receptors and produce estradiol. Therefore, hormonal treatments have been used empirically in AGCT, mainly as a last resort in patients with non-operable AGCT. Hormonal therapies were also considered if the patient did not tolerate or the tumour did not respond to conventional chemotherapy. Treatment modalities included progestins, a gonadotropin-releasing hormone agonist, selective oestrogen receptor modulators and aromatase inhibition. In a systematic review of 19 studies describing the response to hormone therapy, the pooled objective response rate was 71% [19]. However, in a retrospective analysis of 22 patients from a single institute, the objective response rate was paradoxically low (18%) [20]. Similarly, Wilson et al. reported a 14% response rate to aromatase inhibitors in patients with relapsed stage I AGCT [9]. It should be noted that no randomised trials have been conducted with hormonal treatments and the current literature includes only retrospective series and relatively small case reports, so the true efficacy of hormonal therapy in AGCT remains unknown. Once the hormonal pathogenesis has been clarified in more detail and there is evidence to support a randomised trial, hormone therapy may be an option in the treatment of AGCT [18].

The only targeted therapy proven to be effective in advanced ovarian cancer is angiogenesis inhibition with the humanised monoclonal VEGF antibody bevacizumab [18]. Stage IA granulosa tumours have an excellent prognosis after complete surgery and do not require adjuvant therapy (figure 3). For early stages not located in an ovary, the place of adjuvant chemotherapy is not rigorously demonstrated due to the rarity of these tumors and therefore remains controversial. The notion of tumor rupture has been associated with a higher risk of relapse [18,21].

Figure 3: chemotherapy indications according to the stages (Referential version 2018)

STAGE IA-B R0	**STAGE IC1 (PER OP RUPTURE) R0**	**STAGE IC2 A III**	**STAGE IV**
NO CHIOMIOTHERAPY SURVEILLANCE ACTIVE AND PROLONGED	PROFIT/ RISK CASE BY CASE RCP RARE TUMOR	ADJUSTING CHEMOTHERAPY BEP OR CARBOPLATINE-TAXOL NUMBER OF CYCLE ACCORDING TO RESIDUE	PALLIATIVE CHEMOTHERAPY 4 BEP OU 6 CARBOPLATINE - PLACLITAXEL
ACTIVE AND LIFETIME MONITORING CLINICAL EXAM AT LEAST ANNUAL ULTRASOUND ANNUAL TUMOR MARKERS			QUARTERLY MONITORING CLINICAL EXAM TDM TAP TUMOR MARKERS

According to the observatory of rare gynaecological malignancies (Referential version 2018), chemotherapy is indicated in case of stage IC2 to III if residual. In this case, platinum-based chemotherapy is the reference treatment: the most commonly used regimen is the combination (bleomycin, etoposide, cisplatin) in the absence of respiratory (bleomycin), renal (cisplatin) comorbidity and in patients in good general condition. Due to the toxicity of BEP, non-bleomycin alternatives are offered to women over 40 years of age or with pulmonary comorbidity: the use of carboplatin-paclitaxel or PE has been shown to be effective, although a prospective randomised comparison is not yet available. The number of cycles is usually 4 BEP and 6 carboplatin-paclitaxel, but can be reduced in non-residual IC stages to 3 BEP and at least 3 carboplatin-paclitaxel [18,21,22]. Multiple clinical and histological prognostic factors have been studied for their role in the prognosis of AGCT, but the results have been inconclusive and have varied significantly between cohorts. Tumour stage was the only consistent factor that was related to tumour relapse and survival [4,8,16].

Among stage I patients, those with tumour invading the ovarian capsule or tumour rupture (stage Ic) have a significantly increased risk of disease relapse [9,17]. Consistently, tumour capsule rupture has been implicated as an unfavourable prognostic indicator, also in stage I AGCT [17-19]. Interestingly, in a recent study of verified AGCT, there was no difference in the risk of relapse between surgically or spontaneously ruptured tumours [17]. The identification of risk factors in stage I patients is the most clinically important determinant since stage I patients form the majority of AGCT patients. Thus, future clinical and scientific efforts should focus on how to identify and manage these patients who are at increased risk of relapse. In addition, some studies have reported postoperative residual tumour and large tumour size as unfavourable prognostic factors [8,18,19]. Furthermore, it is unclear whether the patient's age at diagnosis affects prognosis, while parity and reproductive status do not seem to influence the outcome of AGCT [4,20].

With regard to histopathological prognostic factors, different histological subtypes have not been associated with prognosis, while high mitotic activity and nuclear atypia predict a worse prognosis [19,21,22]. Multiple histological prognostic factors, e.g. Ki67, p53, epidermal growth factor receptors (EGFR) and the transcription factor GATA4 have been evaluated, but their clinical applicability remains unclear [22-26]. Potential histopathological prognostic factors have not yet been validated in independent validated cohorts limiting their use in clinical decision making.

In the study by Lee et al, it was shown that recurrence rates were directly correlated with stage of disease with a rate of 8.1% in stage I, 9.1% in stage II and 40.0% in stage III. A similar association has been found by other authors [11,12,14,27,28]. Other clinical factors associated with recurrent disease include tumour size, higher body mass index and the presence of residual disease after surgery [2,10,28].

In a retrospective study by Mangili, overall survival at 5 and 10 years was excellent with rates of 97% and 95%, respectively. Saker showed that patients with recurrent GCT had a poorer overall survival (83 vs. 138 months) [12,24]. In the study by Sun et al, 5 and 10 year overall survival rates for all stages were 96.5% and 94.1% respectively [25]. Prolonged surveillance is recommended for GIST, as recurrences can occur very late [18]. Table 1 shows the surveillance modalities according to the Observatory of Rare Gynecological Malignancies [18].

Table 1: monitoring methods (OTMRG) [19]

surveillance	Year 1	from 2 years to 5 years	>5 years
Clinical and biology exam	/4 moth	/6 moth	/year
Scan(stage 1) Endovaginal ultrasound	/4 moth /3-6 moth	/year /6 moth	/year /year

A .CA125, Inhibin B, AMH, progesterone, Δ4 androstenedione, testosterone according to initial secretion

The relative rarity of the tumour and the prolonged course of the disease make studies of new drugs and combinations in prospective clinical trials difficult and time consuming. Large international clinical trials with molecularly defined cohorts of AGCT are needed to validate new treatment strategies for patients with high-risk early and advanced AGCT. The development of effective new treatments should also be based on a deeper understanding of the pathogenesis of AGCT.

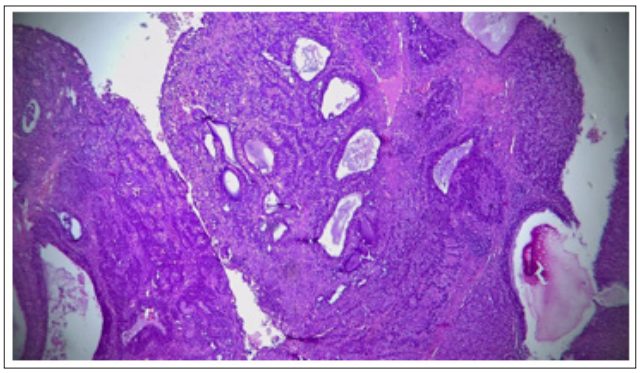

Figure 4: Histological aspect of a granulosa tumour, magnification x4

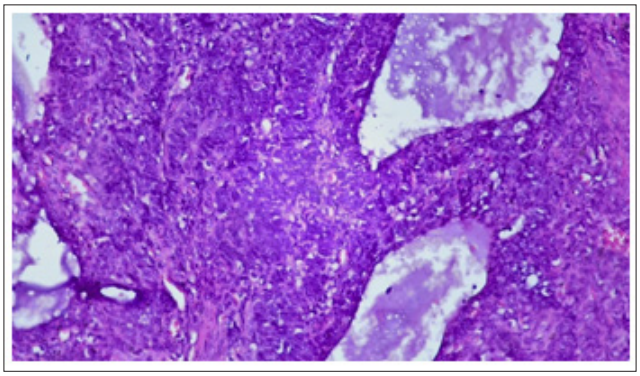

Figure 5: Rising histological appearance of tumour cells with a crumpled ovarian nucleus showing x100 incisions

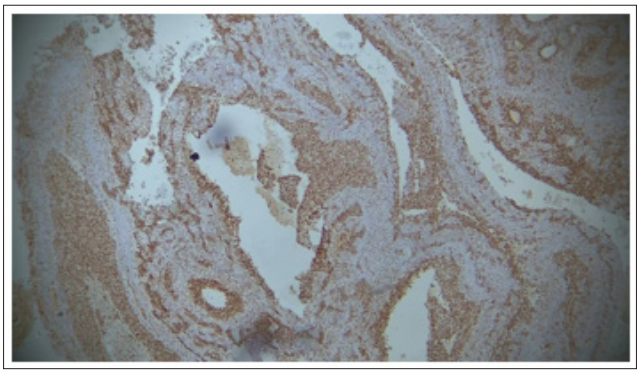

Figure 6: IHC appearance of an adult granulosa tumour showing WT1 expression by tumour cells (magnification x4)

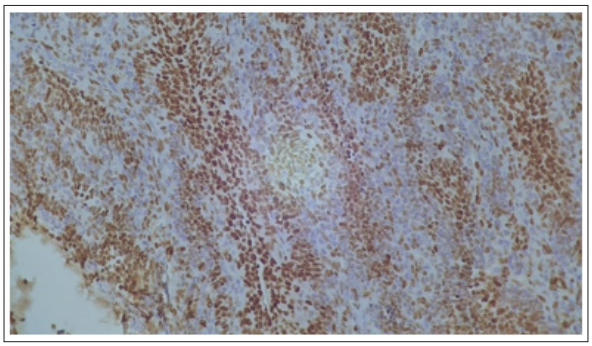

Figure 7 : Wt1x200

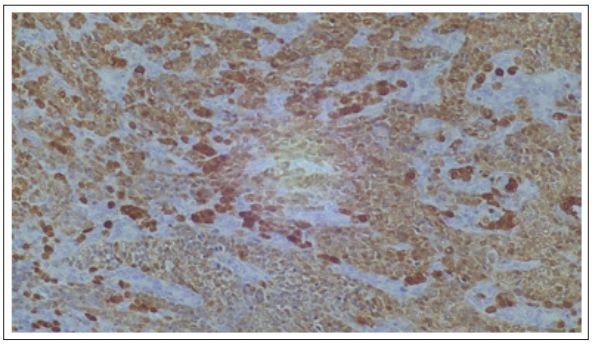

Figure 8: Calrétinine x200

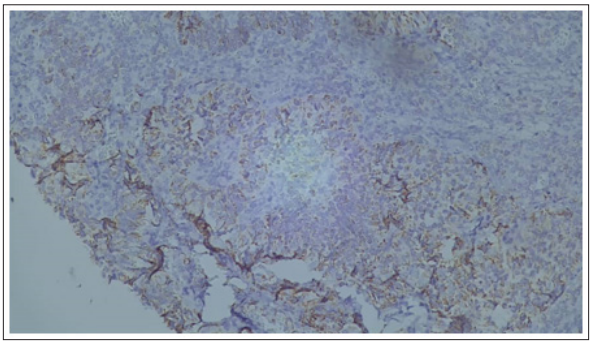

Figure 9: Melan À x200

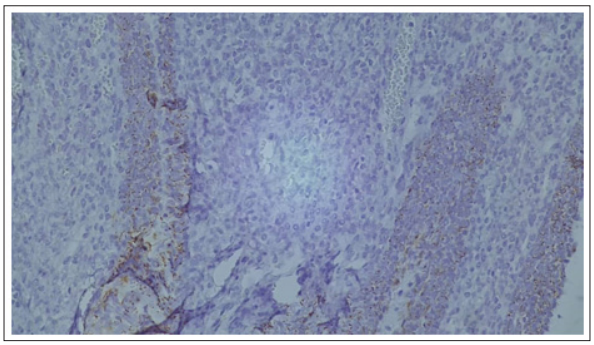

Figure 10: CKAE1/AE3 low expression x200

Conclusion

Granulosa tumours are malignant tumours, often not very aggressive and localised, but their relapse or advanced stage

can be unfavourable or even fatal. The benefit/risk balance is sometimes delicate in young patients with fertility issues or in fragile, comorbid patients; the staging and quality of the initial surgery, often associated with a repeat of 2 looks, and diagnostic confirmation by an expert anatomopathologist are essential to properly classify and treat these patients. Several avenues are being developed to improve the diagnosis, follow-up and treatment of granulosa tumours.

Declaration of interests

The authors declare that they have no conflicts of interest in relation to this article.

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