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Case Report

Pelvic ultrasound scanning in asymptomatic adult-type granulosa cell tumor: A case report and review

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Abstract

Background: Ovarian cancer is common amongst women worldwide. In Indonesia, it is the fourth most common female cancer with a 5-year survival rate of 45%, but can reach up to 92% if treated early. Granulosa cell tumors (GCT) arise from the sex-cord and are considered malignant. This study presents a rare case of asymptomatic adult-type granulosa cell tumor in an elderly lady diagnosed during routine pelvic ultrasound scanning.

Case Illustration: A 65-year-old lady, P2A0, was referred due to left ovarian mass three years before admission. A left adnexal mass was palpated with no sign of internal genital adhesion. Transvaginal ultrasound showed atrophy of uterus and thin endometrial layer. One solid adnexal mass with a cystic part was found on the left adnexal with papillary projection and low resistance index. Histopathological examination revealed adult type-granulosa cell tumor and classical Call-Exner body with grooved nuclei (coffee bean nuclei). Diagnosis of GCT was made by histological findings.

Discussion: Histologically, granulosa cells of adult subtype appear round, pale, with scant cytoplasm, classic coffee bean nuclei and Call-Exner bodies. In contrast, the juvenile subtype has eosinophilic and/or vacuolated cytoplasm with macrofollicular or cystic patterns, composed of immature granulosa cells with frequent mitoses. Call-Exner bodies and coffee bean grooved nuclei are not commonly found.

Conclusion: The diagnosis of GCT was made through histological findings which were consistent with previous findings. Therefore, a laparotomy frozen section can be considered in menopausal women with suspected ovarian neoplasms.

Keywords: *granulosa cell tumor, histopathology, ovarian cancer*

Abstrak

Pendahuluan: Kanker ovarium sering ditemukan pada perempuan di seluruh dunia. Di Indonesia, kanker ovarium merupakan kanker tersering ke-4 ditemukan pada perempuan dengan angka harapan hidup 5 tahun sebesar 45%, namun dapat mencapai 92% bila ditangani secara dini. Tumor sel granulosa (TSG) berkembang dari *sex-cord* dan tergolong ganas. Studi ini menampilkan sebuah kasus jarang tumor sel granulosa tipe dewasa asimtomatik pada perempuan usia lanjut yang didiagnosis selama pemeriksaan ultrasonografi pelvis rutin.

Ilustrasi Kasus: Perempuan usia 65 tahun, P2A0, dirujuk karena massa di ovarium kiri sejak tiga tahun sebelum masuk rumah sakit. Terdapat massa adneksal kiri pada palpasi, tanpa tanda adesi genitalia internal. Ultrasonografi intravaginal menunjukkan atrofi uterus dan lapisan endometrium yang tipis. Ditemukan satu massa adneksa padat dengan bagian kistik pada adneksa kiri dengan proyeksi papiler dan indeks resistensi yang rendah. Pemeriksaan histopatologis menunjukkan tumor sel granulosa tipe dewasa serta badan Call-Exner klasik dengan inti yang berlekuk (*coffee bean nuclei*). Diagnosis TSG ditegakkan dari temuan histologis.

Diskusi: Secara histologis, sel granulosa subtipe dewasa tampak bulat, pucat, dengan sitoplasma sedikit, *coffee bean nuclei* klasik, dan badan Call-Exner. Sedangkan subtipe juvenil memiliki sitoplasma yang eosinofilik dan/atau bervakuol dengan pola makrofolikular atau kistik, tersusun atas sel granulosa imatur dengan banyak mitosis. Badan Call-Exner dan *coffee bean nuclei* biasanya tidak ditemukan.

Kesimpulan: Diagnosis TSG ditegakkan dari temuan histologis yang sesuai dengan temuan-temuan sebelumnya. Oleh karena itu, pemeriksaan potong beku laparotomi dapat dipertimbangkan pada perempuan menopause yang dicurigai keganasan ovarium.

Kata kunci: *histopatologi, kanker ovarium, tumor sel granulosa*

Background

Ovarian cancer is the seventh most common cancer among women worldwide, with a prevalence of about 238,719 cases. It caused 151,917 deaths in 2012.[1] The number of new ovarian cancer cases was 11.7 per 100,000 women per year. The death was 7.4 per 100,000 women per year.[2] In Indonesia, ovarian cancer is the fourth most common female cancer diagnosed with an estimated 10,238 new cases and 7,075 deaths.[1] For all types of ovarian cancer, the 5-year relative survival is 45%. However, it will increase to 92% if it is treated in the early stage. Ovarian cancer is most frequently diagnosed among women aged 55-64 years.[2]

Table 1. Survival by stage

FIGO Stage	5-Year Survival (%)	10-Year Survival (%)
I	90-100	84-95
II	55-75	50-65
III	22-50	17-33 (combined data for stage III-IV)
IV	??	??

Ovarian cancer originated from one of three cell types: epithelial cells, stromal cells, and germ cells. The most common histology findings are epithelial cells (90%), 5-6% sex-cord stromal tumors, and 2-3% of germ cell tumors.[3] As the incidence of sex-cord stromal tumors is rare, most patients are diagnosed with the early-stage disease in contrast to epithelial ovarian cancer. According to INASGO cancer registration, there are 886 cases diagnosed with ovarian cancer in Indonesia during 2011-2013. About 81 cases were non-epithelial ovarian cancer, with 49 of those cases diagnosed as germ cell tumors and the other 42 as sex cord stromal tumors.[4] Sex-cord stromal tumors include granulosa cell tumors (GCTs), fibroma thecomas, and Sertoli-Leydig cell tumors (male characteristics), in which GCTs are more often found to be malignant than thecomas or fibromas.[5]

There are two subtypes of GCTs, which are adult and juvenile. The adult subtypes occur most commonly in middle-aged and older women (median age 50 to 54 years) and comprise 95% of these neoplasms, whereas juvenile types comprise 5% of all granulosa cell tumors.[5] The primary symptom of granulosa cell tumor is post-menopausal genital bleeding attributed to estrogen production. Half of the GCTs are accompanied by endometrial hyperplasia and 10% by endometrial carcinoma. However, in this case, the diagnosis of GCT was not associated with the clinical symptoms or the behavior of the neoplasm.[6] To address this issue, we present a rare case of asymptomatic adult-type granulosa cell tumor in a 65-year-old lady diagnosed during routine pelvic ultrasound scanning.

Case Illustration

A 65-year-old lady, P2A0, was referred from an urban hospital due to left ovarian mass three years before admission. During ultrasound examination, the mass was found to be enlarged in three years. She did not complain of any sign of uterine bleeding, abdominal mass, or abdominal discomfort. She had two living children and no history of hormonal contraceptive use with a BMI of 17.7kg/m^2. The only abnormal finding during the vaginal examination was the presence of a left adnexal mass with no sign of internal genital adhesion. Later, transvaginal ultrasound findings showed uterus atrophy with a 3.5 mm opening (suspected hydrometra) and a thin endometrial layer. One solid adnexal mass with a cystic part sized 4 cm was found on the left adnexal, with papillary projection and low resistance index (RI 0.4). Minimal ascites was found (Figure 1.1-1.4).

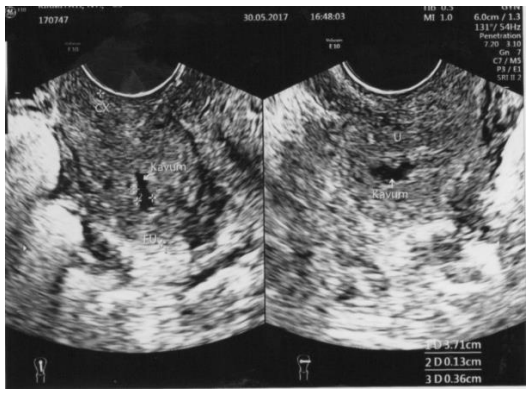

Figure 1.1. Uterine atrophy, hematometra, and thin endometrial layer

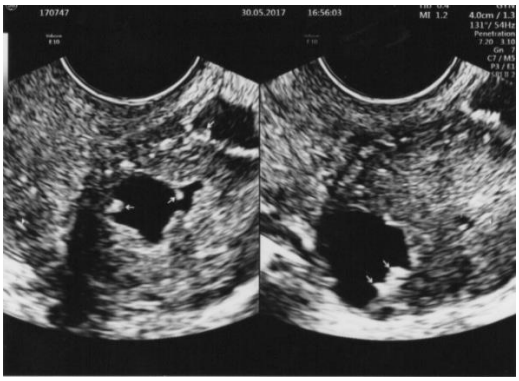

Figure 1.2. Cystic mass with papillary projections

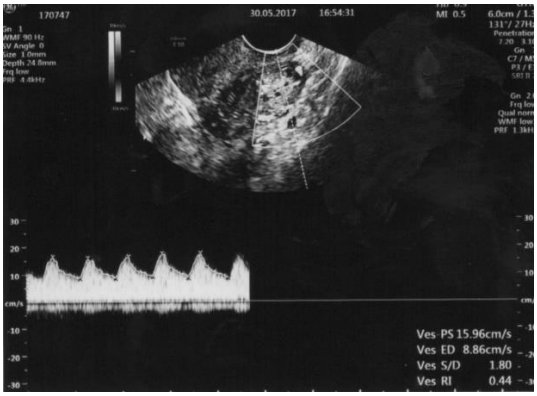

Figure 1.3. Low resistance index

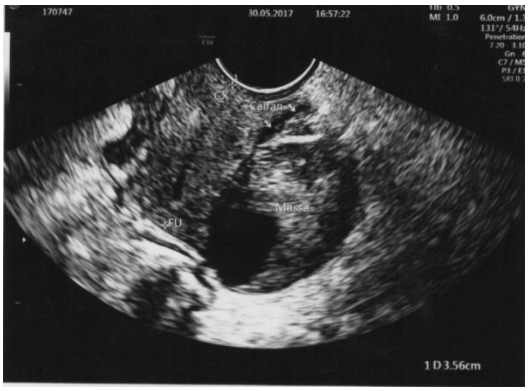

Figure 1.4. Ascites

MRI findings showed a left cystic mass comprised of solid part sized 48x35x46 mm, with an irregular border, fat stranding around the lesion, and minimal fluid collection (Figure 2.1-2). LDH increased to 263, while AFP (2.2 IU/mL), CEA (2.44 ng/mL), and CA-125 (9.6 U/mL) were within normal limit. The intra-operative finding showed a unilocular left solid mass with minimal ascites.

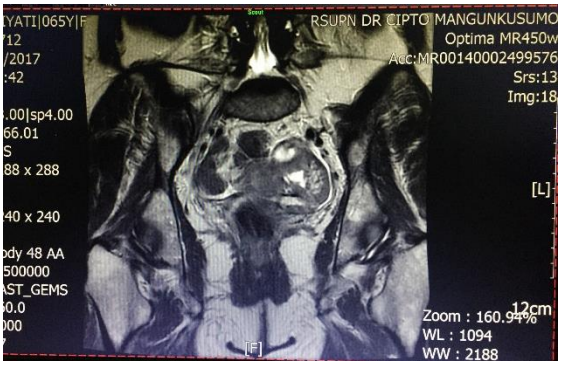

Figure 2.1. MRI finding: left cystic mass with solid part sized 48x35x46 mm with an irregular border

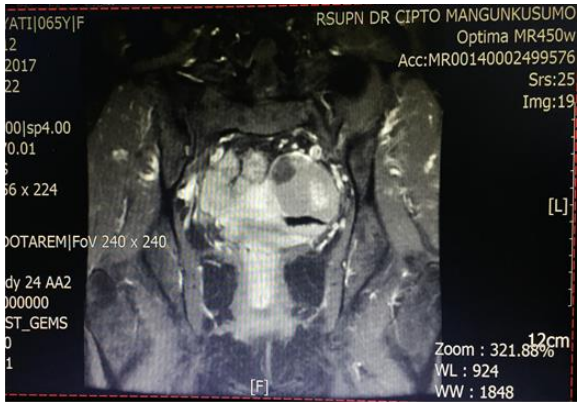

Figure 2.2. MRI finding: hyper-intense left cystic mass with solid part

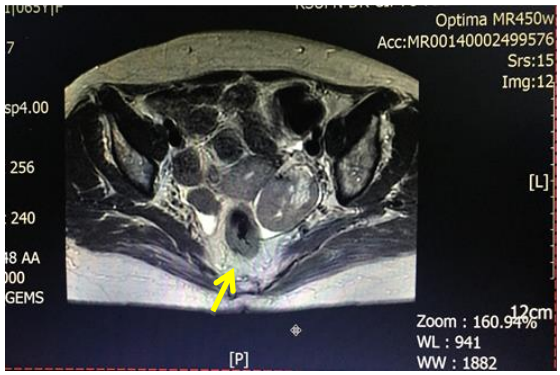

Figure 2.3. MRI finding: Fluid collection in the pelvic region (yellow arrow)

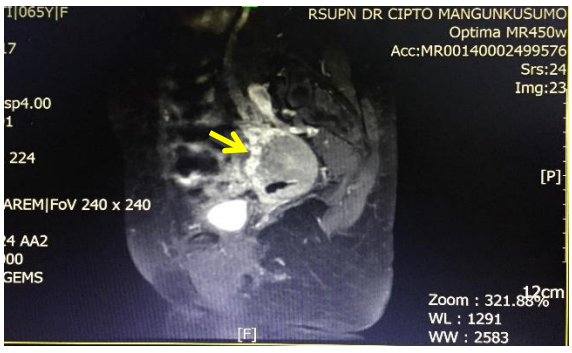

Figure 2.4. MRI finding: fat stranding covering the lesion (yellow arrow)

The solid mass cut-surface revealed a grayish mass with two cystic parts sized 2.5 cm filled with brownish fluid; no normal ovarian tissue was identified. The uterus was atrophic with a thin endometrial layer (Figure 3-4).

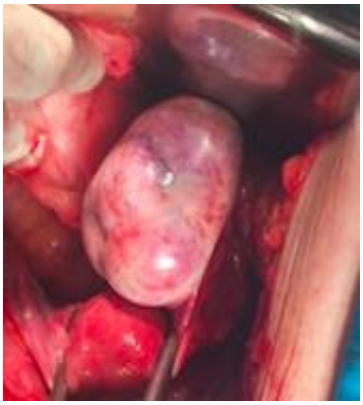

Figure 3. Solid mass with a smooth surface

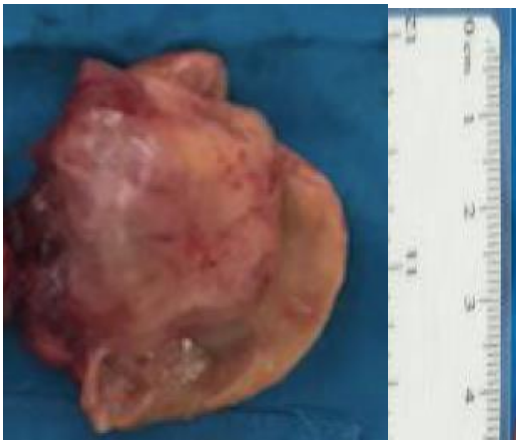

Figure 4. Grayish mass with two cystic parts sized 3 cm filled with brownish fluid

The result from the frozen section showed a granulosa cell tumor with a clinical stage of IA. Therefore, a total abdominal hysterectomy and bilateral salphyngo-oophorectomy were performed. Histopathology examination revealed adult-type granulosa cell tumor and classical Call-Exner body with grooved nuclei (coffee bean nuclei) (Figure 5.1-5.4). After seven months since the surgery, the patient is still alive and in good condition.

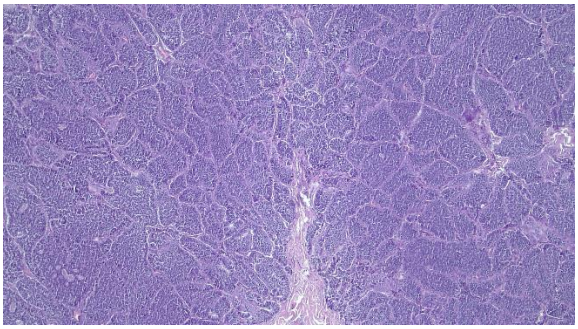

Figure 5.1. Granulosa cell type: nested islands (original magnification 40x)

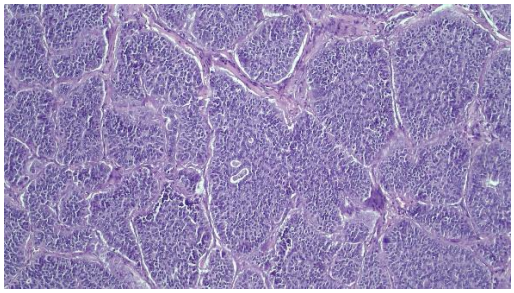

Figure 5.2. Granulosa cell tumor (original magnification 100x)

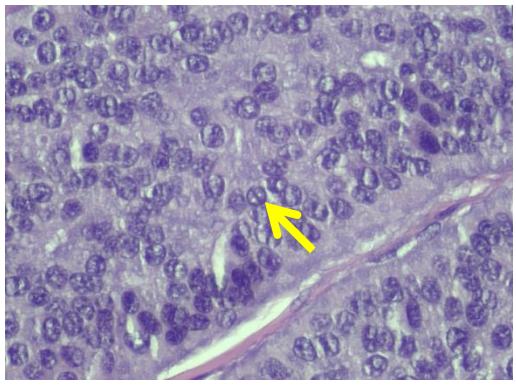

Figure 5.3. Coffee bean grooved nuclei (yellow arrow) (Original magnification 400x)

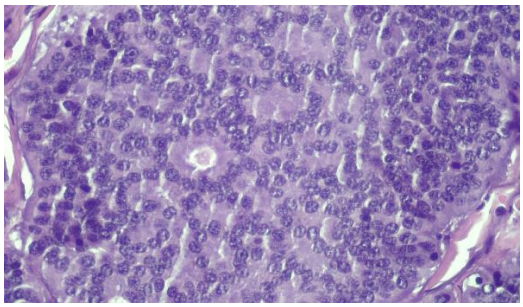

Figure 5.4. Call-Exner bodies resembling primordial follicle (original magnification 400x)

Discussion

Ovarian GCT is a rare neoplasm constituting less than 5% of all ovarian malignancies. GCT occurs at any age, 95% of which are middle-aged and older women (50-54 years) as the adult-type, and 5% occurs among children and young women (juvenile type).[5] Due to estrogen production, occult GCTs can lead to post-menopausal bleeding, although this was not the case in our patient. Most juvenile granulosa cell tumors occurred in children causing a sexual precocity characterized by the development of breasts and pubic and axillary hair.[7] In approximately 10% of the patients, the tumor was either discovered at the time of surgery for abnormal bleeding or found

only after histologic examinations. Endometrial hyperplasia is seen more frequently due to the endogenous estrogenic effect (25-50%) than well-differentiated endometrial carcinoma (5-13%). Other endometrial carcinomas related to GCTs are usually well-differentiated. The early stage is associated with a good prognosis, accompanied by other symptoms such as breast enlargement and tenderness. In our case, the patient had no complaints of uterine bleeding, abdominal pain, nor abdominal mass. The cystic mass was discovered during a routine check-up three years before admission. Thereafter, the size of the tumor had not been increasing in every annual check-up. This could be attributed to its natural history, in which GCT is considered to be slow-growing but with a tendency for a late recurrence.

The spreading type of GCT is a local, direct extension with intraperitoneal seeding. The tumors may also spread hematogenous, and patients can develop metastases in the lungs, liver, and brain years after the initial diagnosis. GCTs are also the most classic late-recurring malignancies in gynecology. Recurrences may not be detected for more than five years after the initial diagnosis. Eighty to ninety percent of GCTs are confined to the ovary. Advanced metastatic disease with ascites is present in about 10% of cases.

Imaging findings in adult GCTs vary widely, ranging from solid masses to tumors with varying degrees of hemorrhagic or fibrotic changes to a multilocular cystic lesion or completely cystic tumors. GCT is divided into two other common forms based on the ultrasound findings; a solid mass with heterogenic echogenicity and a multilocular solid mass with solid tissues around small locules without papillary projections. The latter forms a “Swiss cheese” appearance due to its small locules with variable thickness of solid tissue around the cystic areas. Ultrasound examination of the ovaries may help in assessing the ovarian functions and morphology. Thus, it has a more significant impact when used as a screening method for ovarian neoplasm. These findings were found on this case through ultrasound and MRI. Although not included in the classification, the MRI of this patient also has detected the fat stranding on the adnexal mass.[5,8-10]

In GCTs, several tumor markers can be used to identify the hyper estrogen symptoms such as:[8]

a. Estradiol
   Elevated estradiol levels are not a reliable marker for disease activity since fluctuated levels have also been found in patients with bulky disease or no response to treatment. GCTs do not produce estradiol in approximately 30% of cases due to the lack of theca cells in tumor stroma. It might happen to our patient in which she had no symptoms of uterine bleeding.

b. Inhibin
   This ovarian glycoprotein hormone consists of α-and two β-subunits, suppressing the synthesis and secretion of pituitary follicle-stimulating hormone (FSH). The GCTs have shown positive staining for inhibin-A and the activins. However, inhibin B may be more frequently elevated. Serum inhibin levels will fall following tumor removal; therefore, it can be utilized as a tumor recurrence marker. This tumor marker is more reliable in reflecting disease activity compared to estradiol.

c. Follicle regulatory protein (FRP)
   FRP is secreted normally in regularly menstruating women. It can be produced due to the differentiation of granulosa cells. However, the clinical importance of this tumor marker is not yet known.

d. Mullerian inhibitory substance (MIS)
   Granulose cells produce MIS in developing follicles. In several studies, serum anti-Mullerian hormone (AMH) concentrations were determined in GCTs. Serum AMH was undetectable in normal post-menopausal women and had a mean concentration of <5µg/L in pre-menopausal women. Levels were between 6.8 and 117.9µg/L in patients with progressive granulosa cell tumors. Although the clinical usefulness of MIS is still under investi-gation, this hormone might prove to be a valuable marker of GCT’s activities.

However, these tumor markers level were not evaluated in our patients due to limited resources. Thus, CA-125 is not sensitive to predict GCTs malignancy.[11]

According to the study, the gross appearance of adult-type GCTs is large tumors with an encapsulated structure, forming a smooth or lobulated surface. The cut-surface reveals solid or cystic structure areas in varied proportions, with a grey or yellow hue, depending on the amount of intracellular lipid in the lesion. Some GCTs may form multi-cystic lesions that resemble mucinous cystadenoma or lesions filled with serous fluid. Nevertheless, these types of GCTs are uncommon. Hemorrhagic areas containing cysts with clotted

bleed are mostly found only in larger GCTs, usually without necrosis. Histologically, granulosa cells of the adult subtype appear round, pale, with scant cytoplasm, classic coffee bean nuclei, and Call-Exner bodies. The nuclei of undifferentiated carcinomas are frequently hyperchromatic, ungrooved, and unequal in both size and shape. In contrast, the juvenile subtype has eosinophilic and/or vacuolated cytoplasms with macrofollicular or cystic patterns. They are composed of immature granulosa cells with frequent mitoses; Call-Exner bodies and coffee bean grooved nuclei are not commonly found.[5,10]

The hypersecretion of hormones also causes endometrial pathology. Endometrial hyperplasia and leiomyoma are several examples found in GCT histopathology examinations.[12] Some endometrial hyperplasia can also develop into endometrial carcinoma in 5 to 13% of cases.[12] Pathologic endometrial findings in cases of GCT are suspected in only 5/13 cases during preoperative ultrasound examinations by gray-scale and color Doppler. They were then confirmed histologically in 54% of the patients after biopsy.[10]

Patients with GCTs generally present with a stage-I disease. Therefore, surgical management is often performed, similar to the use of epithelial ovarian cancer treatment. The initial operation is vital for determining which patients are more likely to have a recurrence. A total hysterectomy and bilateral salphyngo-oophorectomy (TAH BSO) should be performed for post-menopausal women, including endometrial biopsy to rule out endometrial cancer. If the patient is young with the desire to preserve fertility, and the disease is confined to one ovary, then unilateral salphyngo-oophorectomy (USO) should be performed (incidence of bilateral tumor is approximately 2-8%). GCT is a potentially responsive tumor to single-agent or combination chemotherapy. Besides, patients with stage I disease have an excellent prognosis (long-term disease-free status is about 90%), making further adjuvant treatment unnecessary.[8]

Several prognostic factors have been reported to be significant for GCTs. The clinical factor which is shown to be related to recurrence is the tumor stage (Table 1). Overall 10-year survival rates for patients with GCT have been reported to lie between 60% and 90%, but the 25-year survival rate is only 40-60%. Tumor size has been reported to have a prognostic significance; tumors with 5 cm or less in size have better progression-free survival and 10-year survival. Nevertheless, some investigators still do not support these findings.

Conclusion

This case report has concluded GCT as the main finding of the patient. These rare, slow-growing tumors are most often found with hyper estrogen symptoms such as post-menopausal bleeding in women and girls. Although it was not performed in this case report, ultrasound of the GCT might either reveal a large solid mass with heterogeneous echogenicity or a multilocular-solid mass accompanied by multiple small locules in color or power Doppler examinations. In this case, the diagnosis of GCT was made through histological findings (coffee bean grooved nuclei, Call-Exner bodies), which were consistent with previous findings. Therefore, a laparotomy frozen section can be considered in menopausal women with suspected ovarian neoplasms.

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