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RESEARCH ARTICLE

Characterization of Ovarian Granulosa Cell Tumors using Magnetic Resonance Imaging

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ABSTRACT

Purpose: To identify the MRI features that aid in the characterization of **ovarian** granulosa cell tumors.

Materials and methods: 11 MR pelvis of an adult woman with **pathology-proven ovarian** granulosa cell tumors with surgical pathology.

We evaluated the patient's age, Ca-125, size, laterality, and with MRI features such as indirect signs (i.e., thickened endometrium > 0.9 cm), morphology (cystic, solid-cystic, or solid), subacute hemorrhage, T2 signal (low or intermediate-to-high), restricted diffusion (B values: 0, 50, 1000 sec/mm³/ADC), and dynamic enhancement (intense or similar to myometrium). Also, the presence of ascites, peritoneal implants, or adenopathy.

Results: The final cohort included 11 women with a surgical-pathological diagnosis of granulosa cell tumors. The median age was 52.4 years (range, 17-80). The Ca-125 level was within normal limits. The median size was 9.4 cm. Most cases were unilateral (81.8%) and more frequent on the left (54.5%).

MRI Analysis: 36.4% had endometrial thickening. **Ovarian** granulosa cell tumors were polymorphous: cystic (54.6%), mixed solid-cystic (9.1%), and solid (36.3%). Most GC had intermediate to high signal on T2 (90.9%), restricted diffusion (81.8%), intense enhancement (81.8%), and 36.4% had intraparenchymal bleeding. 9.1% had associated implants/adenopathy/ascites at diagnosis.

Conclusion: The MRI features characteristic of **ovarian** granulosa cell tumors were the polymorphous morphology, an intense enhancement to the myometrium, restricted diffusion, and the presence of intraparenchymal hemorrhage.

Keywords: Granulosa cell tumor of the ovary; magnetic resonance imaging; ovarian neoplasms; Neoplasms, Germ Cell, and Embryonal

List of abbreviations:

GC: granulosa cell tumors.

MRI: magnetic resonance imaging.

1. INTRODUCTION

The sex cord-stromal tumor represents 7% of all ovarian tumors ¹, and the different histologic subtype includes thecomas/fibrothecomas, granulosa cells, Sertoli-Leydig, sclerosing stromal, and gonadoblastoma ². The most frequent is the thecomas/fibrothecomas, the most common solid benign tumors in women ³, and most are benign and do not require treatment. However, granulosa cell tumors (GC) are the most frequent potential malignant tumor of sex cord-stromal tumors (90%) and 2%-5% of all ovarian malignancies ⁴.

There are two histopathological subtypes of GC ^{5,6}, adult and juvenile, with different clinical implications ¹. GC-adult accounts for 95% and presents between 50 and 55 years of age ¹. Patients can be asymptomatic or have abnormal vaginal bleeding, abdominal pain, or distention due to torsion, hemorrhage, or rupture ¹. GC-adult lesions are variable in size and can measure up to 40 cm ¹, and more than 95% are unilateral ^{1,5}. Contrarily, 90% of GC-juvenile occurs in pre-pubertal girls. In addition, 95% are also unilateral and present at stage I ¹ with precocious puberty ¹.

Up to 80% of GC can produce estrogen ⁷, which can cause endometrial hyperplasia. In addition, it has variable atypia in 24% to 80% of cases, and up to 5% are associated with endometrial adenocarcinoma ^{1,8,6}. The laboratory markers that contribute to the diagnosis are inhibin A and B, secreted by the ovaries in response to follicle-stimulating and luteinizing hormones. On the contrary, ovarian epithelial tumors usually have an elevated Ca-125 ⁶.

Surgical resection is the primary treatment for GC, especially for the localized disease ⁹. Fertility sparing approaches such as unilateral salpingo-oophorectomy and appropriate surgical staging is possible in premenopausal patients. However, in post-menopausal women, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection are performed ¹⁰. Adjuvant treatment with chemotherapy may be helpful in more widespread diseases to prevent recurrence; however, its indication and regimen are not well established ¹¹. GC can even recur 37 years after the initial diagnosis ^{1,8}. Nevertheless, they have an excellent prognosis of about 78% to 91% at stage I. On the contrary, stage III or IV have a 5-year survival of up to 22%, similar to epithelial ovarian cancer ¹.

The radiological evaluation plays an integral part in treatment decision-making, suggesting the probable diagnosis, which carries a different therapeutic approach, and the surveillance after surgery, given the possibility of recurrence. Among the radiological modalities, magnetic Resonance Imaging (MRI) is the imaging modality of choice for evaluating adnexal masses of indeterminate etiology due to the excellent tissue characterization and delineation of the anatomical relationship between the ovaries and the surrounding structures for surgical procedures planning ⁸. Therefore, our objective is to describe the clinical, pathological, and MRI findings of a cohort of patients with GC to familiarize the reader with critical clinical and radiological aspects.

2. MATERIALS AND METHODS

2.1 SUBJECTS

The institutional review board at our institution approved this study and waived the requirement for informed consent. This study was under our country's Personal Data Protection Law (Habeas Data Law).

With the support of the Informatics service of our institution, we searched consecutive adult women (i.e., equal to or greater than 18 years old) with an in-house surgical pathological report of "granulosa cell tumor" between the period January 1, 2016, and December 31, 2020. We retrieved the patients with such a diagnosis and a pelvic gynecological MRI report available before the initial surgery. The time frame between the preoperative MRI and surgery was less than one month. All of the patients had one MRI at baseline acquired in our institution with the same MRI acquisition protocol. The start period corresponds to introducing a picture archiving and communication system (PACS) in this institution.

2.2 MRI ACQUISITION

All MRIs were in-house studies acquired on 1.5 T (Magnetom Avanto and Essenza Siemens, Erlangen, Germany) scanners by using a phased-array body coil. All the sequences obtained were from the aortic bifurcation to the pubic symphysis with a field of view of 22 to 26 mm, 4 mm in slice thickness, and 0 mm in crosstalk. The protocol included T2-weighted images on axial, coronal, and sagittal;

T1-weighted images without fat suppression of fat on axial and with suppression of fat on axial; diffusion images with B values of 0, 50, and 1000 sec/mm² with their correspondent apparent diffusion coefficient mapping (ADC); and one before and five after gadolinium injection T1-weighted volumetric sequences in the axial plane (VIBE) with their correspondent subtraction image s. The dose of gadolinium injected was 0.1 cc/kg of patient body weight in a manual fashion followed by ten ccs of physiological solution, and images were acquired 10 seconds after the bolus injection for a total of 180 seconds.

2.3 MRI ANALYSIS

Two fellowship-trained radiologists with 2 and 4 years of experience in gynecological imaging reviewed independently on a PACS viewing system. Readers were blinded to the final pathology, clinical information, and the original radiology report at the time of review. In cases of discrepancy, a third radiologist with 15 years of experience after fellowship independently reviewed and concluded.

Also, we recorded from the Electronic Medical Record demographic data such as age and the level of the tumor marker Ca-125.

2.4 DEFINITIONS AND CRITERIA

We analyzed the following clinical characteristics and MRI features:

Clinical characteristics:

- Patient age, expressed in years and range.
- Serum level of tumor marker Ca-125, expressed in mean and standard deviation.
- Laterality: unilateral or bilateral, left or right-sided.
- Size: measured in centimeters (cm) in the largest diameter.

MRI features, based on the definition proposed by Bazot et al.⁷.

- Morphological appearance of the adnexal mass:
 - Cystic.
 - Mixed solid-cystic.
 - Solid.
- Presence of indirect findings: endometrial thickening (i.e., more than 0.9 centimeters on a sagittal plane) in post-menopausal women.

- Presence of intratumorally bleeding - subacute hemorrhage (i.e., high signal on T1-fat suppression images).
- Solid tissue present:
 - T2-weighted images: hypointense/low or intermediate-to-high compared to the external myometrium.
 - DWI/ADC: presence or lack of restriction diffusion; qualitative assessment compared to the intensity of the bladder content in B=1000 value.
 - Dynamic enhancement: intense/higher than myometrium or similar to the external myometrium.
- Presence or absence of ascites or peritoneal implants.

2.5 STATISTICAL TESTS

We described continuous variables as median and interquartile ranges and compared them with the Mann-Whitney test. We described categorical variables as absolute and relative frequency and compared them with the Fischer Exact Test. We performed all analyses by Software for Statistics and Data Science (STATA) version 13.

3. RESULTS

3.1 SUBJECTS

The final cohort included 11 women with a surgical-pathological diagnosis of GC [Table 1]. The median age was 52.4 years (range, 17-80). The Ca-125 level was within normal limit s. The median size was 9.4 cm. Most cases were unilateral (81.8%) and more frequent on the left (54.5%).

3.2 MRI ANALYSIS

36.4% of patients had associated endometrial thickening (i.e., more than 0.9 cm).

GC was polymorphous, most commonly (54.6%) cystic [Figures 1 and 2], mixed solid-cystic (9.1%), and solid (36.3%).

Most GC had intermediate to high signal on T2 (90.9%), restricted diffusion (81.8%), and intense enhancement (81.8%). Also, 36.4% had intraparenchymal bleeding.

Finally, only 9.1% of GC had associated implants at diagnosis.

Table 1: Baseline characteristics of the patients analyzed and the frequencies of the MRI features.

Variable		GC (n=11)
Age (years)		52.4 (17-80)
Ca-125 (ng/mL)		8.8 (6.5-17.1)
Size, maximum diameter (cm)		9.4 (4.2-13)
Laterality	Unilateral	9 (81.8%)
	Right	3 (27.2%)
	Left	6 (54.5%)
	Bilateral	2 (11.2%)
Subacute hemorrhage		4 (36.4%)
Indirect signs	Endometrial thickness	5 (45.5%)
Morphology	Cystic	6 (54.6%)
	Cystic-solid	1 (9.1%)
	Solid	4 (36.3%)
T2-signal	Intermediate to high	10 (90.9%)
	Low	1 (9.1%)
Restricted diffusion	Present	9 (81.8%)
	Absent	2 (11.2%)
Contrast enhancement	Higher than myometrium	9 (81.8%)
	Similar to myometrium	2 (18.2%)
Implants	Present	1 (9.1%)
	Absent	10 (90.9%)

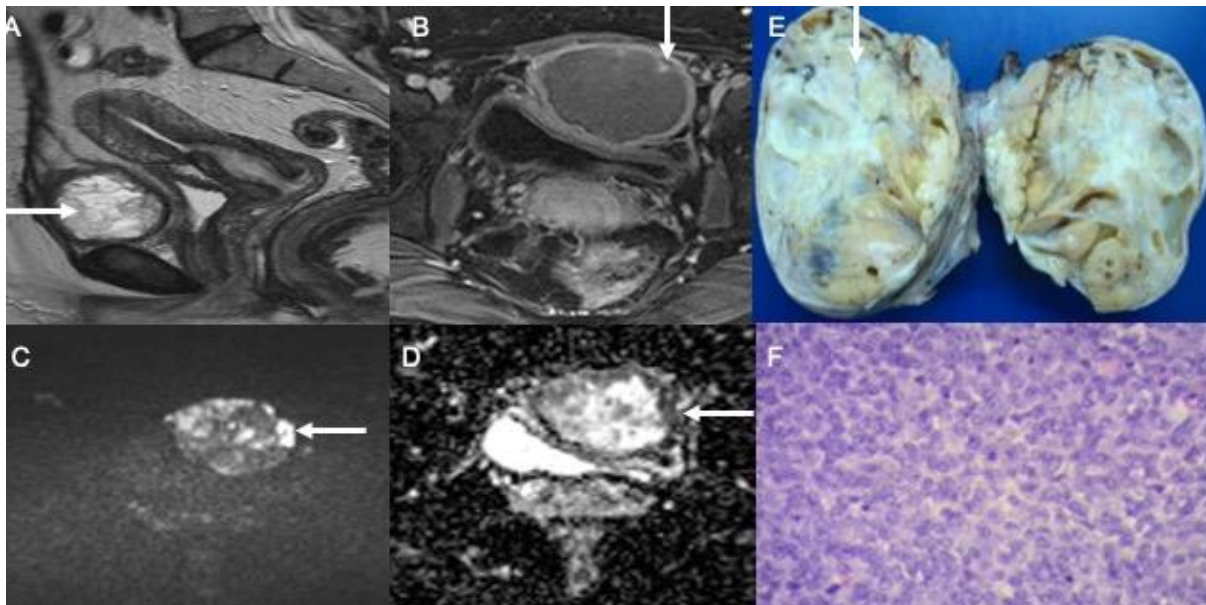


Figure 1.

History: 39-year-old woman in study for incidental lesion found on US. Ca-125 level: 6.5 ng/mL.

MRI female pelvis without and with gadolinium. (A)Sagittal T2-weighted; (B) Axial T1-FS gadolinium; (C) DWI - B value: 1000 sec/mm³; (D): ADC.

Pathological correlation: (E) Gross specimen; (F) Histopathology Hematoxylin/Eosin 100x.

It shows a multiseptated cystic lesion in the left ovary. The septations (arrows) have mild restricted diffusion and similar enhancement to the myometrium. On gross examination, it has a multicystic appearance. On hematoxylin/Eosin, it shows neoplastic cells with eosinophilic cytoplasm and oval nuclei with rare grooves.

Final diagnosis: Granulosa cell tumor, adult subtype.

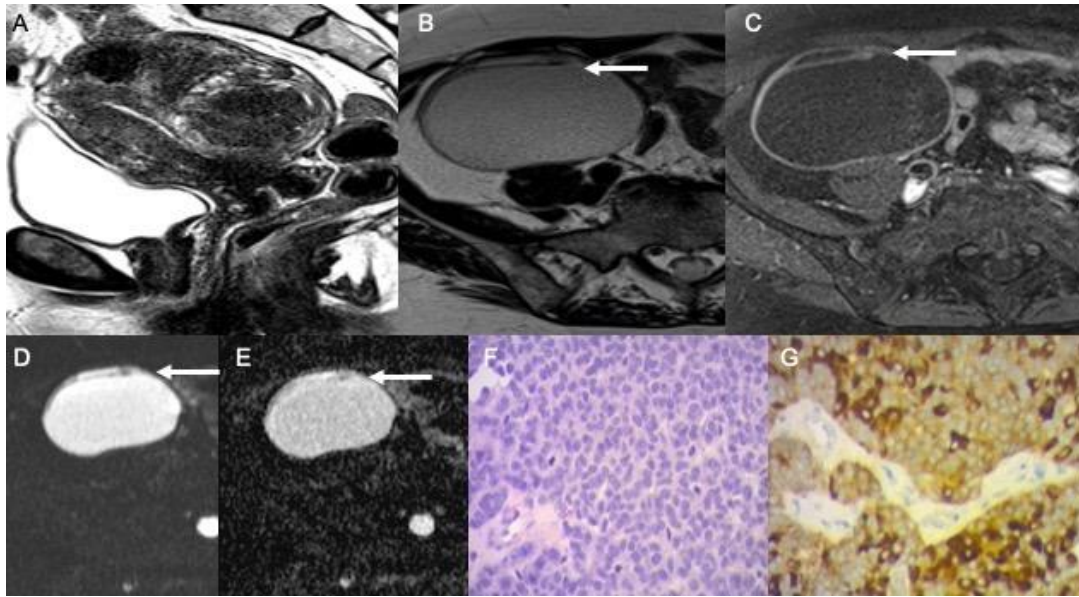


Figure 2.

History: 56-year-old woman in study for pelvic pain. Ca-125 level: 15.40 ng/mL.

MRI female pelvis without and with gadolinium. (A) Sagittal T2-weighted; (B) Axial T2-weighted; (C) Axial T1-FS gadolinium; (D) DWI - B value: 1000 sec/mm³; (E): ADC.

Pathological correlation. (F) Histopathology Hematoxylin/Eosin 400x; (G): Immunohistochemistry.

MRI shows a cystic mass in the right ovary with septation (arrows), which is thin, lacks restricted diffusion, and enhances, similar to the myometrium.

Hematoxylin/eosin shows neoplastic cells with eosinophilic cytoplasm and oval nuclei with rare grooves. There is intense and diffuse positivity for inhibin on immunohistochemistry.

Final diagnosis: Granulosa cell tumor, adult subtype.

4. DISCUSSION

The MR features characteristic of GC were the polymorphous morphology, an intense enhancement to the myometrium, restricted diffusion, and the presence of intraparenchymal hemorrhage.

The clinical characteristics analysis performed is in line with the existing literature regarding the utility of the Ca-125 tumor marker in the evaluation of masses of epithelial origin ⁷. In contrast, in GC, the helpful tumor marker is the inhibin ⁶, which correlates to the reported frequency of GC secreting estrogen is 80 %. Remarkably, such estrogen production can generate indirect findings associated, such as endometrial hyperplasia ⁷, which was present in 36.4 %. Our results align with the literature reported that most GC present at initial diagnosis without associated ascites, abdominopelvic adenopathy, or implants helping to distinguish them from advanced epithelial tumors ⁷.

The appearance of GC in our cohort, in terms of size and morphology, is in line with the existing literature, that GC tends to be larger and has more variable morphology ^{12 2 6 1 3}. Although our sample

of GC is small, we found cases of each type of morphological appearance in concordance with pathological articles ^{1 3}. On the contrary, *Zhang et al.*, in their analysis of 18 patients, found the two most frequent morphological appearances were either solid or predominantly solid masses ¹² [Figure 3]. Of note, no one of the patients analyzed with GC had papillary projections, aiding in the differentiation with ovarian epithelial tumors ⁸.

Similar to *Zhang et al.* and other groups in the field¹², intratumorally bleeding was seen in 36.4% of cases ¹⁴. Some authors have proposed that the former is a predictive feature of recurrence and decreased free survival ¹⁵ [Figure 4].

Moreover, we found that the presence of restricted diffusion is frequently seen in GC (81.8%), similar to the reported by other groups such as *Zhang et al.* ¹², probably concerning the increased cellularity of GC and malignant potential ⁷.

Finally, we found that GC frequently had intense enhancement to the myometrium, a feature did not report before ^{2,12,13,16}, and probably concerning the tumor neoangiogenesis and malignant potential ⁷ [Figures 5 and 6].

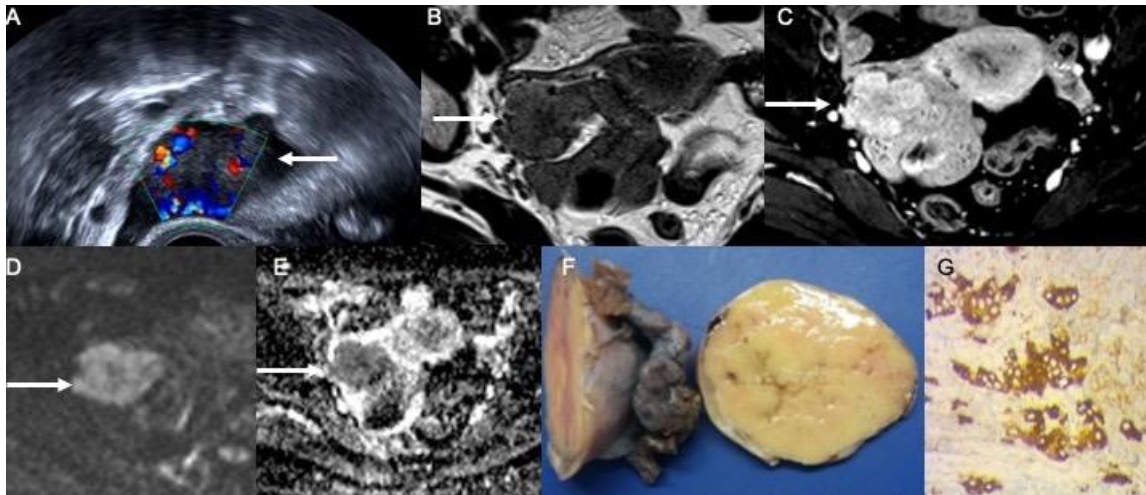


Figure 3.

History: 61-year-old woman in study for vaginal bleeding. Ca-125 level: 9.20 ng/mL.

Transvaginal Ultrasound 2D (A).

MRI female pelvis without and with gadolinium. (B) Axial T2-weighted; (C) Axial T1-FS gadolinium; (D) DWI - B value: 1000 sec/mm³; (E): ADC.

Pathological correlation. (F) Gross specimen; (G) Immunohistochemistry.

It shows a solid lobular mass (arrows) in the right ovary with increased vascularization at Doppler. Further MRI shows that the mass has intermediate to low signal intensity on T2, restricted diffusion, and similar enhancement to the myometrium.

The gross examination shows a solid lobulated mass composed of neoplastic cells with positivity for inhibin in immunohistochemistry.

Final diagnosis: Granulosa cell tumor, adult subtype.

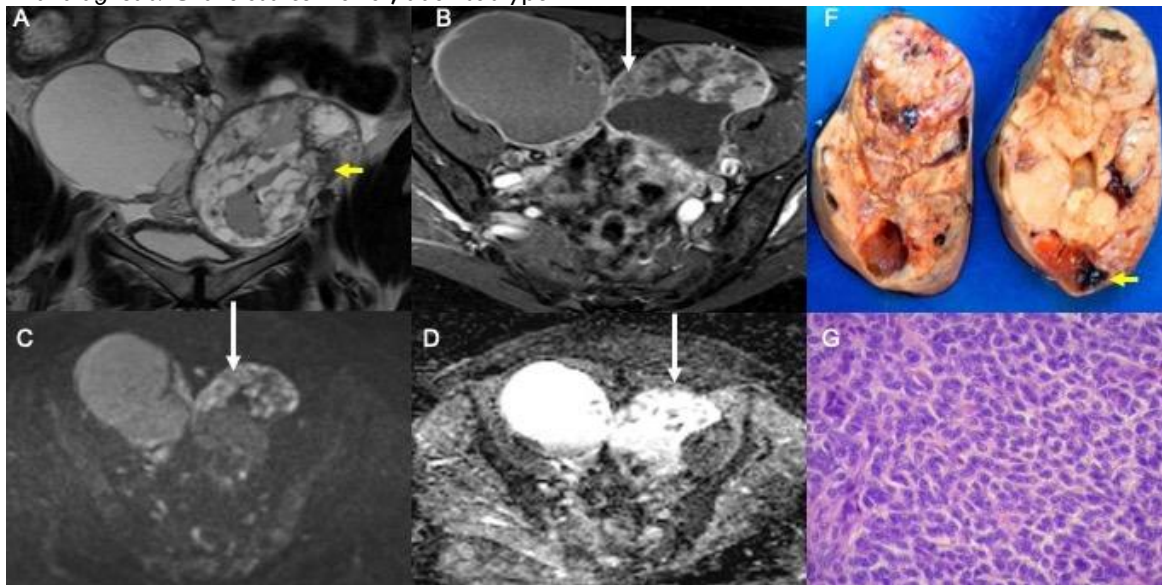


Figure 4.

History: 31-year-old woman in study for palpable mass. Ca-125 level: 21.20 ng/mL.

MRI female pelvis without and with gadolinium. (A) Coronal T2-weighted; (B): Axial T1-FS gadolinium; (C) DWI - B value: 1000 sec/mm³; (D): ADC.

Pathological correlation. (E) Gross macroscopy; (F): Histopathology Hematoxylin/eosin 400x.

MRI shows solid-cystic masses in both ovaries (arrows). The solid component has a homogenous intermediate signal on T2, restricted diffusion, and intense enhancement.

On gross pathology, it is a solid-cystic mass with hemorrhagic areas. On microscopy, neoplastic cells with eosinophilic cytoplasm and oval nuclei with rare grooves composed the tumor.

Final diagnosis: Granulosa cell tumor, juvenile subtype.

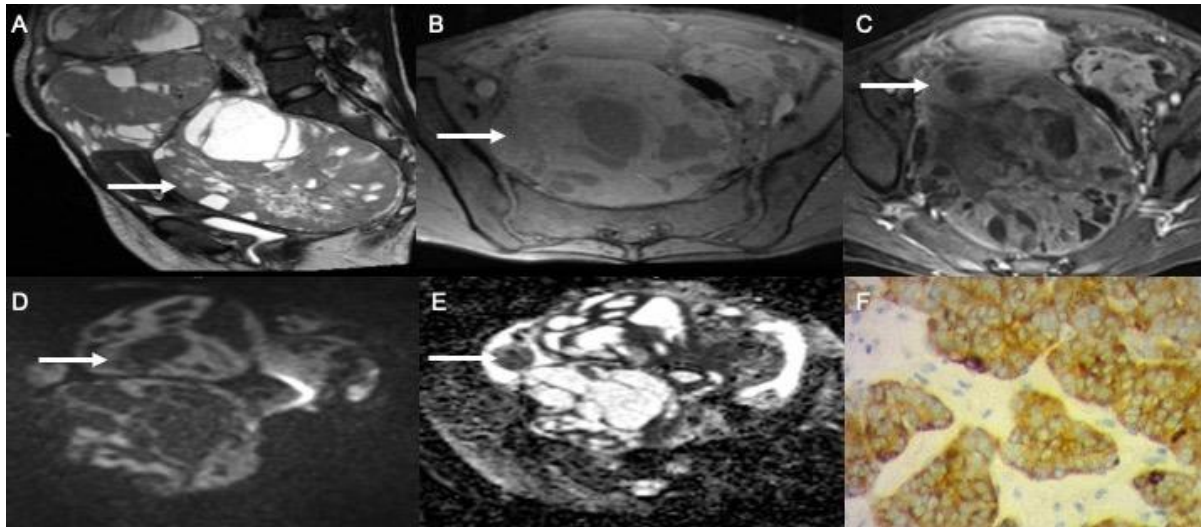


Figure 5.

History: 40-year-old woman in study for pelvic pain. Ca-125 level: 6 ng/mL.

MRI female pelvis without and with gadolinium.

(A) Sagittal T2-weighted; (B) Axial T1 FS-weighted; (C) Axial T1-FS gadolinium; (D) DWI - B value: 1000 sec/mm³; (E): ADC.

Pathological correlation. (F) Immunohistochemistry.

It shows on both adnexa mixed solid-cystic masses. In addition, there are irregularly thickened septations (arrows), which have restricted diffusion and intense enhancement.

There was positivity for inhibin in immunohistochemistry.

Final diagnosis: Granulosa cell tumor, adult subtype.

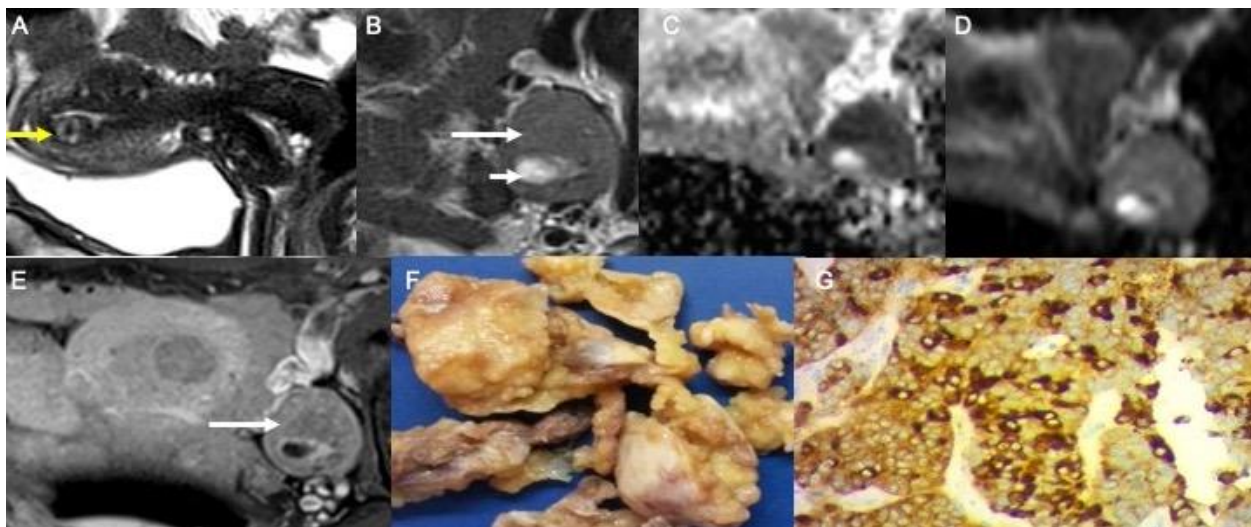


Figure 6.

History: 59-year-old woman in study for characterization of incidental mass noted on US. Ca-125 level: 8.8 ng/mL.

MRI female pelvis without and with gadolinium.

(A) Sagittal T2-weighted; (B) Axial T2-weighted; (C) DWI - B value: 1000 sec/mm³; (D): ADC; (E) Axial T1-FS gadolinium. *Pathological correlation.* (F) Gross specimen; (G) immunohistochemistry.

MRI shows a solid mass (long white arrow) with a small cystic component in the left ovary (short white arrow). The mass has a homogenous intermediate signal on T2, restricted diffusion, and similar enhancement to the myometrium. In addition, there are a few subendometrial cysts, probably representing adenomyosis (yellow arrow).

The mass has been sectioned by half and shows a solid nodular appearance on gross examination. On immunohistochemistry, there is positivity for inhibin.

Final diagnosis: Granulosa cell tumor, adult subtype.

Our study has many limitations. First, there may be a selection bias due to the study's retrospective design. Second, our population of interest in the study is tiny and could not study features to distinguish between GC-adult and GC-juvenile subtypes. Third, we could not provide quantitatively enhancement parameters such as Ktrans, Kep, or Ve because our institution acquired the infusion pump after this project. Also, all the MRIs analyzed were from a single tertiary center highly tailored to specific diseases and conditions, which may limit the generalizability to different settings, i.e., a community hospital and private practice, among others. Finally, we only provided the value of Ca-125, not more specific tumor markers such as inhibin. Since only a few laboratories study inhibin, we only request it in cases of suspected recurrence in our country, but not at the diagnosis.

5. CONCLUSION

The MR features characteristic of GC were the polymorphous morphology, an intense enhancement to the myometrium, restricted diffusion, and the presence of intraparenchymal hemorrhage.

KEY POINTS:

- GC has variable morphology.
- GC has frequent intense and early enhancement.
- GC has frequent intratumoral bleeding.

SUMMARY STATEMENT

The MR features characteristic of GC were the polymorphous morphology, an intense enhancement to the myometrium, restricted diffusion, and the presence of intraparenchymal hemorrhage.

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Conflicts of Interest: None.

Ethical standards: this study was approved by the IRB.

Informed consent: it was waived for this retrospective investigation by the IRB as this study was of minimal risk, and data were deidentified.

Consent for publication: all authors expressed explicit consent for the publication of this manuscript.

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