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Case Report

Unusual radiologic imaging in juvenile granulosa cell tumor with precocious puberty: A unilocular cyst ☆

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ABSTRACT

Juvenile Granulosa Cell Tumor (JGCT) represents 5% of all granulosa cell cancers. Precocious puberty is a frequent feature of this tumor. A 2-year and 2-month-old girl was referred with a diagnosis of suspected ovarian cancer, dysfunctional uterine bleeding, and precocious puberty. Radiologic examination revealed the following: Abdominal ultrasonography showed a solitary anechoic cystic lesion in the pelvic cavity. MRI confirmed the existence of solid components on its walls. JGCT was then confirmed using immunohistochemistry (IHC) markers. JGCT, along with adult granulosa cell tumors (AGCT) are subgroups of granulosa cell tumors (GCTs), which are part of pure sex cord tumors. The 2 forms share imaging findings due to their comparable gross appearance. GCTs require diagnostic imaging tests to distinguish them from other ovarian tumors. Two ultrasound patterns can be identified GCTs, and MRI showed that GCTs are more heterogeneous than other sex-cord stromal tumors (OSCs). In our case, the imaging characteristics for juvenile granulosa cell tumors were nonspecific and these tumors cannot be reliably distinguished from other ovarian neoplasms based on imaging alone. Although GCTs have imaging characteristics that can help to distinguish them from other tumors, confirmation by histopathology and IHC is still mandatory, especially in cases with nonspecific radiological features.

Background

Precocious puberty refers to the manifestation of secondary sexual characteristics before the age of 8 in girls and 9 in boys. The signs of puberty experienced by a girl are characterized by the development of breasts (thelarche), while in boys the development of the testicles in both volume and length. Precocious puberty is classified into 2 types: central and peripheral. Peripheral precocious puberty can be due to 2 types of etiolo-

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gies: acquired or hereditary conditions, and functional tumors or cysts are among the acquired causes [1]. Granulosa cell tumors, part of ovarian sex cord-stromal tumors, are uncommon in children. Classified as juvenile and adult types, 5 percent of granulosa cell tumors are juvenile types. These tumors often cause premature pseudo-puberty, which is associated with hormonal changes [2]. Radiologic findings can be of value in the diagnosis, however confirmation from histopathology and immunohistochemistry (IHC) is the determining factor for the diagnosis. We report a case of a 2-year and 2-month-old girl with precocious puberty confirmed to have juvenile granulosa cell tumor by IHC examination with atypical radiological features.

Case report

A 2-year and 2-month-old girl complained of vaginal bleeding and abdominal enlargement. The first episode of vaginal bleeding was at the age of 4 days and lasted for a week. The patient was consulted to a pediatrician, who diagnosed it as a result of maternal hormones. When the patient was 1-year-old, her parent realized that the patient's breasts began to enlarge, and the abdomen gradually grew in size. Vaginal bleeding occurred again at a week before admission, initially in large amounts, then progressively decreased until less than a pad a day. The patient was then admitted to a general hospital in Lumajang. Subsequently, the patient was referred to our hospital with the diagnosis of suspected ovarian cancer, dysfunctional uterine bleeding, and precocious puberty.

The patient's vital signs and general inspection revealed nothing unusual. The patient's weight was 15 kg and height was 86 cm, normocephalic, and had normal nutritional status. The patient never showed symptoms of headache or visual disturbances. Laboratory evaluations showed a high level of prolactin of 54.41 ng/mL, estradiol of 120 pg/mL, LDH level of 328.5 U/L, and CA-125 of 39.6 mIU/mL accompanied by low FSH 0,045 mIU/mL. LH, while thyroid function test, Quantitative ß HCG, Alfa Feto Protein (AFP) and CEA were within normal limit.

Radiologic examination was also conducted. An abdominal ultrasound revealed a single, unilocular, anechoic cystic lesion at the superior uterus (pelvic cavity) that extended into the abdominal cavity. The lesion had posterior enhancement and was septa-free, solid component not visualized, measuring at ± 10.1 × 4.76 × 9.8 cm (Fig. 1). There was no enlargement of the para-aortic nodes or ascites. Other abdominal organs were normal. Hand X-rays were then used to determine the bone age according to the Greulich and Pyle's classification, with results showing a 3-year-old and 6-month-old girl, which is advanced for her age. The chest X-ray was normal.

Abdominal and pelvic MRI showed an enlarged uterus with a size of ± 2.2 × 3.6 × 4.3 cm (volume ± 17.68 cc), the junctional zone and endometrial line appeared normal, the ratio of the uterine body to the cervix was 2:1 (normal ratio in children is 1:1), the cervix was in the anti-flexion position, without masses, cysts, or calcifications. The cervix and vagina were both normal and had regular borders. At the right ovary a cystic lesion was found, with well-defined borders, no septum or calcification inside, with a size of ± 5.2 × 10.9 × 11.8 cm, along with a solid component on its wall with maximum thickness of ± 1.01 cm (Fig. 2). The cyst extended into the abdominal cavity, compressing the distal and medial ureter, causing dilatation of the right proximal ureter with mild ectasis of the right pelviocaliceal system, and also compressing the bowels to the left side (Fig. 3). The left ovary and pelvic inlet were both normal and no ascites was found. In conclusion, MRI findings revealed a right ovarian cyst causing mild hydroureter and hydronephrosis on the right side with uterine enlargement suggestive of pseudo-precocious puberty.

Surgical management was advised due to a high prolactin level and a risk of malignancy. A laparoscopic procedure with a DJ stent implantation was planned. A uterus the size of a menstruating girl, with no adhesions nor other abnormalities, was discovered intraoperatively (Fig. 4). Bilateral adnexal parametrium was within normal ranges. A ±10 cm cyst was found on the right ovary, with no adhesion or nodule on its surface. Douglas' cavity and omental were both normal. Ultimately, a right ovariectomy via laparoscopy was performed after a direct decompression of the ovarian cyst. The tumor was a FIGO Stage IA tumor, and any additional treatment was not needed.

The cyst was then sent for pathology examination and the result was an ovarian sex cord-stromal tumor of the right ovary (Fig. 5) with high mitotic activity (20 mitosis per 10 high power fields). Immunohistochemistry (IHC) examination showed positive inhibin in the cytoplasm of the tumor cell, calretinin was positive in the tumor cell nucleus and cytoplasm, positive WT-1 in the tumor cell nucleus with negative CK in the tumor cell cytoplasm, and negative CD10 in the tumor cell membrane. All of which suggest a juvenile granulosa cell tumors.

Discussion

The pediatric population rarely develops ovarian cancers. In population-based investigations, malignant ovarian tumors affecting children have increased 10 times at each age interval: in girls 9 years of age or below, the incidence was just 0.102 per 100,000/y; in girls 10 to 19 years of age, it was 1.072 per 100,000/y; and in adult females, the incidence was 11.446 per 100,000/y [3].

WHO classified ovarian cancer into 12 types, including sex-cord stromal tumors which is further divided into 3 categories: 1) Pure stromal tumors 2) Pure sex-cord tumors (which include adult and juvenile granulosa cell tumors, sertoli cell tumors, and sex cord tumors with annular tubules); and 3) Mixed sex cord stromal tumors. The most prevalent type of sex cord-stromal cell tumor is granulosa cell tumor (GCTs). It is divided into 2 subgroups: juvenile and adult variants. GCTs as a low-grade malignant ovarian sex cord-stromal tumors, constitute less than 5% of all malignant ovarian tumors. Juvenile granulosa cell tumors (JGCT) make up 5% of GCTs, and the other 95% of cases are granulosa cell tumors in adults [2,4,5].

Premenarchal girls and young women are susceptible to JGCT, with an average age at diagnosis of 13 years. Precocious puberty, pubic and axillary hair, and clitoral enlargement are common signs since they are commonly observed in

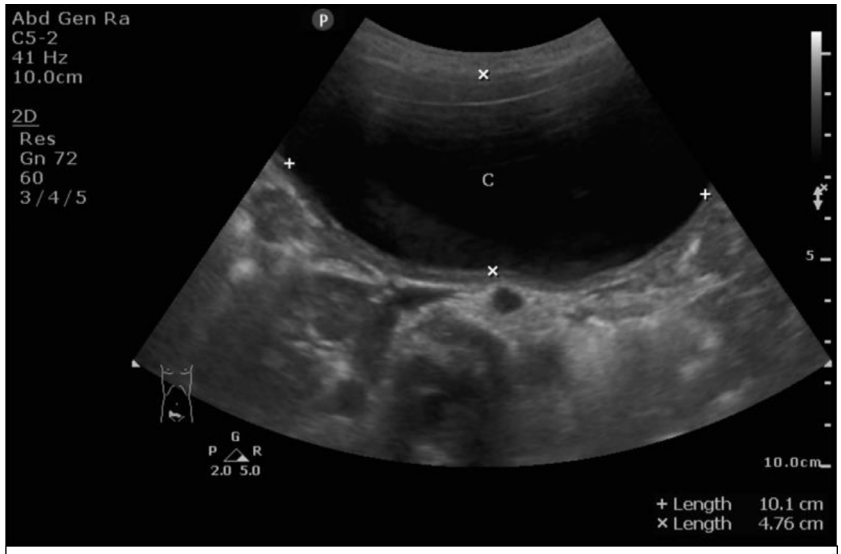

Fig. 1 – Abdominal ultrasound showed a single, unilocular, anechoic cystic lesion in the pelvic cavity that extended into the abdominal cavity.

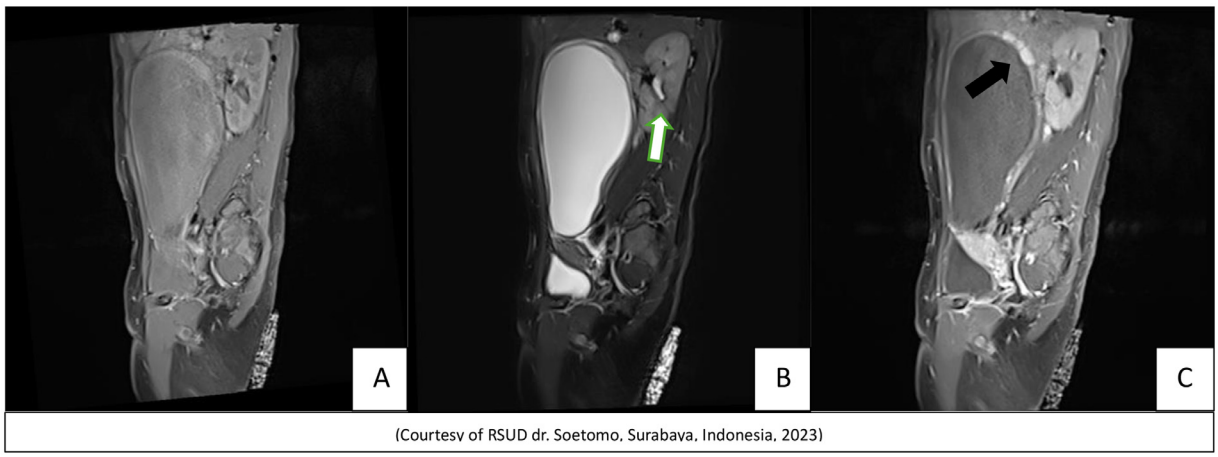

Fig. 2 – The sagittal T1 and T2 Fat-Sat weighted imaging MRI sequence (A & B) showed a large hypointense cystic lesion in the right ovary, hydronephrosis of the right kidney was visible (white arrow). Sagittal contrast-enhanced T1 Fat-Sat sequence (C), showed contrast enhancement in the solid component on the cyst wall (black arrow).

premenarchal girls [6]. There are 2 recognized forms of precocious sexual maturation: central precocious puberty (CPP) and peripheral precocious puberty (PPP). PPP is defined as early pubertal maturation that is unrelated to central hypothalamic-pituitary-gonadal (HPG) axis activation. The etiology of PPP is divided into acquired and hereditary. Functional tumors or cysts is one of the causes of acquired PPP [1].

Estrogen production can trigger precocious puberty in as many as 10% of premenarchal women because JGCT may be hormonally active. In GCTs that are hormonally active, women of reproductive age will begin to notice dysfunctional uterine bleeding and menstrual irregularities [7] Abnormal FSH concentrations in children can help diagnose pituitary issues and may indicate problems with both genders' reproductive systems, infertility, and early and delayed puberty. CA-125 levels may increase due to ovarian capsule stretching, immunoreactive cells in the ascites, or peritoneal irritation [8,9].

Our patient was a 2-year-old and 2-month-old girl with precocious puberty. In this condition, a high level of estradiol and a decreased level of FSH indicated that precocity was not central, instead it was due to the high peripheral estrogen level. Its clinical significance can occur due to the nature of estrogen secretion which causes "pseudoprecocity" because there is no ovulation. Approximately 82% of prepubertal patients will present with symptoms of early puberty accompanied by general signs, including pubic hair growth, vaginal bleeding, breast enlargement, and increased bone aging. The most common symptoms include stomach discomfort and distension [10]. JGCT can also present with several other conditions such as Tuberous sclerosis, nonhereditary congenital syndromes

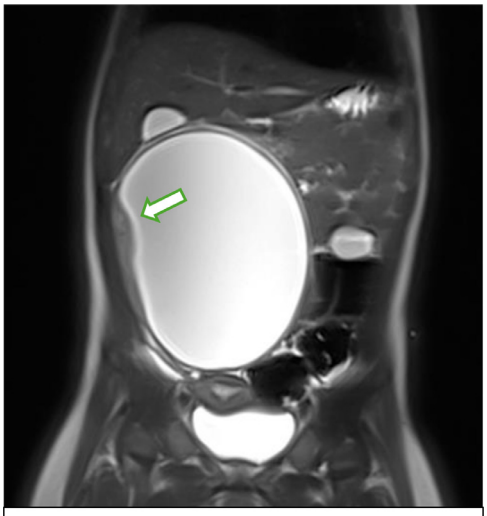

Fig. 3 – The coronal T2 weighted imaging MRI sequence showed the lesion compressing other organs around it to the left side. Areas with thick walls are shown in this image (arrow).

like Ollier's diseases or Maffuci syndrome. Bilateral presentation can be seen in Goldenher and Potter syndrome [11]. In our case, the patient's mother had noticed a breast and abdominal enlargement since she was 1 year old, and vaginal bleeding occurred a week before admission, initially in large amounts which then progressively decreased until less than 1 pad. The patient didn't complain of any stomach discomfort or distension. Normally, increased ovarian estradiol secretion stimulates breast growth in girls at the average age of 10 years. Menarche normally occurs 2.5 years following the start of breast development, at an average age of 12.5 years (range: 9 to 15 years) [12]. The hand X-ray of the patient also supports symptoms of precocious puberty, which indicated the bone age of a 3-year-old and 6 months age girl according to Greulich and Pyle's classification. Based on the clinical and radiological examination, there was no indication that the patient had tuberous sclerosis, Ollier's disease, or Maffuci's syndrome.

Laboratory evaluations showed a high level of prolactin (54.41 ng/mL; normal range: 5.18-26.5) and LDH level of 328.5 U/L. Prolactin (PRL) promotes the development of the mammary and breast glands. In children and adolescents, hyperprolactinemia can cause delayed puberty, gynecomastia, galactorrhea, and primary amenorrhea. As a result, PRL contributes to breast growth as well as gonadal function inhibition [13]. This is associated with earlier breast growth in these patients. In terms of clinical utility, lactate dehydrogenase (LDH) is a fairly nonspecific diagnostic. During apoptosis, the glycolytic cellular enzyme LDH is released from all of the cells in the body. It may be increased in non-malignant conditions including chronic liver disease, stroke, or hemolytic anemia, as well as in all types of malignancies [14].

Granulosa cell tumors are diagnosed based on the clinical presentation of the patients; however diagnostic imaging tests are required. The tumor is frequently unilateral (97%) and measures at an average of 12.5 cm, with macroscopic characteristics comparable to the adult variety. AGCTs can be cystic (30.3%), solid (27.8%), or solid and cystic (41.7%), whereas JGCTs are cystic (14%), solid (37%), and solid and cystic (45%). Although JGCTs differ from AGCTs in terms of clinical and histologic aspects, the 2 forms share similar imaging findings due to their comparable gross appearance. There is no variation in tumor size between the premenarcheal and postmenarche periods [11]. In this patient, the lesion was characterized by a cystic lesion in which the solid component was only found in the wall of the cyst.

Holsbeke et al. described that there are 2 ultrasound patterns which can be identified as GCTs. First, in necrotic zones, there is a huge (pure) solid mass with varied solid tissue echogenicity. The second pattern is a massive multilocular solid mass with mixed cystic fluid or low-level echogenicity. It has a substantial amount of solid tissue as well as papillary projections, which rarely occur. The cystic sections typically contain a significant number of tiny locules, giving the mass the recognizable 'Swiss cheese' appearance. Both types of masses have moderate to high vascularization [8]. Our patient's abdominal US showed a unilocular anechoic cystic lesion with posterior enhancement, without septa, with a size of $\pm$ 10.1 $\times$ 4.76 $\times$ 9.8 cm in the pelvic cavity extending into the abdominal cavity, there was no solid component nor septum. The 2 previously mentioned patterns were not found on this

Fig. 4 – Intraoperative findings. (A) Uterus. (B) Left ovary. (C) Right ovary.

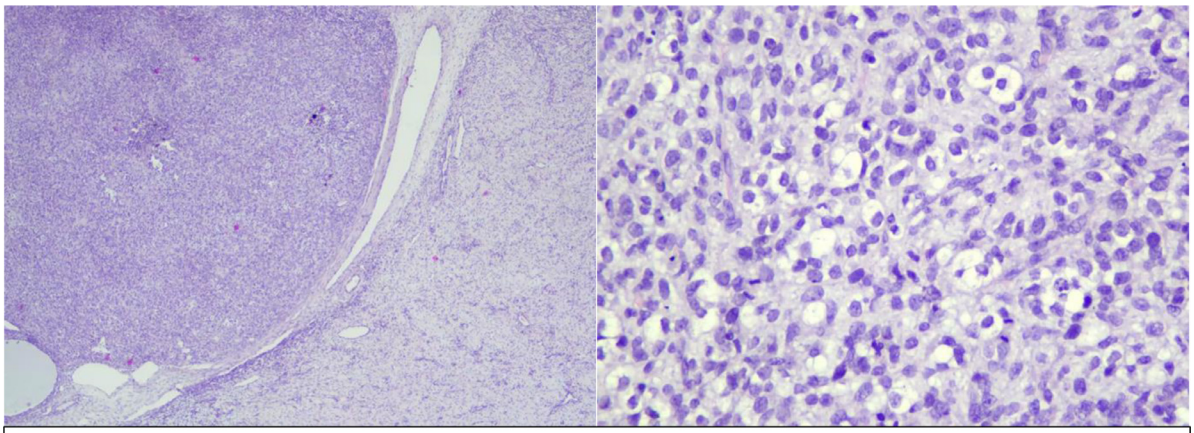

Fig. 5 – Pathology findings of the right ovary at 40x magnification (left) and 400x magnification (right). Mitosis and Tadpole appearance were found on the 400x magnification. Mitosis 20/10 HPF.

patient's ultrasound. This is in line with what was stated by Mulvany et al. that only 3% of GCTs are multicystic on gross examination, and unilocular ones are even unusual [15]. Therefore, we believe that this case can be considered as a good educational resource due to the rarity of unilocular cysts found in JGCT cases.

The presence of a solid component in the right ovarian lesion was confirmed using MRI, which the contrast-enhanced T1 sequence MRI showed contrast enhancement on the posteromedial wall of the lesion. Zhang et al. found that OGCTs ranged from totally solid to fully cystic mass, with variable shapes. Their findings are consistent with the literature, which stated that OGCTs are more heterogeneous than other sex-cord stromal tumors (OSCs). According to reports, a spongelike, multilocular cystic mass filled with blood breakdown products is a common MR imaging indication of OGCT. On T1WI images, more than half of OGCTs showed a high or mixed signal intensity, which could be related to blood degradative components. This trait may be beneficial in distinguishing OGCT from OSCs because it is not observed in the latter group. In terms of lesion enhancement, OGCT demonstrates mild (63.6%) and moderate (36.4%) enhancement when compared to the myometrium. Although there was no significant difference in enhancement type between OGCT and OSC, it could be useful in distinguishing them from broad ligament fibroids, which invariably display considerable enhancement following contrast medium injection [16]. In these cases, neither ultrasound nor MRI can show imaging characteristics that can help distinguish JGCT from other tumors due to its nontypical features.

Yikilmaz et al. reported that in male, JGCT sonographically depicted by the presence of a diffuse multicystic pattern of the tumor referred as "Swiss cheese". Doppler sonography would be useful in differentiating JGCT from other pathologies originating from intra-abdominal solid organs if the vascular supply of tumors originating from the retroperitoneum was demonstrated. From MRI T1-weighted images, the tumor produced a predominantly low but variable signal, indicating the presence of varying levels of mucoid proteins within. A significant rise in signal on T2-weighted images corresponded to a high proportion of fluid within the primary mass. Multiple internal septations of varying thicknesses can be seen, as well as soft-tissue regions (most likely representing granulosa cells) that showed increased signal on both T1- and T2-weighted images. They also reported that there was continuation of the inferior side of the tumor to the inguinal canal via the gubernaculum-like soft tissue architecture, which was confirmed during surgery [17].

This is where the application of histopathology and immunohistochemistry markers, including inhibin, CD99, and calretinin becomes crucial in the accurate diagnosis of GCTs. Because they are spherical, contain a lot of eosinophilic and/or vacuolated cytoplasm (indicating luteinization), and lack nuclear grooves, the neoplastic granulosa cells in juvenile GCTs have very distinct cytology from those in adult GCTs [8]. In histological features, the size and shape of gland-like structures in JGCTs that resemble follicles of the ovary are asymmetrical. Moreover, JGCTs exhibit atypia in their immature nuclei along with elevated mitotic activity [7]. In addition, a positive immunohistochemistry stain for a-inhibin, an ovarian glycoprotein, is an important diagnostic characteristic for GCTs [11]. Due to their lack of specificity, granulosa cells produce follicle regulatory protein, inhibin A and B, and other molecules that can be used to track treatment response or identify recurrence. In patients with JGCT, serum FSH, LH, and GnRH levels are low due to increased inhibin [8]. The specimen in our case was sent for IHC evaluation for inhibin antibody, calretinin, CK, WT-1, and CD10. Macroscopic findings include positive inhibin on the cytoplasm of tumor cells, positive calretinin on the nuclear and cytoplasm of tumor cells, negative CK, positive WT-1 of the nuclear tumor cells, and negative CD10 on the membrane of tumor cells. IHC evaluation of this patient was then concluded as a juvenile granulosa cell tumor (JGCT).

In the case of JGCT, the treatment for every patient may differ based on the patient's age and severity of the condition. The main therapy for the problem is surgery, which includes staging. Standard surgical techniques include bilateral salpingo-oophorectomy and hysterectomy.

Nonetheless, young women have the option of undergoing fertility-sparing surgery, such as a unilateral oophorectomy or unilateral salpingo-oophorectomy. Retrospective studies imply that the cure rate for early-stage illness is essentially identical whether treated unilaterally or bilaterally. Systemic lymphadenectomy is not appropriate for JGCT surgical staging [18]. This case was discussed by a multidisciplinary team. Surgical management with a laparoscopic approach with DJ stent insertion was planned. A laparoscopic right ovariectomy was performed after a direct decompression of the ovarian cyst. The tumor was a FIGO Stage IA tumor, and the patient did not require any additional treatment. Tumors with granulosa cells may exhibit clinically malignant behavior. The age and stage at the time of diagnosis are associated with the prognosis. Nearly 90% of individuals with these cancers have a fair chance of surviving after 10 years. However, even at 10-20 years following the initial diagnosis, patients are prone to late recurrence [18].

Conclusion

We reported a case of a 2-year-old girl with dysfunctional uterine bleeding and precocious puberty. Abdominal US showed a unilocular anechoic cystic lesion with posterior enhancement in the pelvic cavity, the presence of a solid component in the lesion was confirmed by MRI. Laboratory evaluations showed a high level of prolactin, estradiol, LDH, and CA-125 along with low FSH.

Although GCTs have specific imaging characteristics which can help to distinguish them from other tumors, confirmation by histopathology and IHC is still mandatory, especially in cases with nonspecific radiological features.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report.

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