MALIGNANT JUVENILE AND ADULT OVARIAN GRANULOSA CELL TUMORS IN PEDIATRIC PATIENTS - REPORT OF TWO CASES

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Abstract

Juvenile ovarian granulosa cell tumor is a sex chord stromal tumor derived from granulosa cells. It rarely occurs in children. Although it is usually classified as a benign tumor in children due to its good prognosis after surgical intervention, it is a malignant tumor and can be deadly, especially if recurrence occurs. We report two rare cases. The first one is a five-year-old girl with a malignant juvenile ovarian granulosa cell tumor stage 3 FIGO, presenting with abdominal pain in the inferior part of the abdomen and very early pubertal development. On physical examination, she was at stage two puberty. The second case is a 12 years old girl presenting with two periods monthly. An 8.3/5.4cm mass was found at the pelvic region on ultrasound examination. Exploratory laparoscopy with histological examination led to the diagnosis of stage 2A FIGO, combined juvenile and adult ovarian granulosa cell tumor. Conclusion: Precocious puberty accompanying abdominal pain or more than a period in a month is a pointer to juvenile and adult ovarian granulosa cell tumor requiring immediate investigations and patient management. Early diagnosis with the assistance of inhibin test and a FISH test of p53(17p13) aids better management of patients with Juvenile ovarian granulosa cell tumor, preventing tumor recurrence for a favorable outcome. Juvenile and adult ovarian granulosa cell tumors in pediatric female patients can present in different forms but gearing towards menstruation abnormalities.

Keywords: precocious puberty, juvenile ovarian granulosa cell tumor, adult granulosa cell tumor, irregular menstrual cycle, gene P53

Introduction

The incidence of malignant tumors in prepubertal girls is 0.102 per 100.000 girls [1]. Granulosa cell tumor is a malignant sex cord-stromal ovarian tumor classified into adult-type or juvenile-type, which is usually at stage 1 in 90% of cases [2]. Pediatric patients account for 4-5% of ovarian granulosa cell tumors, which are responsible for 10% of very early puberty in prepubertal girls [2,3]. The factors that contribute to poor prognosis in these patients include: high tumor stage, high tumor marker level, large tumor, late diagnosis, presence of cancer-related genetic abnormalities, and recurrence that mainly occurs after puberty [4]. We present a rare case of a 12 years old girl with both juvenile and adult ovarian granulosa cell tumor staged 2A and a second case of a malignant juvenile ovarian granulosa cell tumor stage 3 in a five years old girl presenting with abdominal pain and very early pubertal development, although normal puberty starts in girls between 8-9 years old [5]. Both patients were diagnosed and managed with surgical intervention and chemotherapy.

Case 1

A 5 years old girl presented at our hospital with complaints of abdominal pain for two months and loss of appetite. She had no significant medical or family history, except repeated urinary infection from infancy and dental caries. She was not on any medication. She was the first child to a 22 years old mother, while the father was 30 years old. She weighed 3300g at birth with APGAR score of 9, delivered at nine months, naturally and in cranial presentation. The patient was breastfed for one week before started on artificial milk and diversification, taking all vaccine required and vitamin D. On physical examination, she weighed 20kg and had a height of 117cm, afebrile, with precocious puberty signs: thelarche with eminent breast areola-Tanner 2 and some fine hair strands in the pubic region -Tanner 2. The abdomen was slightly distended in volume and painful at superficial palpation in the left iliac region, with a mass detected at deep palpation.

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She had normal female external genital organs and confirmed as a virgin. Her thyroid function tests were normal. ↓LH-0,1ui/l, ↑ estradiol-58pg/ml, ↑prolactin-22ng/ml, LDH-358u/l, ↑Inhibin B was 34pg/ml. The patient had a urinary tract infection. Ultrasound examination showed a mass in the abdominopelvic region with both cystic and solid components with mild ascites. Karyotype test by the GTG 450 bands showed 46XX karyotype. The cytogenetic analysis with FISH test techniques using metasystem genetic probes detected a deleted p53 (del17p13) gene.

Exploratory laparoscopy revealed a 13.2/7.1cm mass on the left ovary (Figure 1). We performed adnexectomy, excision of the tumor formation and biopsy. The histopathology result showed a juvenile ovarian granulosa cell tumor (Figure 2). The tumor invaded the fallopian tube and the retroperitoneal lymph node - stage 3 FIGO. The ovary was transformed into a tumor, grey smooth and discrete mass surface with multiple zones of ruptured capsules. Multiloculated, inhomogenous section with solid yellowish-white areas mixed and a cystic zone containing serocitrine liquid were also found. Medium-sized cytoplasm was full of eosinophils in the nucleus with moderately atypical mitotic activities in areas over two camps to large sizes with macrofollicular structures of various sizes and forms. Endothelium material of eosinophilia secretion, lined with cellular layers, stroma with fibrothecoma, and some necrotic areas were identified. The tumor section examined appears to compress the ovarian capsule but not exceeding it. Immunochemical examination revealed ER+ 50%, Ki 67+25% and PGR+ 55%. We placed her on chemotherapy: four cycles of PEI, three cycles of paclitaxel +carboplatin and two BEP cycles. At revaluation, after six months of treatment, she had a favorable outcome. Her abdomen was without pain or mass on superficial and deep palpation. Ultrasound showed no secondary intrabdominal parenchymatous lesion, no sign of recurrence of the tumor, the right ovary was normal and the level of Inhibin B was 8.1ng/l. The bleeding also stopped.

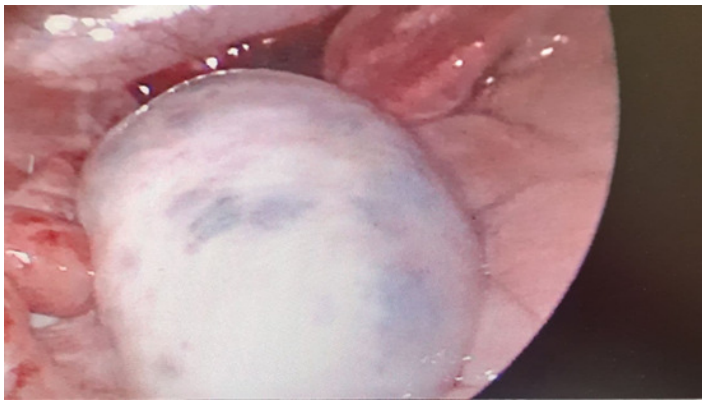

Figure 1. Intraoperative image of the ovary with Granulosa cell tumor.

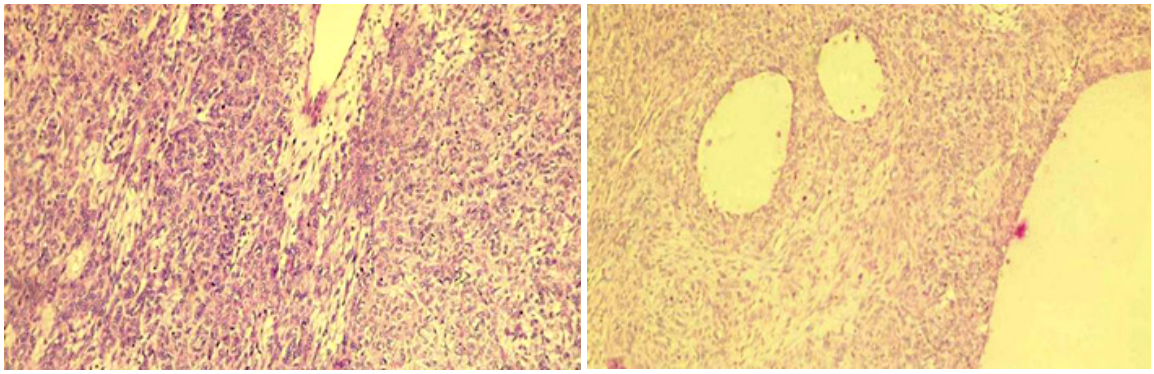

Figure 2. Histopathology of Granulosa cell tumor Hematoxylin-Eosin stains 20X.

Case 2

A 12 years old girl without any significant family or personal medical history, one year after menarche, presented at our hospital with complaints of irregular menstrual cycles, having two periods in a month. She was placed on vitex agnus-castus and progesterone, but symptoms persisted after five months. On physical examination, she weighed 45kg and had a height of 165cm. No abdominal pain or mass at superficial and deep palpation of the abdomen were found. She had normal

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female external genital organs, normal thyroid function test, ↑prolactine:30 ng/ml, ↑ estradiol:120pg/ml, ↑LDH:624u/l. The ultrasound examination revealed a tumoral formation, with cystic and solid components, 8,3/5.4cm in dimension at the right ovary (Figure 3). We performed exploratory laparoscopy and right salpingo-oophorectomy and mounted an abdominal drainage tube, which was removed three days after the operation. We placed her on anti-biotherapy, antalgic and anti-inflammatory therapy. The histopathological examination results revealed ovarian granulosa cell tumors with predominant juvenile and some adult components. They were also present in the fallopian tube and vascular invasion – stage 2A FIGO. Round hyperchromatic nucleus, rare aspects of coffee bean chromatin with eosinophilic cytoplasm and luteinized aspect were present. Solid nodes associated with the presence of some microfollicular focal like call-Exner bodies with unregulated lumen secreting eosinophilia and some papillary structures from the fibrous conjunctive arc and bistratified periphery cylindrical cell were present. There was an area of vascular invasion in the examined fragment, some section of the fallopian tube showed small groups of tumoral cells, 8/10HPF mitosis, and a fragment of lymphatic ganglion and nodes with stasis without tumoral infiltration. Immunochemical examination showed positive K16, inhibin, and calretinin tumor cells (Figure 4).

With favorable evolution, good general state, afebrile, the patient was placed on BEP chemotherapy and discharged. We re-evaluated her after 4 BEP cures, and the treatment was well tolerated with secondary emetic syndrome and slight normochromic normocytic anemia; 10g/dl, with the normal menstrual cycle. Ultrasound examination showed left ovary, uterus, liver, kidney, spleen and urinary bladder without modifications.

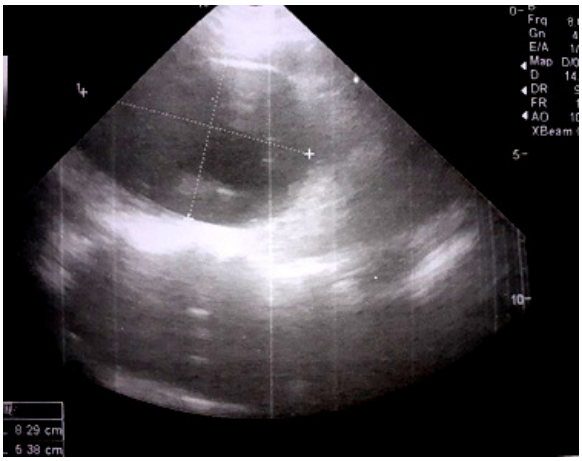

Figure 3. Ultrasound of the right ovary.

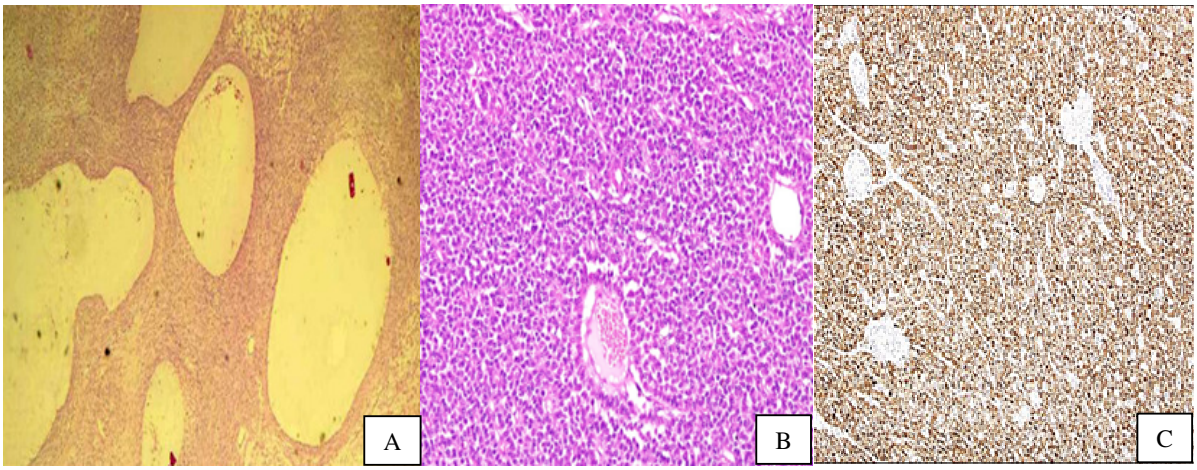

Figure 4. The histopathological result shows Granulosa cell tumor Hematoxylin-Eosin stain 20X A. Ovarian granulosa cell tumor with Juvenile components B. Ovarian granulosa cell tumor with adult components C. Immunohistochemical result showed positive calretinin tumor cell inhibin and KI67.

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Discussion

In patients with granulosa cell tumors, the tumor usually secrets estrogen hormone because the action of cytochrome P450 aromatase is not controlled [4], hence estrogen levels are elevated. The presented cases show that when this pathology appears in prepubertal girls, it can cause very early puberty, while when it appears in pubertal girls, it can cause multiple periods in a month. According to literature precocious puberty is when secondary sexual characteristics are present in a girl before eight years and can be a pointer to the presence of a tumor, such as juvenile ovarian granulosa cell tumor [5]. Mutations of AKT1 and FOXL2 genes have been identified in juvenile and adult granulosa ovarian cell tumors. In a study, Follicular Stimulating Hormones in an eight-year-old girl were responsible of causing juvenile ovarian granulosa cell tumor [6,7]. Call-Exner bodies, coffee-bean, groove nucleus, or microfollicular pattern are present in adult OGCT, but macrofollicular space and round nuclei are present in the Juvenile type. The juvenile type grows aggressively in comparison to the adult one [8,9]. A report shows that ovarian granulosa cell tumor can combine with other tumors like cystadenomas [10]. Mitosis greater than 4/10HPF or a high level of Inhibin B, a tumor marker useful for detecting OGCT, have both proved to be related to the recurrence of ovarian granulosa cell tumor, which results in poor prognosis [11,12]. The inhibin value of the first patient was higher than the average level of 26.5pg/ml in girls at pubertal stage 1 (average age 9), and estradiol level was higher than 40.5, which is the average level for girls at pubertal stage 2 with an average age of 11,4 years old [13]. The 2nd patient returned after four cycles of BEP with a better outcome and had a lower inhibin level, unlike the 1st patient who was on four cycles of PEI, three cycles of paclitaxel +carboplatin, and two cycles of BEP for more than six months, which can be attributed to the high tumor stage and deletion of Tp53 gene. Tp53 gene protein is a tumor suppressor which, if altered, leads to poor prognosis, especially if at stage II-IV or with large tumor sizes like 10-15cm, hence further adjuvant chemotherapy after surgical intervention is given to improve the patient's outcome and prevent recurrence [14, 15]. Malignancy aggression, the affected organs, or tumor size determines the treatment options like tumor excision, adnexectomy, gonadectomy, or hysterectomy, with the efforts to save the gonads and the goal to save the patient's life. Our patients show that juvenile ovarian granulosa cell tumors in females can be present in different forms but gearing towards abnormalities in menstruation according to the given age.

Conclusion

A patient presenting with precocious puberty accompanying abdominal pain is a pointer of juvenile ovarian granulosa cell tumor requiring further investigations and immediate intervention. Early diagnosis with the assistance of inhibin B and a FISH test of Tp53 helps in deciding the best choice of management of patients with juvenile ovarian granulosa cell tumor preventing recurrence for a better outcome. Juvenile ovarian granulosa cell tumor in pediatric female patients can present in different forms, but gearing towards abnormalities in menstruation.

Conflicts of interest

All authors have no conflicts of interest to declare.

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