Postpartum Cystic Juvenile Granulosa Cell Tumor: A Case Report

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Abstract:

Introduction: Juvenile granulosa cell tumor (JGCT) is a subtype of granulosa cell tumors of the ovary. 80% of JGCT occurs at prepubertal period. And, it is considered to be a slow growing tumor. In addition, gross appearance of it is mostly solid. Herein, we report a pure cystic JGCT case that was detected soon after childbirth with huge dimension.

Presentation of Case: We report a 21 year-old woman who presented with abdominal mass during 6th month after childbirth. Ultrasound revealed a cystic mass of approximately 20 cm in diameter originated from left ovary. The patient underwent laparotomy and unruptured left ovarian cystic mass resection was performed. Uterus and right ovary were totally normal and extraovarian spread was not found. Macroscopic examination revealed totally cystic tumor of 25,5x22x10,2 cm with smooth outlines, containing serous fluid. There were papillary projections and small polypoid structures around 1 cm in diameter into the cavity. Histopathologic and immunohistochemical findings were compatible with JGCT. Relaparotomy was performed for staging and the patient was evaluated as stage IA. She is currently under clinical follow up without any further treatment.

Conclusion: It should be noted that JGCT may rapidly grow and reach a higher dimension, occur during pregnancy and at postpartum period, and may present as cystic rather than a solid mass as in our case presented here.

Keywords: Juvenile granulosa cell tumor; Pregnancy; Postpartum

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Consent: We confirm that the patient has given her informed consent for the case report to be published.

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Introduction

Granulosa cell tumors are rare tumors that comprise 1-2% of all ovarian malignancies [1]. Two subtypes as adult and juvenile granulosa cell tumors exist according to their different clinical, histopathological and prognostic features [1]. Juvenile granulosa cell tumor accounts for 5-15% of granulosa cell tumors [2]. Approximately 80% of JGCT occurs during the prepubertal period (mean: 13 year-old) [3]. At this period the presenting symptoms are breast development, appearance of axillary and pubic hair referring to isosexual pseudoprecocity [3]. Postpubertal patients can present with abdominal pain and swelling, irregular menstruel bleeding or acute abdominal symptoms [2]. Ten percent of granulosa cell tumors are reported to present during pregnancy [3]. There are limited data about ovarian neoplasms including JGCT associated with pregnancy in the literature [3-7]. The incidence of ovarian malignancy detected during pregnancy is estimated to range from 1/76 to 1/2328 deliveries [7]. The percentage of malignant tumors ranges from 2.15% to 13.5% of the adnexal masses detected during pregnancy [7]. The most common malignant tumors associated with pregnancy are epithelial tumors (33-65%), germ cell tumors (17-40.9%), sex-cord stromal tumors (9.1-20%), and other tumors (0-13%) may also be seen [8].

The gross features of JGCT are usually similar to adult type. Therefore, generally the neoplasm is composed of both solid and cystic areas (49%). Pure solid (37%) or pure cystic (14%) JGCTs are also on record [9]. Herein, we report a cystic JGCT that was detected soon after childbirth that no mass or symptom was observed during pregnancy in a 21-year-old woman.

Case Report

A 21 year-old woman presented with abdominal mass after giving birth to her second child at 6th month was admitted to the Obstetrics-Gynecology Clinic. Ultrasound revealed a cystic mass of approximately 20 cm in diameter originated from left ovary. The history of the patient was uneventful including the follow up of her pregnancy. CA-125 level was 55 IU/ml (Normal: < 35 IU/ml). The patient underwent laparotomy and unruptured left ovarian cystic mass resection was performed. Uterus and right ovary were totally normal and extraovarian spread was not found. Macroscopic examination revealed totally a cystic tumor of 25, 5x22x10.2 cm with smooth outlines, containing serous fluid (Figure 1a). There were papillary projections and small polyloid structures around 1 cm in diameter into the cavity (Figure 1b). Besides, cystic cavity with hemorrhagic fluid of 2.5x2.2x1.2 cm was encountered (Figure 1b). Histologic sections disclosed solid cellular pattern of tumor protruding to the cavity and localized in the cyst wall (Figure 1c). Tumor cells were oval or round shaped, having hyperchromatic nucleus with minimal atypia and eosinophilic cytoplasm. Tumor cells have lacked nuclear grooves (Figure 1d). Mitotic activity was high, ranging between 15-20/10 high power fields (HPF) (Figure 1d). The stroma was loose or myxoid, or showed fibrothecomatous characteristics. Tumor also consisted of luteinized cells (Figure 1e), and round, oval or irregular shaped follicles containing pale eosinophilic secretion (Figure 1f). Tumor was restricted to the cyst wall. The tumor cells showed cytoplasmic and dot-like immunostaining with pancytokeratin (Figure 2a). Tumor cells have been strongly stained by vimentin, CD99, CD56. Nuclear and cytoplasmic immunoreactivity was seen by calretinin. Inhibin positivity was encountered especially in luteinized cells (Figure 2b). Weak staining was observed by EMA. Chromogranin, synaptophysin and AFP were negative. Histopathologic and immunohistochemical findings were compatible with juvenile granulosa cell tumor. Relaparotomy was performed for staging and the patient was evaluated as stage IA. The patient was under clinical follow up for 7 months with uneventful clinical course and has not received any further treatment.
Figure 1 a. The macroscopic photograph of the cystic lesion with smooth outlines. b. The macroscopic photograph of the inner surface of the lesion. c. The microscopic photograph showing cyst wall and the solid tumor component protruding to the cavity, (Hematoxylin and eosin stain, original magnification, x40). d. Photomicrograph of the tumor cells with eosinophilic cytoplasm and hyperchromatic nucleus that lack nuclear grooves and show numerous mitoses (arrows), (Hematoxylin and eosin stain, original magnification, x400). e. Photomicrograph of the tumor containing numerous luteinized cells that have vacuolised clear cytoplasm, (Hematoxylin and eosin stain, original magnification, x400). f. Photomicrograph of the round, oval or irregular shaped follicles-the cystic spaces containing pale eosinophilic secretion, (Hematoxylin and eosin stain, original magnification, x400).
Figure 2  a. Characteristic dot-like immunostaining with pancytokeratin in the tumor cells, (Avidin-biotin-peroxidase method, original magnification, x200).  b. Immunopositivity with inhibin in the tumor cells especially in the luteinized cells, (Avidin-biotin-peroxidase method, original magnification, x200).
Discussion

98% of JGCTs are unilateral [2]. Generally solid component predominates but it may contain cystic component at various degrees [2]. The diameter of the tumor ranges from 2, 5 cm to 32 cm [2]. As JGCTs can reach a huge size, intraoperative rupture can be seen in 10% of cases. Our patient presented with rapidly growing unilateral ovarian cystic mass at postpartum period; the unruptured tumor was excised totally.

JGCT is histopathologically characterized by granulosa cell proliferation in diffuse or nodular fashion in myxoid or oedematous background [2]. Nodules may become totally hyalinised [2]. Follicular structures of various size and shape are encountered among the nodules or solid cellular areas [2]. However, Call Exner bodies are almost never present or may be very rarely seen [2, 10]. Tumor cells have abundant eosinophilic cytoplasm and round-oval hyperchromatic nuclei which lack nuclear groove that distinguish them from those of adult granulosa cell tumor [2, 10]. Severe nuclear atypia can be observed and mitotic rate is high (1-32/10 HPF) [2]. Scattered luteinized cells can be seen and they become numerous at pregnancy. Immunohistochemically tumor cells are usually positive with inhibin, calretinin, WT-1, CD 56, CD 99, vimentin, S100 and SMA [2]. Dot-like cytoplasmic staining pattern by pancytokeratin as shown in our case is characteristic for granulosa cell tumors [10]. 25-50% of JGCTs may exhibit focal EMA positivity in contrast to other sex-cord stromal tumors. CK 7 and desmin are negative [2, 10].

Differential diagnosis of JGCT from adult type granulosa cell tumor is important. Adult type granulosa cell tumors occur mostly in postmenopausal women although they may be seen at any age [2, 10]. The present case was differentiated from adult type granulosa cell tumor by diffuse cellular pattern of the tumor, presence of follicular structures, lack of Call Exner bodies, and presence of cells without nuclear grooves and high mitotic rate of tumor cells. Thecoma can be considered in differential diagnosis because of the presence of luteinized cells in JGCT but thecomas do not contain follicular structures or high mitotic rate [2]. Besides, the neoplastic cells are characteristically surrounded by reticulin fibers individually in thecoma [2, 10]. JGCT may be confused with yolk sac tumor. However, presence of Schiller-Duval bodies and accompanying other germ cell components, AFP positivity and inhibin negativity are of help in diagnosing the latter [2]. JGCT is sometimes misinterpreted as primary or metastatic malignant melanoma because of the histopathologic features and rare inhibin positivity of melanoma [2]. Immunopositivity with HMB-45 and Melan-A, and the presence of melanin pigment are helpful in differential diagnosis [2]. As JGCT contains luteinized cells, it can be confused with clear cell carcinoma [2]. Clear cell carcinoma occurs in more elderly women. The immunohistochemical demonstration of EMA and CK 7 staining and inhibin negativity make the correct diagnosis possible [2]. Small cell carcinoma of hypercalcemic type may be considered in differential diagnosis of JGCT. It is seen in young women with aggressive course, showing follicle like structures composed of cells with hyperchromatic nuclei and high mitotic rate [2]. However, clinically JGCT is usually associated with estrogenic manifestations and small cell carcinoma exhibits hypercalcemia. Besides, the latter demonstrates inhibin negativity and growth pattern with solid sheets rather than nodules [2].

Adnexal masses during pregnancy is rare, there are some case reports and series in the literature [3-7]. The incidence of the adnexal masses has raised especially after the advent of ultrasound use during pregnancy. In 2011 Aggarwal et al. reviewed the literature (between January 1984–November 2009) about the ovarian tumors in pregnancy. According to this study the prevalence of the adnexal masses ranges from 1/76 to 1/2328 deliveries [7]. A higher prevalence of 1/19–1/88 has been recorded in the studies based purely on ultrasound detection of adnexal masses in pregnancy [7]. The percentage of malignant tumors, both low malignant potential and
ovarian cancer, ranges from 2.15% to 13.5% of the adnexal masses in pregnancy. Studies reporting only malignant ovarian tumors have shown an incidence of 0.073–0.11 cases per 1000 deliveries [7]. Ultrasound based studies have detected a lower incidence of malignancy, ranged from 0 to 3.6% [7]. Some features as solid areas, papillary projections and septations increase suspicion for malignancy on ultrasound. Tumor markers like CA-125 have a limited aid in differentiating benign from malignant tumors in pregnancy as levels increase during pregnancy, especially in the first trimester [7].

The majority of the masses are detected in the first two trimesters (50-80%) of pregnancy. 8% of malignant ovary tumors are diagnosed in the first trimester, 7.3% are diagnosed in the second trimester, 24.2% are diagnosed in the third trimester, and 26.8% are diagnosed in postpartum period [7].

In general, 65-80% of the cases are asymptomatic. However, the patients with malignancy are more usually symptomatic of abdominal mass (> 50%), pain or constitutional symptoms, only 25% of the cases are asymptomatic. Torsion may occur in 3-28% of the patients [7].

The majority of adnexal masses in pregnancy is benign. Dermoid cyst (37-50%) is the most common lesion, cystadenoma (20-24%), endometrioma (5-11%), and functional cysts (6-13%) are also detected during pregnancy in a decreasing order of frequency [11-12].

Primary epithelial malignancies (33-65%) of the ovary are reported to be the most common malignant tumors in pregnancy, followed by germ cell tumors (17-40.9%), sex-cord stromal tumors (9.1-20%), and other tumors (0-13%) [8]. Thirty one malignant ovarian tumours (3.2%) have been reviewed in 12 studies composed of 944 cases with adnexal masses in pregnancy in the literature [7]. These cases included 8 serous cystadenocarcinomas, 5 mucinous cystadenocarcinomas, 4 unspecified epithelial cancers, 4 immature teratomas, 3 Brenner tumors, 3 dysgerminomas, 2 juvenile granulosa cell tumors and 1 embryonal cell carcinoma and 1 Sertoli-Leydig tumor. Zhao et al. have reported 2 cases of JGCT in pregnancy [8]. One of the cases with JGCT presented with abdominal mass and pain during pregnancy, the other case was asymptomatic and presented with adnexal mass detected during cesarean as our case. Also, no hyperestrogenemia or hyperandrogenemia sign has been observed in these cases similar to our case. But these signs should be considered that they might appear in sex-cord stromal tumors complicating pregnancy. Aybatlı et al. have reported a case of 19-year-old woman presented with abdominal ascite and a mass about 10 cm in diameter one year after term pregnancy [1]. Similar to this report our patient presented with a huge adnexal mass at 6th month of childbirth. This suggests that the tumor presumably was present during pregnancy or even before. Most probably it was not noticed because of the small size of the tumor initially or masking of growing uterus at ultrasound. It may also be possible that the tumor appeared after pregnancy and has grown rapidly without any relation with pregnancy.

In general, JGCT is considered as a low malignant potential tumor but it has the risk of local extension and recurrences. Almost all the recurrences of JGCT appear within 3 postoperative years [2]. They are usually slow growing tumors but as in our present case, tumors rapidly reaching huge size can be encountered. The most important prognostic parameter is the stage of the tumor [2]. Most of the cases are diagnosed at early stages (90% of cases at FIGO stage I). The five-year survival rate is about 95% in stage I and stage II tumors, about 59% in stage I and stage II tumors. It is reported that excision of the tumor is almost always curative for stage IA tumors. However the course of the late stage tumors can be mortal [2, 10]. It is suggested that the pregnancy does not modify the prognosis of JGCT [5]. There is no knowledge reported about the effect of pregnancy on the pathogenesis of JGCTs in the literature. It may be considered to be incidental.

In general, the patients are young and the involvement is unilateral, the removal of the involved ovary and salphenx, and complete staging is the preferred surgical approach in order to preserve fertility [2]. Total abdominal histerectomy and bilateral salphingo-oofrectomy, and “debulking”
are performed for late stage patients. Chemotherapy may be indicated.

**Conclusion**

It is noteworthy that JGCT may rapidly grow and reach a higher dimension, occur during pregnancy and at postpartum period, and may present as cystic rather than a solid mass as in our case presented here.

**References**