An Unusual Case of Juvenile Granulosa Cell Tumor of the Ovary

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Abstract

Juvenile granulosa cell tumor is a rare gynecologic malignancy. We describe a case of this tumor arising in a young woman. Initially assigned to Stage IC, the patient returned 3 months later with metastatic disease. Imaging findings in this case are discussed and pathologic examination confirms the diagnosis. The epidemiology, natural history, presentation, histologic and imaging appearances, prognosis and treatment of this malignancy are reviewed.

Case Report

A 19-year-old, gravida 0, para 0, female presented to the emergency room with worsening right sided abdominal pain. She had been previously healthy but with a history of menstrual irregularities and heavy bleeding since age 14. On physical exam, she had noticeable hirsutism, including male-pattern pubic hair growth, and an obvious lower abdominal mass. A contrast-enhanced CT scan of the abdomen and pelvis, and a pelvic ultrasound were performed.

CT scan with oral and intravenous contrast was initially performed and showed a large, multi-lobulated, predominantly low-attenuation mass with numerous septations of varying thickness in the abdomen and pelvis measuring approximately 27 x 22 x 15 cm (Figs. 1-2). There was no calcification appreciated. A moderate amount of ascites and numerous non-enlarged peri-aortic lymph nodes were appreciated. The ovaries were not identified on the CT scan, thus a pelvic ultrasound was performed. This re-demonstrated the large pelvic mass, which appeared complex with both cystic and solid components (Fig. 3). Most walls appeared thick and irregular. Free intra-abdominal and pelvic ascites was again noted. The right ovary was not identified, suggesting ovarian origin for this mass. The left ovary and uterus appeared normal.
Figure 1. 19-year-old woman with juvenile granulosa cell tumor. Contrast-enhanced coronal CT image demonstrating a large, multi-lobulated, low attenuation abdomino-pelvic mass arising from the right ovary.

Figure 2. 19-year-old woman with juvenile granulosa cell tumor. Contrast-enhanced axial CT image demonstrating the multi-lobulated heterogeneous mass with visible intraabdominal ascites.
Figure 3. 19-year-old woman with juvenile granulosa cell tumor. Ultrasound image of the abdomen/pelvis demonstrating a large complex, cystic and solid mass with septations of varying thicknesses.

An exploratory laparotomy found a 27 x 21 x 15 cm right ovarian cystic and solid mass (Fig. 4). Some cysts appear to have ruptured. There is a moderate amount of intraabdominal ascites. Frozen section suggested ovarian malignancy, thus a staging procedure was done. Pelvic and periaortic lymph nodes, as well as omentum and ascites were negative for malignancy. Right salpingo-oopherectomy was performed.

Figure 4. 19-year-old woman with juvenile granulosa cell tumor. Photograph demonstrating the excised right ovarian mass in our patient, measuring 21 x 27 x 15 cm.

The smooth pink-tan mass was 27 cm in greatest dimension and weighed 3482 grams. It was 60% solid and 40% cystic. The cystic portions had ragged, hemorrhagic internal surfaces (Fig. 5). The solid areas contained cells with round nuclei with granular nuclear chromatin, abundant eosinophilic cytoplasm with indistinct borders, and areas of extensive necrosis (Fig. 6A). Frequent mitoses, some nuclear anaplasia were evident. In some areas, cells contain more glassy cytoplasm with some multinucleation. Some cystic spaces contain small amount of gray proteinaceous material. Abundant lutenization of irregular ovarian follicles had occurred. Branching fibrous fronds are present throughout the lesion (Fig. 6B). No Call-Exner bodies were identified. Immunohistochemical staining was positive for inhibin and
focally positive for cytokeratin AE1/AE3.

**Figure 5.** 19-year-old woman with juvenile granulosa cell tumor. Photograph of the cut gross specimen demonstrating heterogeneous internal architecture with solid, cystic, hemorrhagic and necrotic components.

The final diagnosis was juvenile granulosa cell tumor, FIGO Stage IC. The stage is based on the intraoperative findings of tumor on the ovarian surface, but limited to ovary (i.e. no pelvic extension), and no macroscopic peritoneal or regional lymph node metastases. Pathologic findings of lack of microscopic nodal or omental metastasis and negative ascites further clarified the stage. No distant metastases were present.
Figure 6. 19-year-old woman with juvenile granulosa cell tumor. A, Photomicrograph on high power demonstrates anaplastic granulosa cells with dense granular chromatin and abundant eosinophilic cytoplasm with indistinct borders. Numerous mitotic figures and significant nuclear anaplasia are present. B, Photomicrograph on medium power demonstrates the solid component of the tumor containing irregular, rudimentary follicles of varying sizes separated by sheets of cells with high mitotic activity. Fibrous septations course through solid areas.

Given the initial stage of disease assigned to the patient, no further treatment was implemented and a 3 month follow-up CT was done for surveillance. This CT revealed two new low density liver lesions, 3.4 and 4 cm in size, and new soft tissue masses in the splenic hilum, all consistent with metastases. Despite numerous cycles of varying chemotherapy regimens, the most recent CT scan demonstrated enlargement and increased number of both liver lesions and peritoneal implants in the splenic hilum. Additionally, new small loculated fluid collections are now clearly present in the right adnexa suggesting recurrent pelvic disease (Fig. 7). Her serum inhibin level remains elevated.
Figure 7. 19-year-old woman with juvenile granulosa cell tumor. Contrast-enhanced axial CT imaging demonstrating recurrent pelvic disease despite chemotherapy less than 1 year after diagnosis.

Discussion

Granulosa cell tumors are rare sex cord stromal tumors, encompassing 1-5% of all ovarian tumors [1-10]. These tumors are divided into juvenile and adult types, reflecting not only the typical age of presentation, the differentiating histologic characteristics but also the differing natural history [1,2]. The adult form of granulosa cell tumors is the more common type, accounting for nearly 95% of all granulosa cell tumors. They usually present in women over age 40 [1]. Conversely, less than 5% of tumors are the juvenile histological type and occur in mainly prepubescent females [3].

The most common presenting symptoms of both adult and juvenile granulosa cell tumors are abdominal pain and increasing abdominal girth. In 6-10% of cases, tumor rupture causing acute abdomen pain can be the presenting symptom [1,4]. Juvenile granulosa cell tumors can be hormonally active, secreting estrogen and causing 10% of all cases of precocious puberty in premenarchal females [1,4]. Dysfunctional uterine bleeding and menstrual irregularities are frequently seen in women of reproductive age with hormonally active adult granulosa cell tumors [4]. Rare cases have reported androgen-secreting tumors causing virilization [4]. Association with Maffucci’s syndrome and Ollier’s disease has been suggested but not well established [1]. The spread of juvenile granulosa cell tumors is by direct extension and intraperitoneal seeding. Metastases can spread hematogenously and arise in lungs, liver and brain. Lymph node metastases are infrequent; only 8% in one series [4].

Histologically, juvenile granulosa cell tumors are categorized as a subtype of ovarian sex cord tumors. Ovarian follicles of juvenile granulosa cell tumors are irregular in size and shape, lutenization of juvenile-type tumor cells occurs, and the nuclei are immature, show atypia, and a high mitotic rate, in contrast to the adult type which has a low mitotic rate. Call-Exner bodies and grooved, pale, round nuclei are classic features of the more common adult type tumor, and the lack of these features also helps to distinguish the juvenile type from the adult type [2]. A positive immunohistochemical stain for inhibin, an ovarian glycoprotein, is a key diagnostic feature.

Imaging characteristics of adult and juvenile granulosa cell tumors are non-specific and these tumors cannot be reliably distinguished from other ovarian neoplasms on imaging alone. On cross-sectional CT imaging and sonography, their appearance varies widely, but they often appear as a single large multiloculated cystic mass with solid components. They have multiple septations which can be thin, or thick and irregular. The adult form shows more variability with regards to the cystic component and can occasionally appear predominantly solid. Intratumoral hemorrhage, central areas of necrosis and fibrous degeneration can result in a heterogeneous solid appearance [7]. Calcifications or intracystic papillary projections, typical of epithelial neoplasms such as serous or mucinous tumors, are not seen [6].

MR imaging is more distinctive. T1W MR images can demonstrate intracystic high signal suggesting characteristic intratumoral hemorrhage present in up to 71% of cases [4,7]. On T2W images, tumors have a sponge-like appearance, indicating alternating solid and cystic spaces [4,7]. Tumoral secretion of estrogen can cause uterine enlargement and endometrial thickening, which can be additional imaging findings in 50% of patients [8]. 10% of adult type granulosa cell tumors are associated with endometrial adenocarcinoma, thus some investigators have suggested preoperative endometrial biopsy in these patients [8]. Metastasis, though rare at initial presentation, appear as cystic liver masses or peritoneal implants, similar to epithelial ovarian neoplasms [6].

The staging system used for granulosa cell tumors is that applied to other ovarian epithelial tumors, the FIGO staging. Staging determines which patients are at risk for recurrence and those that require
chemotherapy. At presentation, 90% of juvenile granulosa cell tumors are FIGO stage I, confined to the ovary. This stage carries a very favorable prognosis and a 5 year survival rate of 90-100%. Juvenile granulosa cell tumors are less likely than adult granulosa cell tumors to recur after resection of stage I tumors, however if they do, their clinical course is more likely rapid and aggressive, with early relapses and poor outcomes. In one series, relapse occurred in 2 of 4 patients receiving chemotherapy for stage IC tumors [3]. Adult granulosa cell tumors are less likely to be malignant, but have a higher risk of late recurrences [1,3,8,11]. Recurrence depends heavily on stage. A series of advanced stage tumors demonstrated a 41% recurrence rate in patients without macroscopic residual disease, and a 30% mortality rate in this group, despite treatment [1,3,5,9].

A variety of chemotherapy regimens have been used against juvenile granulosa cell tumors with varying success. Multiple studies suggest cisplatin-based multi-drug regimens can be effective in advanced stages of juvenile granulosa cell tumors or to treat recurrences [3,4]. Recently it has been suggested that hormone-based treatments with such drugs as paclitaxel and taxane could be used in combination with platinum-based drugs [4]. The use of radiotherapy as adjuvant treatment has not been convincingly shown to confer any survival benefit to granulosa cell tumors patients at any stage [4,9]. As previously stated, stage I tumors carry a favorable prognosis with 5 year survival between 90 and 100%. Resection of stage I tumors is felt to be curative. 5 year survival for stage II tumors drops considerably to 55-75% and moreso for stage III/IV tumors- 22-50% [7]. Unfavorable prognostic factors may include nuclear atypia, high mitotic rate, extra-capsular extension of tumor within ovary, tumor rupture, and presence of residual disease after surgery [1,3,4,9]. Length of surveillance of patients with Stage I juvenile granulosa cell tumors was initially short, due to the fact that recurrences, while rare, usually occurred within a year. Some advocated that follow-up was only necessary up to 3 years [10], however a recent case report has shown a late recurrence of juvenile granulosa cell tumors 4 years later [11], suggesting longer term surveillance may be necessary in some cases. Tumor markers such as inhibin can also be used to assess for recurrence.

This juvenile granulosa cell tumor may have been a rare, androgen-secreting tumor causing hirsuitism, unfortunately no hormonal levels were obtained. Few cases of this hormonal type of juvenile granulosa cell tumor have been reported. Also, initially this patient was staged at IC, however her disease recurred quickly with both liver and perisplenic peritoneal metastases within 3 months of surgery. This case not only illustrates a rare form of ovarian tumor in young woman, but also demonstrates the unusual aggressive biologic behavior of a stage IC tumor; a situation where surgery has traditionally felt to be curative.

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