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Mixed sex cord–stromal tumor (gynandroblastoma) with malignant morphology involving both ovaries: a case report

Bayan Maraqa, Maxim Al-Ashhab, Nazmi Kamal, Maher Sughayer and Fareed Barakat

Abstract

Mixed sex cord–stromal tumors, which consist of poorly differentiated Sertoli cells and Leydig cells and juvenile granulosa cell tumor tissue, are extremely rare. Most of these tumors are unilateral and stage I at the time of diagnosis; nonetheless, according to the available relevant English-language literature, these tumors maintain a malignant potential. We herein report a case involving a 15-year-old girl diagnosed with a mixed sex cord–stromal tumor (gynandroblastoma with juvenile granulosa cell tumor component). Left salpingo-oophorectomy was initially performed, and the diagnosis of a juvenile granulosa cell tumor was established. Right salpingo-oophorectomy was performed 1 year later, at which time the specimen showed a different growth pattern involving epithelioid cells and tubules, resembling a Sertoli–Leydig cell tumor. Immunohistochemical staining was performed and the specimen was compared with that obtained 1 year earlier. We concluded that the tumors were linked and most likely constituted a gynandroblastoma (mixed form of sex cord–stromal tumor). Although this is an extremely uncommon ovarian tumor, it should be considered when diverse tumor morphology is identified. Bilateral metachronous involvement of the ovaries is possible. The grade of the Sertoli–Leydig cell component may influence the prognosis of such a tumor.

Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan

Corresponding author:
Fareed Barakat, Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, 202 Queen Rania Al-Abdullah Street, PO Box 1269 Al-Jubaiha, Amman 11941, Jordan.
Email: fbarakat@khcc.jo

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Introduction

Ovarian tumors in children and teenage girls are a rare but significant subset of gynecological cancers. They account for 1% of all malignant tumors and have an annual incidence of roughly 2.6 cases per 100,000 girls.[1] Most ovarian tumors fall under the categories of epithelial, mesenchymal, sex cord stromal, and germ cell tumors.[2] Whereas epithelial cell tumors account for 90% of ovarian cancers in all age groups, germ cell tumors predominate in children, accounting for around 70% of such ovarian neoplasms. Mature teratoma is the most common benign tumor, and dysgerminoma is the most common malignant tumor.[1,3]

Gynandroblastoma (mixed form of sex cord–stromal tumor) is a very rare ovarian tumor that has histological components of both a granulosa cell tumor (GCT) and Sertoli–Leydig cell tumor (SLT).[2] Gynandroblastoma comprising poorly differentiated Sertoli cells and Leydig cells and juvenile GCT tissue are tremendously rare, with only 6 of 28 such cases reported in the English-language literature to date. These tumors are usually found in adolescent girls.[4–9]

Patients with gynandroblastoma usually present with stage I disease. Most tumors are unilateral and behave in a benign manner, and only rare recurrences have been reported.[2,10]

We herein report a rare case of gynandroblastoma of the ovary composed of juvenile GCT and SLT elements with bilateral ovarian involvement and malignant behavior in an adolescent. The reporting of this study conforms to the CARE guidelines.[11]

Case Report

A 15-year-old girl presented with left-sided abdominal pain associated with prolonged menstrual bleeding. She had undergone left nephrectomy at the age of 1 year because of a mass lesion; the pathology was unknown but the mass was reportedly benign. A first-degree relative had developed metastatic breast cancer at the age of 30 years. Physical examination was remarkable only for hirsutism.

The patient underwent ultrasound examination, which showed a large mass in left ovary. Computed tomography confirmed this finding. Left salpingo-oophorectomy was performed, and the obtained specimen contained a left ovarian tumor measuring $18 \times 14 \times 7$ cm with a smooth surface. Microscopic examination revealed nodular and diffuse growth of tumor cells with ovoid hyperchromatic nuclei, small nucleoli, amphophilic cytoplasm. Macrofollicle and microfollicle formations containing eosinophilic secretions were identified (Figure 1). The tumor cells were positive for steroidogenic factor 1 (SF-1) and inhibin, focally positive for cytokeratin (CK), and negative for SALL4. Reticulin stain highlighted groups/nests of tumor cells. B-catenin showed a positive membranous staining pattern. Therefore, a diagnosis of juvenile type GCT was established.

One year later, a right ovarian mass was found by ultrasound during a regular follow-up. Serum inhibin and anti-Müllerian

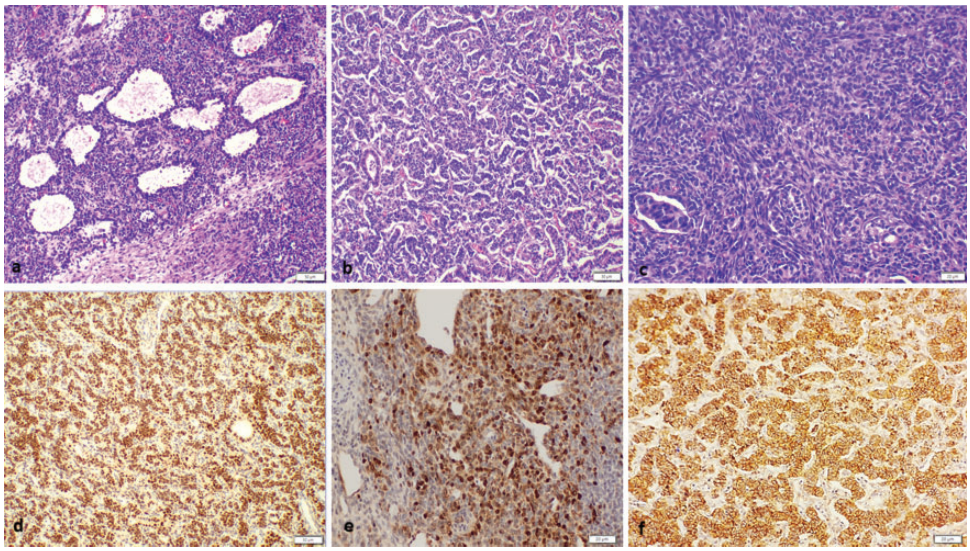

Figure 1. Histological findings of left ovarian tumor. (a) The tumor was composed of cystic follicles (hematoxylin and eosin (H&E), 10×). (b) Focal tubule formation (H&E, 10×) and (c) focal spindle cell areas (H&E, 20×) were identified. The tumor cells were positive for (d) steroidogenic factor 1, (e) calretinin, and (f) membranous B-catenin.

hormone were negative. Pelvic magnetic resonance imaging revealed a pelvic mass measuring approximately 4.5 cm in axial diameter, located to the right of the rectum and probably originating from the right ovary. Right salpingo-oophorectomy was performed, and the specimen contained a tumor composed of poorly differentiated spindle/polygonal Sertoli cells admixed with fewer Leydig cells. Focal tubule formation, cystic follicles, and necrosis were also noted (Figure 2). The mitotic rate was 20 per 10 high-power fields. The tumor cells were positive for SF-1, B-catenin (membranous), alpha-inhibin, and calretinin and negative for SALL4, CK7, and epithelial membrane antigen (EMA).

This tumor was compared with the first tumor diagnosed as juvenile GCT. Areas that were morphologically similar to the new tumor with tubules and cords of Sertoli cells were identified. We concluded that both tumors were related and most likely represented a gynandroblastoma (mixed form of sex cord–stromal tumor).

The patient underwent oocyte cryopreservation and started carboplatin/paclitaxel chemotherapy with no evidence of disease recurrence after 2 years of follow-up.

The patient was evaluated in the genetic clinic and discovered to have a pathogenic *DICER1* mutation (Variant: c.3094-2_3096del). Therefore, she was placed on surveillance guidelines for individuals with a germline *DICER1* mutation.

Materials and methods

In the pathology department of King Hussein Cancer Center, we identified a case of gynandroblastoma (mixed form of sex cord–stromal tumor). The excised tissue was serially sectioned and fixed in 10% buffered formalin overnight. The sections were routinely processed for paraffin embedding and stained using hematoxylin

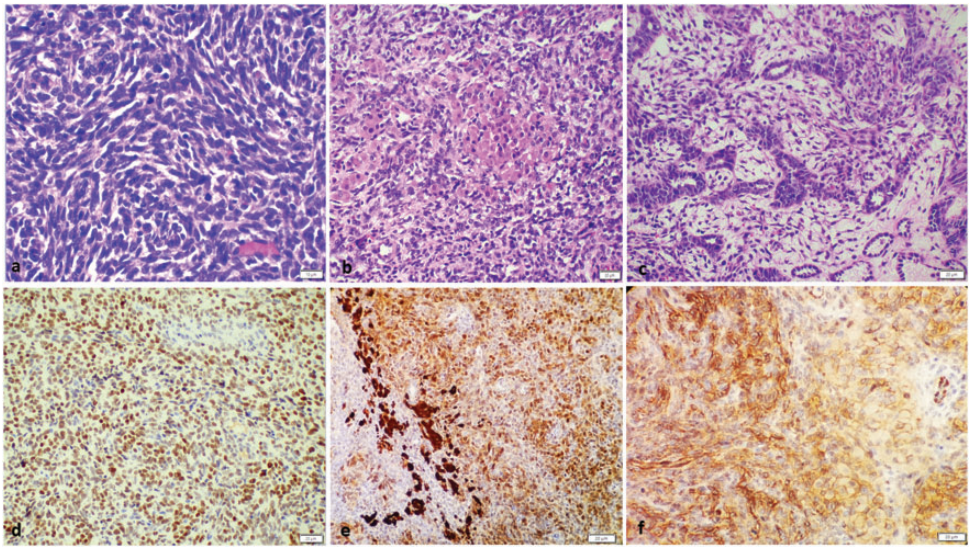

Figure 2. Histological findings of right ovarian tumor. The tumor was composed of (a) poorly differentiated spindle/polygonal Sertoli cells (hematoxylin and eosin (H&E), 40×) admixed with (b) fewer Leydig cells (H&E, 20×). (c) Focal tubule formation was identified (H&E, 20×). The tumor cells were positive for (d) steroidogenic factor 1, (e) calretinin, and (f) membranous B-catenin.

and eosin. Immunostaining was performed on the paraffin-embedded material using the avidin–biotin complex protocol with an iVIEW DAB detection kit (Ventana Medical Systems, Tucson, AZ, USA). We used monoclonal antibodies against SF-1 (Clone ERP19744; Abcam, Cambridge, UK), inhibin alpha (Clone R1; Ventana Medical Systems), pancytokeratin (Clone AE1/AE3/PCK26; Ventana Medical Systems), SALL4 (Clone 6E3; Abcam), B-catenin (Clone 14; Ventana Medical Systems), calretinin (Clone SP65; Ventana Medical Systems), CK7 (Clone B22.1; Ventana Medical Systems), and EMA (Clone E29; Ventana Medical Systems). All immunostains were performed on the Ventana Benchmark XT/Ultra automated immunostainer (Ventana Medical Systems).

Discussion

Gynandroblastoma is a mixed ovarian sex cord–stromal tumor with both male and female components. Two morphologic subtypes of the granulosa cell component can be defined when classifying these tumors, namely the juvenile and adult subtypes; this is important because these two subtypes may differ in behavior and prognosis. Juvenile GCT constitutes a relatively small percentage of all GCTs (about 5%). However, juvenile GCT accounts for approximately 90% of GCTs among prepubertal adolescents and women under the age of 30 years. Most juvenile GCTs are unilateral and appear at an early stage. These tumors are frequently functional and secrete estrogen, which leads to precocious puberty in approximately 80% of patients. Some patients may develop virilization due to the release of testosterone. The absence of a *FOXL2* mutation in juvenile GCT can aid in differentiating it from adult GCT.[12]

Gynandroblastoma generally exhibits adult-type GCT characteristics and is known to have malignant potential. Only a few cases

of juvenile-type GCTs have been reported. These tumors are exceedingly rare. Therefore, there is no consensus on how to assess the likelihood of malignancy in this subtype of gynandroblastoma based on histology.

SLTs can be classified as well, moderately, or poorly differentiated based on the tubular differentiation of the Sertoli cell component.[2] Up to 22% of SLTs have heterologous mesenchymal or epithelial elements. These elements are only found in moderately and poorly differentiated tumors and in tumors with a retiform pattern. In rare cases, they can mimic aggressive tumors such as rhabdomyosarcomas.[13,14] SLT staining is usually positive for inhibin, calretinin, WT-1, and CD56 and negative for EMA. Our patient was found to have a *DICER1* mutation, which has been reported in up to 60% of SLTs in the literature.[15]

DICER1 syndrome occurs in children and young adults. Its clinical presentation may include pleuropulmonary blastoma, cystic nephroma, ovarian SLT, and gynandroblastoma; multinodular goiter; embryonal rhabdomyosarcoma of the cervix; and sarcomas of different sites including the uterine cervix, kidney, and brain.[16] Our patient had a history of nephrectomy as a child, which was probably related to *DICER1* syndrome, and she developed multinodular goiter during follow-up.

We believe that the features of malignant behavior (bilaterality and metachronicity) of the tumor in the present case may have been dictated by the grade of the SLT component (poorly differentiated histologic type 3). In tumors with a low-grade Sertoli cell component, however, whether the juvenile-type granulosa cells found in gynandroblastoma will have a poorer prognosis than the adult granulosa cell component found in classic gynandroblastoma remains unknown.

The pathogenesis and biologic behavior of these two subtypes are still unclear because of the rarity of these tumors and limited numbers of previous reports. More wide-range histologic and molecular studies are needed.

We found five cases of bilateral ovarian involvement by SLTs[17–21] in the English-language literature, three of which were metachronous (asynchronous) and two of which were synchronous. However, we found no previous reports of bilateral ovarian involvement by gynandroblastomas with a juvenile GCT component. To our knowledge, ours is the only reported case of bilateral metachronous involvement of the ovaries by gynandroblastoma with poorly differentiated SLT and juvenile GCT components.

Ordulu and Young[22] reported 38 cases of SLTs that contained follicles resembling a juvenile GCT component. In their opinion, the presence of a juvenile granulosa-like morphology may simply represent another morphology of an SLT rather than a true gynandroblastoma. However, the authors described a multifocal origin within lobules of otherwise typical SLTs, in which the overall tumor features show unusual differentiation within these tumors.

In conclusion, gynandroblastoma with a juvenile GCT component is an extremely uncommon ovarian tumor. When diverse tumor morphology is identified, this type of tumor should be considered. Bilateral metachronous involvement of the ovaries is possible. The grade of the SLT component may influence the prognosis of such a tumor. More comprehensive histologic and molecular studies are required.

Author contributions

Bayan Maraqa was responsible for acquiring the data and drafting the manuscript. Maxim Al-Ashhab was responsible for reviewing the literature and drafting the manuscript. Nazmi Kamal and Maher Sughayer were responsible for critically revising the manuscript. Fareed

Barakat designed, directed, and reviewed the manuscript.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Data availability statement

The original data presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

All treatments were carried out with written informed consent from the patient and her family members. The patient also provided written informed consent for the publication of this article related to her medical records. The study protocol was approved by the Ethics Committee of King Hussein Cancer Center.

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ORCID iDs

Bayan Maraqa https://orcid.org/0000-0001-9455-188X
Maher Sughayer https://orcid.org/0000-0002-9185-9616

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