Pediatric and Developmental Pathology 8, 680–684, 2005
DOI: 10.1007/s10024-005-0055-2

Pediatric Sex Cord-Stromal Tumor with Composite Morphology: A Case Report

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Received June 3, 2005; accepted August 9, 2005; published online October 12, 2005.

ABSTRACT

A 12-year-old female with developmental delay/mental retardation and a family history of gynecologic cancers presented with nonspecific abdominal complaints and was found to have a 4.5-kg, 25- × 23- × 15-cm pelvic mass with solid and cystic components and associated retroperitoneal and mesenteric lymphadenopathy. Laboratory studies revealed increased serum levels of CA-125 and inhibin B. Histologically, the tumor exhibited several different morphologic appearances including adult granulosa cell tumor, juvenile granulosa cell tumor (with areas of marked atypia), and Sertoli cell tumor. Immunohistochemically, the tumor was positive for calretinin, MIC-2 (CD99), S100 protein, PGP 9.5, and neuron-specific enolase. Electron microscopy of the Sertoli cell tumor-like areas showed Charcot-Bottcher filaments, a distinguishing feature of Sertoli cells. Together, these findings supported a diagnosis of mixed sex cord-stromal tumor including granulosa cell tumor of adult and juvenile types and intermediate- to high-grade Sertoli cell tumor, with large areas of markedly atypical sex cord-stromal tumor.

Key words: granulosa cell tumor, ovarian neoplasms, Sertoli cell tumor, sex cord-stromal tumor

CASE REPORT

A 12-year-old developmentally delayed/mentally retarded female presented with vague abdominal complaints including constipation, bloating, and increasing girth. Her medical history was significant for recent onset of menarche at age 12 years with irregular cycles. She had 1 maternal aunt and 1 paternal aunt who were older than 40 years and had ovarian cancer and a grandmother who had endometrial cancer. Physical examination detected a large, firm mass that filled the abdomen and extended from the pubic symphysis to the xiphoid process. Laboratory studies showed increased serum levels of CA-125 (504 U/mL, normal range 0–35 U/mL), inhibin B (2,613 pg/mL, normal follicular phase range 16–290 pg/mL), and lactate dehydrogenase (389 IU/L, normal range 60–200 IU/L). Serum levels of β-human chorionic gonadotropin, α-fetoprotein, testosterone, inhibin A, and total calcium were normal. Computed tomogram demonstrated a 23- × 20- × 12-cm pelvic mass with solid and cystic components and enlarged retroperitoneal and mesenteric lymph nodes.

Exploratory laparotomy of the abdomen and pelvis revealed a 4.5-kg, 25- × 23- × 15-cm, complex right ovarian mass composed of multiple unilocular, smooth-lined cysts filled with brown clear fluid and separated by firm, gray-white, lobulated tissue with focal hemorrhage and necrosis (Fig. 1). The ipsilateral fallopian tube was unremarkable. Tumor implants were found in the rectosigmoid pericolic soft tissue, parauterine soft tissue, omentum, and mesentery. Eleven bilateral peri-

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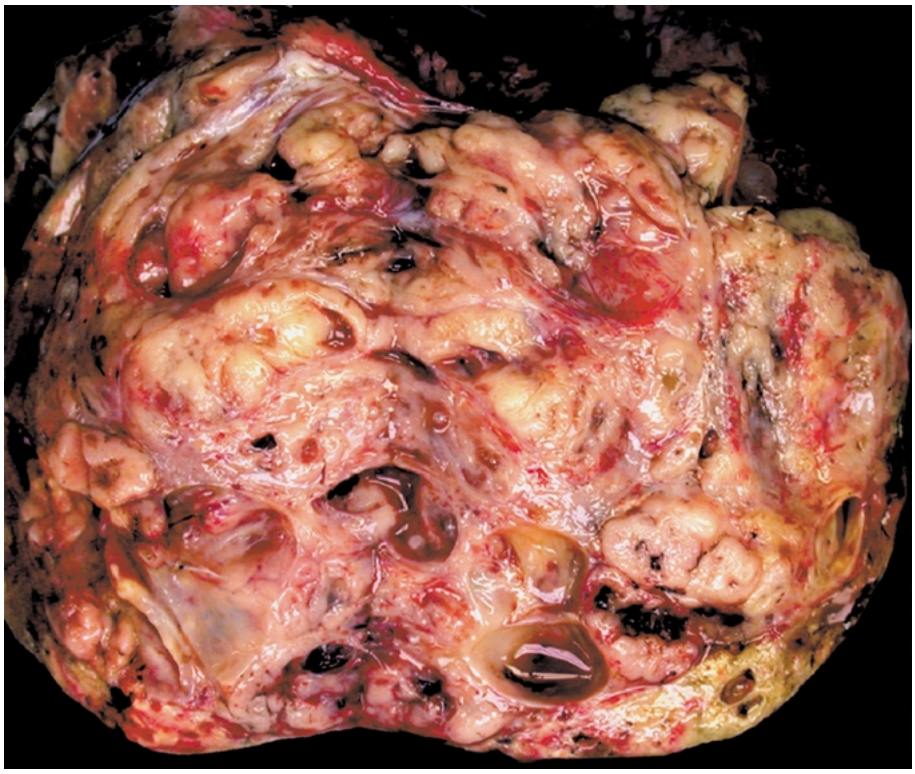

Figure 1. Gross appearance of bivalved right ovarian tumor.

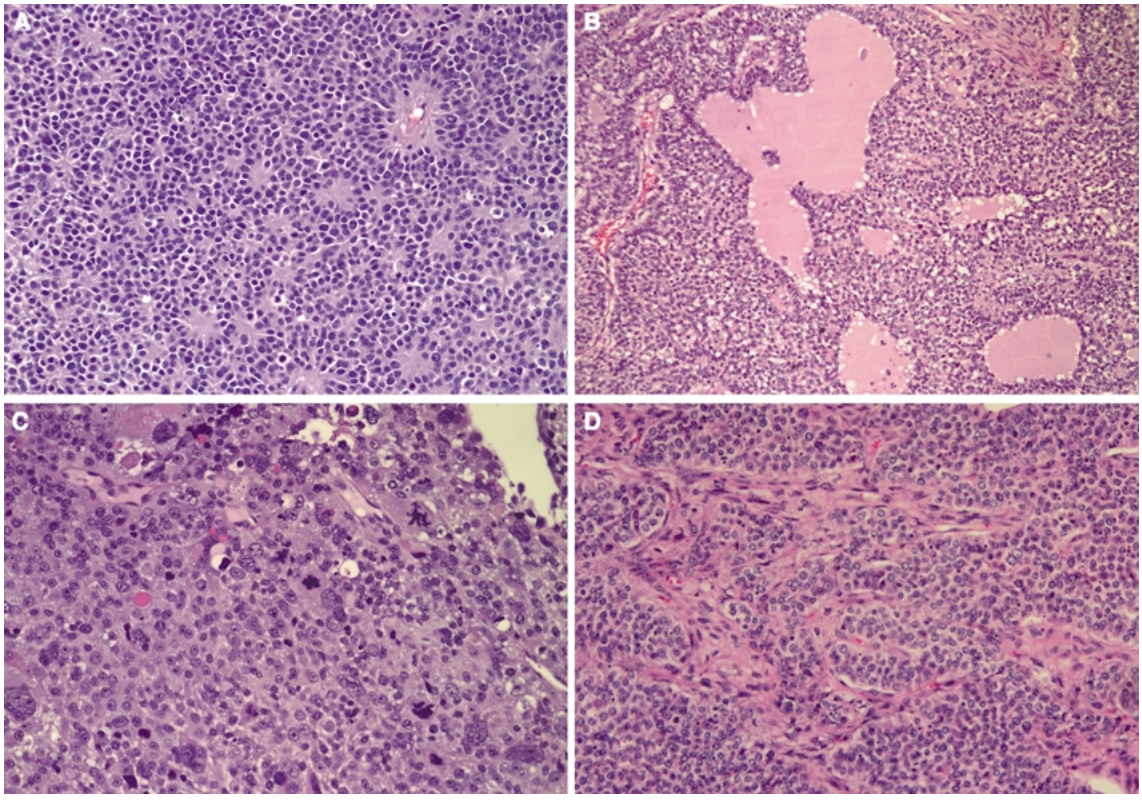

Figure 2. Microscopic appearance of tumor, including areas resembling (**A**) adult granulosa cell tumor with Call-Exner bodies, (**B**) juvenile granulosa cell tumor with irregular follicles, (**C**) markedly atypical areas of juvenile granulosa cell tumor, and (**D**) Sertoli cell tumor. Hematoxylin and eosin, 200× in A, C, D, 100× in B.

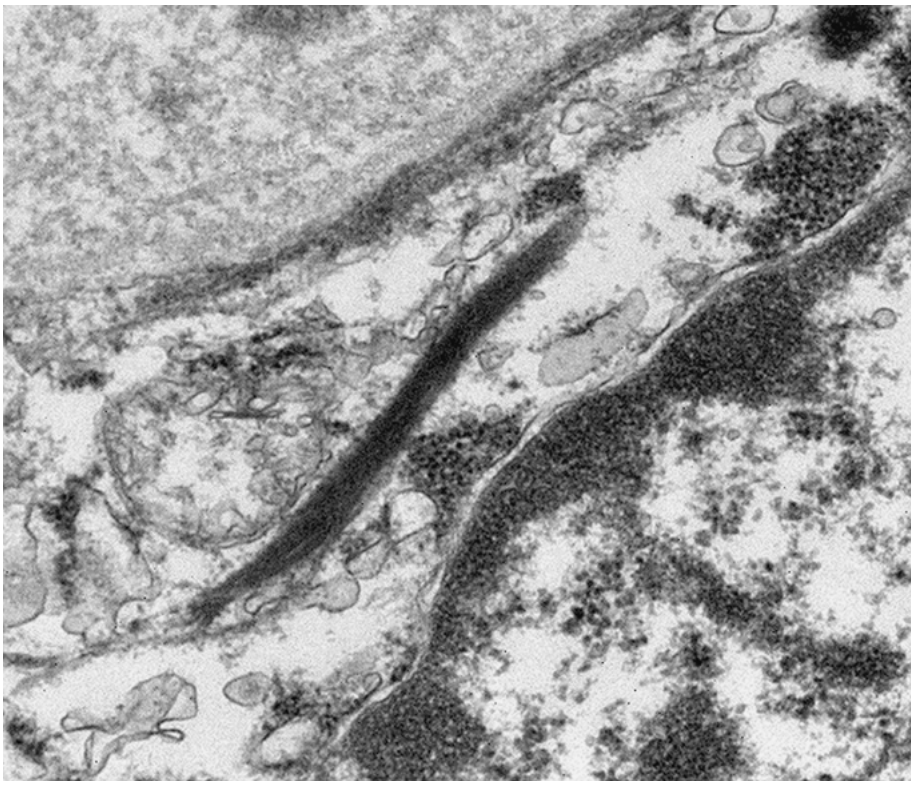

Figure 3. Electron microscopy shows perinuclear, linear filament aggregates consistent with Charcot-Bottcher crystalloids (80,000×).

aortic, mesenteric, and pelvic lymph nodes were negative for neoplasm.

Histologically, the tumor consisted of a spectrum of morphologies. Some areas resembled adult granulosa cell tumor (15%) with trabeculae, diffuse sheets, and Call-Exner body-like structures composed of cells with grooved nuclei and eosinophilic cytoplasm (Fig. 2A). Other areas (10%) showed juvenile granulosa cell tumor with sheets and occasional, large, irregular follicles composed of cells lacking nuclear grooves (Fig. 2B) [1,2]. The predominant appearance (65%) was that of markedly atypical solid areas superficially resembling juvenile granulosa cell tumor (Fig. 2C). Portions of the tumor (10%) resembled Sertoli cell tumor with pale, lipid-filled cells arranged in tubules and trabeculae (Fig. 2D) [3].

Immunohistochemically, the tumor was diffusely positive for MIC-2 (CD99; membranous staining), S100 protein (cytoplasmic), PGP 9.5 (cytoplasmic), and neuron-specific enolase (cytoplasmic) and showed patchy positive staining for calretinin (cytoplasmic); all tumor components expressed each of these antigens, although the most poorly differentiated areas stained less intensely. The tumor was negative for leukocyte common antigen (CD45), α-fetoprotein, epithelial membrane antigen, neurofilament protein, smooth muscle actin, desmin, inhibin-α, chromogranin, synaptophysin, cytokeratin, and c-kit (CD117). Electron microscopy of Sertoli cell tumor-like areas showed rare cells containing electron-dense filaments in a paranuclear distribution. These structures, known as Charcot-Bottcher filaments, are an ultrastructural characteristic of Sertoli cells (Fig. 3). Polymerase chain reaction and western blot studies for the t(11;22) EWS-FLI translocation (performed at the Armed Forces Institute of Pathology) were equivocal.

DISCUSSION

Although the histology of much of the tumor suggested a sex-cord stromal origin, the large areas composed of poorly differentiated small round blue cells raised a number of additional possibilities in the differential diagnosis. In the pediatric population this includes Ewing sarcoma/primitive neuroectodermal tumor, rhabdomyosarcoma, desmoplastic small round cell tumor, and lymphoma. At this age, the most common ovarian neoplasms are germ cell tumors. Small cell carcinoma, hypercalcemic type, was also

considered based on the morphologic appearance of the tumor. Immunohistochemistry helped narrow the differential because lymphoma is unlikely with negative leukocyte common antigen staining, rhabdomyosarcoma is unlikely with negative desmin staining, and small cell carcinoma of the ovary, hypercalcemic type, or desmoplastic small round cell tumor are unlikely with negative epithelial membrane antigen and keratin staining (and a normal serum calcium) [4]. Although the tumor cells were positive for MIC-2 (CD99), PGP 9.5, and S100 protein, EWS-FLI studies were equivocal, which raises the possibility of, but does not confirm, a diagnosis of primitive neuroectodermal tumor. Consequently, the distinctive morphologic features of the granulosa cell tumor-like and the Sertoli cell tumor-like areas, the increased serum inhibin B levels, calretinin positivity by immunostaining, and electron microscopic demonstration of Charcot-Bottcher filaments support a sex cord-stromal origin [4–6]. Gynandroblastoma was also a diagnostic consideration, but this patient's tumor lacked the classic combination of well-differentiated tubular Sertoli cell elements and microfollicularly patterned granulosa cell elements, presented at a later than expected stage, and stained negatively for inhibin-α [7]. Heterologous mesenchymal or neuroblastic components have been described in rare Sertoli-Leydig cell tumors but were not present in this case [8]. Although most ovarian stromal tumors express inhibin-α, this tumor did not; however, this does correlate with the clinical studies showing increased serum levels of inhibin-β but normal levels of inhibin-α [9].

Although the etiology of this patient's developmental delay is unclear, its coincidence with this tumor is intriguing. She was born at 39 weeks of gestation, a 3,610-g product of a pregnancy complicated by non–insulin-dependent gestational diabetes mellitus and mild gestational hypertension. She had an accessory finger that was surgically removed shortly after birth, short fingernails, bilateral clinodactyly, broad thumbs, and large toes. Her mild dysmorphic facial features included synophrys, narrow palpebral fissures, a short forehead, bilateral epicanthal folds and a narrow nasal bridge, heterochromic irides, normally set ears with underdeveloped helical groups, and low anterior and posterior hairlines. The patient also had a pigmented, 2.0-cm birthmark under her left axilla. Ophthalmologic examination was unremarkable and showed no signs of retinal degeneration. At 12 months of age, she was at the 95_{th} percentile for weight despite being at the 50_{th} percentile for height, and she has remained above the 95_{th} percentile for weight ever since. She did not walk until age 16 months and never crawled. At 5 years, she possessed a 100-word vocabulary and was just beginning to formulate short sentences. She experienced menarche at age 12 with irregular cycles since then. Laboratory tests for thyroid and pituitary function were within normal limits. Karyotypic and fluorescence in situ hybridization studies of the Prader-Willi critical region were normal. The clinical possibilities included Bardet-Biedl, Laurence-Moon, and Prader-Willi syndromes. However, no propensity for malignancy has been reported in any of these syndromes. The significance of her family history of frequent gynecologic cancers is unclear in the absence of additional information. A few case reports of similar, histologically diverse ovarian neoplasms have been reported in the pediatric population and suggest sporadic occurrence [10,11].

The final diagnosis was a stage IIIC mixed sex cord-stromal tumor including granulosa cell tumor of adult and juvenile types and intermediate- to high-grade Sertoli cell tumor, with large areas of poorly differentiated, atypical cells resembling juvenile granulosa cell tumor. Most patients with sex cord-stromal neoplasms present early with limited involvement and have a good prognosis, with 5-year survival rates of 80% to 90% for stage I tumors. However, for this patient and others with extraovarian disease (stage II or greater), 5-year survival rates are much lower, in the range of 33% to 50% [12,13]. Although the histologic subtype of granulosa cell tumor does not directly correlate with outcome, high nuclear grade, atypia, and mitotic activity are poor prognostic factors related to advanced stage disease and are prevalent in this tumor [13,14]. The patient was treated with 6 cycles of a chemotherapy protocol comprised of bleomycin, etoposide, and cisplatin. Fifteen months after her initial diagnosis, she was in clinical remission with negative pelvic ultrasound and computed tomographic examinations, an in-

hibin-A level lower than 10 pg/mL, and an inhibin-B level of 40 pg/mL.

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