

Original Article

Histological changes of non-Peutz-Jegher syndrome associated ovarian sex cord tumor with annular tubules in childhood

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Abstract: Ovarian sex cord stromal tumor is a relatively rare subtype of ovarian neoplasms, consisting of only 8% of all primary ovarian neoplasms, among which sex cord tumor with annular tubules (SCTAT) accounts for only 6% of sex cord stromal tumors. The majority of patients with SCTAT are women at reproductive age. Roughly one-third of the patients have Peutz-Jeghers syndrome (PJS), and in cases without PJS, about 15%-20% SCTAT tend to be clinical malignant. Herein we report 3 cases of non-PJS associated ovarian SCTAT onset in childhood, among which, two cases had recurrence and metastasis. And we summarize the pathologic manifests and report our discovery of the pathologic difference between primary and recurrent/metastatic SCTAT in childhood.

Keywords: Sex cord tumor with annular tubules, ovarian sex cord stromal tumor, Peutz-Jeghers syndrome

Introduction

Sex cord tumor with annular tubules (SCTAT) was first described by Scully in 1970 for a peculiar form of ovarian neoplasm [1]. In the past, SCTAT have been placed in the category of unclassified sex cord-stromal neoplasms. In the recently published classification of tumors of female reproductive organs by WHO, SCTAT was classified as pure sex cord neoplasms [2]. It is a rare subtype of ovarian tumor and the majority of patients with SCTAT are women at reproductive age [3]. Roughly one-third of the patients have Peutz-Jeghers syndrome (PJS), and in sporadic cases, about 15%-20% SCTAT tend to be clinical malignant [4].

Case reports

Case 1

A 3 years and 10 months old girl was admitted to our hospital complaining of premature thelarche for 10 months and recurrent and long-lasting vaginal bleeding. Preoperative laboratory testing of hormone demonstrated an increase in serum estradiol (210.75 pg/mL), while LH, FSH, β -HCG and tumor markers were

within normal limits. MR show normal hypothalamus and pituitary. CT revealed right ovary a well-defined oval low-density area, with rim enhancement and punctuate and streak enhancement in it. The uterine was enlarged with liquid in the uterine cavity.

A 6.5 × 5 × 5 cm polycystic mass was enucleated with conservation of the right ovary. The mass was consisted of cysts of different size with clear and transparent liquid.

The hormone level returned to the normal after the operation and she didn't receive chemotherapy. 26 months after the operation, the breast development and vaginal bleeding came again. MR revealed a 13 × 25 × 9 mm cystic mass in right ovary region with thick and significantly enhanced wall. The tumor was staged FIGO IIIa. During the operation, a tumor was found with solid and cystic appearance and an intact capsule on the residual of right ovary as well as numerous seedings on the great omentum and peritoneum. She underwent unilateral salpingo-oophorectomy and omentectomy. After the second operation, she received 7 round chemotherapy following JEB regimen in total. Just after the 5th round chemotherapy,

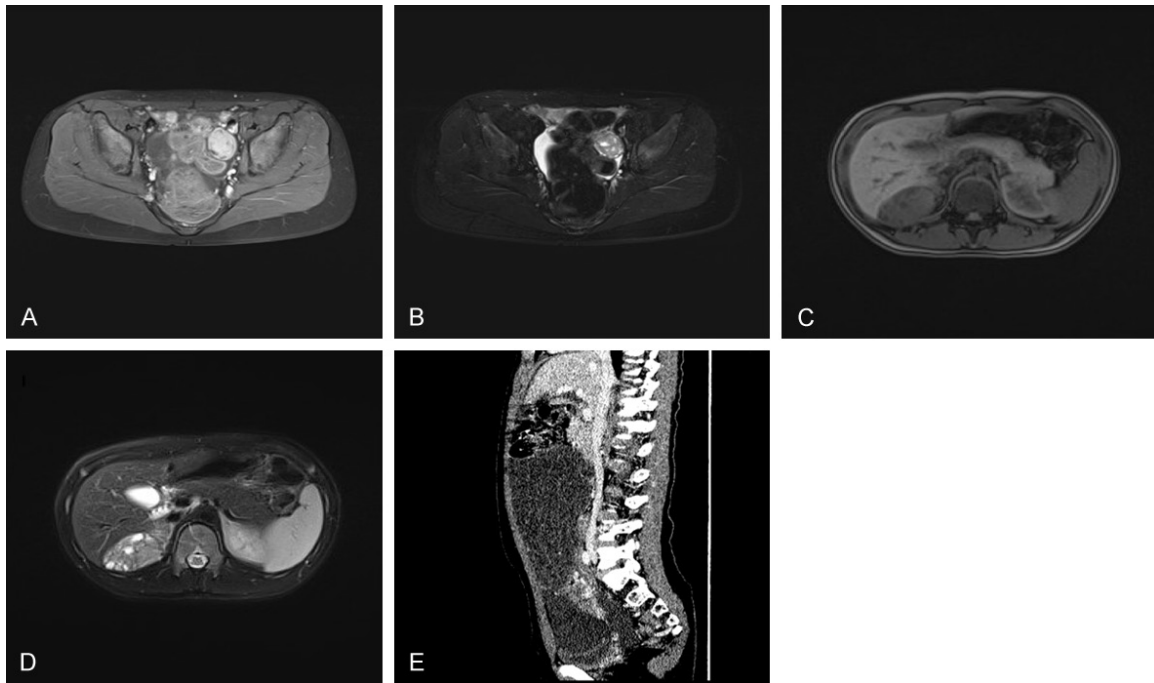


Figure 1. Radiological findings. A, B: Recurrent tumor in case 2. C, D: Metastasis tumor in case 2. E: Primary tumor in case 3. A: MR on fat-suppressed T1WI sequence revealed a 31 mm × 24 mm × 43 mm left ovarian mass with slightly high signal and small patchy low signal. B: MR on fat-suppressed T2WI sequence revealed high signal with patchy higher signal. The mass showed significantly enhanced and clear boundary. C: MR on T1W1 sequence revealed a 52 mm × 29 mm × 61 mm mass with inhomogeneous low signal in the left adnexal region. D: MR on fat-suppressed T2WI sequence revealed high signal mass in the left adnexal region. E: CT showed an enormous cystic mass with flocculent septae in abdominal and pelvic cavity, the mass was 172.5*76.4 mm, and the flocculent partitions were significantly enhanced.

she underwent laparoscopic exploration and found multiple small metastases on the pelvic and abdominal wall. She is now regularly followed-up and does well.

Case 2

A girl aged 6 years and 8 months complaining of 2-month premature thelarche and a little yellowish vaginal secretion was admitted to our hospital. Her breasts staged Tanner III with 2 cm × 2 cm indurations palpated and pubic hairs staged Tanner I. She had no history or family history of gastrointestinal disease and her skin and mucosa seemed normal.

Blood test showed elevated estradiol level (44.00 pg/ml) without FSH and LH presented, no elevated in tumor markers and no response to LHRH test. Pelvic ultrasonography demonstrated a 6 cm × 5 cm × 5 cm polycystic mass in the left ovary and a normal right ovary. MR showed normal hypothalamus and pituitary. She had a little advanced bone age corresponding to 7.5 years old.

At the laparoscopic surgery the left ovary showed a polycystic mass with an intact capsule, and within the mass there were several “enlarged follicles” ranging from 2 cm to 5 cm in greatest dimension. Then she underwent laparoscopic ovarian cyst enucleation.

After the surgery her symptoms relieved and estradiol level returned to the normal. She received hormone therapy instead of chemotherapy in other hospital for 3 years.

She came back at the age of 10 years and 5 months complaining of irregular vaginal bleeding, detection of left ovary solid mass and elevated estradiol level (41.00 pg/mL). MR revealed an 31 mm × 24 mm × 43 mm left ovarian mass with slightly high signal and small patchy low signal on fat-suppressed T1WI (**Figure 1A**) and high signal with patchy higher signal on fat-suppressed T2WI (**Figure 1B**). The mass showed significantly enhanced and clear boundary. There was a 52 mm × 29 mm × 61 mm inhomogeneous low signal on T1WI (**Figure 1C**) and high signal on fat-suppressed T2WI

Table 1. Gross findings of the tumors

Case 1	Primary tumor	Cystic with clear and transparent fluid	6.5 cm*5 cm*5 cm	Grey-red	Soft
	Local recurrent tumor	Solid	1.5 cm*1 cm*1 cm	Grey-yellow	Medium
Case 2	Primary tumor	Cystic, cut surface showed 0.1 cm-0.3 cm small cavities with fluid	3.5 cm*2.5 cm*2 cm	Taupe	Soft
	Local recurrent tumor	Solid	5 cm*4 cm*3 cm	Grey-yellow	Soft
	Metastatic tumor	Solid	10 cm*7 cm*3 cm	Grey-yellow	Soft
Case 3	Primary tumor	Cystic with light yellow fluid	20 cm*15 cm*6 cm	Grey-red	Soft

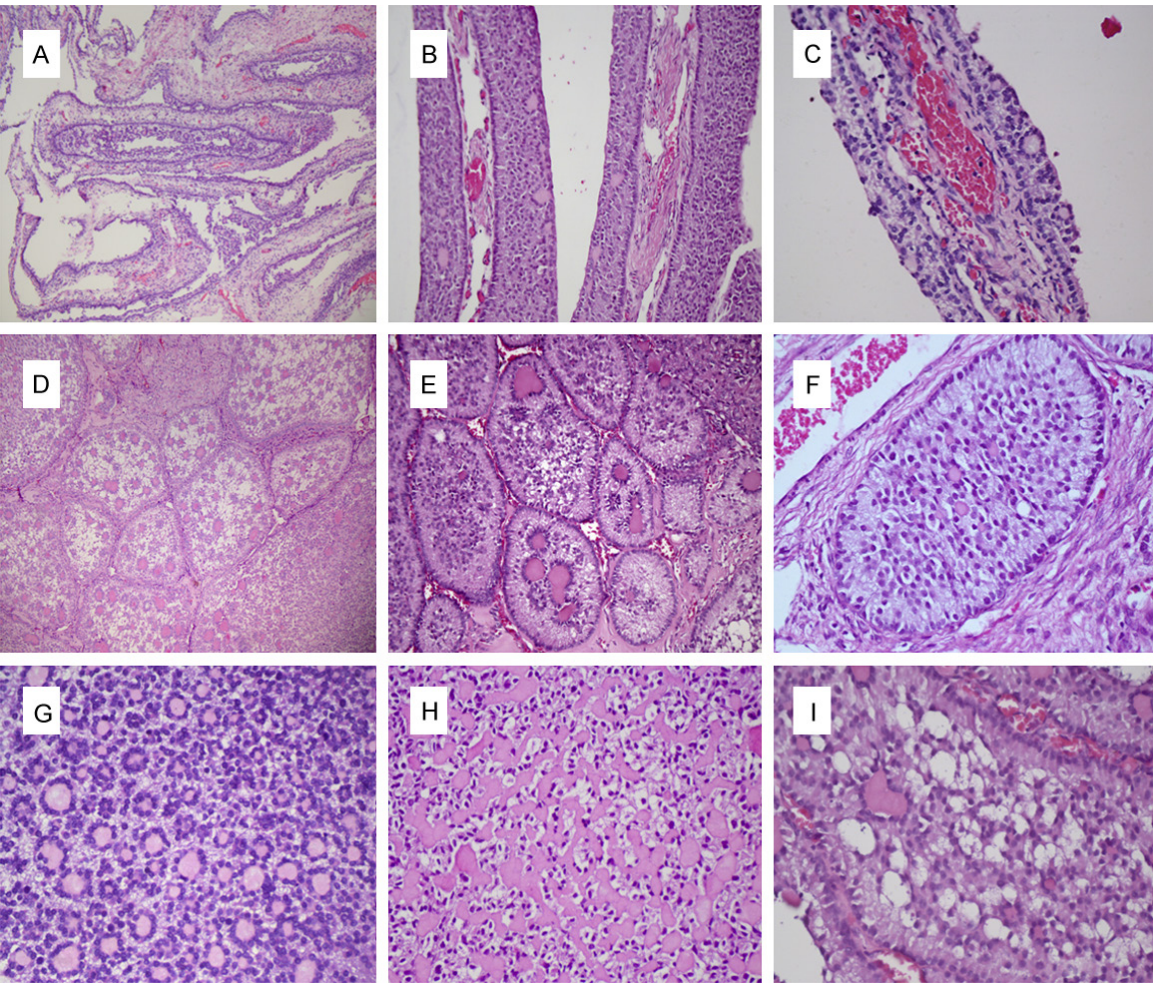


Figure 2. Microscopic findings in HE. A-C: Primary tumors. A: The primary tumors from 3 patients were characterized by multiple layers of tumor cells lining the cysts of different sizes. B: Some of the inner layers of the tumor cells formed tubule-like structures with eosinophilic hyaline bodies. C: The fibrous stroma was hypervascular and congestive. D: The local recurrent tumor. E: The metastatic tumor. The local recurrent tumor and the metastatic tumor had distinct pattern from the primary tumor, demonstrated by rounded epithelial nests of different sizes containing eosinophilic hyaline bodies. F: The partitions surrounding the nests were stromal spindle cells. All the nests had similar structure: inner single layer of neoplastic cells consisting one “tubules” as a unit and outer single layer of cells containing multiple units. G: Simple tubules. H: Complex tubules. I: The neoplastic cells had abundant pale-staining cytoplasm and sometimes it was markedly vacuolated and contained lipids.

mass (**Figure 1D**) in the left adnexal region and several small nodules and medium free ascites in pelvic cavity.

Exploratory laparotomy showed 4 cm × 5 cm × 5 cm enlarged left ovary, and the tumor was solid with an intact capsule and no local inva-

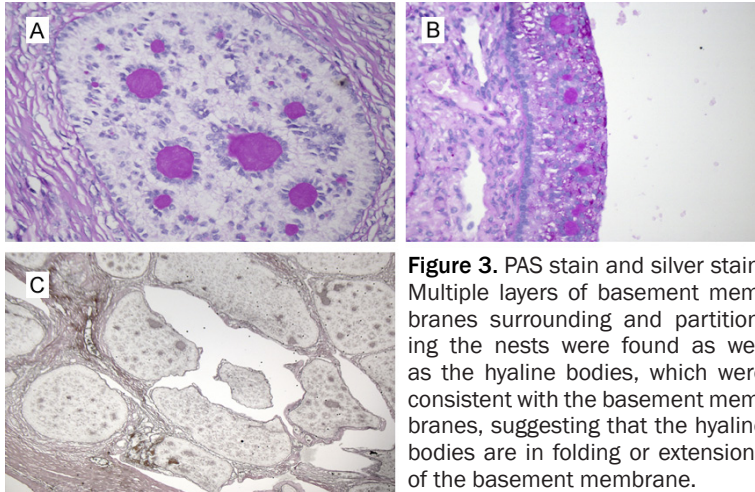


Figure 3. PAS stain and silver stain. Multiple layers of basement membranes surrounding and partitioning the nests were found as well as the hyaline bodies, which were consistent with the basement membranes, suggesting that the hyaline bodies are in folding or extensions of the basement membrane.

sion. The right ovary was 2.5 cm × 1 cm × 1.5 cm and smooth on the surface with follicles found. The ascites was turbid. The peritoneum and mesentery was wildly seeded and there was an 8 cm*6 cm*6 cm retroperitoneal metastatic tumor with no capsule adjacent to right adrenal. She was diagnosed with FIGO stage IIIC and underwent left salpingo-oophorectomy, retroperitoneal mass resection, retroperitoneal lymph node dissection and omentectomy.

Case 3

A 10-year-old complained of abdominal distension with 1 year irregular menstruation history. She had no signs or family history of PJS. During the physical examination, a mass without tenderness and fluctuation was palpated. Her CA125 was 253.90 U/ml, while the CA199 and NSE were slightly elevated. CT showed an enormous cystic mass with flocculent septae in abdominal and pelvic cavity, the mass was 172.5*76.4 mm, and the flocculent partitions were significantly enhanced (**Figure 1E**).

During the operation, the mass was found originated from the right ovary and was polycystic with small partial solid components, occupying most of the pelvis and abdomen. The mass was wrapped by the descended great omentum and there was about 300 mL clear yellowish free ascites. She was diagnosed FIGO stage Ic and underwent right salpingo-oophorectomy and omentectomy.

Her blood CA125 returned to the normal range, CA199 and NSE slightly decreased 1 month after the operation. Now she has finished first

round JEB regimen chemotherapy and does well.

Pathologic manifestations

Gross findings

The primary tumors of all cases are polycystic, while the recurrent and metastatic tumors were solid (**Table 1**).

Microscopic findings

The microscopic difference was consistent with the radiographic difference. The primary tumors from 3 patients were characterized by multiple layers of tumor cells lining the cysts of different sizes (**Figure 2A**). Some of the inner layers of the tumor cells formed tubule-like structures with eosinophilic hyaline bodies (**Figure 2B**). The fibrous stroma was hypervascular and congestive (**Figure 2C**). The local recurrent tumors and metastatic tumors had distinct pattern from the primary tumor, demonstrated by rounded epithelial nests of different sizes containing eosinophilic hyaline bodies (**Figure 2D, 2E**). The partitions surrounding the nests were stromal spindle cells. All the nests had similar structure: inner single layer of neoplastic cells consisting one “tubules” as a unit and outer single layer of cells containing multiple units (**Figure 2F**). In some larger and cellular nests, there were many hyaline bodies and central cystic degenerations, while in some smaller nests; there were few or no hyaline bodies.

In both patterns, the “tubules” which never had real lumens but filled with hyaline bodies are differently shaped-simple and complex, while the complex tubules seemed like simple tubules continuously merged together (**Figure 2G, 2H**). With the PAS stain and silver stain, multiple layers of basement membranes surrounding and partitioning the nests were found as well as the hyaline bodies, which were consistent with the basement membranes, suggesting that the hyaline bodies are in folding or extensions of the basement membrane (**Figure 3**).

The neoplastic cells had abundant pale-staining cytoplasm and sometimes it was markedly vacuolated and contained lipids (**Figure 2I**). The

Table 2. Immunohistochemical manifestations of the tumors

		α -inhibin	CD99	CR	Vim	CK	CAM5.2	CK7	Melan A	SMA	ER	PR	Ki-67
Case 1	Primary	+	+		+			-		-	+	+	+, 10%
	Recurrent	+	+		+	+					-	-	+, 10%
	Metastasis	+	-		+			-			-	-	+, 5%
Case 2	Primary	+	+	+	+	+	+			+	+	+	+, 5%
	Recurrent	+	+	+	+	+	+		+	+	+	+	+, 10%
	Metastasis	+	+	+	+	+	+			+	+	+	+, 10%
Case 3	Primary	+	+	+		+			+		-	-	+, 15%

Note: CR, calretinin; Vim, vimentin; CK, pan cytokeratin; SMA, smooth muscle actin; ER, estrogen receptor; PR, progesterone receptor.

nuclei of the neoplastic cells varied slightly in shape. Many were angulated and had grooves as seen in granulosa cell tumors, while others were oval with smooth contours. All cells had finely and evenly distributed granular chromatin, with small nucleoli.

The pathologic appearance was consistent with a benign tumor. Cytological anaplasia was absent. Only a few mitotic figures were seen in any one tumor and Ki-67 proliferation index was not markedly elevated (see **Table 2**).

Immunohistochemically, the neoplastic cells were positive for broad-spectrum cytokeratin except CK7, calretinin, α -inhibin, vimentin, CD99 and melan A (**Figure 4**), while smooth muscle actin, estrogen receptor and progesterone receptor were sometimes positive (**Table 2**). Notably, the stromal cells are positive for progesterone receptor.

Differential diagnosis

The histologic picture of SCTAT is distinctive and is generally adequate to exclude other tumors in the differential diagnosis. And there are no other specific immunohistochemical targets in SCTAT that can rule out other type of SCSTs.

Other ovarian tumors similar to SCTAT include granulosa cell tumor and gonadoblastoma. The well-defined and PAS-positive hyaline bodies are distinct from the Call-Exner bodies in granulosa cell tumor. Gonadoblastoma is a rare gonadal neoplasm composed of primordial germ cells and sex cord-stromal cells. It is characterized by dual cell populations of larger SALL4-positive germ cells and smaller sex-cord cells. Though numerous round spaces filled with basement membrane material simulate

the hyaline bodies of SCTAT present, it is clinically different and occurs only in patients with abnormal sexual development.

McCluggage reported a series of cases in which incidental microscopic collections of sex cord cells were identified in extraovarian tissues in the absence of an ovarian sex cord neoplasm, most of which closely mimicked SCTAT [5].

Though there is no report by far, the SCTAT can occur in testes theoretically. Sertoli cell nodules in undescended testes should be differential diagnosed with SCTAT that may occur in testes. Histologically, the arrangement of Sertoli cells around the central mass, derived from the basal membrane and PAS-positive, gives the tubules a ringed aspect, which closely mimicked SCTAT [6, 7].

Discussion

SCTAT was first described by Scully in 1970 for a peculiar form of ovarian neoplasm [1]. In the past, SCTAT have been placed in the category of unclassified sex cord-stromal neoplasms. In the recently published classification of tumors of female reproductive organs by WHO, SCTAT was classified as pure sex cord neoplasms [2].

The SCTAT is composed of ring-like, solid, tubular structures, the histological appearance of which is intermediate between granulosa cell and Sertoli cell tumors, and focal differentiation into either of these tumor types may occur [8, 9]. Dai has reported a case of metastatic granulosa cell tumor showing pattern of sex cord tumor with annular tubules and Sertoli cell tumor [10]. It is agreed to some degree that the tumor is composed of primitive cells of sex cord origin which have a potential to differentiate into either granulosa or Sertoli cells [11].

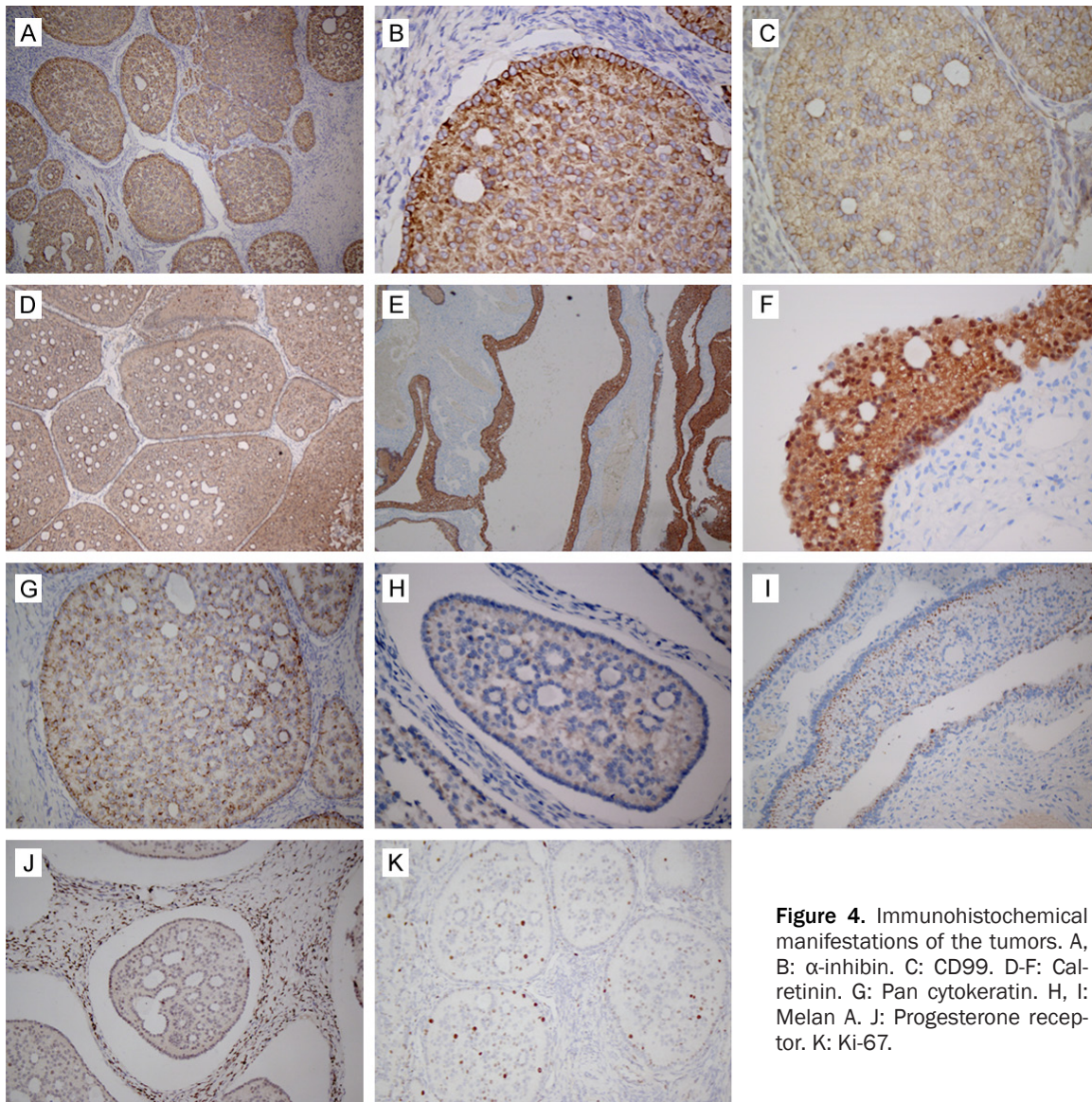


Figure 4. Immunohistochemical manifestations of the tumors. A, B: α -inhibin. C: CD99. D-F: Calretinin. G: Pan cytokeratin. H, I: Melan A. J: Progesterone receptor. K: Ki-67.

Controversy whether the tumors are more closely related to Sertoli cell or granulosa cell tumors exists, and there are evidences supporting both sides [12].

The most frequent clinical manifestations of SCTAT are associated with elevated estrogen and progesterone, including isosexual precocity, menstrual irregularity and post-menopausal bleeding [8, 13]. In our case 2, hyperestrinism with negative for the LHRH test indicates that the tumor has hormone secreting function.

SCTAT is divided into two different variants by whether it is associated with PJS [8], and roughly one-third of SCTAT is associated with PJS. PJS is an autosomal dominant hereditary disorder

with variable penetrance characterized by mucocutaneous melanin pigmentation, hamartomatous polyps of the gastrointestinal tract, and an increased risk for cancer of gastrointestinal and nongastrointestinal sites [14, 15]. Both sporadic and PJS-associated SCTAT have been reported in patients ranging in age from 4 to 76 years old, with most being diagnosed in the third or fourth decade of life [8].

Hart reviewed the data form reported cases and discovered that PJS-associated SCTAT typically was benign, small (<3 cm) or microscopic in size, bilateral and usually with calcific deposits, while sporadic SCTAT was larger, unilateral without calcification [8, 16]. Also, sporadic SCTAT usually have a higher than usual fre-

quency of lymph node spread comparing to other sex cord tumors [17]. But there were exceptions, although rare, reported that are bilateral sporadic SCTAT [18], a unilateral PJS-associated SCTAT about 4 cm in diameter with calcification [19] and malignant ovarian PJS-associated SCTAT [3, 20, 21]. It is worth mentioning that Ayadi has reported a case of bilateral PJS-associated SCTAT who developed a colonic adenocarcinoma in a hamartomatous polyp [20].

Other kinds of tumors of female reproductive system have been reported in association of PJS, including Sertoli cell tumors and minimal deviation adenocarcinoma of cervix [22] and several subtypes of breast cancer [23, 24]. A case of a 58-year-old patient with Peutz-Jeghers syndrome and history of multiple malignancies (thyroid, breast and colon cancer) was diagnosed with endometrial carcinoma and ovarian SCTAT [25]. Zune reported a case of a 4.5-year-old girl with PJS who presented with isosexual precocious puberty due to ovarian lipid-rich Sertoli cell tumor [26]. It is noteworthy that testicular Sertoli cell tumor is also associated with PJS [27, 28], which also focally may have an annular tubular pattern similar to that in the ovarian SCTAT [17].

Germline-inactivating mutations in one allele of the STK11/LKB1 gene (19p13.3) have been found in most patients with PJS [29]. Germline mutations in the tumor-suppressor STK11 gene accompanied by loss of heterozygosity of markers near the wild-type STK11 allele were found in PJS-associated SCTAT, but they were not found in cases of sporadic SCTAT studied [29]. Loss of heterozygosity at 19p13.3 in sporadic SCSTs targets a different gene, which may play a role in the pathogenesis of sporadic SCSTs [30].

Though the histologic appearance of SCTAT is consistent with a benign tumor, SCTAT is now recognized as low-grade malignancies because of its tendency of late recurrence and metastasis. Although the prognosis is relatively favorable, the risk of recurrence is still very high and the recurrent tumors are mainly ipsilateral to the primary tumor as in our cases. Hart first documented the metastatic potential of SCTAT, and speculated the metastasis was via lymphatic vessels [16]. Malignant behavior in SCTAT has heretofore been sporadically reported

[31, 32]. In women with non-PJS associated SCTATs, malignant behavior with metastases may be seen in at least 20% of cases [4]. SCTAT can sometimes combine other ovarian tumors including dysgerminoma [16, 33] and germinoma [1], though the mechanism is unknown.

In summary, we reported 3 cases of SCTAT, two of which with recurrence and metastasis. We described the histological manifestations of SCTAT and for the first time reported the histological difference between the primary tumor and the secondary tumor in childhood.

Disclosure of conflict of interest

None.

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