

## Ovarian Sex Cord Tumor with Annular Tubules - A Case Report and Review of the Literature in Japanese

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### ABSTRACT

A case of ovarian sex cord tumor with annular tubules (SCTAT) in a 41-year-old female is reported. The patient's chief complaint was menstrual irregularity, but the serum values of estradiol and testosterone were not elevated. On gross examination, the left ovary measured 8×7×6 cm in size and its cut surface was yellowish gray or yellow and solid with no cystic area. Histologically, the tumor was composed of simple and complex annular tubules, lined by columnar cells containing abundant lipid droplets. Eosinophilic materials in the center of the annular tubules were continuous with the basement membrane in the periphery, and showed immunoreactivity for type IV collagen. Also, hollow tubules, consisting of columnar cells with a truncated luminal surface and elongated trabeculae, composed of columnar cells with clear cytoplasm, were noted. These structures were reminiscent of Sertoli cell tumor. Based on these histological observations, it appears that SCTAT is a sex cord/stromal tumor made up of cells with differentiation in the direction of Sertoli cells rather than granulosa cells.

**Key words:** Sex cord tumor with annular tubules, Ovary, Sertoli cell tumor, Type IV collagen

Composed of cells with features of the ovarian sex cord/stromal cell, the tumor discussed in this paper constitutes about 5% of all ovarian tumors, and is broadly divided into two groups: those with differentiation in the direction of granulosa and theca cells (female-type cells), Sertoli and Leydig cells (male-type cells). However, some tumors with indistinct differentiation to a specific type of cell occur<sup>20</sup>. Among the latter type of tumors, sex cord tumor with annular tubules (SCTAT) of the ovary, a term proposed by Scully in 1970<sup>21</sup>, is rare. Since the first report of 13 cases by Scully, more than 100 cases have become available in the literatures in English<sup>2-4,6-8,11,13,18,22,26,27</sup>. One third of SCTAT is known to be associated with Peutz-Jeghers (P-J) syndrome<sup>26,27</sup> and almost all female patients with P-J syndrome, if their ovaries have been examined microscopically, may have SCTAT as an incidental microscopic finding<sup>25</sup>. However, only 10 cases have been reported in Japan<sup>1,5,9,10,12,14-17,24</sup>.

So far, histological and ultrastructural observations of SCTAT have demonstrated the ambiguous or biphasic nature of tumor cells, and opinions regarding the histogenesis of this tumor remain controversial. For this reason, SCTAT is categorized as an independent entity among the sex

cord/stromal tumors in the classification commonly used in Japan<sup>23</sup>, and will also be categorized thus in the WHO classification to be proposed in the near future.

We recently encountered a case of SCTAT and in the present report attempt to describe its clinical and pathological findings, briefly reviewing the relevant literature in Japanese.

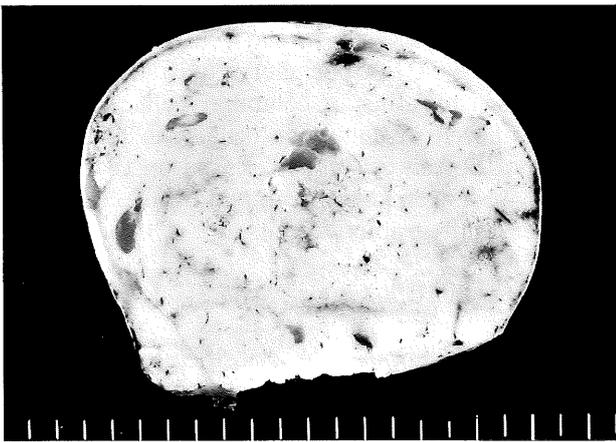
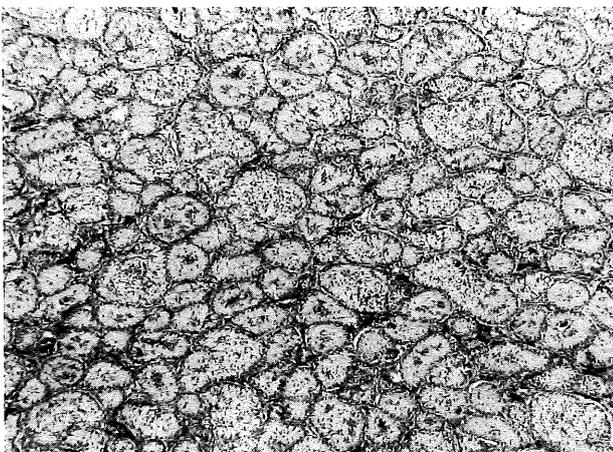
### CASE REPORT

A 41-year-old Japanese woman complained of abnormalities of menstrual duration. Her menarche was seen at 14 years old from which time abnormalities of menstrual duration started. At the age of 22, she received hormonal therapy for two months (precise information not available). She married at the age of 23, and delivered a boy at 29 and twins (a boy and a girl) at 31. At 36 years old, she underwent induced abortion at 13 weeks of gestation. The abnormalities of menstrual duration continued.

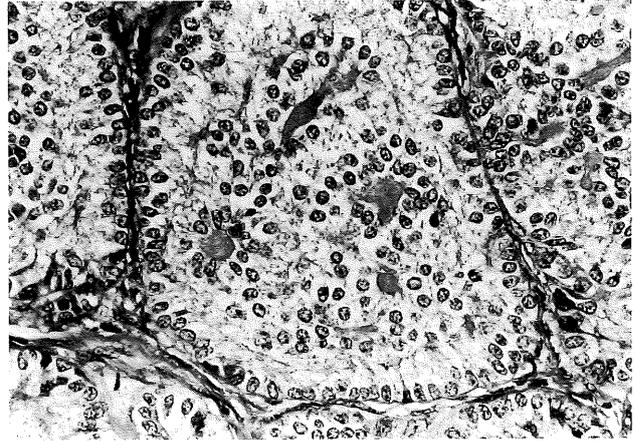
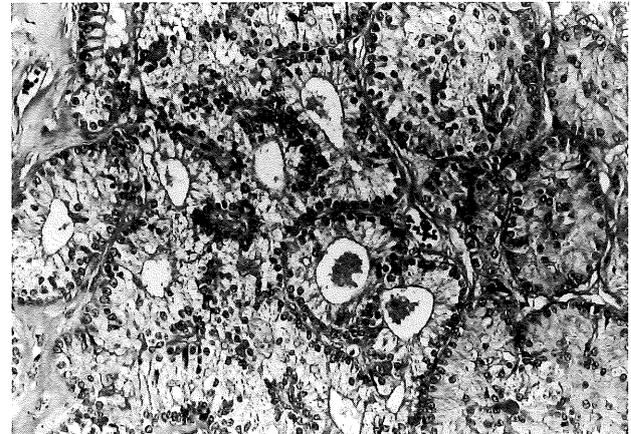
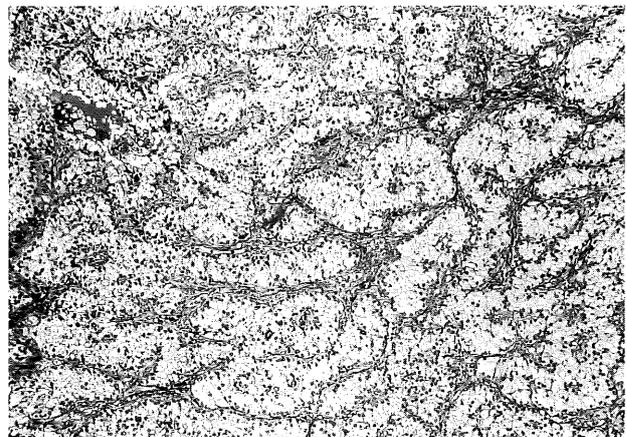
Seven months before admission, she showed amenorrhea and complained of abdominal pain and distension. The ultrasonographical examination revealed a solid tumor located in the left ovary. After admission the diagnosis of malignant ovarian tumor was suggested and she received left salpingo-

**Table 1.** Serum Values of Hormones or Tumor Markers on Admission

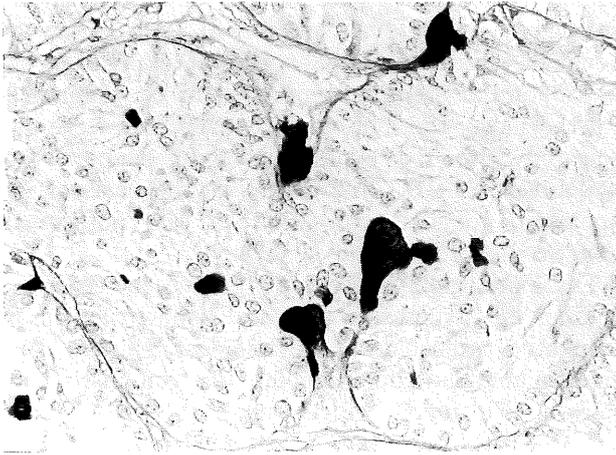
Hormones or Tumor markers	Values	Normal ranges
Estradiol (pg/ml)	73	10–80
Progesterone (ng/ml)	2.2	10–250
Testosterone (ng/ml)	0.5	0.3–1.3
LH (mIU/ml)	2	8–182
FSH (mIU/ml)	2	8–43
Prolactin (ng/ml)	69	3–20
AFP (ng/ml)	4	<10
CEA (ng/ml)	<0.5	<2.5
CA125 (U/ml)	17	<35
CA19–9 (U/ml)	<5	<37
TPA (U/l)	60	<85

**Fig. 1.** Yellowish gray or yellow and solid cut surface.**Fig. 2.** Tumor composed of simple or complex annular tubules with scanty stroma. (H & E stain,  $\times 33$ )

oophorectomy and hysterectomy. On laparotomy, a little serous fluid was noted in the abdominal cavity and there was no peritoneal adhesion. Postoperatively, she showed an uneventful course and was discharged 21 days after the operation.

**Fig. 3.** Annular tubules lined by columnar cells, and eosinophilic and homogenous materials seen in the center. (H&E stain,  $\times 200$ )**Fig. 4.** Hollow tubules, consisting of columnar cells with truncated luminal surface. (H&E stain,  $\times 100$ )**Fig. 5.** Elongated trabeculae, composed of columnar cells with clear cytoplasm focally prominent. (H&E stain,  $\times 100$ )

Clinical observation revealed no evidence of P-J syndrome, including pigmentation of the oral muco-



**Fig. 6.** Eosinophilic materials in the center of annular tubules had immunoreactivity for anti-type IV collagen. (PAP method,  $\times 200$ )

sa and gastrointestinal polyposis. The serum values of hormones and tumor markers examined preoperatively are shown in Table 1. The values of estradiol and testosterone were within the normal limits. Those of progesterone, LH and FSH were lower than the normal limits, but that of prolactin was higher. The values of tumor markers were unremarkable.

#### PATHOLOGICAL FINDINGS

On gross examination the left ovary was  $8 \times 7 \times 6$  cm in size. The ovarian surface was smooth and glistening. On sectioning, the ovarian original structure was totally effaced by yellowish gray or yellow and solid tumor. There was no cystic area (Fig. 1).

On histological examination, the tumor was composed of simple or complex annular tubules, compactly arranged with scanty non-neoplastic ovarian stroma (Fig. 2). These annular tubules were lined by tall or low columnar cells, which had faintly eosinophilic or clear cytoplasm and round nuclei basically located (Fig. 3). Mitotic figures were not seen

in these cells. The basement membrane was seen in the periphery of the annular tubules. Characteristically, eosinophilic and homogeneous materials were observed in the center of the annular tubules, and these materials were often continuous with the basement membrane.

In the other area, histological varieties were observed. Hollow tubules, consisting of columnar cells with a truncated luminal surface (Fig. 4) and elongated trabeculae, composed of columnar cells with extremely clear cytoplasm (Fig. 5) were focally prominent. These findings were reminiscent of Sertoli cell tumor. The transitional appearances between these structures and the above-mentioned annular tubules were noted.

On histochemical examination, no cytoplasm of tumor cells at any part was stained by periodic acid-Schiff (PAS), alcian blue (pH 2.5) or mucicarmine stains, but oil red O stain demonstrated lipid droplets in the cytoplasm of most of the tumor cells. The eosinophilic materials in the center of the annular tubules, as well as the basement membrane in the periphery, were positive only by PAS stain.

Immunohistochemical observations were performed on the formalin fixed - paraffin embedded tissue sections by means of the ABC method. Using antibody to estradiol as well as testosterone (Nichirei Co., Tokyo), no immunoreactivities were detected in the cytoplasm of the tumor cells. On the other hand, immunoreactivity for antibody to type IV collagen (DAKO, Copenhagen, Denmark), a specific protein for basement membrane, was seen at the eosinophilic materials in the center of the annular tubules as well as in the basement membrane of the periphery (Fig. 6).

The uterus was  $8 \times 6 \times 3.5$  cm in size and had no gross abnormalities. The left fallopian tube was stretched along the left ovarian tumor. Histological examination revealed that the endometrium was in the proliferative phase, but no hyperplastic change was seen. In the cervix, mild chronic inflammation was present. The left fallopian tube had no histological abnormalities.

**Table 2.** Summary of Cases from the Literature in Japanese

Authors (year)	Age & sex	Symptoms & signs	Hormonal examination	Site of ovary	Diameter of tumor	Gross finding	P-J* syndrome
Akima (1981)	39F	Amenorrhoea	NS**	right	10cm	NS	NS**
Nakagawa (1982)	19F	Genital bleeding	NS	right	10cm	solid	(-)
Ogasawara (1984)	28F	Amenorrhoea	E $\uparrow$	right	20cm	cystic	NS
Ikarashi (1985)	14F	Irregular menses	E $\uparrow$ P $\uparrow$	right	12cm	solid	(-)
Omata (1985)	64F	Genital bleeding	NS	left	3cm	solid	NS
Yamaguchi (1986)	31F	Genital bleeding	NS	right	hen-egg	NS	(+)
Fujita (1988)	9F	Sexual precocity	E $\uparrow$	left	40cm	cystic	(-)
Ishizaki (1991)	30F	Incidental	NS	bilateral	micro***	-	(+)
Kuhara (1991)	52F	Hypermenorrhoea	NS	left	micro	-	(-)
Nomura (1991)	23F	Genital bleeding	NS	right	5cm	solid	(-)
Present case	41F	Irregular menses	Normal	left	8cm	solid	(-)

\*Peutz-Jeghers syndrome

\*\*not stated

\*\*\*microscopic size

## DISCUSSION

Very few Japanese cases of SCTAT are reported in the literature. To the best of our knowledge, there are only 10, summarized in Table 2. As for the age of patients, one case occurred before puberty and another case occurred after menopause. The prepubertal and postmenopausal cases demonstrate clinical features of hyperestrinism, but women of reproductive years are variable in endocrine activity. The unequivocal association with P-J syndrome is seen in two cases. The size of the tumor is variable from microscopic to 40 cm at the greatest diameter. Gross findings show the tumors to be cystic or solid. These findings differ little from those cases reported in the literature other than Japanese.

The unique histological features of SCTAT have given rise to much discussion of its histogenesis. Originally Scully<sup>21)</sup> thought that this tumor arose from granulosa cells, but grew in a pattern more characteristic of Sertoli cells. Supporting this hypothesis, an ultrastructural study reported by Hertel & Kempson<sup>8)</sup> showed that the predominant cells of SCTAT had features of gonadal stromal cells without the specificities suggestive of either Sertoli or Leydig cells; striking similarities to granulosa cells were noted. In the ultrastructural observations of three cases reported by Crissman & Hart<sup>4)</sup>, the cells of SCTAT had deeply indented nuclei, interdigitating plasma membranes joined by abundant desmosomes and numerous randomly distributed microfilaments that often complexed with desmosomes. These features more closely resembled those of typical granulosa cell tumors than of Sertoli cell tumors, and they proposed SCTAT as a distinctive annular and membranous variant of granulosa cell tumor<sup>7)</sup>. Recently, Kalifat & Brux<sup>11)</sup> also stressed that ultrastructural findings of SCTAT showed granulosa cell differentiation and, to a lesser extent, Sertoli cell differentiation.

On the contrary, Tavassoli & Norris<sup>22)</sup> regarded SCTAT as a variant of Sertoli cell tumor in a report on 28 cases of "Sertoli tumors", appearing as histological patterns of simple tubular, complex tubular and folliculome lipidique. In the ultrastructural study by Astengo-Osuna<sup>9)</sup>, Charcot-Bottcher filaments were observed in the paranuclear region, a characteristic of Sertoli cell tumor; the Sertoli cell nature of SCTAT was postulated. Recently, Ramaswamy et al<sup>19)</sup> encountered a case of androgen insensitivity syndrome, associated with a tumor in the immature gonad, appearing as a mixed form of SCTAT and a large cell calcifying Sertoli cell tumor, thus supporting the concept of a Sertoli line of differentiation of SCTAT.

Matamala et al<sup>13)</sup> reported a case of metastatic, complex sex cord tumor with multiple differentiation. The tumor originally presented itself as a pure granulosa cell tumor, but abdominal metastases revealed a mixed pattern of granulosa and Sertoli cell

tumor admixed with SCTAT. This association seemed to provide a clue for SCTAT being "a peculiar intermediate phenotypical expression of pluripotential stem sex cord cell of the gonads". Furthermore, the fact that some SCTAT were associated with P-J syndrome might support the hypothesis that SCTAT occurs on the basis of inapparent gonadal expression of the autosomal genetic disorder of P-J syndrome<sup>11)</sup>.

The histological findings in the present case, including the structural pattern of hollow tubules or elongated trabeculae and cytological features containing abundant lipid droplets are reminiscent of Sertoli cell tumor, suggesting that SCTAT is a tumor with differentiation in the direction of Sertoli cell tumor. Although the present case could not be examined ultrastructurally, there was no significant evidence indicating the nature of a granulosa cell tumor except for eosinophilic materials like Call-Exner bodies. Also, the present case could not support the intermediate nature of sex cord cell in the tumor cell of SCTAT.

The endocrine function of SCTAT is mainly estrogenic<sup>8)</sup>, but cases showing no endocrine activity have been reported. The nature of SCTAT can be ascertained on the basis of endocrine function. In the present case, no clinical manifestations were seen and immunoreactivities of both estradiol and testosterone could not be detected histochemically. However, formalin fixed-paraffin embedded tissue was used in the immunohistochemical observations in the present study and, therefore, the hormone-producing activity of this tumor could not be completely excluded.

As for the eosinophilic materials in the center of the annular tubules, some ultrastructural observations have been reported. Hertel and Kempson<sup>8)</sup> noted fibrillary to finely granular electron-dense material with no periodicity. Vesicular cytoplasmic fragments were frequently present within the materials. These findings were similar to the Call-Exner bodies in granulosa cell tumor. Crissman & Hart<sup>4)</sup> stated that the hyaline bodies were composed of concentric layers of basal lamina and that the central bodies were continuous with the redundant basal lamina surrounding the cellular nests. In the report by Kalifat & Brux<sup>11)</sup> the hyaline bodies were composed of packed basement membrane and cellular debris secondary to cellular necrosis and these findings were reminiscent of Call-Exner bodies.

In the present case, eosinophilic materials in the center of the annular tubules were fused with the basement membrane in the periphery; the materials, as well as the basement membrane, were stained positively by P.A.S. stain. Furthermore, immunoreactivity for antibody to type IV collagen was noted in the materials as well as in the basement membrane. This observation has not been reported so far, because the immunohistochemical exami-

nation was not performed in most of the previous studies. It is known that basement membrane contains at least four major components: type IV collagen, laminin, entactin and a heparan sulfate proteoglycan. From these facts, it is suggested that the eosinophilic materials in the center of the annular tubules have the same composition as the basement membrane.

As mentioned above, some SCTAT are seen in patients with P-J syndrome, and it was indicated, furthermore, that the clinical and pathological features were different between the cases with P-J syndrome and those without P-J syndrome<sup>26</sup>. In the former, SCTAT was multifocal, bilateral, very small or even microscopical in size, and calcified. They had no malignant potential, although about 15% of cases had "adenoma malignum" of the uterine cervix and a few cases died of it. On the contrary, in the cases without P-J syndrome, SCTAT was unilateral, usually large and occasionally calcified. About 15% of cases were malignant and some were fatal<sup>27</sup>. So far, size of tumor, the number of mitosis, nuclear atypia and vascular or stromal invasion have been taken as indicators of biological nature in SCTAT<sup>6</sup>. Concerning the number of mitosis in the malignant case, various criteria have been proposed, but it is difficult to establish a definite single indicator of malignancy.

The present case displayed no evidence of P-J syndrome and, therefore, according to the indication of Young et al<sup>27</sup>, an adequate follow up is necessary, although mitosis is absent in the histological sections.

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