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Ovarian Sex Cord Tumor With Annular Tubules

Clinicopathologic Report of Two Benign and One Malignant Cases With Long Follow-Ups

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Summary. The clinicopathologic features of three new cases of ovarian sex cord tumors with annular tubules are presented, thereby increasing to 23 the number of the published cases in the world literature. These three observations, along with another one which was previously published, were found in the files of the Institute of Pathology of the University of Lausanne from 1939 to 1978. Forty-seven granulosa cell tumors and eight Sertoli and/or Leydig cell tumors of the ovary were found during the same 40-year period. The patients were 48, 64 and 71 years of age. No sign of the Peutz-Jeghers syndrome was noticed in the three patients. All three tumors caused metrorrhagias as a cardinal sign. They were bulky, unilateral and were formed by solid tissue with cystic spaces. Histologically, the most characteristic pattern consisted of simple and complex tubular structures as described by Scully in 1970. Two patients, in which the mitotic indexes of the tumors were lower than 5 mitoses per 10 HPF, died without evidence of a recurrence 36 and 37 years after surgical ablation of the tumor. The third patient, whose neoplasm featured fewer well differentiated tubular structures than the two previous ones and had a mitotic index of over 70 mitoses per 10 HPF, died from massive abdominal recurrence after 5 years and 5 months.

Key words: Ovarian neoplasms – Pathology.

The ovarian sex cord tumor with annular tubules (SCTAT) was described by Scully in 1970; at the same time, he recognized its frequent association with the Peutz-Jeghers syndrome. Since then, only a few cases have been reported which were or were not combined with this syndrome. Little is known, however, of its evolution as no long follow-up studies have been reported.

The purpose of this paper is to evaluate the frequency of SCTAT with regard to other ovarian neoplasms of the sex cord mesenchyme and to describe 3 new cases with extended follow-ups. One of these behaved in a malignant fashion and caused the death of the patient.

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Materials and Methods

Four cases of SCTAT were found during a review of the ovarian tumors in the files of the Institute of Pathology of the University of Lausanne from 1939 up to 1978. One of them, which was associated with a Peutz-Jeghers syndrome, was previously published (Gloor, 1978) and it is not included in the present series. For the study of the three other cases which are presented here, the original slides were reexamined when available; new ones were prepared and a catamnestic inquiry was undertaken. The mitoses were counted in three series of 10 high-power fields (HPF-400) and the mitotic indexes expressed the minimal and maximal number of mitoses per 10 HPF in each of the three series. Owing to the retrospective character of this study, neither ultrastructural observations nor hormonal determinations could be performed.

Case Reports

Case 1. Following menometrorrhagias, a 48-year old woman, para 2, underwent a supracervical hysterectomy and a left salpingo-oophorectomy for a bulky and partly cystic tumor of the left ovary. There was a cystic and focally atypical hyperplasia of the endometrium. No manifestation of the Peutz-Jeghers syndrome was noticed. The patient died 36 years later, at 84 years of age, from a cranio-cerebral traumatism without evidence of a recurrence of the ovarian tumor. There was no autopsy.

Case 2. A 64-year old woman, para 4, 12 years post-menopausal, presented metrorrhagias. Dilatation and curettage was negative. A left salpingo-oophorectomy was performed for a bilocular cystic tumor of the left ovary. The tumor was thick-walled, partly calcified and was estimated at about 15 cm in diameter. Its pedicle was twisted. No stigmate of the Peutz-Jeghers syndrome was observed. Thirty-seven years later, at 101 years of age, the patient died with signs of cardiac failure without evidence of a recurrence of the ovarian tumor. There was no autopsy.

Case 3. A 65-year old woman, para 9, underwent a left salpingo-oophorectomy for a serous papillary cystadenofibroma of the left ovary estimated at about 10 cm in diameter. No sign of the Peutz-Jeghers syndrome was remarked. At 71 years of age, after metrorrhagias, a total abdominal hysterectomy with a right salpingo-oophorectomy was performed for a tumor of the right ovary. This tumor was partly solid and partly cystic; it measured 13 cm in its largest dimension. The endometrium was proliferative, the glands showing some mitoses; however, there was no cellular nor architectural atypia. The tubal epithelium was high-cylindrical.

Five years and five months later, the patient was reexamined for a massive abdominal recurrence of the tumor of the right ovary which disturbed intestinal function. During operation, solid tissue with small cystic spaces containing an aqueous liquid was found. It adhered to the pelvic walls and infiltrated the sigmoid and a loop of the small intestine which was angulated. The intestinal loop was resected and a colostomy was performed. Several fragments of the tumor were removed, but the bulk of this infiltrating mass had to be left in place. The patient died on the same day. There was no autopsy.

Results

Except for some nuances, the histological features of the three cases including the abdominal recurrence[1] in case 3 are similar and very characteristic (Fig. 1–3): the tumors consist especially of well circumscribed, rounded, oval or polygonal epithelial nests (Fig. 1a, 2a, 3a) which sometimes coalesce into broad fields. These epithelial nests contain hyaline eosinophilic structures composed of small

[1] Courtesy of Prof. Y. Kapanci, Institute of Pathology, Geneva

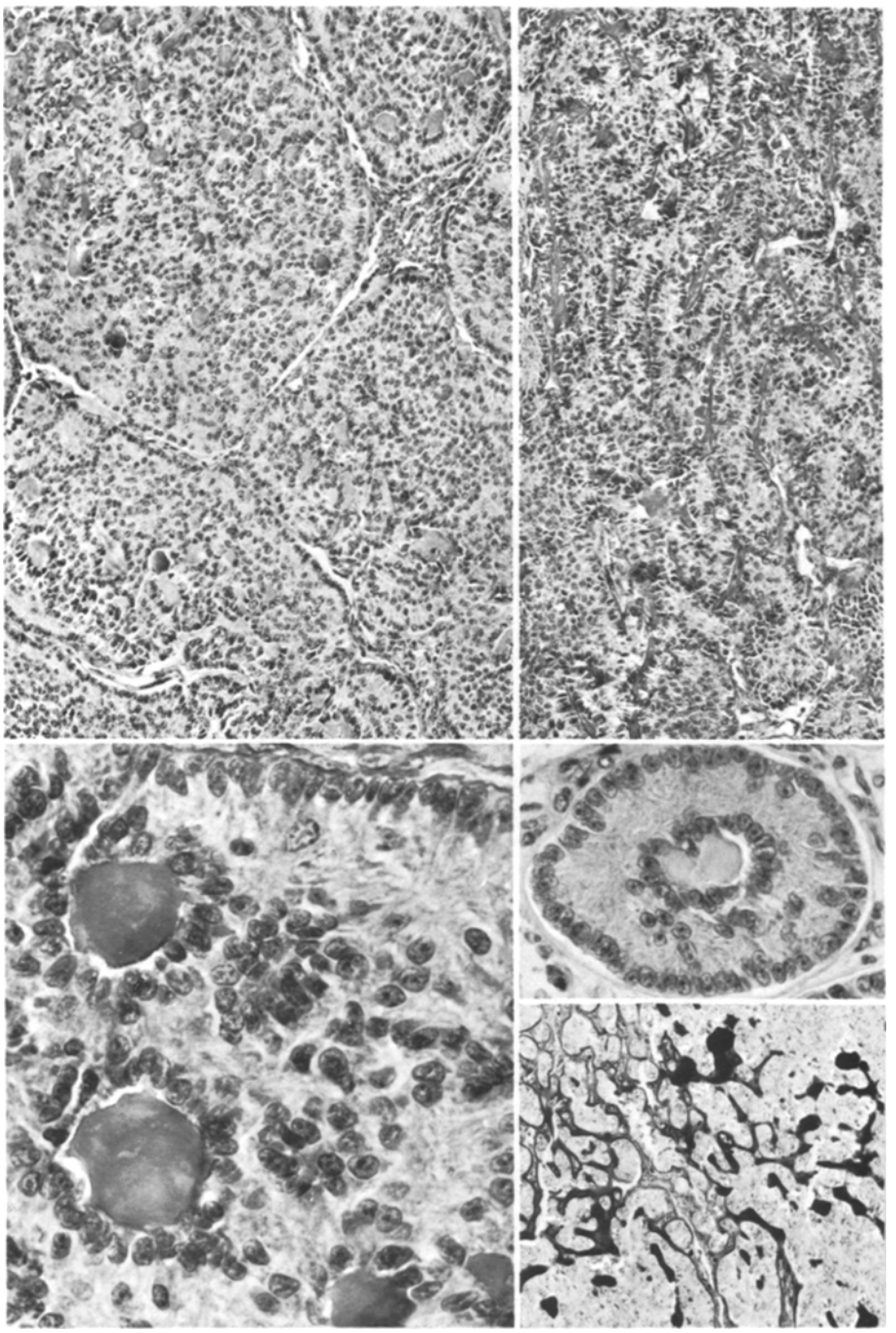

Fig. 1a–e. Case 1. **a** Polygonal nests of complex tubular structures. H.E. ×135. **b** Longitudinal solid tubules. H.E. ×135. **c** Cells palisading around hyaline bodies and along the edge of the epithelial nest (top). H.E. ×535. **d** Annular tubule resembling a wheel. H.E. ×335. **e** Hyaline structures forming a network. PAS ×135

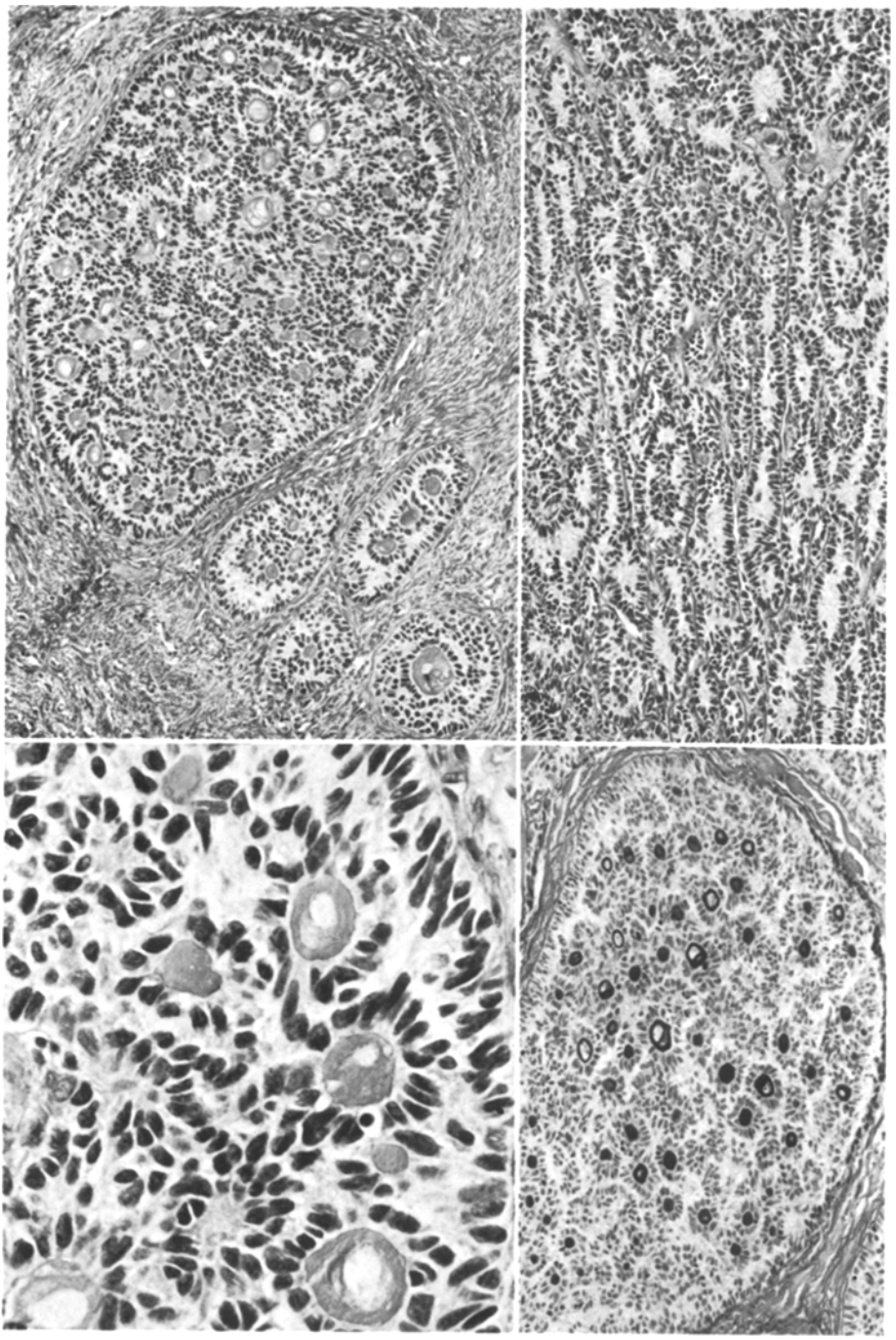

Fig. 2a–d. Case 2. **a** Oval nests of complex tubular structures. H.E. ×135. **b** Longitudinal solid tubules. H.E. ×135. **c** Nest cells palisading around hyaline bodies and along the edge of the nest (right border). H.E. ×535. **d** Hyaline bodies stained with PAS. ×135

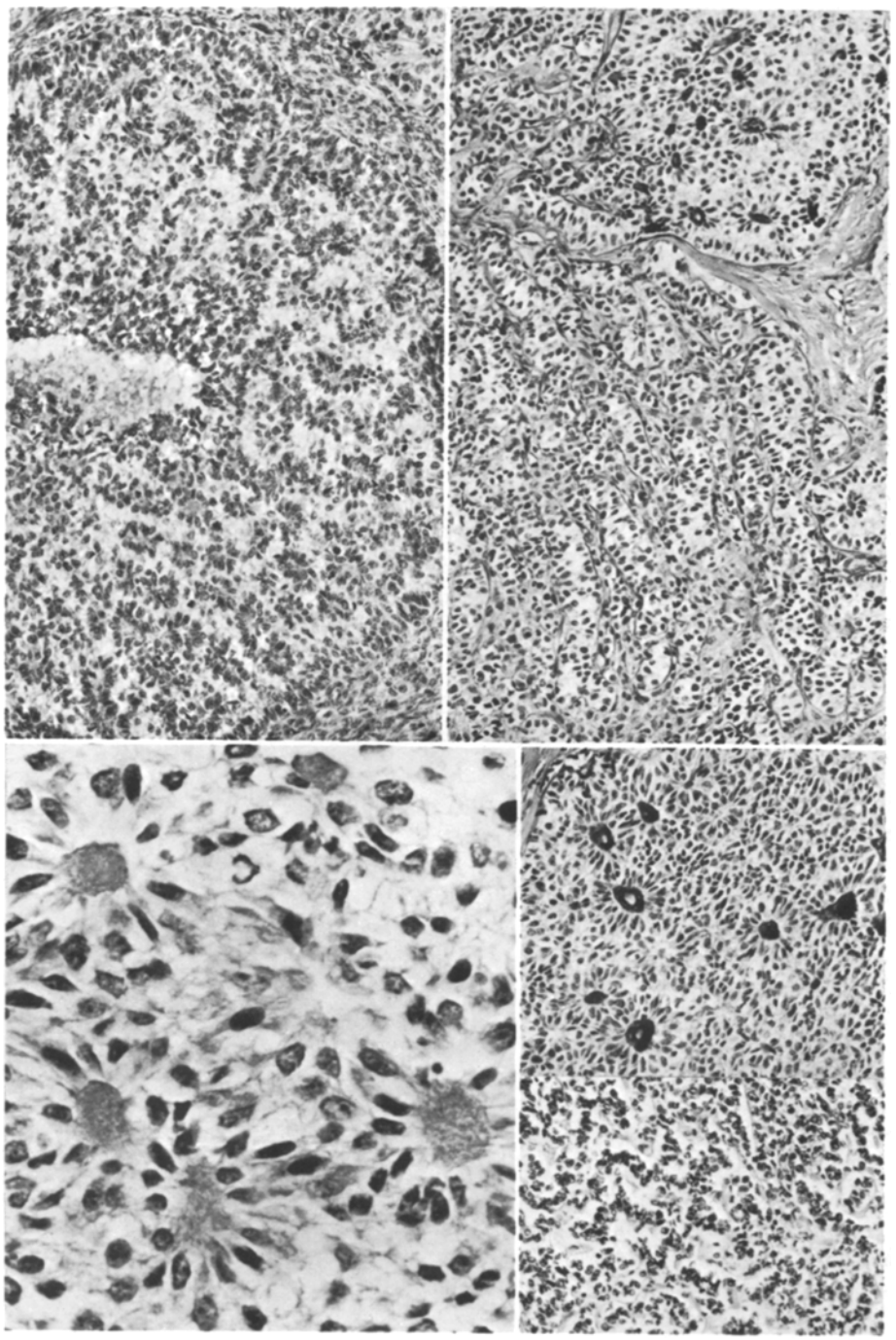

Fig. 3a–e. Case 3 (a,e: ovarian tumor; b–d: abdominal recurrence). **a** A rounded nest of tubular structures. H.E. ×135. **b** Nest of complex tubules (top) and longitudinal tubules (bottom). H.E. ×135. **c** A few hyaline bodies surrounded by palisaded cells. H.E. ×535. **d** Hyaline bodies stained with PAS. H.E. ×135. **e** Narrow ribbons of cells. H.E. ×135

rounded bodies or extensive trabecules that form a network surrounding small epithelial nests and solid tubules (Fig. 1e). This material is heavily stainable with PAS (Fig. 1e, 2d, 3d). The cells which constitute the epithelial nests have an abundant, pale and ill-delimited cytoplasm and an oval, sometimes indented and even cleft nucleus showing little variation in size. One or sometimes two small nucleoli are visible. The nuclei are disposed radially around the hyaline bodies and along the edges of the epithelial nests (Fig. 1c, 2c, 3c). In smaller epithelial nests, the aspect resembles that of a wheel or a ring (Fig. 1d). In other areas, one sees solid tubules (Fig. 1b, 2b, 3b); in case 3, some of them consist of cells with a clear and ballooned cytoplasm probably laden with lipids. Tiny foci of luteinized stroma cells without Reinke's cristalloids are visible in case 1. In case 2, small calcified plaques are apparent in the stroma. In case 3, the only one with a malignant behaviour, the most typical features of SCTAT, namely the complex tubular structures, are less extensively differentiated, both in the primary tumor and the recurrence, than in the two other cases with a benign outcome: in about half the microscopic fields, the tumor is disposed in ribbons of one to several cells in breadth (Fig. 3e) or in diffuse fields. However, the cardinal difference is the mitotic index which is low in case 1 (2–4 mitoses/10HPF) and in case 2 (0–2 mitoses/10HPF), and reaches 71 to 98 mitoses/10HPF in case 3 (malignant). No significant nuclear atypias are noted in any of the three cases.

Discussion

The three cases reported in this study are typical examples of ovarian sex cord tumors with annular tubules. In 1970, Scully described this very rare form of ovarian tumor, the morphology of which is ambiguous and does not exactly correspond to granulosa cell tumors nor to androblastomas. The nomenclature alludes to the "annular tubules" which are observed in cryptorchid testes and which present a certain histological likeness.

The frequency of SCTAT is very low: in his original paper, Scully (1970) indicated that he had found only one case in the files of the Massachusetts General Hospital; nine others were consultation cases and 3 were found in the literature under other names. Since Scully's paper, only a few cases have been reported, in or not in association with the Peutz-Jeghers syndrome (Steenstrup, 1972; Netter et al., 1973; Waisman et al., 1975; Costa, 1977; Hertel and Kempson, 1977; Gloor, 1978). The same tumor has been observed in the ovary of canine species (Norris et al., 1970: Fig. 5). We found four cases, among close to 560,000 biopsies, in the files of our Institute during the 40 last years. One of them, where the tumors were bilateral and microscopic in size, was combined with the Peutz-Jeghers syndrome and was complicated by a bilateral invasive duct breast carcinoma and by a highly differentiated adenocarcinoma of the uterine cervix. This case has already been published separately (Gloor, 1978). The three other cases reported here increase to 23 the number of the published observations in the world literature. It is noteworthy that

during the same period of time, we found 47 granulosa cell tumors and 8 Sertoli and/or Leydig cell tumors of the ovary in the files of our Institute.

The SCTAT may be observed in adults as well as in children. It may produce endocrine symptoms such as irregular menstrual periods even after the menarche, post-menopausal vaginal bleedings, secondary amenorrhea, sterility, precocious pseudopuberty or it may be discovered by chance. These symptoms could result from an estrogen secretion by the tumor as well as, in our cases, the coexistence of an endometrial hyperplasia (case 1) and the presence of an excessively stimulated tubal mucosa according to the age (case 3). On the other hand, neither in our cases nor in those already published, was any sign of an androgen overproduction noticed. To our knowledge, however, there is only one observation in the literature (Waisman et al., 1975) in which preoprative hormonal determinations were performed because of hyperestrinism with precocious puberty. Indeed, in this case, originally diagnosed as a granulosa-theca cell tumor, seric levels of estradiol and of 17-α-hydroxyprogesterone were high but those of testosterone, FSH and LH were normal. Urinary 17-ketosteroid and 17-hydroxysteroid values were normal.

The major clinical interest of SCTAT is its significantly frequent connection with the Peutz-Jeghers syndrome, which was recognized first by Scully (1970) and subsequently has been observed by others. When associated with the Peutz-Jeghers syndrome, the tumors are generally small and most often bilateral if they are carefully looked for. Indeed, because of their small size, they can occasionally be overlooked at the time of the operation and only be discovered on microscopic examination. On the contrary, in cases which are not combined with this syndrome, as in the three present cases, the tumors are unilateral and larger, even bulky. In general, they consist of a solid tissue; occasionally, cystic spaces are observed.

Histologically, the simple or complex tubular structures described by Scully (1970) are the most characteristic architectural patterns: these are epithelial nests containing hyaline bodies and trabecules. Nuclei tend to palisade around the hyaline structures and along the borders of the epithelial nests. As Scully (1977b) points out, the tumor resembles a gonadoblastoma except for the absence of a germ cell component; moreover, at the electron microscopic level, the hyaline bodies, like those of gonadoblastoma, consist of basement membrane material (Waisman et al., 1975). In contrast, typical Call-Exner bodies of a granulosa cell tumor are different: they are made up of an accumulation of cell fragments and amorphous material (Gondos and Monroe, 1971). Solid longitudinal tubules, sometimes consisting of clear cells, are another pattern frequently observed in SCTAT. Calcifications in epithelial nests and smaller or larger, sometimes extensive ones in the stroma, are also a typical feature. In our case 3, other architectural aspects are noticed, which resemble a Sertoli cell tumor or a granulosa cell tumor. The occasional proteiform character of the sex cord tumors of the ovary is well known. This is also true for SCTAT, which can present variable patterns, as Sternberg and Dhurandhar (1977) point it out.

It is not astonishing that the nosology of SCTAT is subject to discussion. Scully (1970, 1977b) thinks that the tumor has a pattern intermediate between

that of a granulosa cell tumor and a Sertoli cell tumor; it probably arises from the granulosa cells, but the histological features are closer to Sertoli cells. Norris and Chorlton (1974) consider it simply as a minor variant of a Sertoli cell tumor.

Ultrastructurally (Waisman et al., 1975; Hertel and Kempson, 1977), the majority of the cells are pale. Most nuclei exhibit deep nuclear clefts. The clear cytoplasmic matrix contains thin fibrils, a few dense bodies, an inconspicuous Golgi apparatus, a few profiles of rough endoplasmic reticulum and sparse mitochondria with parallel tubular cristae. Desmosomes and microvilli are frequently seen between adjacent tumor cells. A few dark cells containing an abundance of delicate fibrils condensed near the cell borders, a greater amount of rough endoplasmic reticulum and a larger number of mitochondria with parallel tubular cristae are also noted, but they form a minority of the cell population. According to Hertel and Kempson (1977), the clear cells, which dominate, differ in several respects from normal testicular Sertoli cells and cells of ovarian and testicular Sertoli cell tumors, but they closely resemble the cells of granulosa cell tumors. The dark cells, which were not described in granulosa cell tumors, are similar to the dark cells of the non-specialized stroma of the ovary.

There is little information available on the prognosis of SCTAT. To our knowledge, no case with a long follow-up has yet been published in detail. Scully (1977a) briefly mentions that certain cases may exhibit a malignant behaviour with an extra-ovarian extension and metastases. In our only case which recurred the differentiation into simple and complex tubular structures is less extensive than in the other two cases (about half the tumorous tissue consists of narrow ribbons of cells and of diffuse fields), but the main difference relies on the mitotic index which is much higher in the malignant case. Unfortunately, we found no indication at all in the literature concerning the degree of mitotic activity in SCTAT. It would be desirable that other cases with a long follow-up be published which take into account morphological parameters that could be useful in the appreciation of the prognosis of this unusual neoplasm.

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