J Korean Med Sci 1998; 13: 89-94
ISSN 1011-8934

Ovarian Sex Cord Tumor with Annular Tubules in a Patient with Turner Syndrome

A case of ovarian sex cord tumor with annular tubules (SCTAT) in a 24-year old woman with Turner syndrome is presented. Close association of dysgenetic gonads and gonadoblastoma has been clearly documented, and there have been sporadic reports of patients with other gonadal tumors. To our knowledge, a case of SCTAT in a patient with 45,X/46,XX Turner syndrome has not been reported. On the basis of histopathologic, immunohistochemical, and ultrastructural findings, we suggest that the SCTAT originated from pluripotential stem cells of the gonads and differentiated into either granulosa cells or Sertoli cells. We postulate a possible relationship between the SCTAT and gonadoblastoma based on the morphologic resemblance and occurrence in dysgenetic gonads.

Key Words : *SCTAT, Granulosa cell, Sertoli cell, Turner syndrome*

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Received : July 4, 1997
Accepted : September 4, 1997

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* This article is based on case first reported in the Korean Journal of Pathology, 1992; 26: 517-23.

INTRODUCTION

Dysgenetic gonads are frequently associated with gonadal tumors (1-3). Most of these tumors are gonadoblastomas, with the possible development of dysgerminoma (4). Other germ cell tumors, including embryonal carcinoma, choriocarcinoma and endodermal sinus tumor, are infrequently developed (5).

Ovarian sex cord tumor with annular tubules (SCTAT) is an unusual variant of sex cord stromal tumors of the ovary (6). The origin of this tumor remains unclear, with some favoring granulosa cell derivation theory (7, 8), and others favoring a Sertoli cell origin (9-11). Also, there have been some postulations that the tumor is composed of pluripotential stem sex cord cells of the gonads which have the potential for differentiating into either granulosa or Sertoli cells (12, 13). We report a 24-year-old patient with 45,X/46,XX Turner syndrome with SCTAT of the right ovary. For determination of the origin of the SCTAT, histological, immunohistochemical, and ultrastructural studies were done. In addition, we hoped to gain some insight into the relationship of SCTAT to gonadoblastoma on the basis of the community in histopathologic findings and occurrence in dysgenetic gonads.

To our knowledge, this is the first reported case of an ovarian SCTAT in a 45,X/46,XX Turner syndrome patient.

CASE REPORT

An 18-year old woman with phenotypic stigmata of Turner syndrome presented with an abdominal mass. The patient complained of secondary amenorrhea which had started 4 years previously. She had reached a final height of 141 cm and a weight of 51 kg at presentation. On physical examination, the patient showed underdeveloped breast, cubitus valgus, webbed neck, lower hair line, scanty axillary and pubic hairs, and low set ears. Peripheral blood karyotype confirmed the Turner's syndrome, showing 45,X/46,XX mosaicism. Ultrasonographic study showed a solid right ovarian mass filling most of the abdomen. Laboratory data showed decreased serum LH (< 1.0 mIU/ml; normal value < 20 mIU/ml) level and FSH concentration (< 1.0 mIU/ml; normal value < 38 mIU/ml). Serum estradiol, CA-125, testosterone were normal. At operation, a large right ovarian tumor (1.1 kg) was resected. Surgical treatment consisted of right salpingo-oophorectomy and appendectomy. Following that surgery the patient did well without any other adjunctive radiation therapy or chemotherapy. The patient was found to have a metastatic tumor in the neck and recurrent neoplasm in the abdomen 6 years after surgery for her right ovarian tumor. An abdominal CT scan showed a 6 cm sized, well demarcated solid mass on the medial side of the right

internal iliac vessel. The neck mass was evaluated on CT scan and was completely resected after fine needle aspiration biopsy for cytologic evaluation. The patient received a regimen of cisplatin, etoposide and bleomycin. After completing the chemotherapy, the size of the abdominal mass was significantly reduced.

RESULTS

Gross findings

The removed ovarian mass measured 23×18×17 cm and was well encapsulated by a thick fibrous capsule. On sectioning, the specimen showed a yellow to light yellow, solid cut surface with small cystic areas and cleft like spaces (Fig. 1). The left ovary was replaced by a fibrous streak 1cm in length. The uterus and fallopian tubes were grossly normal. On pelvic examination she had normal clitoris and vagina. The neck mass underwent excision was well demarcated yellow solid mass, measuring 5×3×3 cm.

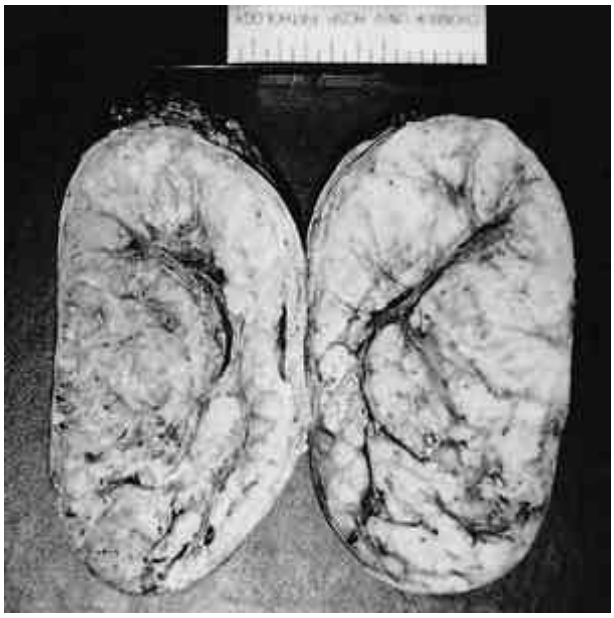

Fig. 1. Ovarian tumor is predominantly solid and cleft like spaces are visible.

Light microscopic findings

Microscopically, the ovarian mass was composed of simple and complex tubules containing eosinophilic hyaline bodies. Occasionally, the hyaline bodies at the center of tubules were continuous with the peripheral basement membrane surrounding the complex tubules. The tubular cells were arranged in antipodal fashion both at the periphery of the tubules and around the hyaline round bodies. The nuclei were round, oval and had a single small nucleolus. Some nuclei showed central grooves or deep indentations as seen in cells of the granulosa cell tumor. Cytologic anaplasia was minimal and mitotic figures were very rare. Ovarian stromal or dense fibrous tissue was noted between the nests of the tumor cells. Peripheral basement membranes and central hyaline bodies were strongly positive with the PAS technique.

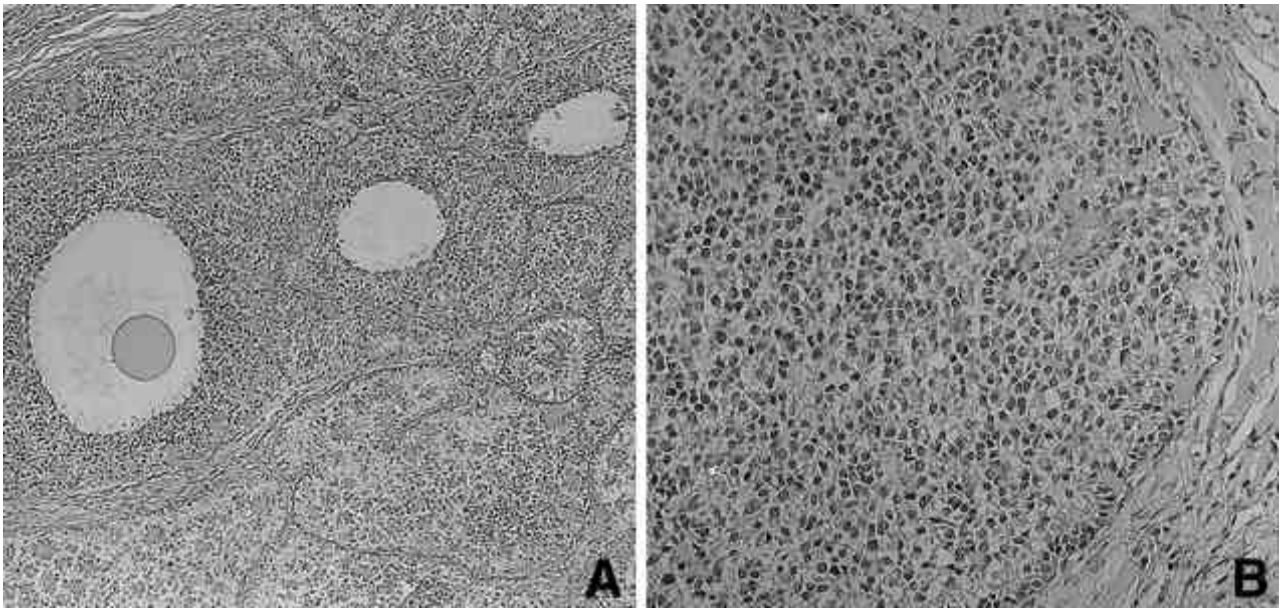

Fig. 2. A. Microcyst formation simulating the macrofollicular pattern of granulosa cell tumor (×40).
B. Solid cellular area simulating the microfollicular pattern of granulosa cell tumor (×100).

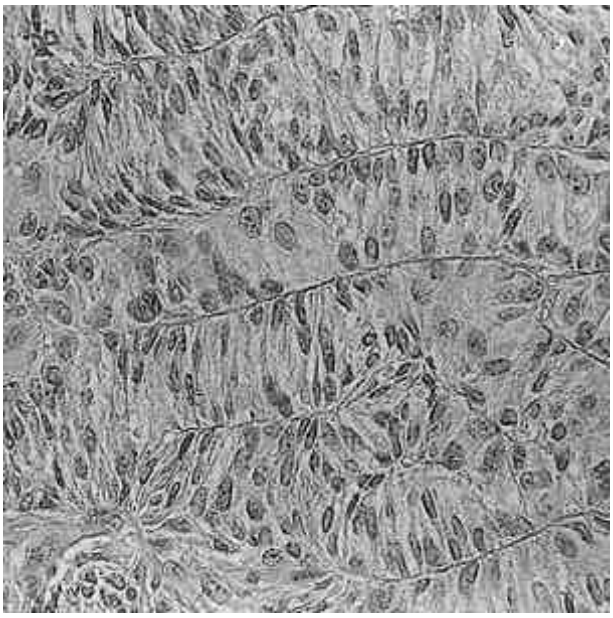

Fig. 3. Elongated tubular differentiation resembling the tubules of Sertoli cell tumor (×200).

Some cells showed positive staining with the oil red O stain. The prominent pattern of the metastatic neck mass was similar to that of the ovarian mass, but several variations from the characteristic pattern were intermixed in close association. One variant pattern was round microcyst formation, containing pale acidophilic material, simulating macrofollicles, as seen in the granulosa cell tumor (Fig. 2A). Solid cellular nests with palisading of nuclei at the periphery and small cavities, simulating Call-Exner bodies in the microfollicular granulosa cell tumor, were also observed (Fig. 2B). A second pattern was composed of elongated solid tubules with cells with pale cytoplasm, resembling the pattern of Sertoli cell tumor (Fig. 3). Most of the tubules were closed type without true lumen, but we could observe two tubules with distinct luminal structures in 1 block of 20 blocks. In a third pattern, hyaline material coalesced to obscure the typical simple and complex tubular structures, creating elongated tubules, or solid tumor cell nests appearance of the Sertoli cell tumor. Multiple foci of lymphatic invasion were observed in the peripheral portion of the tumor. Calcific deposits or germ cells typically seen in gonadoblastomas were not identified.

Immunohistochemical findings

Immunohistochemical stains were performed on formalin-fixed, paraffin-embedded material. The results of immunohistochemical stains of the neck mass were as follows: S-100 protein (Dako, diluted 1:40), progesterone (Immunotech, Marseille Cedex, France, prediluted), estrogen (BioGenex Labs, San Ramone, CA, prediluted), carcinoembryonic antigen (Zymed, San Francisco, CA, diluted 1:100), epithelial membrane antigen (Biomeda, Foster City, CA, prediluted), alpha fetoprotein (Biomeda, Foster City, CA, prediluted), human chorionic antigen (Biomeda, Foster City, CA, prediluted), desmin (BioTech, Santa Barbara, CA, prediluted), and smooth muscle actin (BioGenex Labs, San Ramone, CA, prediluted) were negative; vimentin (Dako, Carpinteria, CA, diluted 1:30) and cytokeratin AE1/AE3 (Signet Labs, Dedham, Massachusetts, prediluted) were positive. Cytokeratin AE1/AE3 showed focal intracytoplasmic paranuclear positivity in cells of granulosa-like nests and elongated Sertoli-like tubules in addition to typical simple and complex tubular areas. The staining patterns of vimentin were similar to those of cytokeratin.

Ultrastructural findings

The tumor cell nests were surrounded by several parallel layers of basal lamina of varying thickness. The central hyaline bodies were composed of necrotic cellular debris and concentric layers of basement membrane material. The basement membranes of the central bodies were continuous with that surrounding the cellular nests. There were some foci of abortive glandular structures forming central small cavities, but no true luminal structure, and apical microvilli or cilia were observed. Two types of cells were noted, predominant clear cells and scattered dark cells. The tumor cells had relatively straight cell borders and were attached to each other by numerous distinct desmosomes. The nuclei were located in the middle or basal portion of the cells, and showed marginal condensation of chromatin with prominent nucleoli. Sometimes, the nuclei revealed complex nuclear membrane which was created by deep indentation or invagination. The cytoplasm contained numerous tubular mitochondria, fragmented cisternae of rough endoplasmic reticulum, membrane of smooth endoplasmic reticulum, and poorly developed Golgi apparatus. Microfilaments were abundant throughout the cytoplasm, and occasionally formed aggregates of parallel array. Free ribosomes were abundant, and showed occasional lipid droplets. There was no evidence of cytoplasmic secretory granules or secretory products. Charcot-Bottcher filaments were readily observed consisting of bundles of electron-dense longitudinal fibrils. The Charcot-Bottcher filaments were mainly located in the paranuclear region, sometimes were discontinuous, ranged from 100 to 200 nm in thickness and 0.8 to 4 μm in length, and they were very similar to the tonofilament as seen in keratinizing squamous cells (Fig. 4). The Charcot-Bottcher filaments were usually observed in cells of smooth, linear nuclear membrane,

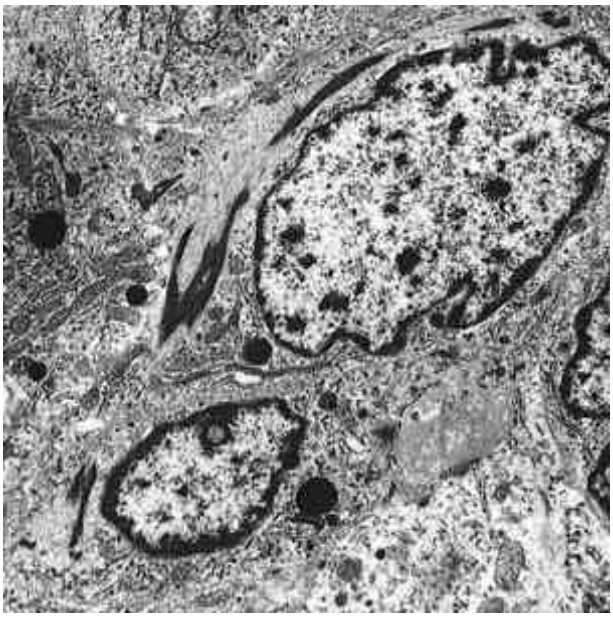

Fig. 4. Electron micrograph of Charcot-Bottcher filaments similar to tonofilament of differentiated squamous epithelium (× 6,000).

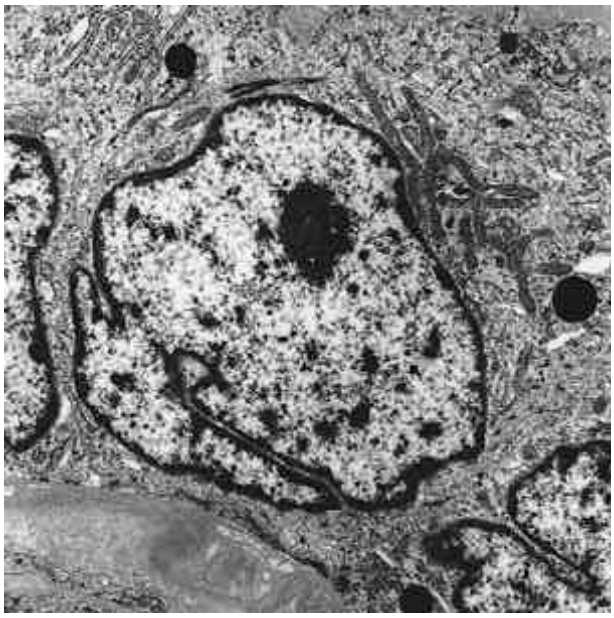

Fig. 5. Charcot-Bottcher filaments in cells with deep indented nucleus (×5,000).

but we could observe bundle of microfilaments, resembling Charcot-Bottcher filaments, located closed to the nucleus in cells of indented nucleus (Fig. 5). The stroma was formed by spindled fibroblasts and collagen fibrils.

DISCUSSION

There is a high risk of neoplasms in case of dysgenetic gonads (1-3). Most of these tumors are gonadoblastomas (4, 5). Troche and Hernandez reported 91 (47%) neoplasms other than gonadoblastoma in an analysis of 140 cases collected from the literature (5). Of these neoplasms 38 were pure dysgerminomas, 34 were gonadoblastomas with dysgerminomatous elements, and 19 were neoplasms composed of other germ cell elements, stromal, or epithelial tumor alone or in association with gonadoblastoma. To our knowledge, the association of dysgenetic gonads with SCTAT has never been described. Tumors in dysgenetic gonads occur almost exclusively in individuals with Y chromosome or fragments of Y chromosome (1-3). In our case, the presence of Y chromosome was excluded by conventional cytogenetic (chromosomal banding) analysis, even though a Y chromosome might be present in a few cells in the gonad, and a possible occult mosaicism is not completely excluded.

In 1970, Scully (14) introduced the term "sex cord tumor with annular tubules" (SCTAT) for a peculiar form of ovarian tumor, which caused much curiosity about the histogenesis and differentiating potentiality (6-13). Although there is considerable disagreement as to whether the cells in a SCTAT are of granulosa (7, 8) or Sertoli type (9-11), there is some consensus that the tumor is composed of primitive cells of sex cord origin which have a potential for differentiating into either granulosa or Sertoli cells (12, 13). Some authors, based on light microscopic findings i.e., the nuclear grooves, the central hyaline bodies resembling Call-Exner bodies, the macrofollicular pattern, the formation of solid nests and the absence of tubular structures which had true lumen, have suggested that the SCTAT differentiated into granulosa cell line (7, 8, 15). Those who believed that the SCTAT cells derived from Sertoli cells based their hypothesis on the morphologic resemblance of SCTAT to Sertoli cells demonstrated by the patterns of palisading of the nuclei, the tubular arrangement with cells of pale cytoplasm and the presence of cytoplasmic lipid (9-11). In our case, the primary ovarian mass was composed of mainly typical simple and complex tubules containing eosinophilic hyaline bodies, but the metastatic neck mass had a somewhat variable histologic patterns: microcyst, microfollicular pattern and elongated solid tubules. Furthermore, we could observe an area of hyaline materials coalesced to obscure the simple and complex tubules, creating elongated tubule or solid tumor cell nests, resembling Sertoli cell tumor. The diversity of morphologic findings of the SCTAT has already been reported by many other authors (6, 11, 14). Hart et al. (7) reported a case of primary ovarian SCTAT displaying divergent sex cord differentiation, but the

supraclavicular and retroperitoneal metastatic lesion more closely resembled a granulosa cell tumor than a SCTAT. Another case presenting as an ovarian granulosa cell tumor followed by SCTAT in the second look operation suggested the potential of divergent differentiation, or intermediate expression of pluripotential stem cells (13).

Despite the fact that many cases of SCTAT have been studied with electron microscopy, the immunohistochemical features of the SCTAT have not been characterized adequately. The presented case shows coexpression of vimentin and cytokeratin (AE1/AE3), and no other immunologic markers which was consistent with other reports (16, 17). Previous immunohistochemical staining of ovarian sex cord tumors has suggested that granulosa cell tumors express vimentin, but not cytokeratin (16). In contrast, Sertoli-Leydig cell tumors show cytokeratin positivity in the tubular cells, which are thought to represent Sertoli cell differentiation (16). But, recent study using a monoclonal or a cocktail of monoclonal anti-cytokeratin antibodies, not a polyclonal anti-cytokeratin, showed a significant proportion of keratin positive granulosa cell tumors (16, 18). Moreover, granulosa cell tumors and Sertoli cell tumors expressed vimentin simultaneously. In our case, the tumor cells resembled cells of granulosa cell tumor and Sertoli cell tumor which showed similar staining patterns, focal cytoplasmic positivity for vimentin and cytokeratin, but a great portion of tumor did not react. The staining patterns of intermediate filaments in our study have similarity in both cell types and hardly distinguish between them, but suggests a complex nature of this tumor.

The authors favoring granulosa cell differentiation of SCTAT have presented some ultrastructural evidence: the deeply indented nuclei, numerous randomly distributed fibrils, abundant desmosomes attaching the interdigitating processes of adjacent cells, and complexes of fibrils with desmosome, the resemblance of the concentric layers of basal lamina of the central hyaline bodies which were characteristic and consistent features of both SCTAT and granulosa cell tumors (7, 8, 19). Those who believed that SCTAT cells derived from Sertoli cells based their opinion on the finding of Charcot-Bottcher filaments, the presence of intracytoplasmic lipid, the tubular arrangement with occasional findings of lumen and microvilli (9-11). They insisted that the absence of the Charcot-Bottcher filaments in other cases may have been due to limited sampling for electron microscopic study (11). There is overlap of the ultrastructural features of granulosa and Sertoli cells (15, 19). They both have an epithelial configuration and may have interdigitating cytoplasmic extensions. A basal lamina separates the Sertoli cells from the interstitium and granulosa cells from the adjacent theca cells. Their nuclei often have irregular configurations with deep invaginations or clefts. These common findings between granulosa and Sertoli cells made it difficult to define the origin of SCTAT as granulosa cell by an ultrastrutural study only. So then, does the presence of Charcot-Bottcher filament in the cells of SCTAT imply its Sertoli origin? According to Crissman and Hart, the characteristic Charcot-Bottcher crystalloids of normal adult Sertoli cells have not yet been reported in Sertoli cell tumors of the testis (15). Tavossoli and Norris gave a critical analysis of the morphology of the Charcot-Bottcher crystalloids (20). The ultrastructural study showed that they were composed of bundles of microfilaments packed together with no specific structure. They lack the typical geometric lattice appearance of a crystalloid and they referred to these structures as Charcot-Bottcher filaments. The Charcot-Bottcher filaments resembled the filaments normally scattered in the cytoplasm and related to the cytoskeleton and the tonofilaments connected to desmosomes (8). In our case, we could observe the overlap of cytologic features of granulosa and Sertoli cells that was previously described, and the finding of paranuclear Charcot-Bottcher filaments in cells with deeply indented nucleus which showed granulosa cell propensity. These findings may be explained by the derivation of both cell types from the same antecedent cell, which has the potential to differentiate in either cell type. The cytoplasmic Charcot-Bottcher filaments in our case are similar to the tonofilament that dispersed in the cytoplasm of differentiated squamous cell. Thus, it is difficult to assume that the Charcot-Bottcher filaments are specific for tumors of Sertoli cell origin.

We were interested in our case in the focus of the histologic resemblance of SCTAT to gonadoblastoma which usually occurred in dysgenetic gonads. These two lesions shared certain histologic features, including rounded nests of sex cord cells with central hyaline bodies, thickened basement membrane, and occasional calcific deposits (4, 6, 14). Unlike SCTAT, gonadoblastomas also contain primitive germ cells within the nests of sex cord cells. The propensity for germinomas and other germ cell tumors to arise from the germ cell elements of gonadoblastoma is well known (4, 5). Hart et al. considered the possibility that SCTAT represents neoplastic transformation of the sex cord element of gonadoblastoma in a patient with combination of germinoma and SCTAT (7). Scully found two cases of germinoma in patients with SCTAT in a study of SCTAT in patients with and without the Peutz-Jeghers syndrome (14). He postulated the possibility that the SCTAT may have been a gonadoblastoma in which the germ cells had dropped or were never seen. We could not find any residual foci of typical gonadoblastoma or calcific deposits in our case. Many

cases of SCTAT associated with Peutz-Jeghers syndrome showed calcific deposits as seen in gonadoblastomas. Such common findings of calcific deposits, which may represent the regression of cellular components, in SCTAT and gonadoblastoma suggest a possible link between the two lesions (7, 14). However, the SCTAT occurring in patients without Peutz-Jeghers syndrome differed in their features; unilaterality, large size, absence of calcification in the majority of cases, compared to that of patients with Peutz-Jeghers syndrome. Until more cases of SCTAT associated with dysgenetic gonads are intensely studied morphologically, a relationship between SCTAT and gonadoblastoma cannot be established.

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