






## Sertoli-Leydig Cell Tumor

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**ABSTRACT** Sertoli-Leydig cell tumors are included under sex-cord stromal tumor of the testis or the ovary. They form less than 0.5% of overall ovarian tumors. They are typically observed in young women (below age 35). Findings such as abdominal distention, pain and virilization are the common reasons of patients' admission to the hospital. Most of the patients have unilateral ovarian mass without extraovarian spread. Generally, Sertoli-Leydig cell tumors have good prognosis. The most important prognostic factors of the Sertoli-Leydig cell tumors are the stage, differentiation, the presence of retiform or heterologous elements. Herein, we presented three different cases; one of which was a well-differentiated Sertoli-Leydig cell tumor, while the second one was an intermediately differentiated Sertoli-Leydig cell tumor. The last one was an Sertoli-Leydig cell tumor with retiform component accompanied by thyroid papillary carcinoma. We present these cases due to their rarity and different clinical presentations.

**Keywords:** Sertoli-Leydig cell tumor; ovary

Pathological diagnosis of ovarian tumors seen in young adults is quite difficult. Sertoli-Leydig cell tumor (SLCT), a rare ovarian sex-cord stromal tumor should always be kept in mind in young cases of ovarian masses, since, beside its broad spectrum differential diagnosis and various variants, distinctive histological grades can complicate the diagnosis as well.<sup>1,2</sup> In this study three distinct SLCT cases, a well-differentiated, of intermediate differentiation and that with a retiform component were reported, emphasizing their differential diagnoses. Additionally we aimed to introduce an interesting clinical presentation of this tumor as seen in our third case with a retiform component which had a thyroid neoplasm.

### CASE REPORTS

#### CASE 1

A 32 year-old woman admitted to emergency clinic with abdominal pain, nausea and vomiting lasting for 3 days. On physical examination, an appendectomy incision scar at the right lower quadrant and rebound tenderness at the left lower quadrant were observed. On the abdominal computed tomography scan of the patient with a preliminary diagnosis of acute abdomen, a hypodense cystic lesion of 67x50 mm and another hypodense cystic lesion of 1,2 cm of diameter were detected in the left and right Douglas

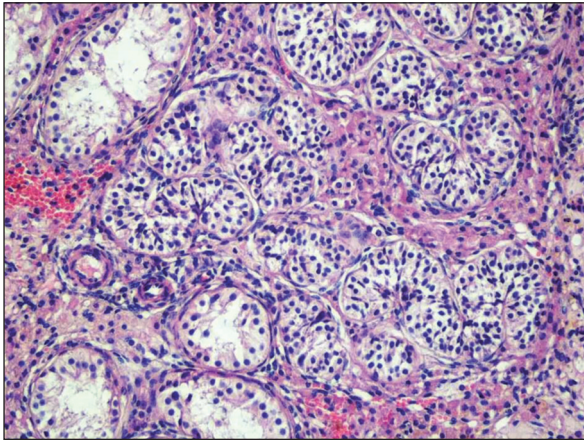


FIGURE 1: Sertoli-like cells and Leydig cells (H&E; x200).

pouch respectively. On the full abdominal ultrasonography (USG), neither uterus nor ovaries were assessed. On rectal USG, on the other hand, right adnexa was assessed without any pathological findings and the left adnexa which sized of 7x3.5 cm was interpreted as consistent with infection or cystic mass. Laboratory findings were as follows: beta-HCG: 0.1 ng/ml (N; 0-5 ng/ml), alpha-fetoprotein (AFP): 1.54 ng/ml (N; 0-10 ng/ml), carcino-embryonic antigen (CEA): 0.98 ng/ml (N; 0.3-8 ng/ml) and CA 125: 184.7 U/ml (N;  $\leq$ 35 U/ml). Upon the above mentioned findings, the patient has undergone bilateral salpingo-oophorectomy with a preliminary diagnosis of left adnexal mass. Macroscopically, the left adnexa was measured 7.5x5x3 cm and the cut surface revealed cystic structures of pinhead size, hemorrhagia and grey-white colored areas. On microscopic examination, the tumoral tissue in the ovary consisted of Sertoli-like cells with basal nucleus and clear cytoplasm arranged in solid or hollow oval-round tubular structures and Leydig cells with granular eosinophilic cytoplasm in fibromatous stroma were observed (Figure 1). The tumor was poorly circumscribed. No cytologic atypia nor mitosis were identified. In immunohistochemical studies, tumor cells were positively stained for inhibin and vimentin, and were focally positive for pancytokeratin (PanCK). Estrogen and progesterone receptors were negative. Based on the histopathological and the immunohistochemical findings, the patient was given the diagnosis of well-differentiated SLCT.

## CASE 2

Hemoglobin and hematocrit values of a 61 year-old woman followed up for diabetes mellitus and hypertension were 7.7 g/dl (N: 13.6-17.2 g/dl) and %26 (N: (%39.5-%50.3) respectively. No significant finding except the Pfannenstiel incision line was observed on physical examination of the patient who was explored for the etiology of anemia who had a history of total abdominal hysterectomy 15 years ago. Ultrasonography examination revealed a heterogeneous mass of 6-7 cm of diameter occupying the Douglas pouch in the pelvic area and on the magnetic resonance (MR) imaging, an additional heterogeneous solitary massive lesion of size of 9x6 cm in the left-half of the pelvis was detected (Figure 2). Since the tumor markers were assessed postoperatively, related values were low as follows: CA19-9: 10.89 U/ml (N;  $<$ 39 U/ml), CA15-3: 5.03 U/ml (N;  $\leq$ 25 U/ml) and CA125: 19.51 U/ml (N;  $\leq$ 35 U/ml). In the course of the operation, the patient has undergone bilateral salpingo-oophorectomy for ovarian bilobular cystic lesion occupying the Douglas pouch. Macroscopically, the surface of the operation material appeared glistening and partly cystic; the cut surface was lobulated and fibrotic with a gray-yellow color. On histopathological examination, tumoral tissue was separated from the surrounding ovarian tissue with quite regular borders and consisted of hyalinizing stroma containing hypocellular nodular structures and more cellular

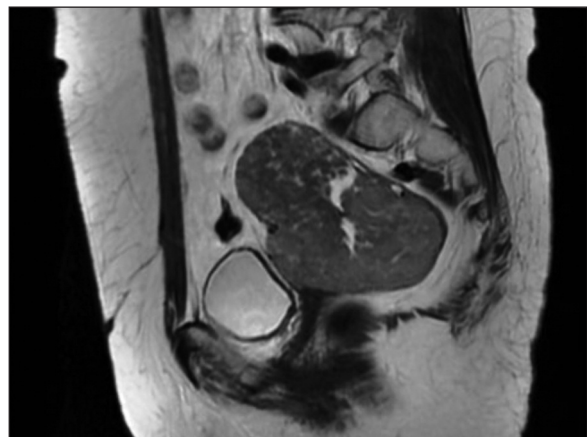


FIGURE 2: Solid mass in left-half of the pelvis on MR.

nodular structures of different sizes. Cellular areas contained solid regions with cleavages and pseudoendometrioid hollow tubules lined with monolayered epithelium, in the periphery of the tumor (Figure 3 A, B). Tumor cells had oval-round nucleus and scanty cytoplasm. Cellular atypia was minimal. Mitotic activity was found as 0-1 in 10 high-power fields. Ki-67 proliferation index (PI) was 3-4%. Tumor cells were positively stained for inhibin (Figure 4 A), vimentin, PanCK and S-100. While focal staining was identified with CD10 (Figure 4 B), no staining was observed with calretinin, CD99 and SMA. Given the morphological

and the immunohistochemical findings, the case was diagnosed as SLCT with intermediate differentiation.

### CASE 3

A 31-year old woman whose slides and blocks were sent to our department for consultation had been followed for 6 years for thyroid papillary carcinoma and she was admitted to the hospital for abdominal pain and distention lasting for the last 6 months. On microscopic examination, Sertoli-like cells and Leydig cell groups arranged as hollow tubular structures, with scanty stroma, without mi-

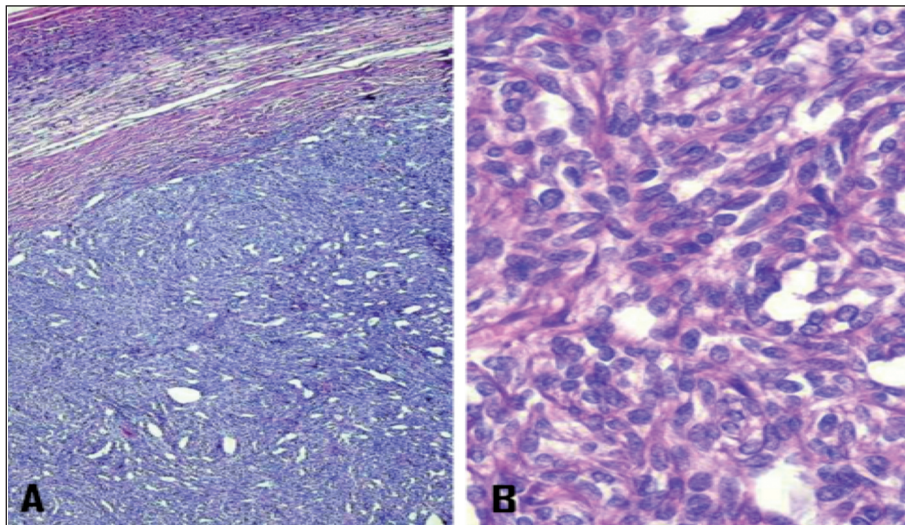


FIGURE 3: A) Tumor and surrounding ovary tissue (H&E; x40); B) Tumor containing solid regions with cleavages (H&E; x200).

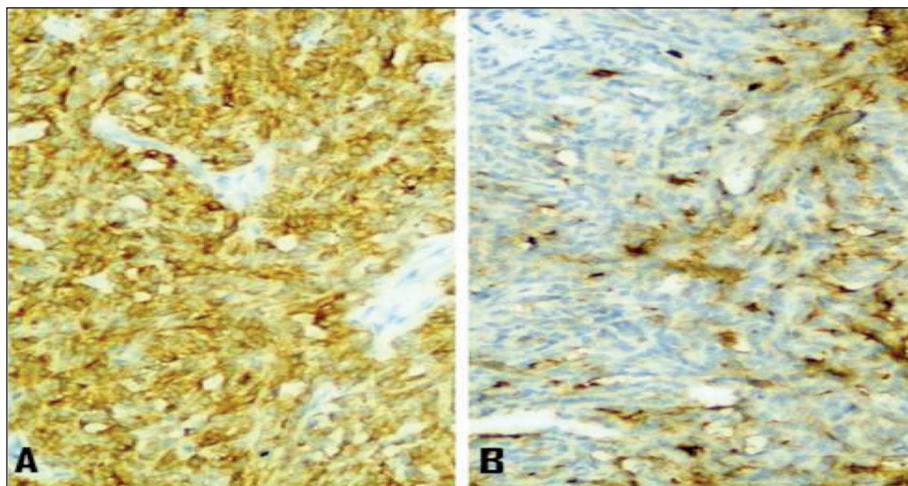
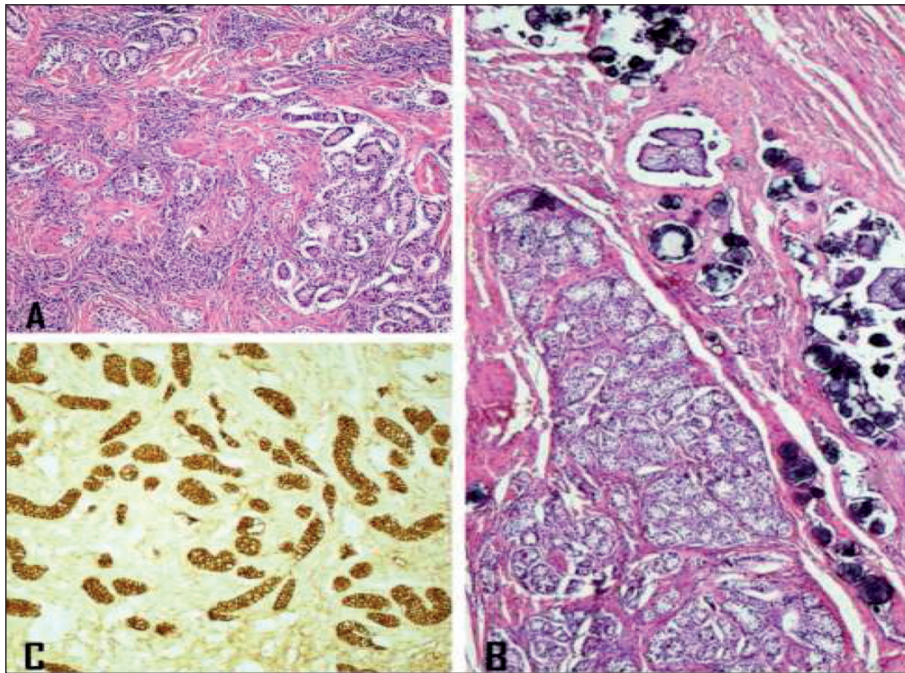


FIGURE 4: A) Inhibin positivity in tumor cells (Inhibin; x200); B) CD 10 focal positivity in tumor cells (CD10; x200).





**FIGURE 5:** A) Sertoli-like cells and Leydig cells (H&E; x100); B) Papillary structures and psammoma bodies (H&E; x40); C) CD99 positivity in tumor cells (CD99; x100).

totic activity and with mild atypia were detected, whereas in about 15% of the tumor, cystic areas comprising slit-like retiform structures lined by flattened epithelium and polypoid and papillary structures accompanied by psammoma bodies were observed in a loose stroma (Figure 5 A, B). These areas were evaluated as retiform components. Immunohistochemical studies revealed vimentin, CD99 (Figure 5 C), WT1, calretinin, CD56 positivity as well as CD10 focal positivity. Progesterone receptor was focally positive in the retiform area, while negative in the remaining areas. Inhibin, AFP and Melan-A were all negative. Ki-67 PI was 1% in both areas. Upon those findings, the patient was diagnosed with SLCT with retiform component.

The patients have given written consent for these case reports.

## DISCUSSION

Sertoli-Leydig cell tumors classified in the ovarian sex-cord stromal tumors account for less than 1% of all ovarian tumors.<sup>2,3</sup> Average age of the young women in whom these tumors are seen is 25. But in

10% of the cases, SLCT may appear in premenarch or postmenopause. As seen in our cases, those tumors have usually unilateral localization; but in rare cases bilateral localizations have also been reported.<sup>4,5</sup> Clinical signs and symptoms comprising secondary amenorrhea and varying degrees of virilization are dependent on the testosterone produced by tumor cells.<sup>6</sup> Rare estrogenic findings may also be observed.<sup>7</sup> Cases without endocrinological findings, such as our first two cases, may manifest with pelvic or abdominal pain or “mass findings”.<sup>8</sup>

These tumors whose clinical course is dependent on the histological differentiation are classified into three groups; well-differentiated (11%), of intermediate differentiation (54%) and poorly differentiated (13%). The latter two categories may contain heterologous elements (22%) and a retiform component (10-15%).<sup>1</sup>

Well-differentiated tumors have primarily tubular pattern and consist of cystic dilated or solid tubular structures lined by Sertoli like cells and variable numbers of Leydig cells. Nuclear atypia is minimal, mitotic activity is rare or absent. In the

tumor of intermediate differentiation, Sertoli cells appearing as immature cells with small, round, oval or angular nucleus in edematous or fibromatous stroma lined with fusiform cells form nests, hollow or solid tubules, thin or thick cords. Some tubules are pseudoendometrioid as seen in well-differentiated tumors. Stroma contains well-differentiated Leydig cells in clusters. Poorly differentiated tumors on the other hand show diffuse growth composed of fusiform cells with brisk mitotic activity arranged in a sarcomatoid pattern. Typical elements are always present in some areas of the tumor. In SLCT cases, inhibin, calretinin, WTI and CD56 show positivity for immunohistochemical staining, whereas with EMA no staining is observed.<sup>1,4,9</sup>

In the retiform variant, tubular structures resembling rete testis are present in some areas of the tumor or sometimes entirely. These are tumors of intermediate or poor differentiation. Elongated, narrow and irregularly branching papillary or polypoid structures project into slit-like tubules. Papillary structures are consisted of thin, branching and stratified cells which are small, blunt or large, edematous or thin resembling serous borderline tumors.<sup>1,9</sup>

The tumors with heterologous elements are of intermediate or poor differentiation. Most frequently they consist cystic glandular structures lined by gastric and intestinal epithelium. In some cases, stromal heterologous tissues such as fetal cartilage and embryonal rhabdomyosarcoma are seen.<sup>1,9</sup>

The differential diagnosis of SLCT includes sertoliform variant of endometrioid carcinoma, trabecular carcinoid tumor, granulosa cell tumor with trabecular pattern and tubular Krukenberg tumor. Findings supporting endometrioid carcinoma are older age of onset, absent virilizing endocrinological findings, presence of large tubular structures in the different areas of the tumor and squamous metaplasia as well as intraluminal mucin, if present. Tumor cells of the endometrioid carcinoma are immunohistochemically positive for EMA and PanCK while negative for inhibin unlike SLCT.

There is no epithelial mucin secretion in sertoliform endometrioid carcinoma unlike SLCT with heterologous elements.<sup>1,9</sup>

Stroma of the trabecular carcinoid tumors are less cellular and more fibromatous. While primary carcinoid tumors comprise teratomatous elements with a frequency of 70%, metastatic carcinoid tumors are bilateral. Presence of round nucleus with regular borders and fine chromatin pattern, and positivity for neuron-specific enolase, chromogranin and argentaffin or argyrophil reaction are all significant findings for distinguishing from SLCT.<sup>1,9</sup>

Granulosa cell tumor with trabecular pattern on the other hand can be differentiated from SLCT with more mature appearances of the cells, presence of angular nucleus or intranuclear grooves as well as Call-Exner bodies, and the absence of Leydig cells. Even rarely, presence of hollow tubular structures in any area of the SLCT is useful for differential diagnosis. Relatively younger age, manifestation of androgenic symptoms, rare presence of fibromatous stroma on the contrary to granulosa cell tumors, more prominent characteristics of Leydig cells compared to granulosa cell tumors and their clustering tendency, and finally, the presence of heterologous and retiform elements support SLCT. But it should be kept in mind that some sex cord cell tumors may morphologically appear between granulosa cell tumor and SLCT or may exhibit characteristics of both tumor types. Tubular Krukenberg tumors may be confused with SLCT with intermediate differentiation, but is usually bilateral and the presence of mucin containing signet-ring cells excludes the SLCT.<sup>1,9</sup>

Differential diagnosis of the variant with heterologous elements includes teratomas, but squamous epithelium, skin appendages and respiratory epithelium seen in teratomas do not exist in SLCT. Retiform variant is a rare presentation of SLCT (10-15%) and associated with some diagnostic challenges due to two major clinical differences compared to typical SLCT: relatively younger age of onset (average ages is 15 compared to 25) and fewer androgenic symptoms.<sup>2,9</sup> While virilization

findings may guide the pathologist to the correct diagnosis in SLCT, their absence and presence of high levels of serum AFP detected in some retiform variant tumors may lead to a mistaken diagnosis of yolk sac tumor. In SLCT, the cells appear less primitive compared to yolk sac tumor. Presence of other typical yolk sac patterns and AFP positivity support the differential diagnosis.<sup>1,2</sup>

Additionally, retiform variant SLCT can be confused with serous surface tumors because of their papillary structures seen on microscopic examination. Relatively lower grade atypia of the papilla lining cells, <30 years of age, virilizing findings and presence of other typical patterns of SLCT exclude serous carcinoma. In the retiform variant, tubular structures present in the cellular mesenchymal background, together with the additional heterologous elements may incorrectly lead to a diagnosis of carcinosarcoma. Unlike carcinosarcoma, both epithelial and mesenchymal areas show benign or borderline appearances and surface epithelium like heterologous elements are not serous but mucinous. Younger age of the patient and inhibin +/-calretinin +/- EMA - immunostaining are distinctive features of this diagnosis. In a young patient, before deciding on the diagnosis of serous borderline tumor, carcinosarcoma or serous carcinoma, retiform SLCT must be ruled out considering these differential criteria.<sup>1,9</sup>

Coexistence of SLT and thyroid papillary carcinoma observed in our third patient is a rare entity and was mentioned in only a few studies in the literature.<sup>10-12</sup> In the literature, there are some studies suggesting the coexistence of SLCT and thyroid anomalies and other probable accompanying neoplasias may be part of a syndrome associated with germline DICER 1 mutation.<sup>10,13,14</sup>

Prognosis of SLCT is considerably correlated with tumor differentiation grade, tumor extension as well as presence of subtypes accompanied by retiform and heterologous elements.<sup>1,9</sup> Majority of the cases are grade I at diagnosis and their prognosis is usually favorable.<sup>4</sup> Cases with a clinically ma-

lignant behaviour are seen at a rate of 10%, while this rate is 25% for retiform variant at the same stage.<sup>1,9</sup> The treatment of choice for relatively poorly differentiated tumors is salpingo-oophorectomy in addition to chemotherapy.<sup>1,4,9</sup>

In this study we aimed to draw attention to the interesting morphological characteristics that lead to challenges and cause mistakes in the differential diagnosis of the ovarian tumors in young patients, reporting an uncommon variant of a rare ovarian tumor, SLCT, together with other cases of varying histological grades. Beside the rare co-occurrence of thyroid papillary carcinoma and SLCT, due to the mutations comprising other organ neoplasias, screening of the thyroid tissue as well as systemic screening may be necessary and useful for SLCT patients.

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#### **Conflict of Interest**

*No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

#### **Authorship Contributions**

**Idea/Concept:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Servet Şişman; **Design:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Servet Şişman, Simten Genç; **Control/Supervision:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Deniz Özcan; **Data Collection and/or Processing:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Servet Şişman, Simten Genç; **Analysis and/or Interpretation:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Deniz Özcan; **Literature Review:** Selma Şengiz Erhan, Servet Şişman, Simten Genç; **Writing the Article:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Servet Şişman; **Critical Review:** Selma Şengiz Erhan, Ayşe Tülay Sayılğan, Servet Şişman, Simten Genç, Deniz Özcan.

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