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OVARIAN SERTOLI-LEYDIG CELL TUMOR: REPORT OF A RARE CASE

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ABSTRACT
Ovarian Sertoli-Leydig cell tumors (SLCT) are extremely rare ovarian tumors belonging to the group of sex cord-stromal tumors and divided into four subtypes, that are well differentiated, moderately differentiated, poorly differentiated, and retiform. They are accounting for less than 0.5% of all primary ovarian neoplasms. Ovarian SLCT often diagnosed at early stage with low-malignant behavior. Accurate diagnosis is very important to determine the management. Due to its rarity, ovarian SLCT have low index of suspicion to be diagnosed. Most of ovarian SLCT are unilateral and presented at young women. Mostly the symptoms are presented with lower abdominal or pelvic mass and often come with virilisation due to androgen production. In the case of moderately and poorly differentiated, sometimes will be found heterologous elements. The presence of heterologous elements or retiform pattern being a bad prognostic feature. Immunohistochemistry staining can be utilized to distinguish ovarian SLCT with other resembling entities.

KEYWORDS: Sex cord-stromal tumor, ovarian Sertoli-Leydig cell tumor, well-diferentiated ovarian Sertoli-Leydig cell tumor, rare ovarian tumors.

INTRODUCTION
Ovarian Sertoli-Leydig cell tumors (SLCTs) are rare ovarian tumors belonging to the group of sex cord-stromal tumors. Malignant sex cord-stromal tumors of the ovary are rare in general, comprising only 1.2% of all primary ovarian neoplasms. Ovarian SLCTs are even more uncommon, accounting for less than 0.5% of all primary ovarian neoplasms. Over 97% of ovarian SLCTs are unilateral.[1–5] The majority are presented at 20-40 years age group.[2,3] Between 40-60% of patients are virilised, include amenorrhoea due to androgen production.[1] The prognosis depends on the patient's age, stage of the tumor and the degree of differentiation with the presence of heterologous elements or retiform pattern.[6] Ovarian SLCTs often present diagnostic dilemma due to their relative infrequency and high degree of morphologic variability. The potential for diagnostic uncertainty and misdiagnosis is amplified in the setting of intra-operative consultation where diagnosis must be made on frozen section material. Here we describe a case of well-differentiation ovarian SLCTs to increase the familiarity of its pathologic and clinical significance.

Case Presentation
The patient is a 31-year-old female with chief complaints abdominal enlargement and did not get her period for the last three months. She felt bloated and mild pain in her abdomen. She has had pregnancy test, and the result was negative. Physical examination revealed a palpable mass in the abdomen above the symphysis, which has limited mobility and non-tender, that suppressed the rectum so that uterus difficult to assess whereas mucosa rectum was smooth. Laboratory results showed high platelet, high erythrocyte sedimentation rate (ESR), high lactate dehydrogenase (LDH), high carcinoembryonic antigen (CEA), and low beta human chorionic gonadotropin (β-hCG). However, cancer antigen 125 (CA-125) and alpha-fetoprotein (AFP) were normal. Abdominal ultrasound and computed tomography (CT) showed a heterogeneous (solid and cystic) mass suggestive from right ovary.

Exploratory laparotomy was performed and found the right ovarian cyst with solid part and left cystic ovarian sized which contained serous fluid. Right salphingo-oophorectomy was performed, including left cystectomy. Frozen section of the resected specimens revealed it as right ovary sex cord stromal tumor, tend to be Sertoli-Leydig cell tumor (Figure 1) and benign left ovary cyst. Cytology examination of peritoneal washings did not reveal any malignant cells.

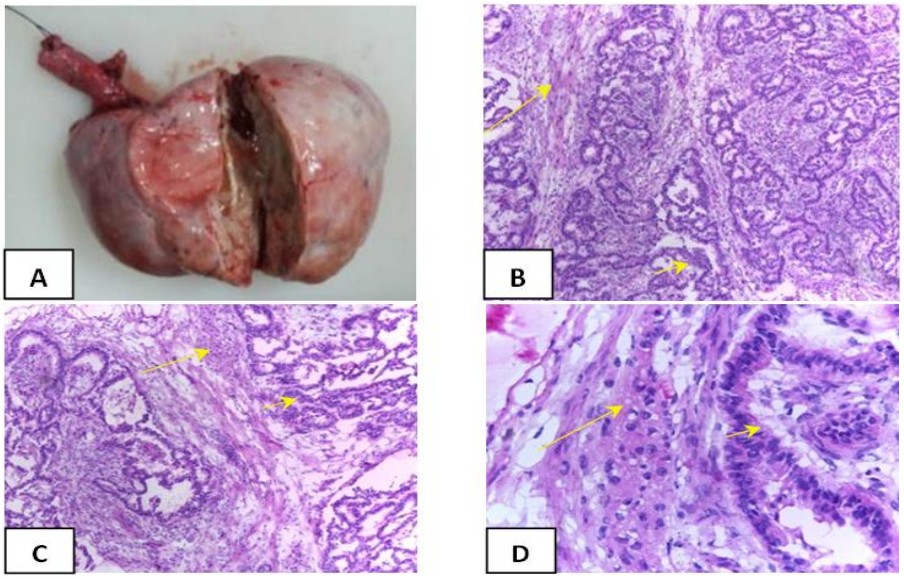


Figure 1: Frozen section examination of right ovary. A. Gross appearance showed a solid firm mass, smooth surface, with solid and multi-cystic parts inside. B-D. Hematoxylin and eosin (H&E) staining, it showed tubules and nest of Sertoli cells (arrows) surrounded by connective tissue stroma with nests of Leydig cells (long arrows). (B. H&E 40x, C. H&E 100x, D H&E 400x).

Right ovarian gross examination of the pathologic showed a 14x10x5 cm, yellow-gray, solid, firm mass with smooth external surface. A cut section of the specimen revealed solid, lobulated as well as multi-cystic areas filled with clear yellowish fluid (Figure 2).

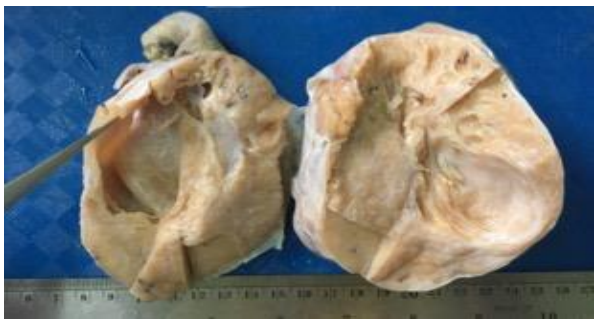


Figure 2: Cut section showed solid parts with multi-cystic areas.

Histopathologic examination showed tubules, solid, trabecular, complex nests of tumor cells with cystic areas. Sertoli cells had uniform round to oval, small to medium size, vesicular, and fine chromatin nuclei with low mitotic activity. Solid connective tissue stroma with nests of Leydig cells that had round, uniform, and vesicular nuclei. The cytoplasm was abundant, clear, and partially eosinophilic. Based on the findings, a final diagnosis of well differentiated right ovarian Sertoli-Leydig cell tumor was made (Figure 3). Left ovarian gross examination of the pathologic showed a cyst, 2 cm in diameter, the external surface was smooth. A cut section of the specimen revealed a smooth internal surface. Histopathologic examination showed features of simple cyst. The histopathologic diagnosis was consistent with frozen section findings.

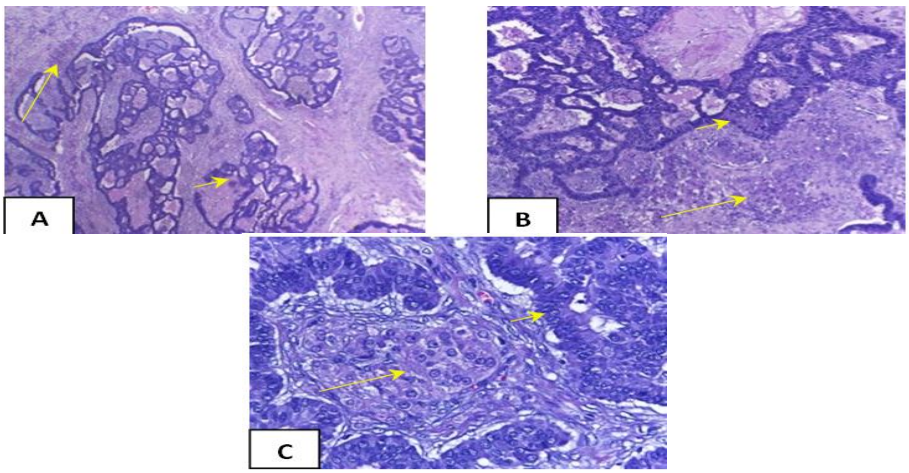


Figure 3: Tumor composed of tubules, solid, trabecular, complex nests of tumor cells (Sertoli cells, arrows). Nests of cells in solid connective tissue stroma (Leydig cells, long arrows) A. HE 40x. B. HE 100x. C. HE 400x.

The postoperative period was uneventful and the patient was discharge on the second day after surgery. After the histopathology report was received, the patient was consulted to Gynecologic Oncologist. Due to the tumor was well differentiated, benign, and unilateral, there was no specific treatment or examination for further diagnosis.

DISCUSSION

Ovarian sex cord-stromal tumors are a heterogeneous group of neoplasms developing from the stem cells furnishing around the oocytes including the cells producing hormones.[2] SLCTs of ovary is an exceedingly unusual neoplasm that belongs to a group of sex cord-stromal tumors of ovary.[7] Approximately 20% of ovarian SLCTs contain heterologous elements such as gastrointestinal epithelium, carcinoid, cartilage, and skeletal muscle.[8]

Ovarian SLCTs occurs in young women, with average age of presentation is 25 years. Well-differentiated tumors occurring in slightly older (mean, 35 years), 75% of the patients are 30 years of age and it is characterized by uncontrolled proliferation of naturally occurring testicular structures (Sertoli and Leydig cells) in ovary, that cause androgen production. It usually present with palpated pelvic mass, abdominal pain and abdominal bloating.[4,7,9] Most of ovarian SLCTs are unilateral and the mean size ranges from 12 to 14 cm, and can reach as huge as 50 cm in poorly differentiated histological variants.[1,4,7] Our case showed 31-year-old woman presented with amenorrhea and an enlarging abdominal mass, measuring 14x10x5 cm. It shows similarity to other reports in terms of age of onset, symptoms, and tumor size at presentation.

Imaging studies can be utilized in the diagnosis of ovarian SLCTs. It may be identified on ultrasound, computed tomography, or magnetic resonance imaging as solid or solid and cystic mass.[1,2] Ultrasound remains the best imaging modality of preference for initial assessment of adnexal masses, due to its high sensitivity, suitability, and cost effectiveness.[7] In this case, the mass was identified as solid irregular mass with cystic part in posterior of uterus from ultrasound examination. While on MSCT scan, the mass was concluded as heterogeneous, solid and cystic, with contrast enhancement, suggestive from right ovary. Therefore, there is a similarity of imaging finding between our case and on the references.

Macroscopically, ovarian SLCTs are frequently unilateral, well-encapsulated, solid, firm, lobulated, and yellow-gray masses. Cut-section surface exhibits varying degrees of greasy/fleshy consistency, and cystic spaces separated by fibrous septae.[7] As in our case, we found the similarity on gross findings, that was unilateral mass, yellow-gray, solid, firm. It also has smooth surface with lump parts. Cut-section showed solid parts, lobulated, and cystic parts with various size.

According to the World Health Organization classification, ovarian SLCTs are categorized as mixed sex cord-stromal tumors. Ovarian SLCTs are divided into four subtypes, that are well differentiated, moderately differentiated, poorly differentiated, and retiform.[1] The tumor cells may be arranged in a variety of architectures including hollow tubules, solid tubules, nests, trabeculae, diffuse, pseudopapillary, follicles, alveolar, and pseudoendometrioid patterns.[10] In well differentiated ovarian SLCTs, Sertoli cells are present in open or closed tubular structures lined by single or multiple layers of cuboidal-columnar cells with well-bounded margins, oval dark nuclei, inconspicuous nucleoli, fine chromatin, eosinophilic or vacuolated cytoplasm, and lack significant nuclear atypia or mitotic activity. There is a delicate fibrous stroma in which Leydig cells are found in small clusters, cords, and singly and typically exhibit polygonal cells with well-defined margins, centric nuclei, prominent nucleoli, and eosinophilic cytoplasm.[1,4,7] The well-differentiated, moderately differentiated, and poorly differentiated forms are assigned based on the degree of tubular differentiation of Sertoli cell component, which decreases with increasing grade, and the amount of primitive gonadal stroma presents within the tumor, which increase with increasing tumor grade. Leydig cells also tend to decrease with increasing tumor grade.[11] In this case, the clinician also sent the specimen for frozen section examination. It showed similar appearance with the histopathologic examination. The tumor cells arranged as open and close tubules, solid, trabecular, complex nests with round to oval and fine nuclei, eosinophilic cytoplasm. It has low mitotic activity. We find some similarities as we called it Sertoli cells in our case which are mostly structured as tubules. Then, in some fibrous stroma, we easily found some small clusters, cords, and singly cells which have the same appearance as Leydig cells. No heterologous elements were identified in this tumor. Accordingly, this case was a well-differentiated ovarian SLCTs.

Distinguish ovarian SLCTs from the resembling entities based on its histologic appearance is very important, not only in histopathologic examination but also in the setting of intraoperative consultation. The incorrect frozen section diagnosis could be lead the clinicians undertake unnecessary extensive surgical resection. However, low index of suspicion of ovarian SLCTs, these microscopic features can be misleading and easily mistaken for a diagnosis of carcinoid tumor and endometrioid carcinoma.[8]

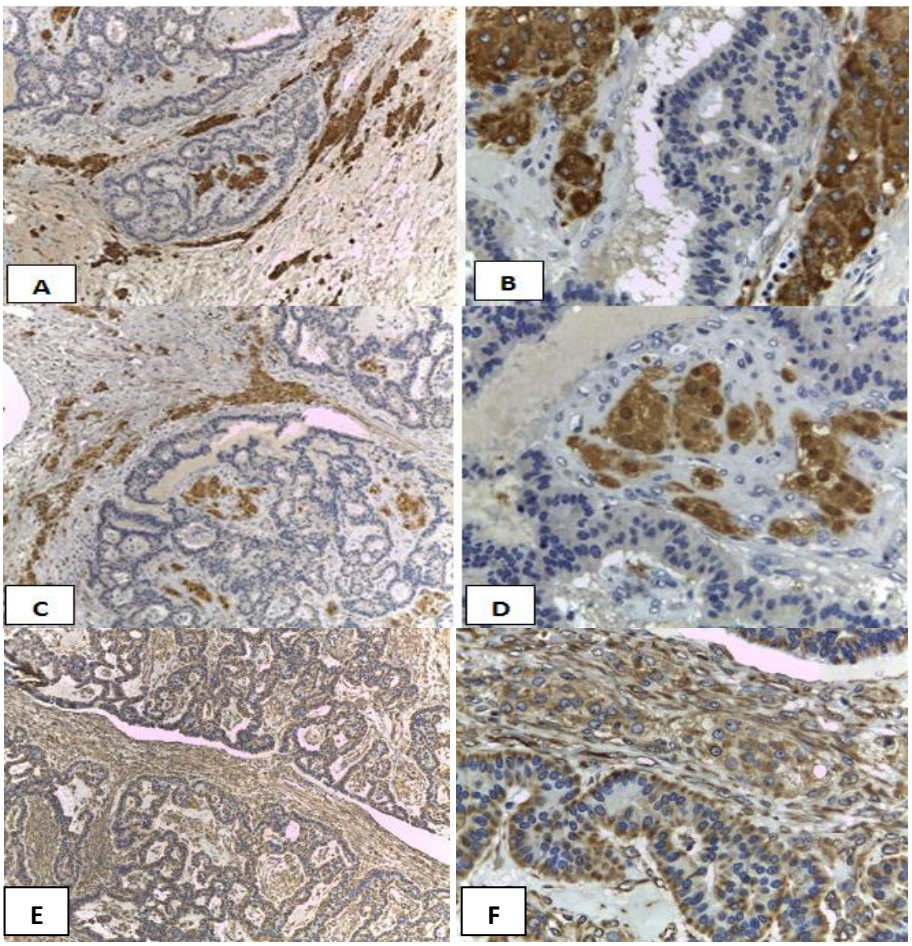
Carcinoid tumor is well-differentiated neuroendocrine neoplasms that are seen in peri- or postmenopausal women, with mean age 53 years. The insular carcinoid is the most common type of primary ovarian carcinoid tumor. It is composed of small acini and solid nest of uniform, round or oval, “salt and pepper” chromatin of nuclei, cytoplasm is abundant. The acini contain eosinophilic secretions that stain positively for mucin.

Mitotic activity is rarely observed. The proportion of stroma is variable.[1,5] Compared with our case, both showed nests of tumor surrounded by fibrous stroma and uniform round to oval nuclei, but the finding of Leydig cells, the absence of asini with eosinophilic secretion, and the fine chromatin of nuclei, was rule out carcinoid tumor histologically. Endometrioid carcinoma can be focally to extensive areas resembling ovarian SLCTs when it contains small, well-differentiated hollow tubules, solid tubules, and the stroma is luteinized. Endometrioid carcinoma can be recognized with its typical glands and squamous differentiation that were not found in our case.

Immunohistochemistry is not a routine procedure for ovarian SLCTs. But it can be utilized to determine the final diagnosis, if there is any doubt on the histologic appearance. The staining that can be used are inhibin, calretinin, vimentin, CD 99, Melan-A, CK7, epithelial membrane antigen (EMA), AE1/AE3, synapthohysin, chromogranin A, and CD 56. Inhibin and calretinin usually positive in Sertoli and Leydig cells tumors, although staining can be patchy and is strongest in Leydig and typically negative for CK7 and epithelial membrane antigen (EMA).[11,12] Sertoli and Leydig cells also positive for vimentin and 50% express CD99. Sertoli cells positive for AE1/AE3. Leydig cells show either minimal staining for CD99, but express Melan-A.[1] In our case, both cells are positive for vimentin and CD99, inhibin and calretinin was negative in Sertoli cells but positive in Leydig cells (Figure 4). Synapthophysin, chromogranin A, and AE1/AE3 was positive in Sertoli cells (Figure 5). CD56 and Melan-A showed positivity in Leydig cells (Figure 6). EMA and CK7 showed negativity in both cells (Figure 7).

The conspicuous tubules, the presence of Leydig cells, and the absence of squamous differentiation in ovarian SLCTs can be useful to differentiate it from endometrioid carcinoma. Whereas, contrast with ovarian endometrioid carcinoma, which positive for CK7 and EMA, but negative for inhibin and calretinin.[11]

The fine chromatin that is lack of granular pattern and the presence of Leydig cells tumor can be used to distinguish ovarian SLCTs with carcinoid tumor. Neuroendocrine markers usually positive in carcinoid tumor. However, previous reports indicate that Sertoli cells tumor frequently exhibit neuroendocrine markers. Leydig cells are probably members of the disperse neuroendocrine system and nomal Leydig cells could be immunoreactive for neuroendocrine markers such as chromogranin A and synaptophysin.[13] Therefore, we used CK7 to distinguish this two entities. CK7 usually positive in carcinoid tumor and negative for ovarian SLCTs.[1] It consistent with this case which was negative for CK7.



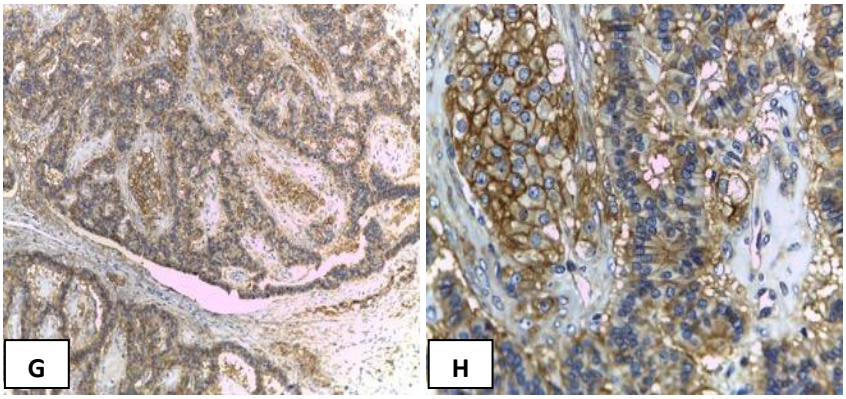


Figure 4. A and B. Inhibin showed strong positivity in Leydig cells and negative in Sertoli cells. C and D. Calretinin showed strong positivity in Leydig cells and negative in Sertoli cells. E and F. Vimentin showed positivity in Sertoli and Leydig cells. G and H. CD99 showed positivity Sertoli and Leydig cells. (A, C, E, G. Magnification power: 100x. B, D, F, H. Magnification power: 400x).

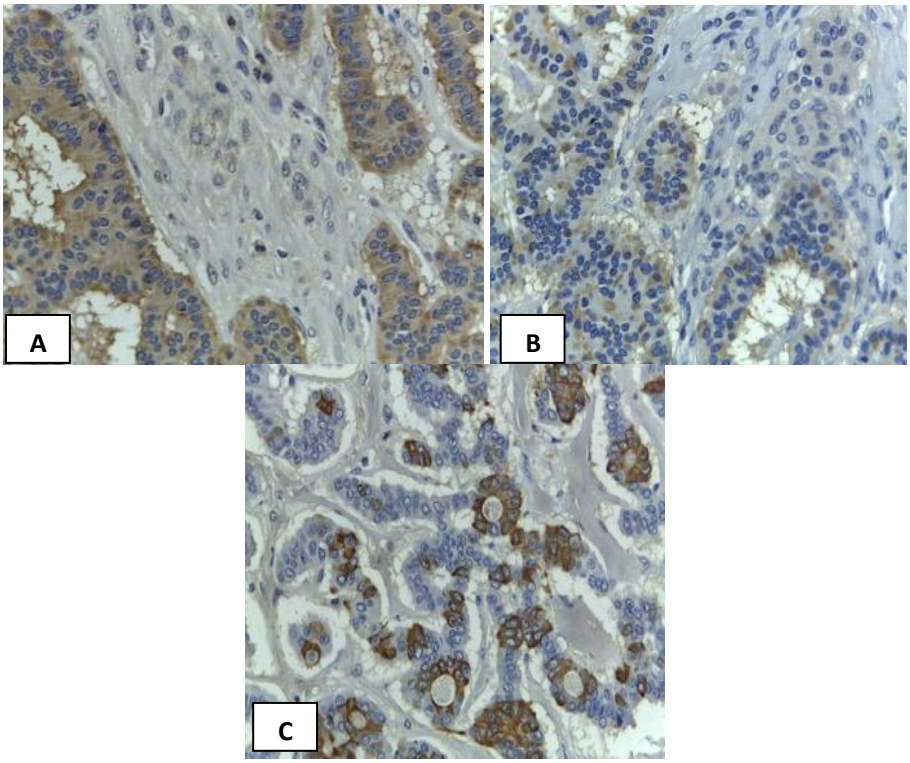


Figure 5. A. Synapthophysin was positive in Sertoli cells (400x). B. Chromogranin A was positive in Sertoli cells (400x). C. AE1/AE3 was positive in Sertoli cells (400x).

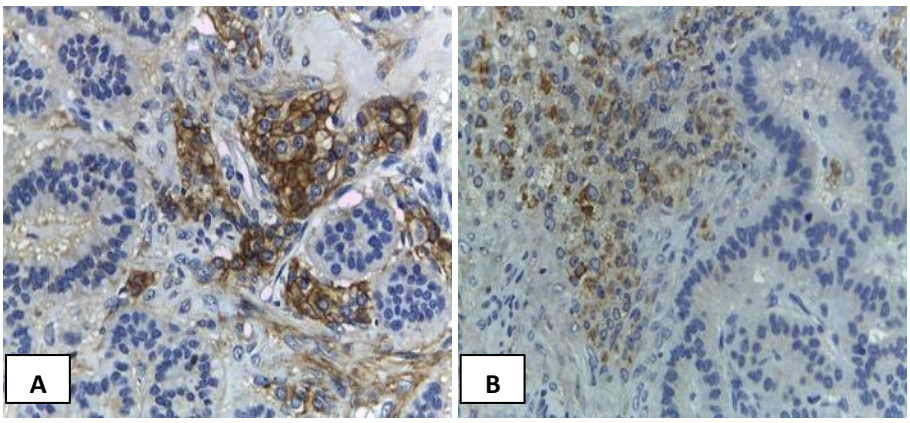


Figure 6. A. CD56 was positive in Leydig cells. B. Melan-A was positive in Leydig cells.

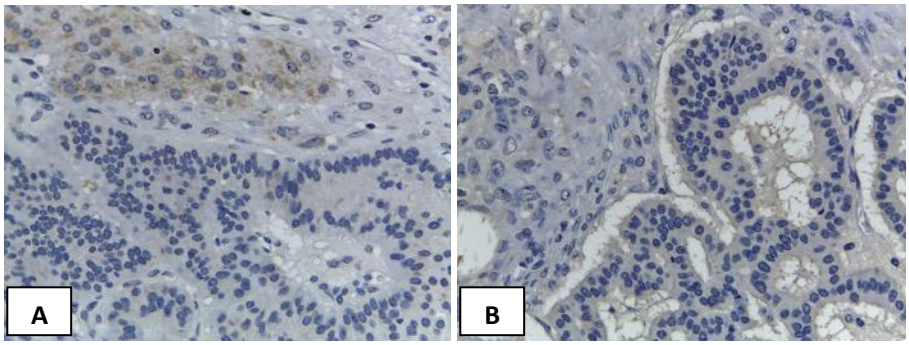


Figure 7. A. CK7 showed negativity in Sertoli and Leydig cells (400x). B. EMA showed negativity in Sertoli and Leydig cells (400x).

Ovarian SLCTs has an overall favorable prognosis. Occurrence of extra ovarian spread of SLCTs are uncommon, accounting for 2-3%. However, prognosis has been associated with the tumor grade and stage at presentation. Well-differentiated SLCTs are associated with zero malignant potential, whereas moderately and poorly differentiated SLCTs are associated with 11% and 59% malignant potential. The 5-year survival rate for well-differentiated SLCTs are 100%, whereas for moderately and poorly differentiated SLCTs are collectively 80%. Based on the tumor staging, the 5-year survival rate for stage I is 95%, whereas for stages III and IV is nearly zero percent.[7]

Well-differentiated to moderately differentiated SLCTs confined to the ovary and without mesenchymal heterologous elements, unilateral salphingo-oophorectomy is the surgical management of choice. In patients with tumor rupture, extra ovarian spread, poorly differentiated forms, or mesenchymal heterologous elements, a total abdominal hysterectomy followed by post-operative chemotherapy, radiation, or a combination of both is the treatment of choice.[11] In our case, it was well-differentiated and confined to the right ovary and the patient proceeded with right salphingo-oophorectomy. In this case, no additional treatment was undertaken for patient after surgery. The patient is in good condition and there is no residual symptoms three months after surgery.

CONCLUSION

Ovarian SLCTs are extremely rare ovarian tumor, accounting for less than 0.5% of all primary ovarian neoplasms. Due to its rarity, low index of suspicion of ovarian SLCTs can be misleading to the other resembling entities and will affect the patient's management. As a pathologist, we must be careful to make the diagnosis, not only in histopathologic examination but also in frozen section examination. We need to correlate the gross and histologically findings with patient's symptoms and history. Immunohistochemistry staining can be utilized to confirm and distinguish ovarian SLCTs with other mimicking entities, but it is not a routine procedure. Prognosis and management for ovarian SLCTs itself, associate with tumor grade and stage at presentation.

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