Review Article

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Sertoli-Leydig Cell Tumor of Ovary, Management and Prognosis: A Review of Literature

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Abstract

Sertoli-Leydig cell tumor of ovary is a rare type of sex-cord stromal tumor. Only few case reports are published in the literature. The majority of the cases occur in young women and are benign and unilateral in location. Nearly, 30-40% of the patients present symptoms and signs of virilization. In most of the cases, histopathologically, the degree of differentiation is intermediate or poor. Majority cases are diagnosed at Stage I and extraovarian spread at the time of diagnosis are very uncommon. The degree of tumor grading/differentiation and staging are important prognostic factors. The rarity of the tumor results in inadequate data regarding management protocol. Surgery is the important initial treatment part. Chemotherapy is indicated in the presence of poor prognostic factors, but, controversy exists. There is a need for more number of studies for a standard treatment protocol including chemotherapy.

Key words: Chemotherapy, Heterologous elements, Ovary, Sertoli-Leydig cell, Surgery, Virilization

INTRODUCTION

Sex-cord stromal tumor consists of granulose, thecal cells, and fibrocytes, derived from stromal component of ovary and testis. It consists of 8% of ovarian cancers and 5% of testicular cancers. The classification is based on the cell/tissue type, i.e., sex-cord, gonadal stroma, and mixed. Granulosa cell tumor, thecoma, fibroma, Sertoli cell tumor, Leydig cell tumor, Sertoli-Leydig cell tumor (SLCT), and gynandroblastoma are the various types of sex-cord stromal tumors. Among these, SLCT consists of 1% of sex-cord tumors. The site of occurrence, i.e., ovary is an extremely rare entity constituting <0.5% of all ovarian neoplasms.[1,2] Although both the Sertoli and Leydig cells are found in the testicle, this tumor can occur in ovary. The majority are presented at young age group (20-40 years age group). SLCTs are usually unilateral at the time of presentation, and bilateral presentation is seen in only 2% of cases.[3] Symptoms and sign of presentation depend on mass occupying lesion or excess hormonal production.[2,4-6] The aggressive nature of the tumor depends on the degree of differentiation on histopathology.[7] Approximately, 90% of the cases are diagnosed at Stage I.[8] A combination of both histopathology and immunohistochemical examination results in more accurate definitive diagnosis of SLCTs.[9]

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DEFINITION

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. The World Health Organization (WHO) classified ovarian sex-cord stromal tumors into four groups such as: Granulose cell tumor, Sertoli-stromal cell tumor, mixed or unclassified type, and steroid cell tumors. SLCT is included under Sertoli-stromal cell tumor. Nowadays, the terminologies such as arrhenoblastoma and androblastoma are replaced by SLCTs. The WHO definition of SLCT is the tumor composed of variable proportions of Sertoli cells, Leydig cells, and in the case of intermediate and poorly

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differentiated neoplasms, primitive gonadal stroma, and sometimes heterologous elements.[10]

CLINICAL FEATURES

Most of the epithelial ovarian SLCTs present at advanced stage whereas sex-cord stromal tumors/SLCTs diagnosed at early stage and with low-malignant behavior. It can occur at any age group between 2 and 75 years. However, majority present at young age with the average age of presentation is 25 years. Symptoms and signs are related to either mass effect or due to excess hormone production. Nearly, 50% of the patients are presented with lower abdominal or pelvic mass with pain due to pressure effect of the mass.[2,5,6] SLCT masses are usually mobile, unilateral, and detected by self or clinical examination.[4] Pain is usually chronic and dull in nature due to capsular expansion and pressure effect on surrounding visceral structures.[4] 15% of the cases are presented with acute abdominal pain due to ovarian torsion, capsular rupture, and bleeding.

More than 50% of the patients are with excess androgen production and presents with virilism, hirsutism, acne, alopecia, breast atrophy, hoarseness of voice, clitoromegaly, and amenorrhea.[4] Patients rarely present with precocious puberty, abnormal uterine or vaginal bleeding, generalized edema, breast hypertrophy, weight gain, endometrial hyperplasia due to estrogen excess production.

Feminine features improved after surgery, whereas, consequence of masculinization disappears slowly.

PATHOLOGY

Morphologically, SLCT resembles the cells of testis under various stage of development, but, ultrastructurally, resembles ovarian granulose cell tumor. Various degrees of differentiation or grading found in SLCTs such as well, intermediate, and poorly differentiated.[11] Both intermediate and poorly differentiated forms are mostly seen. Heterologous elements are found in 20% of cases and include both endodermal and mesenchymal elements.[12] The endodermal elements show both gastric and/or intestinal type of mucin-secreting epithelium, and the mesenchymal elements show immature cartilage, bone, smooth muscle, and skeletal muscle. Endodermal elements are usually associated with intermediate differentiation whereas mesenchymal elements are commonly associated with poorly differentiation and sarcomatoid background.[13] Approximately, 50% of cases come to clinical attention because of progressive defeminisation.[2]

SCLTs are typically well encapsulated solid, firm, lobulated yellow or tan tumor with smooth external surface. Cut section shows greasy/fleshy consistency, straw-colored fluid, and cystic spaces, but necrosis and hemorrhagic areas are less common and mostly seen in poorly differentiated histopathology. Microscopically, there is varying degree of differentiation of tubules lined by Sertoli cells and intervening nests of Leydig cells.[14] Well and intermediate differentiated types have Leydig cells in clusters in interstitial stroma, and Sertoli cells forming tubular structures and mitotic figures are very rare. Poorly differentiated forms lack a classical arrangement between tubules, Sertoli cells, and Leydig cells and the tumor cells have immature differentiation, high nuclear atypia, increased nuclear to cytoplasmic ratio, coarse chromatin, and abundant mitotic figures. In addition, reticular form found in 10% of cases, and microscopically, it is typical, a network of slit-like spaces and cysts containing papillae. Immunohistochemical examination shows positivity for inhibin and calretinin and negative for epithelial membrane antigen.[15] Low-molecular weight cytokeratin (AE1/AE3), CAM5, WT-1, and CD56 markers may be positive.[16,17]

SERUM MARKERS

About 80% of patients with ovarian SLCTs present with increased level of serum testosterone and androstenedione.[18,19] There is increased production of androgen (40% of cases), whereas, excess estrogen production is rare. Inhibins are normally secreted in granulose and Sertoli cells of the ovary, and increased serum levels may be seen in SLCTs.[20-23] Increased serum testosterone level more than 200 ng/dl are commonly found in androgen secreting neoplasm from ovaries or elsewhere.[24] Total inhibin is a sensitive immunohistochemical marker for ovarian sex-cord-stromal tumors.[25,26] Paracrine action of inhibin at theca cells may enhance androgen production.[27]

RADIOLOGICAL INVESTIGATION

During the period of clinical diagnosis of SLCTs, extraovarian spread is rarely seen accounting for 2-3%.[2,5,6]

Ultrasound

Transvaginal ultrasound is the best initial imaging method for the assessment of SLCTs and typically exhibit solid appearance.[4,28] It has high sensitivity, cost-effectiveness, and yields better morphological features of adnexal mass in comparison to abdominal ultrasound.[29] SLCTs may be purely cystic, purely solid, or mixed.[30] It typically shows a solid mass with intramural cystic component. Ultrasound does not rule out the diagnosis of ovarian SLCT in situation of excess androgen, and estrogen.[4] Highly vascular nature of the tumor on color Doppler study suggests malignant nature of the lesion.

Computed tomography, magnetic resonance imaging (MRI), and positron-emission tomography scans are used for better characterization of the primary tumor, detection of locoregional spread, distant metastasis and possible second primary.

Pelvic MRI

The signal intensity of T2-weighed MRI depends on the fibrous component of SLCTs. SLCTs usually has low signal intensity on T2-weighed MRI with few areas of high signal intensity.

Prognosis

The tumor stage (extent) and degree of differentiation (grading) are the most important prognostic factors.[2] The previous study showed well-differentiated (Grade-1) SLCTs were benign, whereas, 11% of tumors with intermediate differentiation (Grade-2) and 59% of poorly differentiated tumors and 19% of cases with heterologous elements were malignant.[2] Local recurrence rarely occurs in well-differentiated early stage SLCTs. Metastasis can occur to omentum, abdominal lymph nodes, or liver, and less likely to lungs, bone, brain, and other parts. The 5-year overall survival is different according to degree of differentiation: 100% in well-differentiated SLCTs and 80% in Grade-2 and Grade-3 patients.[31] The overall 5-year overall survival for Stage I is 95%, whereas, it is zero percent for Stage III and IV patients.[2,5]

Treatment

Till date, there are only a few cases reported in the literature regarding ovarian SLCTs and the insufficient data resulted in lack of standard treatment protocol guidelines.[32] Surgery is the initial treatment of choice in ovarian SLCTs.[9] Adjuvant chemotherapy is still controversy due to inadequate data.

Tumor staging is necessary to know the prognosis of the SLCTs and to guide for further management. Most of the cases are unilateral and diagnosed at Stage I without any extraovarian spread. Therefore, conservative surgery is an appropriate treatment in young patient. Unilateral salpingo-oophorectomy is the preferred surgical method in young woman with stage disease.[33] Few literature reports successful management of ovarian SLCTs by laparoscopic surgery.[34] Adjuvant chemotherapy should be considered in Stage I patient with the presence of risk factors: Intermediate and poorly differentiated tumors, heterologous elements, increased mitotic rate, rupture or spillage of the tumor, and advanced stage/metastatic tumor of any histologic type.[2,5,6,33] Tumor with Stage II or higher, should be treated with total abdominal hysterectomy (TAH) and bilateral salping-oohprectomy (BSO) plus staging surgery (omentectomy, appendectomy, and pelvic lymphadenectomy) followed by adjuvant chemotherapy. Fertility-sparing surgery can be done in patients with well-differentiated histology, but in Grade-2 and Grade-3 patients, unilateral salpingo-oophorectomy with standard staging surgery should be performed.[33,35] Treatment with pelvic lymphadenectomy is still questionable. However, pelvic lymph node metastasis in SLCT is extremely rare and pelvic lymphadenectomy may be excluded from staging surgery.[36] Elder age group or patient with progressive disease should be treated with complete surgery, i.e., TAH plus BSO with omentectomy, appendectomy, and pelvic lymphadenectomy.[17] Combination chemotherapy with BEP regimen (bleomycin, etoposide, and cisplatin) is the most frequently used first-line chemotherapy regimen.[37] Other chemotherapeutic regimens used in SLCTs are CAP (cisplatin, adriamycin, and cyclophosphamide) and PVB (cisplatin, vinblastin, and bleomycin).[38] However, due to rarity of the tumor and less number of reported data, the role of adjuvant chemotherapy is still questionable.

CONCLUSION

SLCT is an uncommon variety of ovarian sex-cord tumor, and most of the cases found unilaterally, present at Stage I, extraovarian spread and lymph node involvement are uncommon. Young female with symptoms of virilization and presence of ovarian mass clinicoradiologically should be considered as SLCT unless otherwise proved. Management is solely based on histopathology and staging/extent of the tumor. Patient desiring fertility is an important issue in the management of SLCTs. Stage I patients should be treated with conservative surgery. Adjuvant chemotherapy should be given in poorly differentiated histology. Adjuvant chemotherapy in intermediate variety is individualized. Stage II or more than it should be treated with TAH plus BSO with standard surgical staging. However, due to rarity of the case, limited research data, there is no standard treatment guidelines regarding surgery and the role of chemotherapy and requires further evaluation.

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