ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-6 | JUNE-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

SERTOLI LEYDIG CELL TUMOUR OF OVARY - A REVIEW

Gynaecology

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ABSTRACT

Sertoli Leydig Cell Tumours are a group of relatively rare ovarian tumours of the sex cord stromal group occurring mostly in young girls and are usually benign and unilateral. The malignant counterpart are usually bilateral, very aggressive and have poor prognosis. Approximately half of these young women present with symptoms of virilization. Histopathologically most of these tumours show intermediate to poor differentiation. The degree if differentiation, tumour grading and surgical staging at diagnosis are the most important prognostic factors. Surgery is the most important treatment modality chemotherapy with BEP regime is indicated when associated with poor prognostic factors, but controversy exists regarding the same. There exists a great need for more number of clinical studies and evidence- based data for formulating a standard treatment protocol including chemotherapy.

KEYWORDS:

Chemotherapy, sex cord stromal tumours, ovarian tumour, sertoli leydig cell tumour,virilization.

INTRODUCTION :-

Sex cord stromal Tumours (SCST) consist of granulosa, theca cells and fibrocytes, derived from the stromal component of the ovary and testes. They consist of approximately 8-10% of ovarian and 5-6% of testicular cancers. (1)

SCST are classified according to the cell or tissue type into the following types :

- **Sex -cord**
- **Gonadal stromal &**
- **Mixed**

The various types of SCST are-

- **Granulosa cell tumours (GCT)**
- **Sertoli- Leydig cell tumour (SLCT)**
- **Thecoma**
- **Fibroma**
- **Sertoli cell tumour**
- **Leydig cell tumour**
- **Gynandroblastoma**

SLCT consist of approximately y of sex-cord tumours. They consist of < 0.5% of all ovarian neoplasms. (2,3). Majority present in the young age group ie. 20-35 years. SLCT are usually unilateral at the time of presentation, with only 2% showing bilaterality. (4). The clinical features depend on excessive hormone production and mass effects.(3,4,5,6,7) the degree of differentiation on histopathology determines the degree of aggressiveness of these tumours. (8). Almost 90% are diagnosed at stage I and carry better prognosis (9). Histopathology when combined with immuno-histochemistry result in more accurate definitive diagnosis of Sertoli-Leydig cell Tumours. (10).

Definition :- Ovarian sex-cord stromal tumours are a heterogonous group of neoplasm's arising from the stem around the oocytes including the hormone producing cells from the ovarian stroma. WHO classifies ovarian sex-cord stromal tumours into 4 histological groups:-

- **Granulosa cell Tumours**
- **Sertoli- stromal cell tumour**
- **Mixed or unclassified type &**
- **Steroid cell tumours**

SLCT is included under the Sertoli- Stromal cell tumour group. Earlier terminologies eg. arrhenoblastoma & androblastoma are replaced by Sertoli- Leydig cell tumous. The WHO definition of SLCT is the tumour is composed of Sertoli cells, Leydig cells in variable proportions & in case of intermediate and poorly differentiated tumours, primitive gonadal stroma & sometimes heterologous elements too are present. (11)

CLINICAL FEATURES:-

Majority of the sex-cord stromal tumours (SLCT) present at young age group (20-40years) with the average age at presentation being 25 years. The symptoms & signs are because of either excessive hormone production or mass effect. Approximately half of the patients present with lower abdominal pain or mass or pelvic heaviness & pain due to the pressure effect of the tumour Diagnosis Mass. (1,3,6,7). SLCT masses usually are mobile, unilateral and may be detected by the patient herself or on clinical examination. (1,5). The associated pain is usually chronic and dull- aching in nature due to capsular expansion and pressure effect on the surrounding visceral structures. (5). Around 15-20% patients present with acute abdomen due to ovarian torsion, rupture of the capsule and internal hemorrhage. (1). More than half of the patients have excessive androgen production and present with features of virilism, hirsutism , acne, temporal balding, alopecia breast atrophy, hoarseness of voice, clitoromegaly and amenorrhea.(1,5). Some of these young girls may present with precocious puberty, abnormal uterine bleeding, generalized edema, breast hypertrophy, weight gain, endometrial hyperplasia and irregular vaginal bleeding due to excessive estrogen production. (1,5,6). It has been observed that the feminine features improve after primary surgery, whereas, the masculine features disappear rather gradually. (1)

PATHOLOGY :-

Sertoli Leydig Cell Tumours morphologically, though resemble the testicular cells under various stages of maturation and development, but histopathologically they resemble the ovarian granulosa cell tumours. SLCT show various degrees of differentiation or grading and are classified according as-

- Well differentiated
- Intermediately differentiated &
- Poorly differentiated (12)

The intermediate and poorly differentiated types are the most commonly encountered types. Approximately 20-25 % tumours show heterologous elements including both endodermal and mesenchymal elements. (11,12). The endodermal elements consist of both gastric and/ or intestinal type of mucin secreting epithelial cells & the mesenchymal elements consist of immature cartilagenous, bone, smooth, muscular and skeletal muscular components. Endodermal elements are usually associated with intermediate differentiation and mesenchymal elements are usually associated with poor differentiation and show sarcomatoid background. (13,14)

SCLTs are usually well- encapsulated, solid firm, lobulated ,light yellow or tan- coloured tumours with smooth external surfaces with

cut-section showing greasy or flashy looking tissue with straw-coloured fluid and cystic soaves with areas of hemorrhage and necrosis sometimes (Mostly encountered in the poorly differentiated variety) .Microscopic examination reveals varying degrees of differentiation of tubules lined by sertoli cells with intervening nests of leydig cells.(13,14,15). The well and intermediately differentiated variety show leydig cells in clusters in the interstitial stroma with the Sertoli cells forming tubular structures interspersed with few mitotic figures occasionally. On the other hand, the poorly differentiated variety lacks a classical arrangement between tubules, sertoli & leydig cells and the tumour cells show immature differentiation,

High nuclear atypia, increase nuclear- cytoplasmic ratio, coarses chromatin with abundance of milolie figures all around. In addition to the above, around 10% cases have a reticular form, which microscopically looks typically like a network of slit- like spaces and cysts containing papillae. (I) immune-histochemical studies show positivity for inhibin & calretinin & negativity for epithelial membrane antigen. (15,16). Low molecular weight cytokeratin (AE1/ AE 3), CAM 5, WT-1 and CD 56 markers may be positive in tumours. (17,18)

SERUM MARKERS:

Almost 75-80% of ovarian SLCT, present with increased serum levels of Testosterone & Androstenedione (19,20) In about 40-50% cases there is excessive androgen production while excessive estrogen production maybe present in about 10-12% cases. (1,12). Increased levels of Inhibin may be seen in SLCTs as it is secreted normally by the sertoli and granulosa cells of the ovary. (21,22,23,24). Total Inhibin is used as a sensitive immune-histo chemical marker for ovarian SCST. (25,26,27) The paracrine action of Inhibin at the theca cells may enhance the androgen production in these tumours. (27,28)

RADIOLOGICAL EVALUATION OF SLCT:-

Ultrasonography:- Transvaginal USG is thought to be the best initial imaging modality for the assessment of SLCT and they typically exhibit solid appearance (5,29). SLCTs may be purely cystic, purely solid or mixed. (31) It typically looks like a solid mass with intramural cystic component. Colour Doppler showing highly vascular nature of the tumour may suggest malignant nature of the tumour(1). CT, MRI and PET scans can be used for better characterization of the primary tumour, detection of local or regional spread, distant metastases and possible second primary may be delineated too

- Pelvic MRI:- The signal intensity of T_2-weighed MRI depends usually on the fibrous component of the SLCTs. Which usually has low signal intensity on T_2-weight MRI with few area of high signal intensity.

PROGNOSIS:- the stage of the tumour and the degree of differentiation (tumour grade) are the two most important prognostic factors (3). It is usually seen that well differentiated (Grade-II) SLCTs were benign and 10-12% of tumour with intermediate differentiation (Grade-II) and 55-60% of the poorly differentiated tumour & approximately 20% tumour with heterologous elements are malignant. (2,3)Local recurrence is rarely seen in well- differentiated early stage SLCTs. Distant metastases can occur to the omentum, abdominal lymph nodes or liver and like commonly to the lungs, bone brain and other parts. The 5 years survival rate is different according to the degree of differentiation –(32).eg

100% in well- differentiated (grade-1)
80% in intermediate (grade-2)
60% in poorly differentiated (grade-3)

The overall 5-years survival rate in stage-I is 95% whereas the same in stage-III and IV is almost zero % (2,3,4,5)

TREATMENT :-

Primary cytoreductive surgery is the initial treatment of choice in ovarian SLCTs. (1,10). Adjuvant chemotherapy is still controversial due to lade of adequate data on clinical trials and studies. (1)

Surging staging is must to assess the prognosis of the SLCTs & for further management since most of the cases are unilateral and diagnosed at stage-I without extra-ovarian spread, therefore, conservative cytoreductive surgery is an appropriate treatment in the young patients.(1) unilateral salpingo- ophyorectomy is the preferred surgical procedure in young patients with stage-I disease (30) there are few literature reports supporting successful management of ovarian SLCTs by laparoscopic surgery (14,31).

Adjuvant chemotherapy should be considered in stage I patients with factors being present-

- Intermediately and poorly differentiated tumours
- Heterologous elements
- Increased mitotic rate
- Capsule rupture or spillage of the tumour &
- Advanced stage / metastatic tumour of any histologic type or variety .(2,3,6,7)

Tumours with stage II or higher, should be subjected to primary cytoreductive surgery consisting of →Total abdominal hysterectomy & bilateral salpingo-oophorectomy (TAH+BSO) plus omentectomy, appendectomy and pelvic lymphadenectomy) followed by adjuvant chemotherapy . Fertility- sparing surgery may be opted for patients with well differentiated histological type, here unilateral saplingo-oophorectomy with standard staging surgery should be done.(1,2,19). Treatment with pelvic lymphadenectomy is still controversial and a hot topic for debate all over the world. However, since pelvic lymph node metastasis in SLCT is extremely rare therefore, pelvic lymphadenectomy may be excluded from staging surgery. (1,6). Patients with older age or with progressive disease are best treated with complete cytoreductive surgery ie. TAH+BSO+ omentectomy+ appendectomy+ pelvic lymphadinectomy(17,18). Combination adjuvant chemotherapy with BEP regimen (Bhomyein, etoposide & cisplatin) is the most commonly used first-line option. (17,18,19). Other regimens eg. CAP (cisplatin, adriamycin+ cyclophosphamide) & PVB (cisplatin), vinblastin+bleomycin) (18,19,20). But the role of adjuvant chemotherapy is still a matter of great controversy because of the rareity of the tumour & like. Data on clinical studies and trials.

Conclusion:-

SLCT, though an uncommon variety of ovarian sex-cord tumour & most of the cases are unilateral, presenting at stage-I, with extra-ovarian spread and lymph node involvement being rare. Young girls with symptoms of virilization and ovarian tumour should be considered as SLCT unless proved otherwise. Treatment should be based on histopathology and surgical staging of the tumour. Since it occurs mostly in young women, preservation of fertility is a big issue in the management of these tumours. Stage –I patients should be treated with fertility- conserving surgery. Adjuvant chemotherapy should be reserved for only poorly differentiated tumours. Adjuvant chemotherapy in patients with intermediate variety of SLCT should be individualized. Stage-II and more disease should be managed with TAH+BSO+ standard surgical staging with cytoreductive surgery. Since there is lack of enough clinical data and reported study results and limited research available worldwide, there is no accepted standard treatment guidelines regarding the optimum surgery and the role of adjuvant chemotherapy & this calls for further research and evaluation.

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