Ovarian Sex Cord-Stromal Tumours: “ Newly Recognised Entities”
S.M.Tamaskar
Department of Pathology, People’s College of Medical Sciences & Research Centre, People’s Campus Bhanpur, Bhopal-462037, (M.P.)

Abstract:
A sex cord-stromal tumour is one that is composed of granulosa cells, theca cells, Sertoli cells, Leydig cells and fibroblasts of stromal origin, singly or in various combinations. A pseudopapillary pattern has been described recently in granulosa cell tumours. This was seen in both juvenile and adult types. Pseudopapillae develop as a secondary or degenerative phenomenon lacking true stromal cores. The distinction of a granulosa cell tumour from a surface epithelial carcinoma can be aided by the use of Epithelial Membrane Antigen (EMA) which is positive in carcinomas and Inhibin and Calretinin is positive in granulosa cell tumours. A negative inhibin on immunohistochemistry does not exclude a diagnosis of granulosa cell tumour. The study by Irving et al (2006) emphasizes the distinction of a group of mitotically active, cytologically bland, cellular fibromatous tumours from fibrosarcomas. These tumours show a mean of 6.7 Mitotic figure (MF)/10 HPF with a range of 4 to 19 MF/10 HPF. Luteinized thecomas occur in younger women than typical thecomas, the mean age being 46 years. A distinct variant of luteinized thecoma is one that is associated with sclerosing peritonitis. Microcystic stromal tumour is a newly recognized entity. Twelve types of this non-functioning, neoplasm have been described, all occurring in adults. Sertoli cell tumours are rare in their pure form. They often present with oestrogenic manifestations in young women. Occasional cases are seen in the Peutz-Jeghers syndrome. 

Key Words: Sex cord-stromal tumours, Breast carcinoma antigen, Granulosa cell tumours.

Introduction:
Ovarian sex cord-stromal tumours constitute a heterogeneous group of uncommon tumours that develop from the cells surrounding the oocytes, including the cells that produce ovarian hormones i.e. the non-germ cell and non-epithelial components of the gonads (Young, 2005). They may be benign or malignant (Scullly & Sobin, 1999; Chen et al, 2003).

Ovarian sex cord-stromal tumours (SCSTs) are relatively infrequent neoplasms that account for approximately 8% of all primary ovarian tumours (Young, 2005). They are a heterogeneous group of neoplasms composed of cells derived from gonadal sex cords (granulosa and Sertoli cells), specialized gonadal stroma (theca and Leydig cells), and fibroblasts (Chen et al, 2003). The morphology of these tumours varies, depending on the cell type or mixture of cell types present, and can range from entirely glandular as in well-differentiated Sertoli cell tumors to entirely spindled as in cellular fibromas. This varied appearance and the fact that some of these tumours are relatively uncommon, can lead to difficulties in diagnosis. In the great majority of cases the patterns are distinctive in routinely stained sections and as in ovarian tumour pathology in general, the importance of thorough sampling cannot be over-emphasized.

Immunohistochemical studies may be useful in those situations when routine microscopic findings fail to indicate a clear diagnosis. Most ovarian sex cord stromal tumours produce steroid hormones. The diagnosis should, therefore, be suspected in patients, who present with signs of estrogen excess (precocious puberty in a child, abnormal uterine bleeding, endometrial hyperplasia/carcinoma), or androgen excess (virilization), especially if an adnexal mass is present (Outwater et al, 1998). These tumours secrete proteins, such as inhibin which can serve as diagnostic markers. Consideration of these characteristics, help in clinically distinguishing sex cord-stromal tumours from germ cell ovarian tumours, the more common epithelial ovarian cancer and the rare small cell carcinoma of the ovary.

Corresponding Author: Dr. S.M.Tamaskar, Professor of Pathology, People’s College of Medical Sciences & Research Centre, People’s Campus Bhanpur, Bhopal-462037, (M.P.)
Phone no: 0755 2730819, 09424439897
E-mail: shailendra_tamaskar2001@yahoo.com
Whenever possible, surgery should be performed to obtain tissue for definitive diagnosis, staging (in the case of malignancy) and treatment. The staging system for ovarian sex cord-stromal tumours is the same as that used for other primary ovarian carcinomas. In contrast to epithelial ovarian cancer, most patients with sex cord-stromal tumours can be diagnosed in early stages; the tumours are of low malignant potential, and there is no known association with inherited breast carcinoma antigen (BRCA).

A sex cord-stromal tumour is one that is composed of granulosa cells, theca cells, Sertoli cells, Leydig cells and fibroblasts of stromal origin, singly or in various combinations. As a result a wide range of patterns are encountered and include a long list of differential diagnoses.

**Granulosa Cell Tumours:**

Granulosa Cell tumours are divided into adult predominant type and rarer juvenile type, based on their morphological characteristics. The designation “juvenile” was coined by Dr Robert Scully (Young & Scully, 1985; Zaloudek & Norris, 1982) because of the recognised features that differed from the adult type like greater irregularity of follicular size and shape, more abundant cytoplasm, more immature nuclei lacking groves and greater mitotic activity. A small “hybrid” group exists where both morphological patterns are seen in the same tumour. There is insufficient information on such uncommon tumours to comment on prognosis.

**Granulosa cell tumour of the ovary with a pseudopapillary pattern:** A pseudopapillary pattern has been described recently in granulosa cell tumours (Aboud, 1997). This was seen in both juvenile and adult types. Pseudopapillae develop as a secondary or degenerative phenomenon lacking true stromal cores. The tumours tended to be cystic, unicocular or multilocular, with multiple papillary-like formations projecting into cystic spaces. In all tumours thorough sampling revealed areas with architectural and cytological features of typical granulosa cell tumour.

**Histopathological examination:**

**Gross:** The tumour is usually unilateral. The cyst wall is lined by multiple papillary projections, ranging in size from 0.1 to 1.5 cm and are typically soft, edematous, fleshy, or rubbery.

**Microscopy:** Microscopically pseudopapillae (lacking fibrovascular cores) are formed by intracystic cellular projections with surrounding necrotic debris and/or undulating folds of neoplastic cells in the absence of appreciable necrosis (Fig. II). Granulosa cell tumours of adult and juvenile type may have a pseudopapillary pattern that can be confused with other ovarian tumours with a papillary architecture (Fig. III). Identification of areas that are more characteristic of granulosa cell tumour resolves most cases, although immunohistochemistry can be used in more problematic tumours.

**Immunohistochemistry:** Useful markers for diagnosis (Mc Cluggage & Young, 2005)
The classification of fibromas has recently been addressed. Many pathologists had been making a diagnosis of fibrosarcoma based exclusively on the mitotic count (> 4 MF/10 HPF). The study by Irving et al. (2006) emphasizes the distinction of a group of mitotically active, cytologically bland, cellular fibromatous tumours from fibrosarcomas (Fig. IV & V). These tumours showed a mean of 6.7 MF/10HPF and a range of 4 to 19 MF/10HPF. This group of patients have a favourable outcome in contrast to fibrosarcoma which show moderate to severe atypia and elevated mitotic rates. Those cellular or mitotically active cellular neoplasms associated with rupture or adherence occasionally recurred, and, therefore, long term follow up of these patients would be appropriate. The term cellular fibromas is reserved for those cytologically bland, cellular neoplasms that have a mitotic count of up to 3 MF/10HPF.

**The tumour has to be differentiated from the following:**
- Endometrioid adenocarcinoma: positive for EMA and CK7.
- Undifferentiated carcinoma with pseudopapillae.
- Retiform variant of Sertoli-Leydig cell tumour: the papillae have stromal cores, often with marked hyalinisation.
- Melanoma may form pseudopapillae.
- Ovarian ependymoma: there are long fibrillary cytoplasmic processes, perivascular pseudo-rosettes and true rosettes; the tumour is positive for glial fibrillary acidic protein.

The distinction of a granulosa cell tumour from a surface epithelial carcinoma can be aided by the use of EMA which is positive in carcinomas and inhibin and calretinin are positive in granulosa cell tumours. A negative inhibin on immunohistochemistry does not exclude a diagnosis of granulosa cell tumour.

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**INHIBIN** : POSITIVE IN 3 OUT OF 3 CASES.
**CALRETININ** : POSITIVE IN 2 OUT OF 2 CASES.
**CLUSTER DIFFERENTIATION 99** : POSITIVE IN 1 OUT OF 1 CASE.
**CAM 5.2** : POSITIVE (Focal positivity) IN 1 OUT OF 2 CASES.

**Fig. III:** Photomicrograph showing Pseudopapillary granulosa cell tumour composed of small papillae with hyalinized cores projecting into larger cyst (A); Clusters of Leydig-like cells (B). The tumour cells were strongly positive for calretinin (C); Melan-A immunoreactivity in Leydig-like cells (D) (H & E, 100 X).

**Fig. IV:** Photomicrograph showing “Mitotically active”, cytologically bland, cellular fibromatous tumours (H & 100 X).

**Fig. V:** Photomicrograph of cellular fibroma of ovary showing hypercellularity and minimal mitotic activity (H & E, 100 X).
**Thecomas:**

Luteinized thecomas occur in younger women than typical thecomas, the mean age being 46 years. They are histologically composed of clusters of large eosinophilic lipid laden or vacuolated lutein cells scattered in the stroma. Luteinization is particularly common in tumours from pregnant women. These tumours may be functional; 10% androgenic, 50% oestrogenic.

There is a distinct variant of luteinized thecoma associated with sclerosing peritonitis (Clement et al., 1994). They are frequently bilateral, typically exhibit a brisk mitotic rate and histologically show a cellular neoplasm that range from fusiform to spindled cells associated with weakly luteinized cells often showing a microcystic appearance (Fig. VI). It is uncertain if these lesions are neoplastic or non-neoplastic. Staats et al. (2008) recommend that thecomatosis be used in parenthesis after the preferred terminology of luteinized thecoma to designate this entity until further information becomes available.

**Sertoli Cell Tumours:**

Sertoli cell tumours are rare in their pure form. They often present with oestrogenic manifestations in young women. Occasional cases are seen in the Peutz-Jeghers syndrome. They usually have an excellent prognosis. Recent McCluggage & Young (2007) studied 54 cases of Sertoli cell tumours in which 6 had foamy cytoplasm and one had clear “lipid-rich” variant. In addition to the tubular morphology, other patterns encountered by them were: cords or trabeculae, diffuse pseudopapillary, retiform, alveolar and spindled (Fig. VII & VIII).

**Stromal Tumours:**

Microcystic stromal tumour is a newly recognised entity Irving & Young (2008). Twelve examples of this non-functioning, neoplasm have been described, all occurring in adults. On microscopy, the tumour is composed of lobulated cellular masses separated by hyaline bands and fibrous plaques. There is a microcystic pattern characterized by small cysts that anastomose with each other focally in areas or sometimes more strikingly. Mitotic figures are rare. These neoplasms are inhibin negative and CD 10 positive.

Fig. VI: Photomicrograph showing lutenized thecoma of ovary (H & E, 100 X).

Fig. VII: Photomicrograph showing ovarian Sertoli cell tumour with lipid rich cells (H & E, 200 X).

Fig. VIII: Photomicrograph showing retiform sertoli-Leydig cell tumour of intermediate (H & E, 100 X).
Moderate to severe cytological atypia, brisk mitotic activity of >5MF/10HPF and sometimes necrosis are features associated with malignancy. It should be differentiated from endometrioid adenocarcinoma and carcinoid tumour. Epithelial membrane antigen (EMA), inhibin and chromogranin are useful immunohistochemical markers in their distinction.

Sertoli-Leydig cell tumours are virilizing in about half of the cases (Young & Scully, 1985). Occasionally tumours may be oestrogenic. Poorly differentiated tumours are composed of immature, cellular mesenchymal tissue with a high mitotic count resembling a sarcoma. Tubular, sex cord-like and other more distinctive patterns are required to establish the diagnosis. Like thecomas and granulosa cell tumours. Sertoli-Leydig cell tumours can also contain cells with bizarre nuclei. Sixteen percent have a retiform component while heterologous elements are encountered in approximately 20% cases. The commonest element is mucinous epithelium of gastro-intestinal type. Mesenchymal heterologous elements are encountered in approximately 5% and they include cartilage and areas of embryonal rhabdomyosarcoma arising on a sarcomatous background. Caution should be exercised before a diagnosis of a pure ovarian sarcoma is made in a young woman and the diagnosis of a poorly differentiated Sertoli-Leydig cell tumour should be considered.

**Gynandroblastoma:**

Gynandroblastoma is a term that does not convey any concrete diagnostic information to the clinician. It is, therefore, preferable to make a primary diagnosis of a mixed sex cord-stromal tumour and then give the components present with a rough indication of the percentage of each component identified.

**Bibliography:**