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# HISTOPATHOLOGY OF OVARIAN SEX-CORD STROMAL TUMOURS: A TERTIARY CARE STUDY IN INDIAN POPULATION

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**ABSTRACT:**

Objective: To study the frequency, histopathology and clinical features of sex cord-stromal tumours of the ovary. Material and Methods: The present study was carried out in the department of pathology in a tertiary care centre for a period of five years, from July 2008 to July 2013. Results: The frequency of ovarian tumours was 2.77% among the gynecological specimens received during the same period. Sex cord-stromal tumours constituted 9.65% of the ovarian tumours. Maximum cases were seen above 60 years of age. Pain and mass in abdomen was the most common presenting symptom. Granulosa cell tumour (63.64%) was the most common sex cord-stromal tumour in our study. Two cases of fibrothecoma (18.18%), one each of fibroma (9.09%) and sclerosing stromal tumour (9.09%) were reported. Conclusion: Histopathology is a time-tested foundation for accurate diagnosis of sex cord-stromal tumours of the ovary. It aids in prompt institution of treatment.

**Keywords:** histopathology, sex cord-stromal tumours, ovary, granulosa cell tumour

## I) INTRODUCTION:

Ovarian neoplasms have become increasingly important not only because of the large variety of neoplastic entities but more because they have gradually increased the mortality rate in female genital cancers.[1] Sex cord-stromal tumours (SST) account for 8% of ovarian neoplasms.[2] Jha et al (2008)[3] recorded an incidence of 3.1% of SST in their study, while these tumours comprised only 3.15% of all ovarian tumours studied by Ashraf et al (2012).[4]

SST 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.[5] Fundamental to the correct diagnosis is a broad appreciation of the spectrum of patterns that may be encountered and the extent to which they overlap with those of other neoplasms. 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 to detect clues to the diagnosis cannot be overemphasized.[6]

This heterogeneity in histological patterns provided the impetus for our study of SST of the ovary at our tertiary care institute over a five year period. We observed their clinical attributes and noted the gross and microscopic features in accordance with the WHO classification of ovarian tumours.[2] Although imaging studies, immunohistochemistry and the emerging

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molecular studies have widened the scope of ancillary testing; their lack of universal availability, cost, skills involved, reinstate the fundamental place of histopathology in the diagnosis of SST of the ovary.

## II) MATERIAL AND METHODS:

The present study was carried out in the department of pathology in a tertiary care centre. The study was prospective (2 years) as well as retrospective (3 years) and was done during the period from July 2008 to July 2013, i.e. 5 years. Ethical clearance was obtained prior to commencing the study.

All the biopsies and resected specimens received in the histopathology section were immediately fixed in 10% formalin for 24 hours. Gross features of the specimens were noted. Multiple sections of the specimens were taken and processed in an automatic tissue processor. After processing, the paraffin blocks were made. Five microns thick sections were cut on a rotary microtome and then stained with Haematoxylin & Eosin. Special stains were done wherever necessary.

Detailed study of the sections was performed under the light microscope, immunohistochemistry was done wherever necessary and then the final diagnosis was given. Typing of the tumours was carried out following WHO classification.[2]

## III) RESULTS:

During this period, 4120 gynecologic specimens were received in the histopathology section, out of which 114 were ovarian tumours (2.77%). SST constituted 11 cases (9.65%) of the total ovarian tumours.

**A) Granulosa cell tumour:** Granulosa cell tumour was the most common SST comprising 63.64% of SST. Their age ranged from 30 to 67 years. The average age of presentation was 44 years **(Table 1)**.

**Table 1: Case wise overview of clinical manifestations of ovarian sex cord-stromal tumours**

| Case No. | Age (years) | Parity | Menstrual phase | Clinical presentation | | | | Histopathological diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | | | Pain and/or mass in the abdomen | Vaginal bleeding and/or discharge | Constitutional symptoms | Asymptomatic | |
| 1 | 30 | 3 | Menopausal | + | + | - | - | Granulosa cell tumour |
| 2 | 52 | 3 | Menstrual | + | - | - | - | Granulosa cell tumour |
| 3 | 16 | 0 | Menstrual | + | - | + | - | Fibroma |
| 4 | 45 | 2 | Menopausal | + | - | - | - | Granulosa cell tumour |
| 5 | 65 | 4 | Menopausal | - | + | + | - | Fibrothecoma |
| 6 | 67 | 3 | Menopausal | - | - | - | + | Granulosa cell tumour |
| 7 | 45 | 4 | Menopausal | + | - | + | - | Granulosa cell tumour |
| 8 | 36 | 4 | Menstrual | - | - | - | + | Granulosa cell tumour |
| 9 | 66 | 4 | Menopausal | - | + | - | - | Fibrothecoma |
| 10 | 30 | 2 | Menstrual | + | - | + | - | Granulosa cell tumour |
| 11 | 18 | 0 | Menstrual | + | - | + | - | Sclerosing stromal tumour |

**Table 2: Gross morphological features of ovarian sex cord- stromal tumours**

| Case No. | Laterality | Consistency | Size (cm) | Histopathological diagnosis |
|---|---|---|---|---|
| 1 | Left | Cystic | 9X8X3.5 | Granulosa cell tumour |
| 2 | Right | Cystic | 17X12X7 | Granulosa cell tumour |
| 3 | Right | Solid | 6X4X2 | Fibroma |
| 4 | Left | Cystic | 22X22X12 | Granulosa cell tumour |
| 5 | Left | Mixed | 7X5X3 | Fibrothecoma |
| 6 | Right | Solid | 10X9X2 | Granulosa cell tumour |
| 7 | Left | Solid | 16X15X4 | Granulosa cell tumour |
| 8 | Right | Solid | 6X4X3 | Granulosa cell tumour |
| 9 | Right | Solid | 7X5X2.5 | Fibrothecoma |
| 10 | Left | Solid | 7X7X5 | Granulosa cell tumour |
| 11 | Left | Solid | 18X17X10 | Sclerosing stromal tumour |

Majority of the patients presented with pain and mass in the abdomen. Irregular menses and ascites were observed in one case each. One case of Granulosa cell tumour with metastasis to the omentum was observed, which presented with the complaints of mass in abdomen and increased frequency of micturition. Grossly, majority of the tumours were lobulated and encapsulated. The smallest tumour measured 6x4x3 cm and the largest tumour measured 22x22x12 cm. The cut surfaces were yellowish. One tumour was hemorrhagic with blood clots, necrotic and few viable yellowish areas. One tumour with metastasis was large, cystic with attached omentum **(Table 2)**. The cut surface was variegated in appearance with multiple cysts filled with serous and hemorrhagic fluid. Rest of the cut surface was gray-white, soft and fleshy with areas of hemorrhage. Microscopically, six of the tumours were composed of cells arranged in microfollicular, macrofollicular, cylindrical, solid and trabecular patterns. The tumour cells were small, round to oval with nuclear grooves and scant cytoplasm. The microfollicles showed central eosinophilic material (Call-Exner bodies) **(Fig 1)**. The tumour with omental metastasis was composed of cells arranged in macrofollicular, cylindrical, solid and trabecular patterns. The tumour cells were small, round to oval with nuclear grooves and scant cytoplasm. Call-Exner bodies could not be seen. Sections from the omentum showed metastasis by tumour cells of similar morphology. Immunohistochemistry was done to confirm the diagnosis. The tumour was positive for inhibin, vimentin, focally positive for calretinin **(Fig 2, 3),** but negative for Epithelial Membrane Antigen. Ki-67 immunostaining was of intermediate index. The IHC profile was consistent with H&E impression of Granulosa cell tumour.

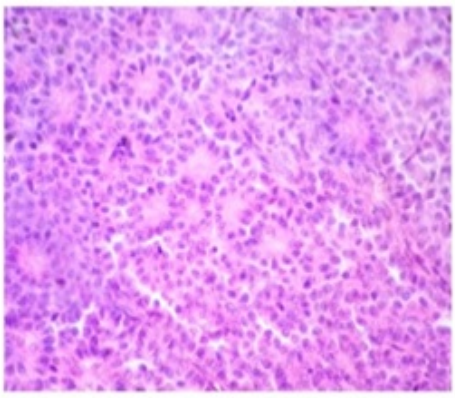

Figure 1 : Photomicrograph of Granulosa cell tumour showing cells arranged in microfollular pattern (Call-Exner bodies) and nuclear grooving imparting the coffee-bean appearance. (400X; H&E)

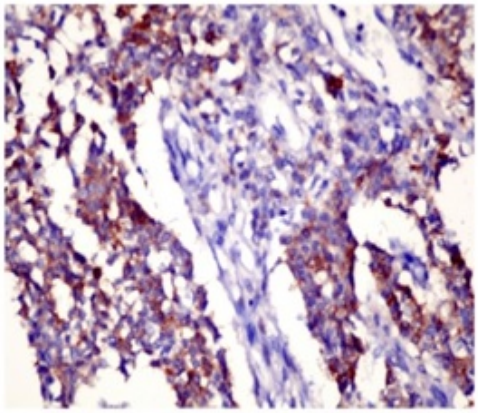

Figure 2 : Photomicrograph of Granulosa cell tumour showing Inhibin positivity. (400X)

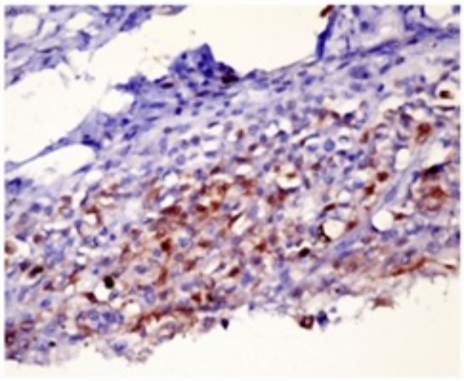

Figure 3 : Photomicrograph of Granulosa cell tumour showing focal Calretinin positivity. (400X)

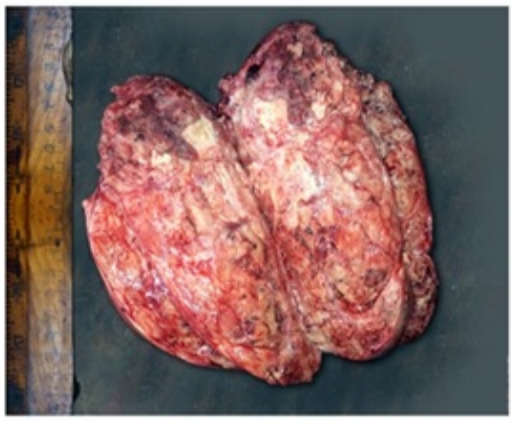

Figure 4 : Sclerosing stromal tumour: Solid, gray white cut surface.

**B) Fibrothecoma:** We recorded two cases in our study accounting for 18.18% of SST. The patients aged 65 and 66 years respectively. The former presented with the complaint of per vaginal spotting. The latter complained of postmenopausal bleeding and was later diagnosed with endometrial carcinoma, a well-documented complication of the unopposed estrogenic effect of thecoma. Both the cases were unilateral.

Grossly, one of the tumours had a bosselated external surface. Cut surface was firm, gray white, nodular with yellowish areas. The other tumour was gray white with multiple cysts on cut surface.

Microscopically, both the masses showed a tumour composed of cells arranged in fascicles. Individual cells were spindle shaped. At places scattered and clusters of theca cells having uniform, bland, oval to spindle shaped nuclei and abundant, pale, vacuolated cytoplasm were seen. Oedema, collagen bands, hyaline plaques were also seen. Reticulin stain showed intercellular fibres surrounding individual cells.

**C) Fibroma:** We came across a single case of right sided fibroma with torsion accounting for 9.09% of SST. The patient was sixteen years of age and presented with pain in abdomen.

Grossly, the tumour was hemorrhagic, solid with a firm and hemorrhagic cut surface. Microscopically it showed spindle shaped cells with elongated bland looking nuclei and indistinct cytoplasm arranged in small bundles and scattered. Extensive areas of hemorrhage were also seen.

**D) Sclerosing Stromal tumour:** A single case of left sided sclerosing stromal tumour was noted by us accounting for 9.09% of SST. The patient in our study was 18 years of age and came with complaint of pain and mass in abdomen.

Grossly, the tumour was large, encapsulated and measured 18x17x10 cm. The cut surface was solid, gray white and oedematous **(Fig 4)**.

Microscopically, the encapsulated tumour was composed of clusters of cells with a dual population: spindle shaped cells and lipid containing round or oval cells. Intervening stroma showed fibrosis, sclerosis and thick walled blood vessels.

## IV) DISCUSSION:

SST of the ovary occur over a wide age range, with individual tumours occurring in different age groups.[7] Maximum cases of SST in our study were seen above 60 years of age. Jha et al[3] found maximum number of cases of SST in patients above sixty years of age. Danish[8] et al found maximum number of these tumours in the age group of 51-60 years.

**A) Granulosa cell tumour:** It shows differentiation toward follicular granulosa cells. Two distinct types exist, known respectively as adult and juvenile.[9]

Granulosa cell tumour was the most common SST comprising 63.64% of SST. Ashraf et al[4] (75%) and Makwana et al[10] (84.61%) also reported granulosa cell tumour as the most common SST.

Granulosa cell tumours occur over a wide age range, with nearly 60% of cases occurring after menopause and 5% before puberty.[7] The average age of presentation of granulosa cell tumour in our study was 43 years. Pectasides et al[11] in their study on 34 patients of adult granulosa cell tumours, in 2008, recorded a median age of 51 years. In a study by Andrade et al[12] on 20 Adult granulosa cell tumours, the median age was 53 years. Kuladeepa et al[13] recorded a mean age of 47 years among the granulosa cell tumours studied by them. Zaman et al[14] recorded an age range of 25 to 65 years with a mean age of presentation of 39.14 years.

In the present study, there was one case of granulosa cell tumour with metastases to the omentum. Immunohistochemically, the tumour was positive for inhibin, vimentin, focally positive for calretinin but negative for Epithelial Membrane Antigen. The IHC profile was consistent with H&E impression of granulosa cell tumour of ovary. In the study by Haroon et al[15], detailed immunohistochemical analysis of 163 granulosa cell tumours showed all the tumours to be positive for Inhibin and 90% for Calretinin.

**B) Fibrothecoma:** Many tumours contain a mixture of fibroblasts and theca cells and are termed fibromathecomas.[16] Some authors use the term fibrothecoma for tumours in the intermediate zone between fibroma and thecoma.[6]

Two cases of fibrothecoma were reported in our study (18.18% of sex cord-stromal tumours). Makwana et al[10] reported a frequency of 15.39% in their study.

The patients were 65 and 66 years of age. The latter complained of postmenopausal bleeding and was later diagnosed with endometrial carcinoma; Kuladeepa et al[13] reported a single case of fibrothecoma in a 55 year old woman. In a study by Haroon et al[15] on 47 fibrothecomas, age range was 2 to 80 years with median age of 48 years. One case in their study was associated with endometrial hyperplasia.

**C) Fibroma:** This tumour is composed of spindle cells forming variable amounts of collagen.[17] They are most common in middle age (mean 48 years). Less than 10% occur before the age of thirty.[2]

We reported a single case of fibroma in a 16 year old girl. Zaman et al[14] noted a single case of fibroma in a 41 year old woman. In a study by Haroon et al[15] on 98 fibromas, age range was 12 to 79 years with median age of 42.2 years.

**D) Sclerosing stromal tumour:** It is a benign ovarian neoplasm that shares many features

with fibroma and thecoma. However it occurs in a younger age group.[9]

One case of Sclerosing stromal tumour was noted by us in an 18 year old patient. Grossly the tumour was large, encapsulated. In a study by Kaygusuz et al[18] on sclerosing stromal tumours in young women, the ages of the patients varied between 18 and 25 years (mean age-20 years). Haroon et al[15] in their study on 26 sclerosing stromal tumours of the ovary, reported a median age of 22.5 years. In all the tumours in their study except one, the capsule was intact.

**V) CONCLUSION:**

One of the key take-a-ways from this study is the rarity of sex cord-stromal tumours observed in the Indian population. Keeping in mind the lack of trustworthy screening procedures, this study stresses on the need to be well versed with the gamut of differential diagnosis available so that one is conscious while reporting an ovarian tumour. The importance of taking into account the clinicopathological findings as well as resorting to immunohistochemical studies where deemed appropriate, in aiding the diagnosis and subsequent treatment is reaffirmed.

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