

Sex Cord - Stromal Tumours : Pathological Considerations

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INTRODUCTION

Sex cord - stromal tumours account for about 8% of ovarian neoplasms. This category includes tumours composed of granulosa cells, theca cells, Sertoli cells, Leydig cells and fibroblasts of stromal origin, singly or in various combinations.¹

The WHO histological classification of tumours of the ovary groups sex cord-stromal tumours as follows:

Sex cord - stromal tumours

Granulosa-stromal cell tumours

- Granulosa cell tumour group
 - Adult granulosa cell tumour
 - Juvenile granulosa cell tumour
- Thecoma-fibroma group
 - Thecoma, not otherwise specified
 - Typical
 - Luteinized
 - Fibroma
 - Cellular fibroma
 - Fibrosarcoma
 - Stromal tumour with minor sex cord elements
 - Sclerosing stromal tumour
 - Signet-ring stromal tumour
 - Unclassified (fibrothecoma)

Sertoli-stromal cell tumours

- Sertoli-Leydig cell tumour group (androblastomas)
 - Well-differentiated
 - Of intermediate differentiation
 - Variant with heterologous elements (specify type)
 - Poorly differentiated (sarcomatoid)
 - Variant with heterologous elements (specify type)
 - Retiform
 - Variant with heterologous elements (specify type)
- Sertoli cell tumour
- Stromal-Leydig cell tumour

Sex-cord stromal tumours of mixed or unclassified cell types

- Sex cord tumour with annular tubules
- Gynandroblastoma (specify components)
- Sex cord stromal tumour, unclassified

Steroid cell tumours

Stromal luteoma

- Leydig cell tumour group
 - Hilus cell tumour
 - Leydig cell tumour, non-hilar type
 - Leydig cell tumour, not otherwise specified
- Steroid cell tumour, not otherwise specified
 - Well differentiated
 - Malignant

Granulosa cell tumours

Granulosa cell tumours, first described by Rokitansky in 1855 constitute 2-3% of all ovarian malignancies². They are characteristically of low-grade malignancy with a favourable prognosis. However, recurrences after more than 10 years are not uncommon. A special feature of Adult Granulosa Cell Tumours (AGCT) is the appearance of metastases long after treatment of the primary tumour³. The overall survival with granulosa cell tumours is better than that with epithelial ovarian cancer (EOC) as the hormonal symptoms make an early diagnosis possible. Stage for stage the survival is equal².

Clinical presentation

Most granulosa cell tumours occur in adult women (peak incidence 45 -55 years) and somewhat more than half occur after the menopause⁴. Patients present with complaints of an endocrinological disturbance (50%), non-specific abdominal symptoms (20%) or both (30%). Ascites accompanies nearly 10% of tumours. Acute abdominal pain due to hemorrhage into the tumour or rupture of a cystic neoplasm may also be seen, particularly in young women during pregnancy.

Menorrhagia and post-menopausal vaginal bleeding are the common endocrinological manifestations seen⁵. Elevated serum levels of estradiol and estrone are often found. Occasional tumours present with signs of virilization, especially those that are unilocular cysts.

Pre-pubertal girls and adolescents, having a distinctive tumour type designated as "juvenile granulosa cell tumour", present with isosexual precocious pseudopuberty. The majority of granulosa cell tumours removed or diagnosed during pregnancy belong to this type.

Serum inhibin, a polypeptide secreted by granulosa cells, is a useful tumour marker⁶.

Gross features

The tumours vary in size from small subclinical lesions to huge masses filling the abdomen, with a mean diameter of about 13 cm⁷. The external surface may be smooth or bosselated. The cut surface is partly solid and partly cystic. Solid areas are yellowish in colour while cystic spaces contain proteinaceous fluid or altered blood. Thin-walled parilocular cystic granulosa cell tumours may be mistaken grossly for benign serous tumours. Hemorrhage and necrosis are common. Most tumours are unilateral (98%) and are confined to the ovary (90%).

Microscopic features

The hallmark of granulosa cell tumours is the conspicuous presence of cells (at least 10% in the material examined) that resemble those of the follicular granulosa or their luteinized variants. Other cells of ovarian stromal origin and similar to those in the theca interna or externa of the developing follicle commonly accompany them and may be a dominant component without negating the diagnosis. Tumours with a small granulosa cell component (less than 10%) are designated as 'fibromas with minor sex cord elements'⁵.

Granulosa cells characteristically have scant cytoplasm and a round to oval nucleus with a longitudinal groove. When luteinized, the cells develop abundant eosinophilic or vacuolated cytoplasm; the nuclei become round and lack nuclear grooves. A reticulin stain is helpful since granulosa cells typically grow in aggre-

gates bound by reticulin fibers whereas thecomas have fibrils surrounding individual cells.

Histologically granulosa cell tumours can be divided into well-differentiated, moderately differentiated or poorly differentiated forms.

Well-differentiated granulosa cell tumours exhibit one or more of 'microfollicular', 'macrofollicular', 'trabecular' or 'insular' patterns.

The microfollicular variant shows multiple small, rounded spaces containing eosinophilic PAS-positive material and often nuclear debris, surrounded by radially oriented granulosa cells. These spaces, known as Call-Exner bodies are found in only 30 to 50% of tumours.

The macrofollicular variant shows cysts of differing sizes lined by multilayered, well-differentiated granulosa cells often surrounded by a layer of theca-like cells. In the uncommon totally cystic granulosa cell tumours, the lining cells of the cysts may so closely resemble those of non-neoplastic ovarian follicle cysts that differentiation on purely histological criteria is difficult.

The trabecular variant shows cells arranged in anastomosing ribbons that may be one to several cells wide.

Insular variants consist of islands of polyhedral granulosa cells with peripherally palisaded nuclei, separated by a fibroma-like or thecoma-like stroma. Call-Exner bodies are common in this variant.

Additional features thought to be degenerative in nature include occasional cells with large bizarre nuclei, multinucleated giant cells and central sclerosis within islands of granulosa cells. These do not alter the classification, typing or grading of the tumour in which they are found.

Moderately differentiated granulosa cell tumours are characterized by fine, narrow undulating cords of granulosa cells with little intervening stroma, producing a 'watered-silk' or gyriform appearance. An insular pattern may also be seen, but with scant stroma.

Poorly differentiated diffuse or sarcomatoid forms show sheets of uniform cells resembling a low-grade round cell or spindle cell sarcoma. Mitoses are generally fewer than 5 per 10 high-

power fields. Reticulin stain outlines groups rather than individual cells.

Juvenile granulosa cell tumours are characterized by nodular or diffuse cellular growth punctuated by macrofollicles of varying size and shape. A fibrothecomatous stroma with variable luteinization is common. The typically rounded neoplastic granulosa cells have abundant eosinophilic and/or vacuolated cytoplasm. Almost all nuclei lack grooves. Mitoses are more prominent than in AGCT, about 7 per 10 high-power fields.

Isolated cases of granulosa cell tumours with combined benign mucinous tumour or with focal mesenchymal differentiation have been reported.

Immunohistochemistry

Granulosa cell tumours are immunoreactive for CD99 (100%), alpha-inhibin (100%), vimentin (95%), smooth muscle actin (90%), S100 protein (50%) and calretinin. The tumour cells are negative for cytokeratin7, epithelial membrane antigen and carcinoembryonic antigen^{1,5}.

Differential diagnosis

It is important to distinguish granulosa cell tumours from other morphologically similar ovarian tumours, which have a significantly poorer prognosis, the most important of these being hypercalcemic small cell carcinomas and poorly differentiated surface epithelial carcinomas.

The nuclear appearance is the most important feature that helps in distinguishing AGCT from small cell carcinoma (SCC). Nuclei in granulosa cell tumours are typically bland and often grooved, with few mitoses. Nuclei of SCC show hyperchromasia, variation in size and shape, are rarely grooved and have numerous mitoses which are frequently atypical. SCCs generally stain for epithelial membrane antigen but not for inhibin while granulosa cell tumours show the reverse pattern of staining.

Undifferentiated surface epithelial tumours show diffuse cytoplasmic positivity for cytokeratin whereas granulosa cell tumours are typically negative or show focal punctate cytoplasmic staining.

Granulosa cell tumours with an insular pattern may be confused with carcinoid tumours. The cells in carcinoid tumours, however, have well defined cell margins, eosinophilic cytoplasm and more regular rounded nuclei than those of AGCT. In addition, immunohistochemistry for chromogranin is positive in carcinoid tumours. Distinction from androblastomas (Sertoli-Leydig cell tumours) may be difficult. Call-Exner bodies are not found in androblastomas. Hollow tubules and Leydig cells (containing Reinke crystals) are not seen in granulosa cell tumours. This distinction may be impossible in poorly differentiated cases and such tumours should be designated as sex cord-stromal tumours of indeterminate differentiation.

Prognosis

All granulosa cell tumours are considered as low-grade malignancies. The spectrum of differentiation correlates poorly with the clinical outcome. For example, juvenile granulosa cell tumours, although appearing poorly differentiated and pleomorphic, typically have a high cure rate except in advanced stage cases.

Adverse features include ²

- extra ovarian spread at laparotomy (stages 2 - 4)
- spontaneous rupture of tumour in stage 1a cases
- tumour diameter > 5 cm
- mitotic figures > 5 / 10 high power fields

Dissemination is mostly by coelomic spread usually within the pelvis or lower abdomen. Rarely distant metastases have been reported in the lungs³, brain, bone and liver. Delayed local recurrence (average of 8 to 9 years) is far more common than metastases.

Thecoma-fibroma group

Tumours forming a continuous spectrum from those composed entirely of fibroblasts and producing collagen to those containing mainly theca cells constitute this group. With the exception of fibrosarcomas, these are benign tumours with an excellent prognosis.

Fibromas are the most common subtype among the sex cord-stromal tumours and account for almost two thirds of neoplasms in this group⁵.

Clinical presentation

Fibromas typically occur in patients over forty years. Forty percent of those over 10 cm in diameter are associated with ascites and 1% are associated with Meigs' syndrome (ascites and pleural effusion).

Gross features

The majority of fibromas are unilateral (92%), and are uniformly solid, firm white tumours. Focal or diffuse calcification may be seen in less than 10%.

Microscopic features

The classic appearance is that of spindle cells producing collagen, arranged in a storiform pattern. Mitoses are absent or rare. Cellular fibromas have relatively scanty collagen and show closely packed spindle cells with nuclei which are more rounded than in a typical fibroma; an average of 3 or fewer mitoses per 10 high power fields may be seen.

Fibrosarcomas typically show 4 or more mitotic figures per 10 high power fields as well as moderate to marked nuclear atypia.

Genetic susceptibility

Ovarian fibromas are common in females with the nevoid basal cell carcinoma syndrome. Tumours in such patients are bilateral (75%), almost always calcified and tend to occur in a younger age group.

Immunohistochemistry

Fibromas express vimentin and may be immunoreactive for alpha inhibin.

Thecomas

Thecomas are stromal tumours composed of lipid containing cells resembling theca interna cells, with a variable admixture of fibroblasts.

Clinical presentation

They are about one third as common as granulosa cell tumours¹. The majority occur in post-menopausal women (mean age 59 years). Typical thecomas may be discovered incidentally or produce signs and symptoms of a pelvic mass. About 60% of patients have symptoms related to estrogen production including abnormal uterine bleeding. About 20% of post-menopausal women with thecoma have endometrial adenocarcinoma or rarely a malignant mullerian mixed tumour or endometrial stromal sarcoma.

Gross features

Thecomas usually measure 5 to 10 cm and have a cut surface which is solid and yellow, occasionally with hemorrhage or necrosis. They are almost invariably unilateral.

Microscopic features

Thecomas show sheets of cells with uniform, bland oval to spindle shaped nuclei with abundant pale vacuolated, lipid-rich cytoplasm. Individual cells are invested by reticulin. Mitoses are absent or rare.

Immunohistochemistry

Thecomas are immunoreactive for vimentin and alpha inhibin.

Stromal tumours with minor sex cord elements are fibromas or thecomas which contain scattered sex cord elements (resembling either granulosa cells or Sertoli cells) occupying less than 10% of the area of the tumour. These are designated as. These tumours behave more like fibroma-thecoma than like sex cord-stromal tumours.

Sclerosing stromal tumours are benign tumours which arise from perifollicular myoid stromal cells – a population of muscle-specific actin-positive cells in the theca externa.

Clinical presentation

These tumours are unique amongst sex cord-stromal tumours in that they occur mainly in younger women (80 % occur in patients under 30 years of age) and show a lack of hormonally related abnormalities.

Gross features

They are unilateral, solid, distinctly lobulated, firm tumours, sharply circumscribed from the ovarian parenchyma, averaging 3 to 5 cm in diameter. The cut surface is pale, fleshy and variegated with focal yellowish areas.

Microscopic features

They have a pseudolobular pattern of cellular zones separated by broad swathes of acellular sclerotic or edematous connective tissue. The cells are typically rounded to polyhedral with vacuolated or eosinophilic cytoplasm or are spindle-shaped fibroblasts. They have small, dark, non-grooved nuclei. Mitoses are rare. The

edema seen in these tumours is zonal in contrast to that in massive ovarian edema or an edematous fibroma.

Immunohistochemistry

These tumours are immunoreactive for desmin, smooth muscle actin and inhibin⁹.

Differential diagnosis of tumours in the thecoma-fibroma group⁹

The most common problem is distinguishing fibroma from thecoma. Because a spectrum exists between the two, any distinction is necessarily arbitrary. Tumours are in the fibroma category unless a distinct theca cell component is identified. The term fibrothecoma has been used for tumours in the intermediate zone between fibroma and thecoma.

Fibromatosis of the ovary may closely resemble fibroma. Fibromatosis, however, envelops ovarian follicles whereas fibroma typically displaces them. Massive edema of the ovary is similarly distinguished from an edematous fibroma.

A storiform pattern in a fibromatous tumour of the ovary does not warrant a diagnosis of fibrous histiocytoma.

Luteinized thecoma, an uncommon member of this group, is characterized by lutein cells present singly or in clusters. Luteinized thecomas must be distinguished from stromal hyperthecosis, which is almost always bilateral, in contrast to luteinized thecoma.

The stromal cells in hyperthecosis lack the mitotic activity which may be a striking feature of luteinized thecomas. Also, stromal hyperthecosis does not cause obliteration of the ovarian architecture.

Sertoli-stromal cell tumours

Sertoli-Leydig cell tumour group (androblastomas)

Sertoli-Leydig cell tumours (SLCTs) account for less than 0.2% of ovarian neoplasms.

Clinical presentation

The average age of patients is 25 years⁹. Approximately 50% of patients show initial signs of hirsutism or virilization. Patients without endocrine manifestations have symptoms due to a pelvic or an abdominal mass. Elevated se-

rum alpha fetoprotein (AFP) levels may be seen.

Gross features

SLCTs have an average diameter of 10 cm. They are firm, solid, yellow or tan tumours with a smooth external surface. Cysts may be present but are less common than in GCTs. Tumours with a prominent mucinous component may resemble mucinous epithelial tumours. Hemorrhage and necrosis are uncommon except in poorly differentiated subtypes. Ninety-eight percent are unilateral.

Microscopic features⁹

SLCTs have been divided into five subtypes according to the WHO classification.

Well-differentiated SLCTs have hollow or solid tubules similar to those in well-differentiated Sertoli cell tumours, but the stroma contains numerous cells resembling Leydig cells. Crystals of Reinke have been identified within these cells in only a minority of cases.

SLCTs of intermediate differentiation have a lobulated appearance with cellular areas separated by hypocellular fibrous or edematous stroma. Within the cellular areas cords, thick columns, nests or uncommonly solid or hollow tubules are seen. These are composed of cells with small round nuclei and scanty cytoplasm, suggestive of immature Sertoli cells. The Sertoli cells are interspersed with varying numbers of Leydig cells and indifferent stromal cells. Some tumours have foci of small spindle shaped cells with appreciable mitotic activity.

Poorly differentiated SLCTs are characterized by spindle shaped cells that are highly active mitotically, suggesting fibrosarcoma. Tubules and sex cord like aggregates as well as Leydig cells, which may be minor in extent, are necessary to establish the diagnosis.

Retiform SLCTs constitute about 10% of all SLCTs. Patients are on average ten years younger than those with other types of SLCTs. The retiform pattern (so-called because of resemblance to the rete testis) is seen usually as a variable component in an otherwise moderately or poorly differentiated SLCT. This pattern is typified by a network of slit-like spaces and cysts, often containing papillae, imparting a resemblance to a malignant epithelial neoplasm.

SLCTs with heterologous elements. Heterologous elements are found in about 20% of all SLCTs, and have been encountered only in tumours of intermediate or poor differentiation or in retiform tumours. The most common heterologous component is mucinous epithelium of gastrointestinal type. Mesenchymal heterologous elements in the form of immature skeletal muscle, cartilage or both may be seen.

Immunohistochemistry

SLCTs are usually positive for inhibin. The epithelial-like areas show positivity for both broad spectrum and low molecular weight cytokeratins (AE1/AE3) and CAM5.2. Such areas are consistently negative for epithelial membrane antigen.

Differential diagnosis

Differentiation between granulosa and Sertoli Leydig cell tumours may be impossible in the poorly differentiated forms. A history of virilization should not justify a label of SLCT for a tumour that would be better categorized as sex cord-stromal tumour of indeterminate type.

Carcinomas, primary or metastatic may be mistaken for a moderately differentiated SLCT. The age ranges and clinical settings should facilitate the differentiation. Squamous metaplasia or luminal mucin may be seen in endometrioid carcinomas. Positivity for cytokeratin and epithelial membrane antigen favour a diagnosis of carcinoma.

Prognosis

The incidence of clinical malignancy in these tumours is 10-30%. Patients with early stage disease and well-differentiated tumours rarely experience recurrences. Eleven percent of tumours with intermediate differentiation and 60% of poorly differentiated tumours are likely to progress clinically. Tumours which show extraovarian spread or metastases at the time of laparotomy usually are fatal. Recurrence or metastasis in early stage disease usually becomes apparent within twelve months, often before six months and are often preceded by an

exacerbation of the patient's virilization. Metastases have been seen in the omentum, abdominal lymph nodes or liver and less often in lungs, bone, intestine, kidney, mediastinum or brain. Sertoli cell tumours are uncommon and present with estrogenic effects in two thirds of cases with tumours occurring at an average age of 27 years. Almost all tumours reported have been unilateral.

Leydig (hilus) cell tumours are also most uncommon. Most are benign and are masculinizing but about 10 to 20% are associated with estrogenic effects, most readily recognized in the endometrium as hyperplasia or carcinoma.

Other sex cord-stromal tumours

Gynandroblastomas, sex cord-stromal tumours with annular tubules, unclassified sex cord-stromal tumours and steroid cell tumours are infrequently encountered ovarian neoplasms each with its own unique histological appearance. On account of their rarity, these tumours should figure infrequently in the differential diagnosis of sex cord-stromal tumours.

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