Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Solid Tumour Section

Review

Ovary: Sex cord-stromal tumors

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Published in Atlas Database: November 2003

Online updated version : http://AtlasGeneticsOncology.org/Tumors/OvarSexCordStromID5223.html
DOI: 10.4267/2042/38058

Identity

Note: Sex cord-stromal tumours develop from the gonadal stroma, and are a type of ovarian tumour. They account for 5-10 % of all ovarian neoplasms.

Classification

Ovarian sex cord-stromal tumours are subdivided into the following clinicopathological entities:
- Granulosa cell tumour,
- Theca cell tumour,
- Thecoma,
- Fibroma,
- Sertoli-Leydig cell tumour,
- Sex cord tumour with annular tubules,
- Lipid cell tumour,
- Gynandroblastoma.

Clinics and pathology

Etiology

There appear to be several established clinical syndromes associated with several subtypes of sex cord-stromal tumours.
30% of patients with sex cord tumours with annular tubules have **Peutz-Jeghers syndrome** (PJS), an autosomal dominant disorder characterised by multiple gastrointestinal hamartomatous polyps, increased risk of various neoplasms, and melanocytic macules of the lips, buccal mucosa, and digits. Peutz-Jegher females are also susceptible to granulosa cell tumours. When associated with this syndrome, the tumour is usually small, benign and bilateral. Meanwhile in the absence of this syndrome, it is usually large and unilateral, and malignant in 20% of cases.

There have also been clinical reports of several other types of sex cord-stromal tumours being less frequently associated with PJS including:
- oxyphilic Sertoli cell tumour;
- Sertoli cell tumour (lipid-rich);
- malignant Sertoli-Leydig cell tumour and
- ovarian fibroma.

10% of patients with lipid cell tumours have Cushing Syndrome.
Fibromas are associated with Meigs Syndrome. The phenotype of Meigs syndrome is a benign ovarian tumour (fibroma), with ascites and pleural effusion that resolve within several weeks to months following surgical resection without any recurrence. Thus it imitates a malignant tumour, but has a very good prognosis. Indeed, following resection, life expectancy is similar to the general population.
Ovarian fibromas occur in 75% of female patients with **Gorlin syndrome** (also known as Nevoid basal cell carcinoma syndrome). Gorlin syndrome is an autosomal dominant disorder that predisposes to basal cell carcinomas of the skin, ovarian fibroma and medulloblastoma.
2 theories account for the aetiology of sex cord-stromal tumours hypothesising that they develop either from:
(1) mesenchyme of the developing genital ridge, or
(2) precursors of the mesonephric and coelmic epithelium.
No definite aetiologies have been established for granulosa cell tumours, although chromosomal abnormalities and abnormal autocrine and endocrine signalling have been suggested.

Epidemiology

The frequency of sex cord-stromal tumours is similar

throughout the world. There does not appear to a racial predisposition, in contrast to epithelial ovarian cancers. Every year, 15-20,000 new cases of sex cord-stromal tumours are diagnosed in the USA. Sex cord-stromal tumours appear in any age group but usually in the 4th and 5th decades. Fibromas are usually detected in the fifth decade of life. The mean age of presentation of Leydig cell tumours is 50. The median age of diagnosis of adult granulosa cell tumours is 52, and is 53-years for theca cell tumours. Theca cell tumours account for 1 % of ovarian neoplasms, and are rarely diagnosed in women under 30-years of age, unless they have luteinized thecoma which is more apparent in younger women. However, Sertoli-Leydig cell tumours tend to present at a younger age, usually in the third decade of life.

Clinics

Granulosa cell tumours usually follow a nonaggressive clinical course. However, they may become malignant or recur (up to 30 years after the initial diagnosis). 65% of granulosa cell tumours occur in postmenopausal females. Juvenile and adult granulosa cell tumours, fibromas, and Sertoli-Leydig cell tumours are usually unilateral. Granulosa-theca cell tumours are usually large and benign, with cystic degeneration (http://chorus.rad.mcw.edu/doc/00506). Intra-abdominal bleeding following rupture is often the presenting symptom of patients with granulosa cell tumour. Both adult and juvenile granulosa cell tumours are indolent. Approximately 10% of granulosa cell tumours occur in pregnant patients, and should be surgically removed at 16-18 weeks of gestation.

The excess oestrogen produced by some stromal tumours, such as adult granulosa cell tumours and thecomas, causes isosexual precocious puberty, postmenopausal bleeding, menorrhagia, menometrorrhagia, amenorrhea, endometrial hyperplasia or cancer or fibrocystic breast disease (http://chorus.rad.mcw.edu/doc/00506). Thecomas usually develop in postmenopausal women, on average grow to 7-8 cm, and >97% of cases are unilateral. Most thecomas are hormone producing and cause postmenopausal bleeding in two-thirds of patients. Luteinized thecomas are usually androgenic, and these tend to present in younger women. Approximately 40% of patients with Sertoli-Leydig cell tumours and most patients with Leydig cell tumours show virilization. This is attributable to the Leydig cells which produce androgens. Lipid cell tumours usually cause virilization. A subset of patients with Sertoli-Leydig cell tumours secrete excess oestrogen.

Pathology

All ovarian sex cord-stromal tumours are derived from the stroma of the developing ovary. The gonadal stoma is primitive, and consequently can develop in a testicular or ovarian differentiation pathway.

Adult and Juvenile Granulosa cell tumour

Adult granulosa cell tumours contain granulosa cells in the presence or absence of theca cells. Granulosa theca cell tumours are composed of at least 25% theca cells in addition to the granulosa cells. Varying histologies have been reported in adult granulosa cell tumours, including well-differentiated histologies such as microfollicular, macrofollicular, trabecular and insular, and less well diffentiated subtypes including diffuse and watered-silk (gyriform). Call-Exner bodies are pathognomonic of granulosa cell tumour, and are found in the microfollicular pattern, the most common histological subtype. Call-Exner bodies consist of small rings of granulosa cells surrounding eosinophilic fluid and basement membrane material (http://www.emedicine.com/med/topic928.htm#target1). Macrofollicular granulosa cell tumours contain one or more large cysts lined with granulosa cells. Granulosa cells are organised into nests and bands in the trabecular and insular histologies, with an intervening fibrothecomatous stroma present in the trabecular type. The diffuse subtype contains sheets of cells arranged in no pattern (http://www.emedicine.com/med/topic928.htm#target2), and the watered-silk entity contains cells arranged in single file in lines (http://www.emedicine.com/med/topic928.htm#target4). Both the well-differentiated and the less well-differentiated adult granulosa cell tumours contain large, pale, ovoid or angular nuclei with nuclear grooves.

Few mitotic figures, mild nuclear atypia and little cytoplasm are usually found, however luteinization can sometimes be evident.

The gross appearance of juvenile granulosa cell tumours is similar to the adult counterparts-both comprise a mixture of solid and cystic components with many haemorrhagic areas. However the similarity ceases at the gross level, as morphologically both types differ greatly. Juvenile granulosa cell tumours contain round hyperchromatic nuclei, nuclear grooves are usually absent, severe nuclear atypia, contain more mitotic figures, more cytoplasm (which is dense).

Fibromas

Fibromas are benign and are classified as such if they contain <3 mitoses per high-power field. Malignant fibromas are called fibrosarcomas, and are classified as such if they have > 4 mitoses per high-power field. Less than 5% of fibromas are malignant.

Thecomas

Thecomas or theca cell tumours contain exclusively theca cells. Thecomas are solid, tan or yellow-orange tumours. They are highly similar to fibromas, except that thecomas secrete excess oestrogen. Thecomas are usually benign, and are characterised by <3 mitoses per high-power field. Malignant thecomas have >3 mitoses

per field. Microscopic analysis reveals round or ovoid cells with pale nuclei and a lipid-rich cytoplasm. Hyaline bands frequently intersperse cells (http://www.emedicine.com/med/topic928.htm#target5). Luteinized thecomas contain lipid rich cytoplasmic cells and a more fibromatous stroma (http://www.emedicine.com/med/topic928.htm#target6). Less than 5% of thecomas are malignant.
http://pathy.med.nagoya-u.ac.jp/atlas/misc/thecoma.html

Sertoli cell tumours
Sertoli cell tumours contain Sertoli cells in a tubular arrangement.

Sertoli-Leydig cell tumours
As the name suggests, Sertoli-Leydig cells contain both Sertoli and Leydig cells. They are subclassified in accordance with the WHO as follows:
1. well-differentiation (predominant tubular pattern)
2. intermediate differentiation (sheets of immature Sertoli cells with some stroma)
3. poor differentiation (immature Sertoli cells with little or no stroma)
4. containing heterologous elements with retiform pattern.
Less than 5% of Sertoli-Leydig tumours are malignant.

Leydig cell tumours
Leydig cell tumours contain Leydig cells, and are usually benign. When located in the hilus they are described as hilus cell tumours. Leydig cell tumours contain Reinke crystals.

Lipid cell tumours
Lipid cell tumours are characterised by round Leydig-like cells, luteinized stroma, adrenocortical cells and the absence of Reinke crystals. 30% of lipid cell tumours are malignant.

Gynandroblastoma
These are rare ovarian tumours which contain granulosa stromal cells and Sertoli stromal cells. 100% of gynandroblastomas are malignant.

Sex cord tumour with annular tubules (SCTAT)
Histologically SCTAT is intermediate between granulosa cell tumour and the Sertoli cell tumour. It is characterised by sex cord cells in the form of a ring with nuclei orientated around a central hyalonized body.

Treatment

Surgery may be the only treatment necessary. Surgical intervention of patients with sex cord-stromal tumours is age dependent. Trans abdominal hysterectomy or bilateral salpingo-oophorectomy is appropriate for women beyond childbearing age, whereas unilateral oophorectomy is appropriate for younger women. There is a paucity of data on treatment of advanced or recurrent stromal tumours due to their rarity, varied histology and indolence.

Combination chemotherapies have yielded some responses in each subtype of sex cord-stromal tumour.
Pelvic radiation has also been used for localised tumours.
No effective treatment is available for metastatic lipid cell tumours.

Evolution

20% of lipid cell tumours metastasise. In the low percentage of granulosa cell tumours showing aggressive behaviour, any organ can be affected by metastatic disease, although it is usually confined to the pelvis and abdomen.

Prognosis

The prognosis of sex-cord-stromal tumours is good, as these tumours usually present when confined to a single ovary, and are responsive to chemotherapy.
Patients with **juvenile granulosa** cell tumours have a good prognosis-mortality is only 1.5% for patients with stage IA. For individuals with **granulosa cell tumours**, diffuse growth pattern, increased mitotic figures and cellular atypia correlate with poor prognosis. >90% of adult and juvenile granulosa cell tumours are diagnosed at stage I. 5-year survival rates are 90-95 % for stage I tumours, but only 25-50% for those presenting with advanced disease. **Adult granulosa cell tumours** usually develop in postmenopausal women, recur after longer time intervals, (average of 5-years), and the average survival following recurrence is 5-years. Meanwhile, most juvenile granulosa tumours develop in individuals under 30-years of age, recur within 3-years and then are rapidly fatal. Individuals with completely resected granulosa cell tumours with normal DNA diploid content, have a much better prognosis than when residual tumour remains after laparotomy, and the DNA content is aneuploid.
Theca cell tumours have an excellent prognosis, with 5-year survival rates of nearly 100%, as they are usually benign.
The prognosis of **Sertoli-Leydig cell tumours** is governed by the stage and differentiation of the tumour. 97.5% of such tumour entities are stage 1, the remainder being advanced-stage.

Cytogenetics

Cytogenetics Morphological

Trisomy 12 is a recurrent finding, often as the sole anomaly in benign sex cord-stromal tumours including fibromas, fibrothecomas, thecomas, granulosa cell tumours. The consistent occurrence of trisomy 12 in different subtypes of sex cord-stromal tumours suggests a common mechanism of oncogenesis within this diverse group of neoplasms. Numerical abnormalities of chromosome 12 can readily be demonstrated by interphase cytogenetics.

Trisomy 12 and 14, and monosomy 22 are the characteristic recurrent cytogenetic aberrations in granulosa cell tumours. There has been a single case of a Sertoli cell tumour in which cytogenetics was performed. Supernumerary i(1q) was present as the sole abnormality. Monosomy 22 was identified as the sole anomaly in a mixed germ cell-sex cord-stromal tumour in the ovary, by both karyotyping and CGH, which may suggest a common pathogenetic mechanism for both tumour types. Monosomy 22 was also identified as the sole abnormality in a fibrothecoma. Monosomy 22 and trisomy 14 may be early events in the pathogenesis of adult granulosa cell tumour, and particularly adult granulosa-thecoma cell tumours.
Other abnormalities found include:
44,XX,dup(p13p31),del(3)(p14),add(10p),-16,-22 in one case of fibrothecoma,
57,XX,+4,+5,+6,+10,+12,+12,+14,+17,+18,+19,+20 in another fibrothecoma case,
+4,+9,+12 in fibrothecoma,
trisomy 12 and 4 as only cytogenetic aberrations in a thecoma.

Cytogenetics Molecular

CGH and FISH analysis of an ovarian metastasising Sertoli-Leydig cell tumour demonstrated trisomy 8 as the sole anomaly, suggesting that the molecular pathogenesis of Sertoli-Leydig cell tumours differs from the other subtypes of sex cord-stromal tumours.
In a study, FISH using DNA-specific probes for chromosome 12, 17, 22 and X on granulosa cell tumours revealed monosomy 22 in 6/20; trisomy 12 in 5/20; monosomy X in 2/20 and monosomy 17 in 1/20. They also analysed this series of tumours by CGH and identified gains of chromosome 12 (6/20) and 14 (6/20) and losses of chromosome 22 (7/20) and X (1/20) as the predominant findings. These findings corroborate previous reports of the prevalence of trisomy 12 and 14 and monosomy 22 in granulosa cell tumours.

Genes involved and proteins

Note
Involvement of the follicle stimulating hormone receptor, FSHR, gene in granulosa cell tumours has now been excluded. An initial study found mutations in 9 out of 13 sex cord tumours, which were later shown to arise from contamination in the tissue processing procedures. Other studies have confirmed the absence of somatic mutations in the FSHR in sex cord-stromal tumours, and in particular granulosa cell tumours.
Activating mutations of the G-protein subunit, G-alpha I-2, have been found in 30% of ovarian sex cord tumours, however none were found in a series of 13 granulosa cell tumours. Data for involvement of the mutations in G-alpha I-2 (Gia2) gene, in ovarian granulosa cell tumours is contradictory. However, 2 studies have excluded any major involvement of this gene in the genesis of ovarian granulosa cell tumours.
As discussed earlier, sex cord tumours with annular tubules are present at increased frequency in individuals with PJS, which is caused by germline inactivating mutations of the STK11 gene at 19p13.3. A study investigated whether LOH was present in 2 cases of PJS associated sex cord-stromal tumours, and in 5 sex cord-stromal tumours in individuals without PJS. LOH was identified in both tumours associated with PJS. Neither LOH nor somatic mutations of STK11 were present in the sporadic tumours.
Immunohistochemistry has demonstrated that 32/33 granulosa cell tumours, and 10/11 Sertoli-Leydig cell tumours show inhibin alpha (INHA) immunopositivity, and 18/33 granulosa cell tumours and 6/11 Sertoli-Leydig cell tumours MIC2 (CD99 antigen) immunopositivity. Knockout mouse models null for the INHA gene develop granulosa cell tumours suggesting that this gene may act as a tumour suppressor gene. To find supporting evidence that this was the case in human granulosa cell tumours, it has been investigated whether LOH of the INHA locus at 2q33-qter was evident in a series of 17 granulosa cell tumours. However LOH was found in only one case, suggesting that this gene does not function as a tumour suppressor gene in granulosa cell tumours in human, contrary to the findings in the mouse model. However this supports the observation of elevated expression of inhibin which has been reported previously in these tumours. Thus there appears to be an apparent dichotomy between the human granulosa cell tumour and the mouse models.
A study to address whether trisomy 12 was associated with amplification of the KRAS2 oncogene (12p12.1) demonstrated no relationship in 2 fibromas and 1 granulosa cell tumour with trisomy 12 (taking the ploidy level into account). Cyclin D2 (CCND2) has been suggested as the candidate gene on 12p, and has been reported to demonstrate increased expression. Granulosa cell tumours demonstrated increased expression of FSHR, CCND2, RII-beta and COX-2 (PTGS2), whereas they showed decreased expression of SGK and LHCGR (luteinizing hormone/choriogonadotropin receptor) compared to normal ovarian tissue by RT-PCR. Altered expression levels of the following genes have also been found in granulosa cell tumours: Mullerian inhibiting substance; inhibin; p53; ERBB2; and MYC. A role for the INK4 family of cyclin-dependent kinase inhibitors has also been suggested in granulosa cell tumours.
The role of mutations of WT1 in sex cord-stromal tumours was investigated. Of 11 granulosa cell tumours, 3 Leydig cell tumours and 1 Sertoli-Leydig cell tumour, none harboured a mutation in the zinc finger domain where >90% of WT1 mutations are found in sporadic Wilms' tumours, despite most of the

tumours expressing WT1 mRNA. However loss of the normal wild type allele of WT1 was observed in a granulosa cell tumour present in a patient with Denys-Drash attributable to a germline mutation of WT1.
Studies on the role of TP53 mutations in granulosa cell tumours have been contradictory. It was found that over-expression of TP53 was not characteristic of 19 ovarian granulosa cell tumours; whereas other workers found a correlation between expression of mutated TP53 with poor prognosis, which was supported by other findings. Neither point mutations (exons 5-8 analysed only), nor LOH of TP53 were evident in a series of 17 granulosa cell tumours, suggesting that they have a distinct molecular pathogenesis to that of epithelial ovarian tumours. Mutations outside the hotspot exon 5-8 were not excluded by their study, but are unlikely to be significant since an association between TP53 and granulosa cell tumour by immunohistochemistry was not demonstrated in the first study.

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This article should be referenced as such:

Lee-Jones L. Ovary: Sex cord-stromal tumors. Atlas Genet Cytogenet Oncol Haematol. 2004; 8(1):48-53.