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Solid Tumour Section

Review

Ovarian tumours: an overview

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Identity

Note

Ovarian tumours are a group of neoplasms affecting the ovary and have a diverse spectrum of features according to the particular tumour entity. They include benign, low-malignant potential/borderline and malignant subtypes.

Classification

Ovarian tumours are subdivided into 5 main categories according to the World Health Organization's classification system:

Epithelial tumours, which account for about 75% of all ovarian tumours, and 90-95% of ovarian malignancies.

Sex cord-stromal tumours, which account for about 5-10 % of all ovarian neoplasms.

Germ cell tumours, which account for about 15-20 % of all ovarian neoplasms.

Metastatic tumours, accounting for about 5% of ovarian malignancies, and usually arise from breast, colon, endometrium, stomach and cervical cancers.

Other, a small number of other types of neoplasms which develop from ovarian soft tissue or non-neoplastic processes.

Clinics and pathology

Etiology

There are several tumour predisposition syndromes associated with the development of some ovarian tumours.

For ovarian sex cord-stromal tumours these include:

Peutz-Jeghers syndrome,

Cushing Syndrome,

Meigs Syndrome and

Gorlin Syndrome (for further details see Sex Cord-Stromal tumour Review).

There have also been accounts of fibromas, a type of sex cord-stromal tumour affecting more than one family member, implying a genetic predisposition in a subset of cases.

About 5-10% of **ovarian epithelial tumours** are associated with one of three syndromes:

Hereditary breast-ovarian cancer syndrome;

Hereditary nonpolyposis colon cancer; and

Site-specific ovarian cancer syndrome (for further details see Ovarian Epithelial Tumour Review).

Ovarian germ cell tumours, in contrast, rarely develop in individuals with tumour predisposition syndromes. However there have been several reports of ovarian germ cell tumours affecting more than one family member, suggesting a genetic predisposition in a minority of cases. Furthermore, constitutional chromosomal abnormalities involving partial or entire Y chromosome gains, and also dysgenic gonads, are more frequently associated with the development of ovarian germ cell tumours.

Epidemiology studies have shown a correlation between increased risk of ovarian epithelial tumours with increased number of ovulation cycles. Other factors which increase the likelihood of developing ovarian epithelial tumours include: use of talc on perineum and vulva, asbestos, pelvic irradiation, viruses, high-fat diet and lactose consumption. Reducing the number of ovulation cycles by multiparity, breast-feeding and oral contraceptives, decreases the probability of ovarian cancer.

Epidemiology

Generally ovarian tumours are more prevalent in the upper socioeconomic groups, and account for approximately two-thirds of cancers in the 40-65 age

group. The incidence of ovarian tumour starts increasing in the third decade, and progressively increases to peak in the seventh decade. The different subtypes of ovarian neoplasms are more prevalent in different age groups.

Ovarian germ cell tumours usually affect young women (mean age of presentation is 19 years) with an incidence of 20 per million at 18 years (age of peak presentation).

Sex cord-stromal tumours, meanwhile, usually present in the 4th and 5th decades and

Ovarian epithelial tumours are usually found in post-menopausal women (mean presentation age is 56 years). The median age for ovarian adeno-carinoma is 60-65 years.

There is no racial predisposition to **ovarian sex cord-stromal tumours or ovarian germ cell tumours**. However there is a racial predisposition for **ovarian epithelial tumours** with higher risks for Caucasians and lower risks for black women. Clear cell adenocarcinoma, a subtype of ovarian epithelial tumours, is more prevalent in Japanese than in Western women.

Clinics

Ovarian tumours are generally difficult to detect until they are advanced in stage or size, as the symptoms are vague and manifest over time. The principal symptoms include: fatigue, shortness of breath, increased abdominal girth, weight loss, non-productive cough, bloating, and amenorrhea for premenopausal women and menstrual irregularity. Most ovarian neoplasms cause symptoms by exerting pressure on contiguous structures, resulting in increased urinary frequency, pelvic discomfort and constipation. Abdominal swelling results from enlargement of the tumour. Upper abdominal metastases or ascites cause nausea, heartburn, bloating, weight loss and anorexia. Irregular vaginal bleeding can be observed. Shortness of breath is a symptom of patients with ascites or hydrothorax. Some tumours, including subtypes of sex cord-stromal tumours, produce excess oestrogen which results in isosexual precocious puberty, postmeno-pausal bleeding, menorrhagia, menometrorrhagia, amenorrhea, endometrial hyperplasia/cancer or fibrocystic breast disease. Some subtypes of sex-cord stromal tumours produce androgens which causes virilization.

Pathology

Diverse histopathologies are evident reflecting the different cell origins of the tumours: germ cell tumours develop from the primitive germ cells of the embryonic gonad, sex cord-stromal tumours develop from the stroma of the developing ovary, and epithelial tumours arise from the epithelial cells. Examples of both gross and microscopic images of these clinical entities can be viewed at the following websites:

Internet Pathology Lab for Medical Education

eAtlas of Pathology (Univ of Connecticut).

Treatment

Some ovarian tumours, notably the sex cord-stromal tumours, require ***surgical intervention*** only. Meanwhile others require chemotherapy post-resection; this applies to all germ cell tumours and the vast majority of ovarian epithelial tumours (with the exception of some stage Ia patients). In young patients with germ cell and sex cord-stromal tumours, unilateral salpingo-oophorectomy is performed in order to preserve fertility. Meanwhile when fertility is not a concern, such as in women beyond childbearing age, total abdominal hyster-ectomy and bilateral salpingo-oophorectomy is performed. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is performed upon diagnosis of ovarian adenocarcinoma.

Ovarian germ cell tumours are highly responsive to ***chemotherapy and radiotherapy***, although the former is preferable in order to conserve ovarian function. Ovarian epithelial tumours are initially highly responsive to chemotherapy, but most patients relapse and fail to respond to subsequent chemotherapy regimes. Postoperative radiotherapy is also provided for ovarian adenocarcinoma patients in order to treat minimal residual disease. Platinum-based chemotherapy is used to treat both ovarian germ cell and epithelial tumours. There is very little data available on the treatment of advanced/recurrent ovarian sex cord-stromal tumours due to their rarity and varied indolence, but some responses have been obtained with combination chemotherapy in each subtype. However there is currently no effective treatment for metastatic lipid cell tumours.

Evolution

The growth potential of ovarian neoplasms differs according to their subtypes, as does their ability to metastasise.

Ovarian epithelial tumours initially spread by direct seeding of the peritoneal surfaces, with mucinous tumours generally forming large masses and serous tumours spreading more diffusely.

Ovarian germ cell tumours metastasise intraperitoneally or hematogenously, with the exception of dysgerminomas which metastasise via the lymphatic system (and are the only type of ovarian tumour to do so). In general, most ovarian germ cell tumours do not metastasise, with the exception of the lipid cell entity which metastasises in 20% of cases, and a very low percentage of granulosa cell tumours (whose metastatic spread is usually limited to the pelvis and abdomen).

Prognosis

The prognosis of both **ovarian germ cell tumours and ovarian sex cord-stromal tumours** is generally good, as these tumour entities usually present at stage I, are benign and are highly responsive to treatment.

Meanwhile the situation is very different in **ovarian carcinomas**, which often present at advanced stages with extensive metastases. If ovarian epithelial tumours are diagnosed at stage I (growth limited to the ovaries), 5-year survival rates are >90%, in stark contrast to <25% 5-year survival rates for those diagnosed at advanced stage. Before 45 years of age over 98% of ovarian neoplasms are benign.

Genetics

Note

The contribution of genetic predisposition to the genesis of ovarian tumours varies widely according to the particular subtype.

There have been several reports of **ovarian germ cell tumours** affecting more than one family member, whereas genetic predisposition has only been implicated in one particular subtype of ovarian sex cord-stromal tumours, fibromas.

However, genetic predisposition is far more prevalent in **ovarian epithelial tumours**. Indeed, genetic factors are the most important risk factor for ovarian epithelial carcinoma, and approximately 5-10% of ovarian epithelial cancers are thought to have a hereditary component. Having 1 or 2 first-degree relatives with ovarian cancer increases the lifetime risk to 3-5% and 39% respectively. As mentioned in the aetiology section, three hereditary syndromes are associated with familial aggregation of ovarian carcinoma: hereditary breast-ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome (HNPCC, also known as Lynch Cancer Family syndrome II), and site-specific ovarian cancer syndrome. All 3 patterns of familial ovarian carcinoma are consistent with autosomal-dominant transmission. The age of diagnosis of hereditary epithelial ovarian cancer is approximately 10 years earlier than its sporadic counterpart. BRCA1 and BRCA2 genetic testing identifies individuals who are more likely to benefit from screening for ovarian epithelial tumours.

Cytogenetics

Cytogenetics Morphological

There is a paucity of cytogenetic data available on **ovarian germ cell** and **sex cord-stromal tumours**. Trisomy 3, 8, 12, 14 and isochromosome 12p are recurrent findings in ovarian germ cell tumours. Trisomy 12 is a frequent finding, often as a sole anomaly, in the different subtypes of ovarian sex cord-stromal tumours. Trisomy 12 and 14, and monosomy 22 are characteristic recurrent cytogenetic aberrations present in the granulosa cell tumour subtype of ovarian sex cord-stromal tumours. Despite the heterogeneity of ovarian tumours, trisomy 12 is frequently found in the different subtypes of borderline and benign ovarian tumours of germ cell and sex cord-stromal origin, suggesting a common pathogenesis, at least for the initial stages of tumourigenesis. Trisomy 14 is also a common finding in both ovarian germ cell tumours and sex cord-stromal tumours.

There is far more cytogenetic data available on **ovarian carcinomas** (epithelial tumours) due to their higher incidences, with over 400 published karyotypes. Published cytogenetic data on ovarian epithelial tumours are detailed on Mitelman Database of Chromosome Aberrations in Cancer. The cytogenetic aberrations are non-random and complex. However, no pathognomonic rearran-gements have been identified thus far. The karyotypes often show severe aneuploidy, with hypodiploid or near-triploid stemline chromosome numbers. The different subtypes of ovarian carcinoma show no marked cytogenetic differences, except seropapillary tumours more frequently display chromosome aberrations than the other subtypes. A correlation exists between karyotypic complexity and tumour grade. Simple chromosome changes (numerical changes only or a single structural rearrangement) were found in well-differentiated carcinomas, whereas complex karyotypes were found in poorly differentiated tumours. Patients with aberrant tumour karyotypes, particularly complex ones, were associated with short survival. The most prevalent numerical changes are gains of chromosomes 1, 2, 3, 6, 7, 9, 12 and 20 losses of chromosomes 4, 8, 11, 13, 14, 15, 17 and 22. Structural rearrangements primarily involve deletions and unbalanced translocations involving 1p, 1q, 3p, 3q, 6q, 7p, 10q, 11p, 11q and 12q.

Cytogenetics Molecular

There are limited FISH, CGH and allelotype studies on **ovarian germ cell tumours** and **ovarian sex cord-stromal tumours**.

Of the rudimentary CGH data presently available on ovarian germ cell tumours a high incidence of the gain of the entirety or the short arm of chromosome 12 was found. Other findings were similar to those previously reported for testicular germ cell tumours (i.e. gains of 8, 21 and 1q, and loss of 13).

The limited CGH data available on ovarian sex cord-stromal tumours supported the cytogenetic findings, demonstrating gains of chromosomes 12 and 14 and losses of chromosomes 22 as the predominant findings.

In contrast, there is a plethora of CGH and allelotyping data implicating many genomic regions in **ovarian epithelial tumours**. Interphase cytogenetics demonstrated a high frequency of gain of copy number of 20q13.2 (70%), AIB1 (20q12) and cyclin D1 (CCND1 at 11q13, 72%) in ovarian epithelial tumours which were associated with poor prognosis. For a comprehensive overview of the imbalances identified by CGH in published reports of ovarian epithelial tumours see http://www.helsinki.fi/cmg/cgh_data.html. The commonest imbalances detected by CGH of epithelial neoplasms were gains of 8q, 1q, 20q, 3q and

19p in 69-53% of a series of 106 tumours and under-representations of 13q, 4q and 18q in 54-50% of cases. Under-representation of 11p and 13q and over-representation of 8q and 7q correlated with undifferentiated ovarian carcinoma, whereas 12p under-representation and 18p over-representation were more commonly associated with well-differentiated and moderately differentiated tumours. In a study correlating CGH genomic imbalances with clinical endpoints in 60 ovarian carcinomas, the following associations were found:
Loss of chromosome 4 with high-grade tumours
Gains of 3q26-qter, 8q24-qter and 20q13-qter and low-grade and low-stage tumours
Deletion of 16q24 and >7 independent genomic imbalances and reduced survival times.
Tumour grade correlated better with genomic progression than clinical stage.

Genes involved and proteins

Note
The molecular pathogenesis of **ovarian sex cord-stromal tumours** and **germ cell tumours** are relatively understudied. Several genes have been analysed for somatic mutations and/or LOH, with largely negative findings. Due to the extensive similarity between ovarian and testicular germ cell tumours in terms of their cytogenetic, pathological and biological features, it is thought that the genes involved in their pathogenesis will be similar. P53 mutations are rare in germ cell tumours
However P53 mutations are commonly found in **ovarian epithelial tumours**, suggesting that these tumours have a distinct molecular pathogenesis to the other subtypes. Other genes involved in the molecular aetiology of ovarian epithelial tumours include: CDKN2A, RB, GATA4, RNASET2, BRCA1, KRAS, MYC, ERBB2, CSF1R, ECGF1, EGFR, MYC, SRC, PI3K, AKT2, FGF3 and MDM2.

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