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Solid Tumour Section

Review

Ovary: Germ cell tumors

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Identity

Note

Ovarian germ cell tumours (OGCT) are a type of ovarian neoplasm principally affecting young women. They are derived from primitive germ cells of the embryonic gonad, and may undergo germinomatous or embryonic differentiation. They differ in clinical presentation, histology and biology, and include both benign (predominantly) and malignant subtypes. Germ

cell tumours (GCT) account for 15-20% of all ovarian neoplasms, and constitute the second largest group of ovarian neoplasms. Less than 5% of ovarian cancers are of germ cell origin.

Classification

Note

OGCT are subdivided into the clinicopathological entities listed in Table 1.

Subtype	Frequency of OGCT	Benign/ Malignant	Uni- or Bi-lateral	Tumour Markers Expressed	Metastasis Route
Dysgerminoma	35-50%	Malignant	10-15% are bilateral	Serum lactic dehydrogenase and serum hCG	Lymphatic system
Endodermal sinus tumor, (EST)	20%	Malignant	Usually unilateral	AFP (commonly), alpha 1-antitrypsin (rarely)	Intraperitoneally and hematogenously
Embryonal carcinoma	Rare	Malignant	Usually unilateral	AFP and hCG	Intraperitoneally
Polyembryoma	Rare			AFP and hCG	
Choriocarcinoma	Very rare	Malignant	Usually unilateral	HCG	
Teratoma	Immature account for 20% of malignant GCT	Benign or malignant	12-15% are bilateral	Immature teratomas sometimes secrete AFP, serum LDH and CA-125	
Mixed GCT	10-15%	Dependent upon the cell types present		Dependent upon the cell types present	

Table 1 Subtypes and characteristics of ovarian germ cell tumours (data derived from Rice, 1999 and John Hopkins Pathology, 2001).

Clinics and pathology

Etiology

No factors have been associated with the aetiology of GCT, apart from an increased incidence associated with dysgenetic gonads. 5% of patients with dysgerminomas are associated with constitutional cytogenetic abnormalities involving the entirety or part of the Y chromosome; 46,XY (testicular feminisation), gonadal dysgenesis and mixed gonadal dysgenesis (45,X, 46,XY). However 95% of females with dysgerminomas are cyto-genetically normal. In genetic syndromes with a high risk of cancer, rarely are GCT found. GCT may be found infrequently in individuals with Li-Fraumeni.

Epidemiology

GCT predominantly affects young women, but they do sometimes occur in infants and older women. GCT account for over 60% of ovarian neoplasms in children and adolescents, one-third of which are malignant. The frequency of OGCT is invariable throughout the world. There does not appear to be a racial predisposition, in contrast to epithelial ovarian cancers. The incidence of OGCT increases in incidence from the age of 8-9 years, and peaks at 18 years (20 per million). The mean age of presentation of OGCT is 19 years. The incidence of OGCT is much lower than that of testicular germ cell tumours (TGCT). At 19 years of age the incidence of GCT in males is 44.5 per million, whereas it is only 10.4 per million in females. In the US, the incidence of GCT has not increased during the last thirty years.

Clinics

Most GCT are benign and unilateral, with the exception of dysgerminomas. Patients usually present at stage I. Abdominal pain or adnexal torsion is the commonest presenting symptom of GCT, however they may be asymptomatic. The mass may cause acute pain due to torsion, rupture, or haemorrhage. Patients may also have abdominal distension, vaginal bleeding or fever. Teratomas are usually diagnosed in premenopausal women without presenting symptoms. Complications of mature cystic teratoma (dermoid cyst) include torsion, rupture, infection and haemolytic anaemia. Approximately 50% of prepubertal girls with nongestational choriocarcinoma are isosexually precocious. Only 1-2% of dermoid cysts become malignant, usually in postmenopausal women. Patients with ESTs frequently present following spontaneous rupture and haemorrhage.

Pathology

Teratomas

Teratomas develop from totipotential germ cells, and consequently contain all three germ cell layers: ectoderm, mesoderm and endoderm. Teratomas are

classified into immature (malignant), mature (dermoid cyst) and monodermal (struma ovarii, carcinoid).

Dermoid cysts contain mature tissue, and upon gross examination skin, teeth, bone, hair, sebaceous glands and neural tissue predominate; whilst cartilage, respiratory and intestinal epithelium are also common. They are cystic tumours with a firm capsule.

Monodermal teratoma comprise mainly one tissue element. For example the most common type of monodermal teratoma, Struma ovarii, is comprised of at least 50% mature thyroid tissue (of any type). Argentaffin cells in dermoid cysts are usually the site of origin for ovarian carcinoids, although this is rare.

Immature teratomas account for approximately 20% of all malignant GCT. They are classified as Grade I, II or III if they have 0 or 1, 3 or less, or 4 or more low-power fields (x-40) containing immature neuroepithelium per section, respectively. Immature teratomas are solid tumours containing immature or embryonal tissues. Immature neuroepithelium is the predominant immature tissue found.

Dysgerminoma

Dysgerminomas have a solid, lobulated, tan, flesh-like gross appearance with a smooth surface. Microscopically dysgerminoma cells are round and ovoid, contain abundant cytoplasm, irregularly shaped nuclei, >1 prominent nucleolus. These cells have a propensity to aggregate forming cords and sheets. Lymphocytic and granulocytic infiltration of the fibrous septa is often evident.

Endodermal Sinus Tumor (EST)

Gross examination of EST, also known as yolk sac tumour, demonstrates smooth, glistening, hemorrhagic and necrotic surfaces. Histology reveals a wide range of patterns (microcystic, endodermal sinus, solid, alveolar-glandular, papillary, macro-cystic, hepatoid, primitive endodermal). The classic pattern contains Schiller-Duval bodies (central capillary surrounded by simple papillae) and eosinophilic globules containing AFP. Intracellular and extracellular hyaline droplets (periodic acid-Schiff positive) are also seen in EST.

Embryonal Carcinoma

Gross examination of embryonal carcinoma reveals a solid, hemorrhagic, necrotic tumour, resembling a larger form of EST. Embryonal glands, glandlike clefts (embryoid bodies), and syncytiotrophoblastic giant cells are present microscopically.

Choriocarcinoma

Choriocarcinoma is a very rare solid, hemorrhagic tumour, composed of malignant cytotrophoblast and syncytiotrophoblast. Nongestational and gestational choriocarcinoma have identical histologies.

Mixed Germ Cell Tumour

As the name suggests, mixed germ cell tumours contain >1 histological type. Dysgerminoma with EST, and immature teratomas with EST are frequent combinations.

Polyembryoma

Histological analysis of polyembryoma demonstrates erythroid bodies in different stages of presomite development.

Treatment

The treatments used for OGCT have largely been based on those used for the more prevalent TGCT.

In young patients **surgery** should be conservative in order to preserve fertility. Consequently unilateral salpingo-oophorectomy is performed for all stages of dysgerminatous and nondysgerminatous GCT. Even if extra-ovarian disease is present, the contralateral ovary and uterus should not be removed as these tumours are curable with chemotherapy. However if fertility is not of concern, total abdominal hysterectomy and bilateral salpingo-oophorectomy, together with removal of as much tumour tissue as possible, is recommended for stage II, III and IV of dysgerminatous and nondysgerminatous GCT.

Chemotherapy is preferable, despite these tumours being highly radiosensitive (except EST and embryonal carcinoma), in order to preserve ovarian function. All patients irrespective of tumour histology, except those with immature teratomas (stage IA, grade I), receive post-operative chemotherapy, for adjuvant or curative purposes. Adjuvant chemotherapy is given to patients with completely resected stages I, II or III ESTs, mixed cell tumours, embryonal carcinomas, choriocarcinomas and immature teratomas due to high recurrence rates. All non-dysgerminatous GCT receive the same chemotherapy regimes based on a combination cisplatin therapy. Combination therapies include vinblastine, bleomycin, and cisplatin (VBP); bleomycin, etoposide and cisplatin (BEP) and also etoposide and cisplatin (EP). Combination chemotherapy is given to patients with bulky residual disease, extra abdominal metastases, or those who failed primary treatment with a curative intent. Survival rates for nondysgerminatous ovarian germ cell malignancies has increased dramatically with the use of platinum-based combination chemotherapy. Approximately 15-25% of dysgerminomas recur, but these are usually treated with a curative outcome.

The survival rates for dysgerminomas presenting at early and advanced stages are 95% and >80% respectively.

The survival rates for stage I and II ESTs are reported to be 60-100%, whereas for those with stage III or IV disease the prognosis is less favourable (50-75%).

Survival rates for embryonal carcinoma are slightly higher than those for ESTs.

The prognosis of immature teratomas is governed by grade and stage. Grade 1, stage I have 100% survival rate, whereas stage III, grade 1 has only a 50% chance of survival. Meanwhile, most patients with mature teratomas show long survival times.

The prognosis is better for gestational choriocarcinoma than nongestational carcinoma.

The prognosis for mixed GCT is dictated by the proportion of the more malignant component and the stage.

Evolution

The means by which OGCT metastasise are summarised in Table 1. Dysgerminomas are the only type of ovarian tumour to metastasise lymphatically. Malignant degeneration of 1-2% of mature teratomas occurs, usually into squamous cell carcinoma.

Prognosis

The prognosis of OGCT is excellent, as most cases are benign. When malignant they are very aggressive, but the prognosis is still good provided it is treated without delay with combination chemotherapy.

Genetics

Note

There have been several published reports of ovarian germ cell cancers affecting more than one family member. The rarity of these cancers, (lifetime risk is 0.07%), and the close relationships between affected individuals suggests that a susceptibility gene to germ cell malignancies may be responsible in some families. In addition, several cases of families with both males and females diagnosed with germ cell malignancies have been published, suggesting a common genetic aetiology and susceptibility. Linkage analysis of familial TGCT has identified Xq27.

Cytogenetics

Cytogenetics Morphological

There is a paucity of cytogenetic data available on OGCT. Of 25 mature and immature teratomas displaying abnormal karyotypes, 16 had numerical changes only. Trisomy 3, 8, 12 and 14 were the most common numerical changes identified. Isochromosome 12p, i(12p) is the only recurrent structural rearrangement in OGCT, particularly in dysgerminomas and malignant GCT with a yolk sac component. I(12p) is more prevalent in TGCT, present in 80% of all such tumours. The presence of this anomaly in both testicular and ovarian GCT suggests that they may arise from a similar pathogenesis process. A representative example of isochromosome 12p, i(12p), is shown in Testicular Germ Cell tumor. Interphase cytogenetics using a chromosome 12 centromere and a 12p locus-specific probe can be used to detect this abnormality. Trisomy 12 has been found in several immature teratomas, supporting the importance of

this chromosome in the onset of a subset of OGCT.

Immature teratomas frequently have chromosomal abnormalities (63%), of which gains of chromosomes 3, 8, 12 and 14, losses of chromosomes 4 and 13, and several structural rearrangements including i(12p) are common. It has been proposed that cytogenetically abnormal immature teratomas are more likely to recur than their cytogenetically normal counterparts.

Over 300 mature teratomas have undergone cytogenetic analysis and only 4% have had aberrant karyotypes, displaying numerical alterations only, none of which are recurrent. The few cases in which abnormalities have been identified were as follows: trisomy of chromosome 8 (2 cases), 13 (1 case), 15 (1 case), 20 (1 case) and double trisomy of chromosomes 7 and 12; losses of chromosomes 3, 6, 7, 11, 16, 17, 21 and 22; structural rearrangements involving +mar (2 cases), add(1)(q11) (1 case), der(6)(t1;6)(q11q22) (1 case), i(12)(p10) (1 case) and +del(20)(q11) (1 case).

Mature teratomas that have undergone malignant transformation display multiple numerical and structural chromosomal anomalies principally involving chromosomes X, 1, 3, 4, 5, 9, 10 and 11. Several similarities were found when comparing the benign cystic and malignant component of an ovarian teratoma. It is noteworthy that the benign component had multiple anomalies (13 non-random structural and numerical changes), which raises the possibility that multiple anomalies in the benign component predispose the tumour to malignant transformation.

Complex numerical and structural chromosome changes were apparent in mixed mesodermal tumors, but there is insufficient data to address whether this tumour subtype has a different composition of chromosomal abnormalities than the other subtypes. Abnormalities of chromosome 12 were found in two of six cases of ovarian choriocarcinomas. 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 patho-genetic mechanism for both tumour types.

From the cytogenetic data available to date, it appears that similarities exist between OGCT and TGCT. Isochromosome 12p, i(12p), gains of chromosomes 1, 8, 21 and loss of chromosomes 6 and 13 have been reported in both.

Cytogenetics Molecular

There have only been a limited number of studies employing comparative genomic hybridisation (CGH) to investigate OGCT, and no allelotyping studies have been undertaken.

27 ovarian GCT were analysed by CGH, of which 12 were dysgerminomas, 6 were ESTs, 3 were mixed GCT and the remainder were immature teratomas. The data was grouped for the dysgerminomas, ESTs and mixed GCT and the most frequent finding was gain of 12p, (14/19), 8 of which showed gain of 12p only, (which may result from

i(12p)), 4 showed gains of the entirety of chromosome 12 and 2 showed high level amplification of 12p11-p12. 12p gain is a frequent finding in TGCT, and amplification of 12p11-p12 has also been found in a few such cases. Other recurrent abnormalities were found in this group which have also been previously reported as recurrent findings in TGCT. These include gain of entire chromosome 21 (42 % of malignant OGCT vs. 45% TGCT), gain of chromosome 8 (42% OGCT vs. 45% TGCT), gain of 1q (32% OGCT vs. 36 TGCT) and loss of chromosome 13 (26% OGCT vs. 38% TGCT). There did not appear to be a correlation between the pattern of chromosomal imbalances and histological subtype, except for distal 1p deletion, which was exclusively found in two ESTs. Meanwhile, only 1 of the 6 immature teratomas revealed an abnormality, gain of chromosome 14.

A study summarised these findings according to histological entity. Every dysgerminoma (n=12) analysed showed chromosomal imbalances, with an average number of 10 changes per case. Gains were more common than losses. The most frequent anomalies were gains of 12p (8/12), 12q (9/12), 21q (8/12), 22q (7/12), 20q (6/12), 15q (5/12), 1p (4/12) and 6p (4/12) and the whole of chromosomes 19 (6/12), 7 (5/12), 8 (5/12) and 17 (5/12). Losses of chromosome 13 were seen in 7/12 of the cases. All 4 ESTs analysed displayed copy number changes, with an average of 6 per case. These included gain of 12p (3/4), 1q (3/4), 3p (2/4), 11q (2/4), Xp (2/4), and loss of 18q (2/4). Fewer changes were observed in the immature teratomas, with an average of 1.4 per case. 4 of the 9 immature teratomas had no copy number change. Gain of all or parts of 1p, 16p, 19 and 22 were identified in 2 of the cases with anomalies.

Thus both studies frequently found 12p gains in several subtypes of OGCT, except for immature teratomas, and suggest that immature teratomas follow a different pathway to that taken by other malignant OGCT (and TGCT).

Several interphase cytogenetic studies have been performed on paraffin sections using centromeric probes to determine the copy number of chromosomes, and probes specifically designed to identify the i(12p). A study showed over-representation of chromosomes 7 and 12, and under-representation of chromosome 18, all of which are characteristic features in the male counterpart testicular seminoma.

Genes involved and proteins

Note

There is very little data available on the molecular mechanisms involved in the initiation and progression of OGCT. However, TGCT have undergone more extensive analyses. TGCT and OGCT have very similar pathological, biological, and cytogenetic features, thus it is highly likely that the genes involved are similar.

To date, no gene has been unambiguously identified to be involved in the initiation or progression of TGCT. Several genes including KRAS2, JAW1 and SOX5 have been suggested as the candidate genes on 12p in TGCT. The candidate genes were searched in the 12p11.2p12.1 amplicon, and suggested that DAD-R is the most likely candidate. Overexpression of BCAT1, CMAS, EK11, KRAS2 and SURB7 was demonstrated in a series of TGCT. LOH of regions frequently involved in TGCT is looked, in a panel of 35 OGCT. The results showed LOH of 3q27-q28 (50%), 5q31 (33%), 5q34-q35 (46%), 9p22-p21 (32%) and 12q22 (53%), and were found in all subtypes of OGCT. These data suggest that these loci may be harbouring tumour suppressor genes involved in the initiation and progression of OGCT and TGCT.

Ovarian teratomas develop in transgenic mice lacking a functional c-mos proto-oncogene. However, analysis of twenty teratomas for mutations of c-MOS did not identify any, suggesting that mutations of c-MOS do not play a significant role in the development of human ovarian teratomas.

Amplification of MYCN was found in 3/3 immature teratomas, but in 0/5 dermoid cysts and 0/5 mature teratomas. Less than 3% of GCT have mutations of p53. A somatic novel missense mutation (G to C at nucleotide 2467) of c-KIT has been identified in one ovarian mixed dysgerminoma/EST, which resulted in constitutive activation of KIT kinase activity.

There has been a single report of a germline BRCA1 mutation in a 16 year-old woman with dysgerminoma. This mutation was present in numerous relatives with different cancers including breast and ovarian cancer. It is unclear whether the dysgerminoma was a consequence of the germline mutation, or whether germline BRCA1 mutations are responsible for a small proportion of dysgerminomas and other types of OGCT.

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