Ovary: Choriocarcinoma

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Identity

Alias
Choriocarcinoma of the ovary; Ovarian choriocarcinoma

Note
Choriocarcinoma of the ovary is a highly malignant ovarian tumor which is characterized pathologically by the presence of trophoblastic malignant cells, and biochemically by the production of the pregnancy hormone human chorionic gonadotrophin (hCG) in the absence of an ongoing pregnancy. Choriocarcinoma tends to be invasive and to metastasize early and widely through both the venous and lymphatic systems. This disease is classified two types in origin, gestational choriocarcinoma and nongestational germ cell tumor. Nongestational pure choriocarcinoma is so rare that the prognosis, chemo-sensitivity, and genetics analysis of nongestational type have not been decided compared with that of gestational type. It is necessary, but difficult to distinguish nongestational choriocarcinoma from gestational choriocarcinoma except by DNA analysis.

Classification

Classification of choriocarcinoma of the ovary is based on gestational or not. It is very difficult to differentiate a pure ovarian carcinoma with a non-gestational origin from a gestational one using histopathological investigation. It can be diagnosed with only in a patient who is sexually immature, unable to conceive, or has never had sexual intercourse, unless DNA analysis is not performed.

The gestational type includes an ovarian metastasis from primary uterine choriocarcinoma which occurs in association with a normal pregnancy or spontaneous abortion, complete hydatidiform mole, or partial mole, and primary gestational ovarian choriocarcinoma which arises from ectopic pregnancy in the ovary.

The nongestational type is as a component of a mixed germ cell tumor and a pure ovarian choriocarcinoma is a very rare malignant tumor.

Clinics and pathology

Etiology

By far the most important risk factor for gestational choriocarcinoma is the nature of the preceding pregnancy. A hydatidiform mole carries with it a 1,000 - to 2,000 fold increased risk of choriocarcinoma, one of the most striking cancer risk factors identified in humans. In nongestational choriocarcinoma, no factors have been associated with the etiology of germ cell tumor, apart from an increased incidence associated with dysgenetic gonads.

Epidemiology

Gestational type

Women over the age of 40 are at increased risk for gestational choriocarcinoma. The reported prevalence of choriocarcinoma varies widely throughout the world, being greatest in Asia, Africa, and Latin America and substantially lower in North America, Europe, and Australia. Choriocarcinoma occurs with a frequency of 1:20,000 to 1:40,000 pregnancies in the United States and Europe. Estimates for the incidence in Asia, Africa, and Latin America have generally been higher; rates as high as 1 per 500 to 1,000 pregnancies have been reported, although marked regional variations do occur. Gestational choriocarcinoma follows normal pregnancy (25%), spontaneous abortion (25%), and hydatidiform mole (50%), but only about 3-5% of all molar pregnancies eventuate in choriocarcinoma. Gestational
primary ovarian choriocarcinoma is extremely rare, with an estimated incidence of 1 in $3.7 \times 10^4$ pregnancies.

Nongestational type
Nongestational choriocarcinoma arises in women under 40 years old because of germ cell tumor, and the frequency is reported less than 0.6% of all ovarian tumors. Goswami et al. reported the mean age 13.6 +/- 6.9 years old.

Clinics
Clinical symptoms are variety in gestational type, because choriocarcinoma is likely to metastasis to multiple organs, such as lung, liver, and brain. More than 90% of patients with extraterine gestational choriocarcinoma will have lung metastasis. In nongestational type, predominant presenting symptom is lower abdominal pain. Common complaints includes atypical genital bleeding, amenorrhea, nausea, and vomiting because of high level of hCG. Choriocarcinoma is often diagnosed by the finding of an elevated hCG level in association with metastatic lesion detected radiographically. The levels of serum or urine beta-hCG are good tumor marker for the progression or remission of disease.

Pathology
There is no difference in pathological appearances between gestational type and nongestational pure choriocarcinoma. On gross examination, a circumscribed hemorrhagic mass is observed. Microscopically, hemorrhage and necrosis are found, and tumor cells resemble placental trophoblastic cells: cytotrophoblast (CT), intermediate trophoblast (IT), and syncytiotrophoblast (ST). The CT and IT tend to grow in clusters and sheets separated by ST. The typical pattern of choriocarcinoma has been called "two cell pattern", "biphasic"-terms that reflect the relatively regular, alternating arrangement of CT and ST in the tumor interspersed with intermediate trophoblast. Nuclear pleomorphism, hyperchromasia and nuclei are prominent. Immunohistochemically, beta-hCG is expressed in syncytiotrophoblastic cells, but not cytotrophoblastic cells.

Treatment
Gestational choriocarcinoma is treated with methotrexate-based chemotherapy, for example MEA (methotrexate, etoposide and actinomycin-D), EMA/CO (methotrexate, etoposide, actinomycin-D, cyclophosphamide and vincristine), or EP/EMA (etoposide, cisplatin, methotrexate and actinomycin-D). However, nongestational ovarian choriocarcinoma (germ cell tumor) is so rare that there is lack information on therapeutic options. Germ cell tumors of the ovary are treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. A complete staging operation is indispensable for management and prognostication. In young patients, stage I germ cell tumors can be treated with conservative surgery, i.e., unilateral oophorectomy or salpingo-oophorectomy. Postoperative chemotherapy is recommended by combination chemotherapy with the BEP (bleomycin, etoposide and cisplatin) or methotrexate-based regimen.

Prognosis
The prognosis of gestational choriocarcinoma is getting better by advances of combination chemotherapy. The survival rate is increasing and 96.4% in 15 years since 1985. Nongestational pure choriocarcinoma of the ovary is so rare that it is not known whether the prognosis is worse than gestational choriocarcinoma or not. Some papers reported that nongestational choriocarcinoma of the ovary has worse prognosis and is less sensitive to methotrexate-based chemotherapeutic regimens than gestational neoplasm. But they did not diagnose definitely by DNA polymorphism analysis. It is important to clarify whether the tumor arose from a gestational or nongestational origin in order to understand the prognosis of this disease accurately.

Genetics

Note
To differentiate gestational from nongestational tumors, it is necessary to determine whether a paternal contribution is present in the genome of the tumor. Examination of genetic polymorphisms from the tumor and comparison with those found in the patient and her partner should define the presence or absence of paternal DNA and establish whether or not a tumor is gestational. An extensive literature search including Medline demonstrated only five reported cases of nongestational ovarian pure choriocarcinoma diagnosed with DNA polymorphic analysis from 1985 to 2007.

Cytogenetics

Note
Gestational choriocarcinoma shows wider variations in karyotype, most being aneuploid, with some in the hyperdiploid and hypotetraploid range. Many forms of chromosomal gains, losses and rearrangements are observed, but no specific chromosomal abnormality has yet been identified.

Cytogenetics Morphological

Gestational type
A study by Matsuda et al. suggested that chromosome 7 contained a putative tumor suppressor gene for choriocarcinoma. Furthermore, by using a panel of microsatellite markers located on chromosome 7, they identified the critical region on chromosome 7 (7p12-7q11.23) which was biallelically deleted in choriocarcinomas. Another study by Ahmed et al., using the comparative genomic hybridization
technique, demonstrated amplification of 7q21-q31 and loss of 8p12-p21 in choriocarcinomas which did not occur in hydatidiform moles.

**Genes involved and proteins**

**Note**

**Gestational type**

In the tumor suppressor genes, p53 (located on chromosome 17 and encodes for a 53 kDa nuclear phosphoprotein that binds to DNA and inhibits the progression of the cell cycle from G1 to S phase), the p21WAF1/CIP1 (a downstream effector of p53 and mediates growth arrest by inhibiting the G1 cyclin-dependent kinase), the retinoblastoma (Rb) gene (a reaction to the inactivation of Rb protein by forming a complex with over-expressed mdm2 proteins) were upregulated in choriocarcinoma than in normal placenta, and the DOC-2/hDab2 gene was downregulated. In oncogenes, the expression of c-myc, c-erb-B-2, c-fms and bcl-2 oncoproteins were studied in normal placenta, partial and complete moles, and choriocarcinoma. The study suggested that synergistic up-regulation of c-myc, c-erb-B-2, c-fms and bcl-2 oncoproteins may be important in the pathogenesis of complete mole and choriocarcinoma.

**References**


This article should be referenced as such: