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Gestational Trophoblastic Disease

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Introduction

Gestational trophoblastic disease (GTD) refers to a group of benign and malignant tumors that develop in the uterus from placental tissue. Pathogenesis of GTD is unique in that maternal tumors arise from gestational tissue that can have locally invasive or metastatic potential. Historical data on incidence of GTD varies widely by region, with higher incidence reported in Asia compared with Europe and North America. These differences are thought to be due at least in part to varying diagnostic criteria, reporting practices, quality of epidemiological data, and diet and nutrition. In the United States, the reported incidence of GTD is approximately one out of every 1000 pregnancies.

Molar pregnancies can be considered as low malignant potential even though they can be a locally aggressive proliferation, with myometrial invasion and systemic metastases. On the other hand, chorionic carcinomas and implantation site tumors are true neoplasms. All of these entities are characterized by focal or diffuse proliferation of trophoblasts.

Trophoblast cells possess several properties that make them unique. They produce the implantation of the embryo within the endometrium and produce chorionic gonadotropin in sufficient quantity to maintain the pregnancy. The normal trophoblast lacks expression of antigens such as those of the HLA and ABO systems, which prevents maternal immune rejection of the embryo. Normal trophoblastic tissues are only capable of invading the maternal decidua, veins, and myometrium. The normal trophoblast continually embolizes trophoblast cells into the maternal venous system where they are filtered by the pulmonary circulation and rarely gain access to the rest of the systemic circulation. These properties of the normal trophoblastic cell are exaggerated in all forms of gestational trophoblastic disease.

Complete and partial hydatidiform mole, invasive hydatidiform mole, and chorionic carcinoma exhibit proliferation of both cytotrophoblast and syncytiotrophoblastic cells, which maintain chorionic gonadotropin secretion.

Hydatidiform Mola

Its incidence ranges between 0.26 and 2.1 per 1000 pregnancies. Some studies have documented an increased risk for women at each end of reproductive life. It has a 30-fold increased risk in women over 50 years of age and six times in women under 15 years of age.

Several studies have indicated that a history of previous abnormal pregnancies increases the risk.

Detailed histopathological studies together with sophisticated cytogenic techniques have established the presence of two different molar syndromes. The complete mole is associated with a paternal diploid genotype, whereas the partial mole is associated with a triploid that incorporates an extra paternal chromosomal complement.

Complete hydatidiform mole

A classic histological triad is presented in the complete mole, it includes diffuse hyperplasia of both cytotrophoblast and syncytiotrophoblastic elements, generalized edema of the chorionic villi and absence of the central vessel. This results in the characteristic macroscopic description of a "bunch of grapes" with no embryo.

Complete moles result from an empty egg (with no maternal genetic component through an unknown mechanism) fertilized by a single sperm. If the paternal 23X chromosome set reduplicates, the normal 46-chromosome component is re-established. Zygotes with genotype 46 YY are nonviable.

Invasive mole

These moles have the characteristics of complete moles in conjunction with invasion beyond the placental site, directly into the myometrium. Venous metastases to the genital tract and lungs are rare. The diagnosis of myometrial invasion is extremely difficult to make on the basis of uterine scrapings. Local penetration through the myometrium may result in uterine rupture or intraperitoneal hemorrhage.

Partial hydatidiform mole

The embryo survives much longer than complete moles, with embryonic death typically occurring at 8 weeks' gestation. There is frequently gross or microscopic evidence of a fetus. Fetal veins are frequently identified and contain nucleated fetal erythrocytes. Histologic features may vary, depending on the gestational age at the time of evacuation. The hydropic change progresses in severity as gestation progresses.

Partial moles result from fertilization by two sperm from one egg with retention of the maternal haploid set. For unknown reasons, 69 XYY partial moles are rare, with 69XXX and 69XXY being the most common.

Treatments of the Mola

Treatment of hydatidiform mole consists of surgical evacuation of the uterus followed by careful monitoring of serum chorionic gonadotropin levels. Although complete and partial moles have different cytogenetic, histopathologic, and clinical features, their management is similar. Partial moles are probably underdiagnosed and may comprise 1% to 2% of all miscarriages.

Complete hydatidiform moles have diffuse, often hydropic, degeneration of the chorionic villi, with trophoblastic proliferation, producing more clinical signs and symptoms. Vaginal bleeding is the most common of the symptoms, frequently producing anemia. Almost half of the patients with complete moles will have a uterine size larger than expected for the time of gestation, due to expansion of the uterus, either by molar tissue or intrauterine bleeding. Unilateral or bilateral ovarian enlargement caused by thiolutin cysts is detected clinically in approximately 25% to 33% of patients with complete moles and is usually associated with chorionic gonadotropin levels above 100,000 mIU/ml. Preeclampsia and/or hyperemesis occur in approximately 25% of patients with a complete mole.

Techniques for evacuation include induction of labor with oxytocin or prostaglandins, cervical dilation followed by uterine curettage or suction, and hysterectomy. If the patient does not want pregnancy, the preferred method is hysterectomy, with the mole in situ. However, most women with moles can be carefully evacuated using suction regardless of uterine size.

Mola complications

Tecolutein cysts when they exceed 5 or 6 cm, they are clinically evident, they are detected in 25% to 35% of cases. Ovarian enlargement correlates with a marked elevation of chorionic gonadotropin levels above 100,000 mIU/ml.

Respiratory Distress Syndrome. Pulmonary complications may be seen in patients with a uterine size of 16 weeks' gestation.

Pregnancy Hypertension Up to 25% of women with complete hydatidiform moles treated in referral centers will present with signs or symptoms of preeclampsia, consisting of hypertension, hyperreflexia, and proteinuria.

Hyperthyroidism Less than 10% of patients with complete moles have symptoms of hyperthyroidism.

Chorion Carcinoma

The incidence of chorionic carcinoma was 2.46 cases per 100,000 pregnancies in the United States. There was an increased risk among women over 45 years of age. Women of color had about twice the risk of white women. In this study, an increased risk was seen in women who had miscarriages before pregnancy. It is a malignant transformation of molar tissue or a new lesion arising spontaneously from the placenta of a full-term pregnancy or miscarriage. It is characterized by a dimorphic proliferation of cyto and syncytiotrophoblastic elements. Chorionic villi are not present. Gestational carcinoma rapidly invades the veins, producing blood-borne metastases. Metastatic sites tend to have areas of central necrosis. Chorionic gonadotropin secretion is produced by both cytotrophoblast and syncytiotrophoblastic elements. The value of this tumor marker correlates well with the volume of disease and is a sensitive marker of response to chemotherapy. Choriocarcinoma usually progresses rapidly, and metastatic disease is fatal without treatment.

Risk Factors for Post molar Trophoblastic Disease

Several factors have been associated with the risk of developing gestational trophoblastic disease (GTD). Many investigators have reported that increasing maternal age is associated with an increased risk of sequelae. This risk appears to increase as the patient enters the perimenopausal age.

The presence of uterine enlargement and the presence of thecolutein cysts are also risk factors. Other clinical risk factors for post molar GTE include extremely high titers (>1,000,000 mIU/ml) of gonadotropin levels, development of pulmonary complications during molar evacuation, eclampsia, and uterine subinvolution with hemorrhage after evacuation.

Follow-up after molar evacuation

Using chorionic gonadotropin levels is the only reliable method for early detection of malignant sequelae after mole evacuation. A baseline level should be obtained 48 hours after evacuation and weekly serial levels until normal levels are obtained. They are then repeated at 1-to-2-month intervals to ensure remission is over 6 to 12 months.

Diagnosis of post molar TGE

Approximately 20% of the s patients undergoing evacuation of a complete hydatidiform mole will develop GTD. 70% to 90% of these consist of moles histologically defined as persistent or invasive, while 10% to 30% are chorionic carcinomas. Criteria for the diagnosis of post molar GTE include high levels of chorionic gonadotropin (level > 20,000 mIU/ml) after 4 months of evacuation, progressive increase in gonadotropin values, histological evidence of invasive mole, chorionic carcinoma or tumor of the site. of implantation or evidence of metastatic disease.

Pregnancy after a mole

Most women treated for mola are in their early reproductive years and desire future pregnancies. Patients after evacuation of complete hydatidiform moles have a risk of preterm birth, spontaneous abortion, and congenital malformations equal to that of the general population. Therefore, after a woman has had a molar pregnancy, she must be informed of the possibility of having future normal pregnancies, but she must also know that she has an increased risk of having new molar pregnancies. The placenta and product of conception should be examined histologically at the time of delivery or evacuation of the pregnancy.

Gestational Trophoblastic Disease

Diagnosis is made in various circumstances:

1.- when a woman presents sustained values of human chorionic gonadotropin.

2.- When she develops a metastatic disease after the evacuation of a hydatidiform mole, a local disease is diagnosed after a normal pregnancy.

Malignant GTD may be confined to the uterus or metastatic at the time of diagnosis. Frequently, patients who develop it after non-molar pregnancies present with signs and symptoms that include gastrointestinal or urological bleeding, hemoptysis, or cerebral hemorrhage. Irregular bleeding from the

uterus or amenorrhea may also be presenting signs. Under these circumstances, the diagnosis of malignant GTD is facilitated by a high level of human chorionic gonadotropin and the exclusion of a normal pregnancy. The possibility of metastatic GTE should be emphasized in any woman of reproductive age with metastases to the lungs or distant sites with an unknown primary. ETG can invade the myometrium and penetrate the small uterine vessels. Venous metastases then occur, resulting in retrograde metastasis in the lower genital tract through the vaginal venous plexus, direct spread to the parametrium or distant to the lungs. Hematogenous systemic metastasis usually occurs only after a pulmonary metastasis has already been established.

The selection of initial therapy and survival are closely related to the identification of poor prognostic factors in patients with metastatic disease.

Three systems are frequently used to classify patients with malignant GTD: the recently modified FIGO clinical classification system that is based on prognostic factors that correlate with failure or success of single-agent therapy from the National Cancer Institute (NCI), and the prognostic index of the World Health Organization (WHO).

FIGO staging

Stage I Strictly confined to the uterine corpus

Stage II Extended outside the uterus, but limited to genital structures

Stage III Extended to the lungs with or without involvement of the genital tract

Stage IV All other metastatic sites

Assigned sub stadiums for each stadium, as follows:

A: No risk factors present

B: A risk factor

C: Both risk factors

Risk factors used to assign substages:

1. Pretreatment serum chorionic gonadotropin > 100,000 mIU/mL

2. Disease duration > 6 months

NCI system

I. Nonmetastatic GTE: No evidence of disease outside the uterus

II. Metastatic GTE: Any metastasis

Metastatic TGE with good prognosis

1. Short duration (< 4 months)

2. Low serum hCG level (< 40,000 mIU/ml)

3. No liver or brain metastases

4. No history of full-term pregnancy

5. No prior chemotherapy

Poor prognosis TGT: Any risk factor

1. Long duration (> 4 months since the last pregnancy)

2. High pre-treatment serum HCG level (>40,000 mIU/ml)

3. Brain or liver metastases

4. History of full-term pregnancy

5. Previous chemotherapy

A complicated scoring system has been adopted by the WHO, based on a retrospective analysis of Bagshaw's experience at Charing Cross Hospital in London. Multiple factors were found to have prognostic significance when analyzed separately, including patient age, type of pregnancy, time interval between pregnancy and development of GTD, human chorionic gonadotropin levels, maternal and paternal blood types, number, and location of metastases, ta size of the major tumor, and treatment with previous chemotherapy.

PROGNOSTIC SCORING INDEX FOR GTN[a]

Prognostic factor	Risk score			
	0	1	2	4
Age (years)	<40	≥40	--	--
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	--
Interval from index pregnancy (months)	<4	4-6	7-12	>12
Pretreatment hCG (IU/L)	$<10^3$	10^3 to $<10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size, including uterus (cm)	<3	3-5	>5	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1-4	5-8	>8
Previous failed chemotherapy	--	--	Single drug	Two or more drugs
Total score	--	--	--	--

Non-Metastatic Gestational Trophoblastic Disease

Most patients in this category are diagnosed after molar evacuation, especially in relation to proliferative or invasive moles. All patient series published by Hammond et al. describe the use of methotrexate and actinomycin D in the treatment of these patients and reported 100% remissions after primary treatment with single-agent regimens.

Prognostic Factors

Human Chorionic Gonadotropin Level

Human chorionic gonadotropin is a sensitive and specific marker for monitoring patients with GTD. The levels presumably reflect the total burden of tumor mass. Women with human chorionic gonadotropin levels greater than 100,000 IU/24-hour urine had a 41% remission rate versus 91% for those with lower levels.

Duration of the disease

The duration of GTD, measured by the time elapsed since the termination of the previous pregnancy, or the duration of symptoms until the initiation of treatment, indirectly reflects the potential for the development of spontaneous drug resistance.

Location of metastases

Lung metastases have a good prognosis, several studies have documented the high risk of brain, liver, and kidney metastases.

Type of previous pregnancy

Women with GTD after a molar pregnancy frequently experience a delay in diagnosis, which allows dissemination, transforming into metastatic disease.

ABO blood group

Bagshaw documented a worse prognosis among women with blood type B or AB or maternal/paternal pairs 0 x A or A x 0.

Tumor size and number of metastases

In addition to human chorionic gonadotropin levels, the size of the largest tumor and the number of metastatic sites or number of identifiable metastases should be recorded.

Prior chemotherapy

The failure of primary chemotherapy is, subject to discussion, the single most important risk factor in patients with GTD.

Treatment

Before current and effective chemotherapy regimens became widely available for STD disease, surgical treatment of invasive nonmetastatic mole cured 85% of patients while clinically localized choriocarcinoma was cured in 41% of cases. Since the introduction of methotrexate to treatment, most centers have reported close to 100% cure in patients with non-metastatic disease using monochemotherapy regimens alone.

Methotrexate and actinomycin are the agents used for these cases

Methotrexate

It has been used since the 1950s with excellent results and almost 100% cure in patients with localized disease. The dose to be administered is 0.4 mg per kg of intramuscular weight for 5 days, with repeated cycles every 12-14 days. Toxicity of this regimen includes alopecia in all cases, mucositis, and significant neutropenia along with skin toxicity in nearly 70% of cases, gastrointestinal side effects seen in 50% of cases, and thrombocytopenia in approximately 40%.

Intramuscular methotrexate is also used at a dose of 1 mg. per kg given on days 1, 3, 5 and 7 alternating with intramuscular folinic acid at a dose of 0.1mg. per kg on days 2, 4, 6 and 8. In general, a single cycle is administered in non-metastatic cases and the regression curve of chorionic gonadotropin is observed, administering two additional cycles after normalization.

Actinomycin

Patients with metastatic TGT can achieve remission of primary and secondary disease with actinomycin as a single agent, at an intravenous dose of 9 to 13 μg/kg/d for 5 days, with an interval of 14 days. The most common toxicity was nausea and vomiting, hair loss, and bone marrow depression.

Methotrexate-Actinomycin alternated

The use of alternate courses of active agents in the treatment of women with GTD may decrease the incidence of failure of therapy caused by drug resistance and may decrease toxicity.

5-Fluorouracil

etoposide

Treatment of Low-Risk Trophoblastic Disease

According to the WHO system, most patients who have a good prognosis according to the clinical classification are low-risk patients.

As seen above, in patients with low-risk metastatic disease, initial single-agent therapy is a reasonable option, intramuscular methotrexate for 5 days is the indication as the initial regimen, and actinomycin is reserved for second-line treatments, too. Methotrexate and folinic acid have been used alternately for 8 days, producing averages of complete remissions of approximately 50% to 68%. All patients with methotrexate-resistant disease were subsequently cured with actinomycin in 5-day cycles or combination therapy.

Treatment of High-Risk Trophoblastic Disease.

These patients benefit much more from polychemotherapy.

Chemotherapy with the MAC scheme consists of methotrexate 0.3 mg/kg, IM; actinomycin 0.5 mg, IV and chlorambucil 0.2 mg/kg, PO (or cyclophosphamide 250 mg/IV), each for 5 days. Cycles are repeated every 14-21 days and in most studies in which patients had brain and liver metastases, radiation therapy was added. Using this regimen or its variations, remissions are reported in approximately 60-80% of patients with high-risk metastatic disease. This schedule has significant toxicity, particularly if cycles are repeated in less than 21 days. In the mid-1970s, Bagshaw proposed a complex scheme that alternated 8 drugs: methotrexate, actinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine (CHAMOMA), to be used in patients with high-risk metastatic disease.

The other widely used scheme is the EMA-CO scheme, etoposide, methotrexate, actinomycin, methotrexate with folic acid rescue, vincristine, and cyclophosphamide.

High-Risk Metastatic Locations

Central Nervous System Metastasis

Whole-brain irradiation is used to control the nervous system, among patients receiving methotrexate or schemes such as EMA-CO , whole-brain radiation has been incorporated into the primary treatment of these patients.

liver metastases

They are found in approximately 2% to 8% of patients with ETG. Liver involvement is a poor prognostic factor.

Drug Resistant Disease

High-risk metastatic TGT patients who have failed primary chemotherapy are very challenging and have a very poor prognosis. Details of prior therapy should be fully reviewed to identify potentially active agents that have not been used. Surgical removal of drug-resistant foci is an action that should be considered in cases of limited systemic metastases.

Patients treated with chemotherapy for malignant GTD should be monitored at least weekly using chorionic gonadotropin.

After completion of chemotherapy, patients are monitored with serial human chorionic gonadotropin values at 2-week intervals for the first 3 months after completion of chemotherapy, and at least monthly for the first year of follow-up.

Additional Agents/Regimens with Potential Activity in Treatment-Resistant GTN

Several additional treatment regimens have been shown to have some activity when treating resistant GTN, including high-dose chemotherapy (HDC) with peripheral stem cell transplant, immunotherapy, and other chemotherapy regimens. For a subset of patients with resistant disease despite multidrug chemotherapy, HDC with autologous stem cell support has been reported to produce sustained complete responses.

A retrospective study of 32 patients with refractory choriocarcinoma or poor- prognosis PSTT/ETT who underwent HDC with peripheral blood stem cell support reported a sustained complete response in 7 patients, with 13 of 32 patients' disease remaining free at the time of analysis following HDC with or without additional therapy.

Pembrolizumab is a monoclonal antibody that inhibits programmed cell death protein 1 (PD-1), which functions as a checkpoint protein for regulation of various immune cells, including T cells with potential antitumor activity. Programmed death ligand 1 (PD-L1) is strongly expressed by GTN.

Outcomes were recently reported for four patients with drug-resistant GTN who received pembrolizumab, including two cases of metastatic choriocarcinoma and two cases of metastatic PSTT or mixed PSTT/ETT.109 All patients had tumors with high levels of PD-L1 expression. Durable response to pembrolizumab was observed in three of the four cases. The patient whose disease did not respond to pembrolizumab had strong PD-L1 tumor expression but an absence of tumor-infiltrating lymphocytes. Based on these data, the NCCN Panel also added nivolumab, another PD-1 inhibitor, to the list of regimens that may potentially be effective against treatment-resistant GTN.

Avelumab, a PD-L1 inhibitor, may also be effective against treatment-resistant GTN. Results from a phase II study enrolling 15 patients with GTN who experienced disease progression after single-agent chemotherapy suggested that avelumab was effective in normalizing hCG levels in approximately half of the patients.

Gemcitabine, capecitabine, and fluorouracil may also have potential for treating GTN in this se thing. Limited data have suggested activity of gemcitabine, administered with or without a platinum agent. Additional support for the potential activity of these regimens in GTN can be found in the data for treating germ cell tumors. Successful use of capecitabine as single-agent salvage chemotherapy has been reported. Groups in Asia have also reported on fluorouracil, primarily in combination with dactinomycin.

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