Gestational trophoblastic disease

Ka Yu Tse

Karen KL Chan

Kar Fai Tam

Hextan YS Ngan

Abstract

Gestational trophoblastic disease is a rare pregnancy-related disorder and its incidence is about 1 in 1000 livebirths in the West. It comprises of partial mole, complete mole, invasive and metastatic mole, choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour. Novel immunohistochemical technologies have helped in the diagnosis of the disease and some of the genes may also serve as prognostic markers. Partial and complete moles can be treated by suction evacuation and most patients do not require further treatment. However, 10–20% of them may develop gestational trophoblastic neoplasia. The Gynecological Oncology Committee has adopted a staging system with incorporation of the modified World Health Organization scoring system. Low-risk disease is treated by single-agent chemotherapy while high-risk disease is treated by multi-agent chemotherapy. The overall cure rate is more than 90% and most patients can preserve fertility and anticipate normal pregnancy outcomes. Nevertheless, the disease can recur. Referral to a specialist centre is important to ensure proper monitoring and management.

Keywords choriocarcinoma; epithelioid trophoblastc tumour; gestational trophoblastic disease; hydatidiform mole; placental site trophoblastic tumour

Introduction

Gestational trophoblastic disease (GTD) consists of a spectrum of pregnancy-related disorders ranging from benign hydatidiform mole, clinically malignant conditions like invasive mole and metastatic mole, to neoplastic conditions including choriocarcinoma, placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). GTD can be subdivided into those with and without chorionic villi (see Table 1). In 2003, the World Health Organization (WHO) also developed a classification system (see Table 2). GTD was once a potentially fatal disease entity, however, with more understanding about the disease, most patients can now be treated conservatively and have a favourable prognosis.

Types of gestational trophoblastic disease

With villi
Hydatidiform mole: complete mole, partial mole
Invasive mole
Persistent mole
Cholangiocarcinoma

Without villi
Placental site nodules and plaques
Placental site trophoblastic tumour
Epithelioid trophoblastic tumour
Choriocarcinoma

Table 1

Hydatidiform mole

Epidemiology

Hydatidiform mole can be classified into complete and partial moles. Molar pregnancy is a rare disease. Its incidence varies worldwide, being seven to 10 times higher in Southeast Asia than in Europe and North America. For example, the reported incidence is 1 in 125 livebirths in Taiwan, while it is 1 in 1000 in Europe and 1 in 1500 in the United States, respectively. The incidence in certain Asian countries shows a decreasing trend probably related to the change of lifestyle, diet and environment. However, the accuracy of these epidemiological data depends on how vigilant and reliable the registry system is. Besides, the incidence of molar pregnancy may be under-estimated if the tissue masses are not saved for histological examination after miscarriage or termination of pregnancy.

Molar pregnancy is more common at the extremes of ages. Previous history of molar pregnancy increases the risk of

WHO classification of gestational trophoblastic disease

Hydatidiform mole: complete mole, partial mole
Invasive hydatidiform mole
Choriocarcinoma
Placental site trophoblastic tumour
Trophoblastic lesions, miscellaneous
Exaggerated placental site
Placental site nodules and plaques
Unclassified trophoblastic lesion

WHO, World Health Organization.

Table 2

Ka Yu Tse *MBBS MMedSc MRCOG is at the Department of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, Hong Kong.*

Karen KL Chan *MBBChir MRCOG is at the Department of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, Hong Kong.*

Kar Fai Tam *MBBS MRCOG is at the Department of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, Hong Kong.*

Hextan YS Ngan *MBBS MD FRCOG is at the Department of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, Hong Kong.*

recurrent molar pregnancy to 1.8%, around 20 times higher than the background risk. Case-controlled studies had suggested that vitamin A precursor carotene deficiency was associated with increased risk of complete mole but not partial mole. Recent genetic studies also showed that mutation in NLRP7 (formerly known as NALP7) gene – a CATERPILLER protein family involved in pathogen-induced inflammation and apoptosis – on chromosome 19q13.4 was associated with familial and recurrent hydatidiform mole. In addition, the use of oral contraceptive pills increases the risk of molar pregnancy (relative risk (RR) 1.3–2.6) and such risk appears to increase with the duration of the use of the pills. On the other hand, it is still controversial about the effects of parity, blood group, paternal age, smoking and alcohol consumption in molar pregnancy.

Pathology

Cytogenetic studies have shown that complete mole has a diploid karyotype and is paternal in origin. It is the result of fertilisation of an empty ovum by a haploid sperm, which then duplicates its chromosomes and the karyotype configuration of the complete mole zygote is 46, XX. In about 4–20% of cases, an empty ovum is fertilised by two haploid sperms resulting in 46, XX or XY. In partial mole, a haploid ovum is fertilised by two sperms. The zygote, therefore, becomes triploid containing 69, XXY, XXX and rarely XYY.

Complete mole is characterised by gross villous vesicles although sometimes these may not be present in early gestation. Histologically, there are diffuse hydropic villi and trophoblastic hyperplasia. The cytotrophoblasts may show nuclear pleomorphism. There are no foetal tissues identified. In contrast, gross villous vesicles are only occasionally seen in partial mole and these tend to be smaller and less numerous compared with complete mole. Normal gestational products like gestational sac, embryo, foetus or placenta may be present. Hydropic villi and trophoblastic hyperplasia are less conspicuous in partial mole and foetal tissues like erythrocyte may be found. There may also be scalloping of chorionic villi and trophoblastic stromal inclusions. Hydropic abortion may mimic complete and partial moles. Gross examination of hydropic abortion shows 'normal'-looking products of gestation and the amount of tissues tends to be scanty. The villi show hydropic change, which may be balloon-like and cisterns are absent. The trophoblasts are usually attenuated and trophoblastic hyperplasia may only be seen in miscarriage with aneuploidy. Immunostaining may be helpful. Ki-67, a proliferation marker, was positive in $<25\%$ of cytotrophoblastic nuclei in hydropic abortion compared with $>65\%$ in molar pregnancies. p57 (KIP2) is a paternally imprinted gene and is maternally expressed. Complete mole is composed of paternal DNA and so there is absence of p57 (KIP2) nuclear staining in the cytotrophoblasts and villous stromal cells. On the other hand, since partial mole and hydropic abortion contain maternal DNA, p57 (KIP2) is positive.

Presentation

The most common presentation of molar pregnancy is vaginal bleeding complicating pregnancy. Some may also have passage of vesicles and the uterus may be larger than date on examination. With more popular use of early ultrasound, molar pregnancy may just be incidentally shown and the patients may not be symptomatic at all. And due to the early diagnosis, florid symptoms of hyperemesis gravidarum, hyperthyroidism, early-onset pre-eclampsia, thromboembolism, large ovarian theca lutein cysts and neurological and chest symptoms due to brain and lung metastasis are rarely seen nowadays.

Investigation

Ultrasound is commonly performed in pregnancy. Complete mole may be diagnosed by features such as anembryonic pregnancy, delayed miscarriage and snow-storm appearance. It is difficult to detect partial mole by ultrasound, although some have described soft markers such as cystic spaces in placenta, ratio of transverse to antero-posterior diameters of the gestational sac more than 1.5. In general, the detection rate of molar pregnancy by ultrasound is poor. In one retrospective study involving more than 1000 patients, the sensitivity, specificity, positive predictive value and negative predictive value for ultrasound in detecting hydatidiform mole were 44%, 74%, 88% and 23%, respectively.

Human chorionic gonadotrophin

Human chorionic gonadotrophin (hCG) is a glycoprotein produced by syncytiotrophoblasts. It contains α and β subunits joined by non-covalent bonds. In normal pregnancy, most hCG is intact. In GTD, there is a higher proportion of β-hCG compared with that in normal pregnancy. β-hCG not only reflects trophoblastic activity but also promotes tumourigenesis. Various forms of β-hCG exist in GTD, including free-β, β-core, nicked free-β and carboxyl-terminal fragment. Therefore, an ideal hCG assay for GTD should detect all forms of β-hCG. False-positive and false-negative results can occur. Phantom hCG (pseudohypergonadotropinemia) is a result of the presence of heterophilic antibodies in serum giving rise to a falsely elevated hCG. If there is discrepancy with the clinical presentation, hCG levels should be measured again with a different immunoassay. The other alternative is to measure the urine hCG level because heterophilic antibodies are not excreted into the urine. The serum hCG can also be diluted serially. The lack of dilutional parallelism also indicates the presence of phantom hCG. On the other, high dose hook effect can occur with a falsely low serum hCG level. When the serum hCG level is too high, there are not enough antibodies in the solution to bind the hCG molecules and hence much of them are being washed away without being measured. If very high hCG is suspected, the laboratory should be informed and the serum should be diluted before measurement.

It had been shown that 46% of 153 patients with complete mole had elevated hCG level over 100,000 IU/l before evacuation. However, there is no consensus on a cut-off level for making the diagnosis. Besides, hCG level can also reach to 100,000 IU/l at 7–10 weeks in normal pregnancy. While hCG may not be diagnostic of molar pregnancy, it should be measured as a baseline for subsequent monitoring if molar pregnancy is suspected before evacuation.

Treatment

Uterine evacuation of the uterus can obtain tissues for histological diagnosis and treat the condition completely under most circumstances. Medical induction and cervical priming by prostaglandins are not recommended for molar pregnancy because of the theoretical risk of myometrial contraction and tumour embolism