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REVIEW

The genetics of gestational trophoblastic disease: a rare complication of pregnancy

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Gestational choriocarcinoma is usually a rapidly spreading fatal disease, but it is curable if diagnosed early and treated. It is a unique malignancy that is a partial or complete allograft with a genotype that is not the same as the host genotype. It is most often preceded by an abnormal molar pregnancy. The surprising and unique androgenetic origin of complete hydatidiform molar pregnancies was first revealed by Kajii and Ohama in 1977. We describe the current understanding of the morphology, epidemiology and genetics of gestational trophoblastic disease that followed the milestone findings by Kajii and Ohama.

Keywords Choriocarcinoma, gestational trophoblastic disease, androgenetic hydatidiform mole, *NLRP7*, genomic imprinting

Gestational trophoblastic disease (GTD) encompasses a heterogeneous family of diseases, which includes hydatidiform moles, invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These proliferations arise from placental villous trophoblast and vary in propensity for local invasion and metastasis. The benign forms of GTD include complete and partial hydatidiform molar pregnancies. The malignant forms, which include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor, can progress, metastasize, and lead to death if not treated. However, because of advances in medicine, most cases of malignant GTD can now be successfully treated and cured. Approximately 10% of complete hydatidiform moles transform into one of the malignant forms of GTD (1). And although it is true that most women with malignant GTD can expect to be successfully treated with modern chemotherapy, more than 10% of these patients in some parts of the world still die. This is usually due to delayed diagnosis and inadequate follow-up care (2).

This spectrum of pregnancy-related disorders is unique and interesting. First, hydatidiform moles and gestational choriocarcinoma have rarely been recognized in any other species. Additionally, gestational trophoblastic tumors are naturally occurring allografts, arising not from the patient's own tissue but from a conceptus with a different genotype. It is thought that this genetic difference facilitates rejection of the tumor cells and contributes to their highly favorable response to cytotoxic chemotherapeutic drugs. Also, because all gestational trophoblastic tumors produce human chorionic gonadotropin (hCG), it can be used as a unique biochemical marker and aid in the early detection, diagnosis, and follow-up of these tumors and possible metastatic disease. Blood serum levels can be monitored for the presence of hCG (especially in postmolar cases), leading to early diagnosis and successful treatment. Untreated choriocarcinoma can rapidly spread and is fatal. This is exemplified by rare but unfortunate reports of dissemination of choriocarcinoma from organ transplant donors to recipients. Organs, including lung, kidney, and liver, from patients with undiagnosed choriocarcinoma have been inadvertently transplanted into recipients, in some cases tragically leading to rapid death of the recipients (3,4). Cases such as these emphasize the need for complete medical history of the donor, along with a thorough physical examination. Caution is needed when screening a female donor of childbearing age who has a history of menstrual irregularities, especially following a pregnancy or abortion. Appropriate screening tests such as β-hCG should be performed.

The androgenetic origin of complete hydatidiform moles (CHMs) was first revealed by Kajii and Ohama in 1977, based on chromosomal polymorphisms (5). This was a very surprising finding at that time because androgenetic conceptions with exclusively paternal chromosomes were not described earlier in humans or any other animal species.

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This result was rapidly confirmed by other groups (6–11). Elegant nuclear transplantation experiments performed in mice were reported in the 1980s that clearly described the fate of androgenetic as well as parthenogenetic diploid embryos and provided the proof that both the paternal and maternal genetic contributions are necessary for normal development (12–14). In this review, we describe the current understanding of the genetics of trophoblastic disease that followed the milestone findings by Kajii and Ohama.

Hydatidiform mole: complete and partial

Pathology and genetics of hydatidiform moles

Hydatidiform mole is the most common form of GTD, with an incidence of 1–3 out of every 1000 pregnancies (1). These abnormal conceptions have excessive placental development and little or no fetal development. Detailed morphology and genetic analysis in the late 1970s delineated two major types, namely, complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM). These two differ clinically with distinctive pathologic and genetic features (15,16).

In general, CHM is characterized by rapid hydatidiform change affecting the entire placenta. Histologically, there is marked villous hydrops and extensive circumferential villous trophoblastic hyperplasia, central villous cistern formation with compression of the villous stroma and random karyorrhexis, and little or no embryonic development. Genetically, CHMs are usually diploid and androgenetic in origin, with either a 46,XX or 46,XY karyotype (17). In our laboratory, we have collected data on 433 cases of CHMs since 1978. Of the androgenetic CHMs with cytogenetic analysis, we found 247 cases of diploid XX and 29 cases of diploid XY. In addition, there were three 92,XXXX cases, one 92,XXXY case, and one 92,XXYY case. Approximately 80% of androgenetic CHMs arise from the duplication of the haploid genome of a single sperm, whereas the other 20% appear to arise from dispermy, the fertilization of the egg by two sperm (18–20). Despite the androgenetic nature of the nuclear genome in CHM, the mitochondrial DNA has been shown to be maternally derived (21,22). The fate of the maternal genome in a CHM is still unclear. Originally, it was assumed that an error in meiosis II produced an anucleate egg, which was then fertilized by one or two sperm. More recently, arguments against the existence of "anucleate" eggs have resulted in an alternative theory, the postzygotic diploidization of a triploid conception (23). This theory originates with the formation of a diandric triploid conception usually by fertilization of a single oocyte (M) by two sperm (P_1 and P_2) or by a diploid sperm (P_1P_2). Triploidy is a relatively frequent fertilization error and occurs in approximately 1–2% of all human conceptions (23). The triploid zygote with three pronuclei (M, P_1, and P_2) can maintain the triploid state and produce a diandric triploid zygote (MP_1P_2) or the tripronuclear zygote could undergo abnormal cleavage resulting in 1n, 2n, and 3n derivatives. Some of these 1n and 2n cells may develop into hydatidiform moles or mosaicism involving an androgenetic cell line (Figure 2). Because the first zygotic division is orchestrated by the paternal centrosomes, cleavage errors often occur in cases of dispermic triploid zygotes due to the presence of two active centrioles in one ovum. During the first cleavage, the tripronuclear zygote can undergo abnormal division resulting in a 2n biparental derivative (MP_1) and a 1n derivative (P_2) that can undergo endoreduplication (P_2P_2). One sperm (P_1) contributes to a biparental genome and the other sperm (P_2) gives rise to a homozygous androgenetic mole. Abnormal division of the tripronuclear zygote could also result in the elimination of the maternal pronucleus (M) and the formation of a 2n heterozygous androgenetic mole (P_1P_2). Postzygotic diploidization of triploids provides a natural explanation for 2n homozygous and heterozygous androgenetic moles and may also explain unusual cases of chimerism, 2n/3n mosaicism, 2n/2n androgenetic/biparental conceptions, and 2n/2n molar/twin conceptions. In addition, this theory does not require the fertilization of an "empty egg". Evidence for the natural occurrence of anuclear oocytes has never been observed. Examples of cases that could have originated from the diploidization of triploids and support this theory have been reported in several studies (24–30). However, not all features of the genetics of CHMs can be explained by the postzygotic diploidization of triploids theory, namely, the 4:1 frequency of homozygous versus heterozygous androgenetic CHMs.

Partial hydatidiform moles (PHMs) demonstrate slow hydatidiform change, affecting only some of the placental villi. Microscopic examination of the villi shows focal trophoblastic hyperplasia, trophoblastic pseudoinclusions, and occasional cistern formation. Some fetal development is possible. The most common karyotype for PHM is triploid (69,XXX, 69,XXY, or 69,XYY), with the extra haploid genome being paternal in origin (8,9). The majority of these diandric triploid PHMs have been shown to arise from fertilization with two sperm, and less frequently by a diploid sperm (31). The existence of diploid PHMs is under debate, as some reported diploid PHMs may actually represent misdiagnosed diploid hydropic abortions, twin pregnancies, undetected mosaic cases, or early CHMs.

Diagnostic techniques for hydatidiform moles

Improved ultrasound techniques have led to earlier termination of molar pregnancies, and their classic morphologic and histologic features may not be as evident earlier in gestation. Updated criteria for the histologic features of first-trimester moles are helpful (32); however, additional diagnostic techniques may be necessary to properly diagnose CHM versus PHM versus hydropic abortion. In addition, mosaic conceptions involving a diploid androgenetic cell line or diploid/triploid mosaic cases can pose even greater diagnostic confusion. Since CHMs and PHMs are genetically distinct, techniques that make use of those unique differences can be useful. Immunostaining techniques for maternally expressed genes such as $p57^{KIP2}$ have proven to be valuable diagnostic tools for discriminating CHMs from other hydropic conceptions with a suspicious questionable molar phenotype, because most CHMs contain only paternal genes (33,34). In addition, $p57^{KIP2}$ analysis can also detect mosaicism involving androgenetic and biparental cell lines and can further assess the distribution of these cells within the placental villus structure. However, $p57^{KIP2}$ staining cannot distinguish PHMs from nonmolar hydropic abortions. Occasionally, $p57^{KIP2}$ expression patterns can be erroneously interpreted because of a loss