Molecular Diagnosis of Hydatidiform Moles is Ready for Primetime

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In recent months, two specialty pathology journals chose article images of molecular diagnosis of hydatidiform mole as the journal front covers: the March issue of The International Journal of Gynecological Pathology [1] and the July issue of the Journal of Molecular Diagnostics released [2]. Such emerging interests in the molecular diagnosis of hydatidiform moles may be explained by one simple reason that is our inability to accurately diagnose these common conditions by traditional histology and ancillary studies.

Hydatidiform moles are generally subclassified into complete and partial moles. While histological diagnosis of well-developed complete mole is generally reliable, increasingly evacuated at a much earlier stage nowadays, an early complete mole is often mistaken as a hydropic abortus or a normal pregnancy by both clinicians and pathologists [3]. Partial moles are even more problematic with both under and over diagnosis in about 50% of the cases in the current practice [4]. Yet, it is clinically important to distinguish a hydatidiform mole from a non-molar hydropic abortus, primarily because of the associated risk of development of postmolar gestational trophoblastic neoplasia [3-6]. Accurate subclassification of hydatidiform moles is also important as a complete mole has a much higher risk of progression to gestational trophoblastic neoplasia (18 to 29%) [5] than a partial mole (1.0 to 5.6%) [5,6]. On the other hand, over-diagnosis of molar pregnancy is not without clinical consequence, as all such patients should enter the trophoblastic disease surveillance program that can be particularly burdensome and costly [5]. Thus, reliable diagnostic approaches of molar pregnancy with improved sensitivity and specificity are highly desirable.

It has been firmly established that the pathogenesis of hydatidiform moles requires specific abnormal genetic compositions present in conception. Molecular investigations in the 1970’s established the genetic bases for the pathogenesis of hydatidiform mole [7]. In contrast to a normal diploid gestation of monogygic and monooandric parental compliment (46, XX or XY), essentially all complete hydatidiform moles have a diandric, paternal-only genome, with either 46, XX diploid karyotype arising from the fertilization of an unenculated egg by one spermatozoon followed by duplication (monospermic or homoygous, 80%), or 46, XX or XY karyotype arising from the fertilization of an unenculated egg by two spermatozoa simultaneously (dispermic or heterozygous, 20%) [8]. A rare exception is the existence of biparental (monogygic and monooandric genome) complete mole, which is frequently recurrent with strong familiar tendency and associated with mutations of NAPL7 [9].

The genetic profile of partial hydatidiform moles is triploid with a diandric, monogygic genome arising from the fertilization of a haploid egg by either two spermatozoa (dispermic or heterozygous, 90%) or one spermatozoon with duplication (monospermic or homoygous, 10%) [8]. The resulting conception is triploid with diandric and monogygic haploid genomes, 69, XXX or XXY karyotype. It is important to note that one-third of triploid early missed abortions are digynic and monooandric, but is not partial hydatidiform moles [4]. Therefore, at genetic level, determination of the parental source of the haploid sets is crucial for the separation of a partial mole from a nonmolar triploid gestation.

Various genetic and molecular approaches were explored in the past to improve the diagnosis of hydatidiform moles. Flow cytometry is the most common method for ploidy analysis for the separation of a partial mole from a complete mole or a diploid non-molar hydropic abortus by demonstration of triploidy. Conventional karyotyping is the most accurate chromosomal enumeration method that may be used to confirm the presence of triploidy in a partial mole or diploidy in a complete mole. Interphase FISH can be used for the determination of the number of haploid chromosome sets. However, all these methods cannot distinguish a diploid complete mole from a more common nonmolar hydropic abortus, and is unable to separate a true diandric-monoandric partial mole from a digynic-monoandric non-molar gestation. Cytogenetic studies based on analysis of pericentromeric chromosome heteromorphisms can be used to identify the parental source of chromosomes and may specifically diagnose and subtype hydatidiform moles [7,10]. However, similar to the conventional karyotyping, it requires fresh chorionic villous samples and in vitro cell culture. Polymorphic deletion probe (PDP) fluorescence in-situ hybridization based on copy number variants are highly polymorphic and has been recently applied for the diagnosis of molar gestations using paraffin embedded tissue specimens [11]. Using such PDP probes, however, the diagnostic sensitivity was quite limited: 40% of complete moles and 46.2% of partial moles [2], likely due to small number of polymorphic PDP probes in the study.

DNA genotyping provides the best measurement of genetic variation between members of a species and therefore, can be used to identify parental source of genomic haploid set(s) in a hydatidiform mole. Different molecular methods have been explored, including DNA restriction fragment length polymorphism; enzyme polymorphism and single nucleotide polymorphism [11]. Recently the short tandem repeats (STR) polymorphism analysis has emerged as the most sensitive and specific genotyping method for diagnosis of hydatidiform moles [12] and its diagnostic power and clinical applicability have been confirmed by several studies [8,13,14]. A potential pitfall for the genotypic diagnosis of hydatidiform mole is the presence of a small subset of complete mole of biparental origin, histologically indistinguishable from the diandric uniparental complete mole and DNA genotyping is not helpful [9].

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Although hydatidiform moles are evacuated at a much earlier gestational age in modern medicine, their associated risks for post-molar gestational trophoblastic neoplasia have not been changed [5]. In the absence of typical clinical and imaging features, the role of the pathologist has become even more crucial. Pathologists need to have a high index of suspicion for early complete hydatidiform moles, which are easily misinterpreted as hydropic abortions or even normal pregnancies. When in doubt, ancillary studies such as p57 immunohistochemistry and STR genotyping should be used to rule out a molar gestation. Although inconclusive, recent clinical data support the notion that heterozygous (dispermic) complete moles is more aggressive than the homozygous (monospermic) ones [15]. Therefore a precise genotyping of every complete mole may be desirable. Genotyping diagnosis is highly recommended when a partial mole is suspected. Even with careful histological examination and ploidy analysis, pathologists can only reproducibly recognize up to 50% of partial moles [4]. The money saved by avoiding over-treating nonmolar patients should easily offset the cost of STR genotyping, which runs about 450$ under the current billing codes. With rapidly increasing gestational age in modern medicine, their associated risks for post-molar gestational trophoblastic neoplasia have not been changed [5].

References