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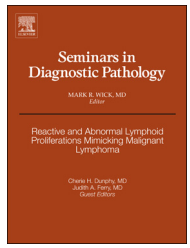

Immunohistochemistry and other ancillary techniques in the diagnosis of gestational trophoblastic diseases

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ABSTRACT

Gestational trophoblastic disease (GTD) encompasses entities ranging from ubiquitous hydatidiform moles to rare neoplastic gestational trophoblastic tumors. In practice, the histological diagnosis of GTD continues to have significant diagnostic inaccuracy with marked inter- and intra-observer variability, even among expert pathologists. Studies in correlation with genotypic evidence have confirmed a lack of accuracy in diagnosis of hydatidiform moles using histology alone. Applications of new immunohistochemical markers and molecular techniques have significantly enhanced the diagnostic precision of various GTDs in recent years. p57 Immunohistochemistry is a highly useful marker in confirming complete hydatidiform mole. PCR-based DNA genotyping has emerged as a powerful diagnostic measure to precisely classify both complete and partial hydatidiform moles. With acquisition of molecular diagnostic capabilities at most medical centers, these ancillary techniques have been increasingly integrated into the routine diagnostic workup of GTD. We propose an algorithmic approach combining histology and these ancillary tests to provide the best diagnostic practice possible. Under this algorithm, all cases with histological suspicion for complete mole are subject to p57 immunohistochemical confirmation, and all cases with histological suspicion for partial mole undergo DNA genotyping workup. Beyond hydatidiform mole, recognition of gestational trophoblastic tumors requires a high index of suspicion and application of immunohistochemical markers of trophoblast is helpful to accurately diagnose these rare tumors.

Introduction

Gestational trophoblastic disease (GTD) encompasses a spectrum of proliferative disorders of the placental trophoblast, including hydatidiform moles—non-neoplastic proliferations of the chorionic villous trophoblast—and trophoblastic tumors, such as choriocarcinoma, epithelioid trophoblastic tumor (ETT), and placental site trophoblastic tumor (PSTT). The pathological diagnosis of these entities, especially hydatidiform moles, rarely can be made on morphology alone; most often, it requires the use of various ancillary techniques to demonstrate the unique underlying genetic abnormalities of these lesions.

Abortion specimens with hydropic chorionic villi are routinely encountered in general and gynecological pathology practice. For prognostic and clinical management purposes, it

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is crucial to diagnostically separate the non-molar, hydropic abortions from hydatidiform moles, as the latter are associated with increased risk of persistent GTD and gestational trophoblastic neoplasia (GTN) and require comprehensive clinical follow-up of the patient. Complete moles progress into persistent/invasive mole in approximately 15–20% of cases and into gestational choriocarcinoma in 2–3%,[1–4] while the risk of persistent GTD after a partial mole ranges between 0.5% and 5%.[5,6] The histomorphologic features of hydatidiform moles and other hydropic non-molar products of conceptions often overlap and have a low sensitivity and specificity, particularly for partial hydatidiform mole.

There have been tremendous advances in our understanding of genetic basis of GTD over the past three decades, followed more recently by development of ancillary diagnostic testing methods, including DNA ploidy analysis, immunohistochemical detection of imprinted genes, and most recently, DNA short tandem repeat genotyping. Diagnostic algorithms have been proposed in the pathology diagnostic workup of GTD using a combination of traditional morphologic assessment and ancillary studies to offer the highest diagnostic accuracy.

Genetic background of molar gestations

Complete and partial hydatidiform moles have characteristic parental contribution to their genome. Complete hydatidiform moles (CHM) are entirely paternally derived, most often with a diploid homozygous 46XX genotype.[7] Approximately 10–20% of CHM are heterozygous and have a 46XX or 46XY genotype,[7,8] and less common tetraploid complete moles with a paternal-only genome also exist.[9] A very rare exception to this genetic profile is biparental CHM, containing both maternal and paternal genome (monoandric monogynic), resulting from homozygous or compound heterozygous mutations of the NLRP7 gene on chromosome 19q13.4.[10,11] In addition to the different pathogenetic implications, the molecular genetic subtypes of complete moles also bear clinical significance: heterozygous (dispermic) complete moles have been reported to have a more aggressive behavior than the homozygous (monospermic) ones.[12,13] Biparental complete moles have a strong familial tendency and are nearly always followed by recurrent complete moles in subsequent pregnancies.[14]

Partial hydatidiform moles (PHM) also have paternal dominance in their genome; they are typically triploid with one set of maternal and two sets of paternal chromosomes, most often (approximately 90% of cases), resulting from two sperms fertilizing a haploid ovum (dispermic, heterozygous PHM) and less commonly (10%) arising from one sperm followed by duplication of the paternal chromosome set (monospermic, homozygous PHM).[15,16] In addition, rare tetraploid partial moles with three haploid paternal chromosome sets have also been reported.[17,18] Digynic monoandric gestations (with two sets of maternal and one set of paternal chromosomes), on the other hand, constitute roughly one-third of all triploid gestations; they are not genetic partial moles and are not associated with increased risk of gestational trophoblastic disease or trophoblastic neoplasia.[15,19,20]

Histopathology of hydatidiform moles and their mimics

Evaluation of histomorphologic features is the first and most basic step in the pathology diagnostic work-up of molar gestations. While well-developed complete moles have easily recognizable characteristic morphology, i.e., marked villous hydrops with cistern formation and diffuse circumferential trophoblastic hyperplasia (Fig. 1A and B), early complete moles and especially partial hydatidiform moles can pose a significant diagnostic challenge based on morphologic features alone.

Complete hydatidiform moles that are evacuated early (at less than 12 weeks gestational age) may have more subtle histologic findings with polypoid or "cauliflower-like" villous shape and mild to moderate circumferential trophoblastic hyperplasia. The villous stroma is usually less hydropic, instead it appears hypercellular with a myxoid matrix and prominent karyorrhexis (Fig. 1C and D).

Majority of partial hydatidiform moles, on the other hand, show relatively non-specific histomorphology—two villous populations, villous hydrops, mild to moderate trophoblastic hyperplasia, irregular villous contours, and trophoblastic pseudo-inclusions—which often overlaps with other non-molar genetically abnormal gestations or hydropic abortions (Fig. 2).[21–24] The size of chorionic villi in PHM ranges between 1 and 6 mm.[24,25] Cistern formation may be seen in nearly 60% of cases, which in combination with a maximum villous size of $\geq$2.5 mm has been shown to have a 90% positive predictive value for partial mole, when compared with trisomy syndromes and non-molar hydropic abortions.[25] Chromosomal trisomies (especially trisomies 7, 8, 13, 15, 16, 18, 21, and 22) can be microscopically indistinguishable from PHM, as they often show abnormal villous shape with trophoblastic pseudo-inclusions as well as villous hydrops.[25–29] Another particularly important entity in the differential diagnosis of PHM is digynic triploidy, which mimics partial moles both at the morphologic and DNA ploidy level (see below). Hydropic non-molar abortions may simulate complete and partial hydatidiform moles, mainly due to the presence of hydropic villi, and less commonly, cistern formation and irregular villous shape with trophoblastic pseudo-inclusions.

The distinction between partial and very early complete hydatidiform moles may be facilitated by identification of fetal tissues, which are generally absent in complete moles. However, fetal vessels and nucleated red blood cells have been rarely described in very early CHM,[30–32] and in rare cases of CHM arising from a twin gestation.[20,30]

The histological diagnosis of hydatidiform moles continues to suffer from poor inter-observer agreement when based solely on morphology even among gynecologic pathologists, and significant under- and over-diagnosis of molar gestations —especially PHM exists, leading to adverse clinical consequences.[33,34]

A high index of suspicion at the time of morphologic evaluation is crucial to initiate further diagnostic work-up and utilize ancillary techniques for the correct diagnosis and classification of hydatidiform moles.