Molecular Diagnosis of Placental Hydatidiform Mole: Innovation and Outcomes

Terence J. Colgan, MD; Abdul Noor, PhD; Shabin Nanji, MBB Chir; Martin C. Chang, MD, PhD; Elena Kolomietz, PhD

Department of Pathology and Laboratory Medicine, Sinai Health System, University of Toronto, Toronto, ON

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> "Aim for the right diagnosis, right treatment and right care at the right time, based on the needs of each individual."[1]

INTRODUCTION

Placental hydatidiform mole is an abnormal growth of the placenta and occurs in about 1 to 2 of every 1000 live births.[2] Molar disease can give rise to life-threatening gestational trophoblastic disease. Complete mole has a diandric diploid origin and leads to gestational trophoblastic disease (GTD) in up to 20% of cases. In contrast, partial mole has a diandric triploid origin and is followed by GTD much less often. Obstetrical ultrasound and serum beta human chorionic gonadotropin levels during the first trimester may lead to a suspicion of mole, but definitive diagnosis is made by pathologic examination of the pregnancy-loss specimen.[2,3] Management guidelines for women with molar disease recommend clinical and biochemical monitoring and contraception/abstinence—only to be discontinued 6 months after achieving 3 negative weekly human chorionic gonadotropin levels.[3]

Key Words: Hydatidiform, non-molar abortus, genotyping, p57 immunohistochemistry

Corresponding author: Dr. Terence J. Colgan, Department of Pathology and Laboratory Medicine, Sinai Health System, University of Toronto, Toronto, ON.
Terence.colgan@sinaihealthsystem.ca

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The Diagnostic Challenge

The histopathologic diagnosis of placental mole, even by experts, is imprecise.[4] The greatest challenge is distinguishing partial mole from non-molar abortus, although classification of a mole as partial or early complete mole can also be difficult. Immunohistochemistry for p57, the product of the maternally expressed gene CDKN1C, greatly facilitates the recognition of complete moles, but 20% to 30% of suspected molar cases are still incorrectly classified even using both histology and immunohistochemistry.[5] Furthermore, through the use of obstetrical ultrasound pregnancy losses which may be suspicious for mole are submitted for pathologic examination much earlier in gestation when morphologic features are much less well developed. Pathologists are cognizant of this diagnostic uncertainty, and when presented with a challenging case of atypical villous morphology suspicious for mole, often will report using the phrase "suspicious for molar disease" or similar terminology. We developed a laboratory diagnostic pilot program which aimed to eliminate the ambiguity in the diagnosis of molar disease.

The Innovation

A quantitative fluorescence-polymerase chain reaction assay, AneuFast (Genomed, Wollerau, Switzerland), had been adopted by our laboratory as the primary prenatal screening test for common aneuploidies consistent with Canadian recommendations.[6] In 2011, our laboratory adapted AneuFast as a genotyping method for suspected moles using DNA extracted from microdissected maternal and conceptus tissues from formalin fixed paraffin embedded tissues.[7,8]

The Five-Year Pilot Study

In 2012, a placental molar laboratory diagnostic service using traditional histopathology and adjunctive molecular

techniques was introduced as a pilot program for the Sinai Health System and external laboratories (consult cases) under SHS research ethics approval (MSH REB 11-0166). Pregnancy-loss specimens were referred to the service if an initial histopathologic assessment revealed atypical villous morphology prompting concern about mole or yielding a preliminary diagnosis of mole. Atypical villous morphology, also known as dysmorphic villous morphology, included variable degrees of villous enlargement, irregularity, hydropic change, cisternal formation, trophoblastic inclusions, and/or trophoblastic hyperplasia. Diagnostic criteria for complete mole, partial mole, and non-molar abortus were adopted, as shown in Table 1.[9] In brief, molecular diagnosis using p57 immunohistochemistry for suspected complete moles or genotyping for suspected partial moles and non-molar abortus was the preferred method of diagnosis. Diagnosis by histopathology alone—the usual practice—was used and accepted if paraffin blocks were unsuitable or unavailable.

Table 1. Sinai Health System laboratory criteria for the diagnosis of placental hydatidiform mole and non-molar abortus[a]

Complete hydatidiform mole: Preferred (Molecular): Atypical villous morphology suggestive/diagnostic of complete mole with absent (< 10%) p57 immunohistochemical staining of villous mesenchymal and cytotrophoblast cells.
Acceptable: Classic histopathology of either late mole (diffuse villous cisternae with atypical trophoblastic proliferation) and/or early mole (myxoid hypercellular club-shaped villi with nuclear debris).
Partial hydatidiform mole: Preferred (Molecular): Atypical villous morphology suggestive of partial mole with diandric triploidy (or triploidy) by genotyping analysis.
Acceptable: Atypical villous morphology classical for partial mole (dual population of villi, some having being irregular with clefts and inclusions and mild trophoblastic proliferation), if informative genotyping not available.
Non-molar abortus: Preferred (Molecular): Atypical villous morphology with biparental inheritance, with or without aneuploidy.
Acceptable: Atypical villous morphology without diagnostic features of partial mole (if informative genotyping not available).

[a]adapted from McConnell et al.[9]

Outcome One: Improved Diagnostic Specificity

During the pilot study, 443 pregnancy-loss specimens suspicious for mole, or with a preliminary diagnosis of mole, were analyzed by the placental molar service. There were 161 SHS cases and 282 cases from 46 external laboratories in 6 provinces. The research ethics board only permitted access to clinical history stated on the pathology requisition or consult. Preoperative clinical history was available in 288 of the 443 cases (65%). Molar disease was clinically suspected in 163 of the 288 cases (57%). In the remaining 125 cases (43%), the stated history was missed/incomplete/therapeutic abortion.

The proportion of cases with a final diagnosis of complete mole in SHS cases (39 out of 161, or 24%) was similar to that of consult cases (74 out of 282, or 26%). In contrast, the final diagnosis of partial mole was made in 66 out of 161 SHS cases (41%), while partial moles composed a lower proportion for consult cases (75 out of 282, or 27%). The differing proportions of partial mole in SHS and external laboratory cohorts suggests that external laboratories' pathologists have a lower threshold for suspicion of mole when presented with atypical placental villous morphology than SHS pathologists. The final diagnosis by case source and diagnostic methods is shown in Table 2. In brief, 189 out of 443 (42.6%) cases suspicious for molar disease were non-molar abortus on final analysis. Women with non-molar abortus could return to normal reproductive activity and avoid unnecessary follow-up for mole, which from the health system perspective is "cost avoidance." Molecular testing using p57 immunohistochemistry always yielded informative results, while molecular testing using genotyping in partial moles and non-molar abortus yielded informative results in 196 out of 243 attempts (81.6%). Measures are being undertaken to increase the proportion of cases which are successfully genotyped.

Outcome Two: Improved Obstetrical Care

In contrast to other QF-PCR methods, which have been used to genotype moles,[9–11] the AneuFast QF-PCR has been specifically designed to detect common aneuploidies, but is not available in the United States. Aneuploidy has been identified in 22 out of 114 (19.3%) of genotyped non-molar abortus cases in the pilot study (Table 2).[12] This information may be useful in subsequent counseling and in the direction of preimplantation genetic diagnosis. Specific aneuploidy types that may be caused by unbalanced form of familial chromosome rearrangement (e.g., Robertsonian translocation type trisomies) are identified in about a quarter of these aneuploidy cases.

New Opportunities

New clinical and research opportunities for molar disease would become available if molecular techniques for

ABBREVIATIONS

GTD	gestational trophoblastic disease
SHS	Sinai Health System
QF-PCR	Quantitative fluorescence-polymerase chain reaction