Diagnostic reproducibility of hydatidiform moles: molecular genotyping significantly improves morphologic assessment

Mamta Gupta, Lee Wu, Anna Yemelyanova, Russell Vang, Robert Kurman and Brigitte Ronnett.

1Department of Pathology, Johns Hopkins Medical Institution, Baltimore, MD, United States.

Background: Distinction of hydatidiform moles (HM) from non-molar specimens (NM) and sub-classification of HMs as complete hydatidiform mole (CHM), early CHM (eCHM), and partial hydatidiform mole (PHM) are important for clinical practice yet diagnosis based solely on morphology is affected by interobserver variability. Molecular genotyping can distinguish these entities by discerning androgenetic diploidy, diandric triploidy, and biparental diploidy to diagnose CHMs, PHMs, and NMs, respectively. This study analyzes the accuracy and inter-observer variability of diagnosis of HMs among experienced gynecologic pathologists relative to genotyping results.

Design: 80 genotyped cases (1 representative slide per case), including 10 CHMs, 17 eCHMs, 27 PHMs, and 26 NMs, were selected from a consecutive series of 200 potentially molar specimens previously diagnosed using p57 immunostaining and genotyping. Slides were classified by 3 pathologists, masked to p57 immunostaining and genotyping results, into 1 of 4 categories: CHM, eCHM, PHM, or NM. Genotyping results were used as the gold standard (true) diagnosis; diagnostic performance was analyzed using kappa (k) statistics.

Result: Using 4 categories, agreement between the individual pathologist's diagnoses and molecular genotyping was fair-moderate (k=0.29-0.49; 50-64%). Using 3 categories (CHM and eCHM combined), agreement was fair-good (k=0.32-0.60; 55-74%). Using a consensus diagnosis (that rendered by 2/3 reviewers), agreement was moderate (k=0.56; 64%) using 4 categories and good (k=0.63; 70%) using 3 categories. Agreement varied from moderate to poor among the individual diagnostic categories, with kappa values of 0.42, 0.40, 0.13 and 0.15 for CHM, eCHM, PHM, and NM, respectively, and 0.59 for CHM and eCHM combined. For 6 cases (1 CHM, 3 eCHMs, and 2 PHMs), there was no consensus diagnosis. Using 3 categories for the 74 cases with consensus, the consensus diagnosis correctly classified 83% of CHMs and eCHMs combined, 84% of PHMs, and 62% of NMs.

Conclusion: Diagnostic reproducibility of HMs by morphology is only fair-good even for experienced gynecologic pathologists, with good agreement only modestly achieved by consensus. Distinction of PHMs and NMs is the most problematic, dominated by over-diagnosis of NMs as PHMs, but failure to recognize all CHMs/eCHMs persists. Genotyping provides a definitive diagnosis for the nearly one-third of cases that are misclassified by morphology.