Access this article online

Quick Response Code:

Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_64_23

Downloaded from http://journals.lww.com/pjog by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/28/2023

Precision medicine in gestational trophoblastic disease

Agnes L. Soriano-Estrella[1]

Abstract:

Precision medicine is a form of medicine that utilizes information about a person's own genes to prevent, diagnose, or treat disease. In trophoblastic disease, precision medicine is important for accurate diagnosis, risk stratification, prognostication, and management. Immunohistochemistry, particularly $p57^{kip2}$, has become an important ancillary procedure for the accurate identification of complete hydatidiform mole (HM). Molecular genotyping, on the other hand, is now considered the gold standard for the accurate classification of HM. Both tests are important for prognostication and the determination of the appropriate follow-up plan. For gestational trophoblastic neoplasia, immunohistochemical markers can confirm the histologic diagnosis of its various types. Molecular genotyping differentiates gestational from nongestational tumors with overlapping histology and allows for precise identification of the index or causative pregnancy of a choriocarcinoma.

Keywords:

Gestational trophoblastic disease, gestational trophoblastic neoplasia, hydatidiform mole, precision medicine

Introduction

Precision medicine, otherwise known as personalized medicine, utilizes information about a person's genes, environment, and lifestyle to accurately diagnose disease and tailor fit treatment and prevention strategies. This approach is in contrast to a one-size-fits-all approach, which puts little consideration for individual differences.[1] In trophoblastic disease, precision medicine would mean accurate diagnosis of the various subtypes of hydatidiform mole (HM) for appropriate prognostication and treatment planning. For gestational trophoblastic neoplasia (GTN), precision medicine refers to the identification of the specific type of GTN, correct risk stratification, and identification of patients at risk for chemotherapy.

Precision Diagnosis of Hydatidiform Moles

HMs are abnormal conceptions characterized by excessive proliferation of trophoblasts on histopathologic examination. They are distinguished from other forms of gestation by placental overexpression of paternally derived genes.[2] The two types of HM, complete and partial, are distinct entities that differ in clinical presentation, cytogenetics, gross morphology, and histopathologic characteristics.

The clinical diagnosis of HM is based largely on typical signs and symptoms supported by elevated serum beta-human chorionic gonadotropin (hCG) titers and typical sonographic findings. Most cases of HMs present with vaginal bleeding with or without passage of vesicular products of conceptions. Complete HMs (CHMs) classically present with uterine enlargement greater than expected for age of gestation, presence of theca-lutein

[1]*Department of Obstetrics and Gynecology, Division of Trophoblastic Diseases, Philippine General Hospital, University of the Philippines, Manila, Philippines*

Address for correspondence:
Dr. Agnes L. Soriano-Estrella, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines, Taft Avenue, Ermita, Manila 1000, Philippines.
E-mail: alsorianoestrella@up.edu.ph

Submitted: 27-Aug-2023
Revised: 07-Sep-2023
Accepted: 11-Sep-2023
Published: 27-Sep-2023

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Soriano-Estrella AL. Precision medicine in gestational trophoblastic disease. Philipp J Obstet Gynecol 2023;47:95-8.

Downloaded from http://journals.lww.com/pjog by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/28/2023

cysts, excessive nausea and vomiting, hyperthyroidism, pregnancy-induced hypertension, and an abnormally high hCG level.[3] However, with the widespread use of ultrasound, CHMs are being diagnosed early and before the onset of the classic signs and symptoms.

The clinical presentation of partial HMs (PHMs) is more subtle compared to CHM and is, thus, often misdiagnosed as a missed abortion. Ultrasonography also often misses the diagnosis, especially if a fetus is detected.

Histopathologic analysis is necessary not only to confirm the diagnosis but also to identify the correct molar subtype. Well-developed CHMs are characterized by enlarged edematous villi with cistern formation, moderate to marked circumferential trophoblastic hyperplasia, cytologic atypia, stromal karyorrhexis, and trophoblastic pseudoinclusions.[2] On the other hand, characteristic morphologic features of PHMs include the presence of large, irregular, hydropic villi admixed with small, immature, fibrotic villi; cisterns in some enlarged villi; markedly irregular villi with scalloped borders and trophoblastic pseudoinclusions; and generally, focal, mild circumferential trophoblastic hyperplasia. Due to the early diagnosis of CHM, histopathologic features are less well developed and may now closely resemble PHM or nonmolar gestations presenting with hydropic villi.[2]

A number of studies have demonstrated that there is diagnostic variability for HM based on routine assessment of hematoxylin- and eosin-stained (H and E) slides, even among experienced pathologists with specialized training.[4-7] Accurate identification of the type of HM, however, is important due to differences in prognosis and recommendations for follow-up. Molar pregnancies are associated with an increased risk for persistent trophoblastic disease (PTD) and GTN, with CHM carrying a higher risk for malignant degeneration than PHM. CHMs progress to invasive mole (IM) in around 15%–20% and into GTN in 2%–3% of cases. On the other hand, the risk for PTD after a PHM is from 0.5% to 5%.[8] Due to the lower risk of progression to malignancy, various experts have recommended a less stringent and shorter postevacuation monitoring for patients with PHM. The Philippine Society for the Study of Trophoblastic Diseases, in its latest clinical practice guideline, has recommended only one more follow-up titer after a normal hCG result among patients with confirmed PHM.[9] Hence, there is a need for other ancillary tests.[9]

Genetic Basis of Hydatidiform Moles

Over the years, there have been tremendous advances in our knowledge of the genetic basis of HMs, leading to the development of ancillary tests to enhance diagnostic accuracy.

There are two types of CHM, the sporadic and the familial biparental CHM (FBCHM). Sporadic CHMs can either be homozygous or heterozygous, depending on the source of paternal chromosomes. Homozygous (monospermic) CHMs arise from fertilization of an empty ovum by a haploid sperm that duplicates its DNA. The karyotype, in this case, is 46, XX. Heterozygous (dispermic) CHMs arise from the fertilization of an empty ovum by two haploid sperms, resulting in either a 46, XX or 46, XY karyotype.[8,10-13] In both scenarios, all 46 chromosomes are paternal in origin, giving rise to a condition known as androgenetic diploidy.[12] Recent studies have shown that the heterozygous CHM, which accounts for roughly 10%–15% of CHM, carries a higher risk for malignant degeneration.[14]

The FBCHM is an autosomal recessive disease caused by mutations in the *NLRP7* gene (OMIM 609 661) and less frequently in the *KHDC3 L* gene (OMIM 611 687), which are believed to be responsible for setting or maintaining the maternal imprints in the oocytes.[10-12,15,16] Clinical and histopathological characteristics are similar to the androgenetic sporadic CHM; genetic analysis would reveal a chromosomal complement from both parents. This type of CHM is unique in that patients have recurrent CHM with little or no chance of a normal pregnancy.[16]

PHMs arise as a result of fertilization of a healthy ovum by two sperms (dispermic, heterozygous PHM) or by one sperm that reduplicates itself (monospermic, homozygous PHM).[8,10,12] Both instances give rise to a triploid karyotype with paternal dominance, a condition called diandric monogenic triploidy. It must be remembered that around a third of triploid gestations have two sets of maternal and one set of paternal chromosomes (digenic, monoandric gestations). These are not partial moles and have no associated risk for PTD or GTN.[8]

Ancillary Tests for Precise Diagnosis

p57^{kip2} immunohistochemistry

P57^{kip2} or p57 is a cyclin-dependent kinase inhibitor encoded by the gene CDKN1C on chromosome 11p15.5. It is paternally imprinted and maternally expressed. Due to its preferential expression from the maternal allele, all gestations with a maternal genetic material such as PHM, FBCHM, hydropic nonmolar abortions, and trisomies express p57 in the placental villi, stromal cells, and cytotrophoblast. In sporadic CHM, p57 is not expressed in cytotrophoblast and villous stroma, and staining in these cells is lost. Staining is, however, preserved

Downloaded from http://journals.lww.com/pjog by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/28/2023

in the decidua and extravillous trophoblast, which act as internal controls for p57 immunostaining.[2,17,18] Major professional organizations, including PSSTD, now recommend the combination of H and E staining and immunohistochemistry with $p57^{kip2}$ to support the diagnosis of sporadic CHM.[9]

Molecular genotyping

Molecular genotyping is now considered the gold standard for the accurate classification of HM. The process can establish ploidy and, correctly, identify the parental genetic contribution to the villous tissue, thus precisely diagnosing the various forms of molar gestation.[2]

Prediction of Neoplastic Transformation of Hydatidiform Mole

It is currently believed that the neoplastic transformation of a HM to GTN requires activation of oncogenes and suppression of tumor suppressor genes. Prior studies investigated the expression of several gene products, such as c-ras, c-erbB-2, p53, and nm23, with varying results.[18] St Laurent *et al*., recently, described two new potential biomarkers of pre-GTN CHM cases: decreased 14q32 miRNA expression and loss of DIO3 expression by immunohistochemical staining.[19] Further studies are, however, needed to substantiate their result.

Precision Diagnosis of Gestational Trophoblastic Neoplasia

GTN encompasses the malignant end of the spectrum of gestational trophoblastic diseases. These tumors are locally proliferative with the ability to invade normal tissue and the potential to spread outside of the uterus.[20] It includes IM, choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The morphological appearance of these tumors may be mimicked by nongestational tumors that show trophoblastic proliferation or nonmalignant tumor-like conditions.[2] In addition, the various types of GTN may need to be differentiated from one another due to differences in management and prognosis.

Utility of Immunohistochemistry for Accurate Diagnosis

Immunohistochemical markers can confirm the histologic diagnosis of the various types of GTN. Commonly, a panel of immunomarkers is used for accurate diagnosis.

The syncytiotrophoblasts of CC have strong staining for hCG. All of the trophoblastic tumor cells should stain strongly and diffusely for cytokeratin in all trophoblast cells. Inhibin, on the other hand, is negative.[21] Ki-67 is diffusely expressed in approximately half the cell.[22] GATA-3 is a new addition to the panel of stains to confirm the diagnosis of CCA. Approximately 80% of CC shows nuclear positivity of variable intensity.[23] One study, which included 19 CC and 10 PSTT/ETT, described the usefulness of SALL-4 expression in differentiating CC from PSTT/ETT. All cases of CC were positive for SALL-4 while none of the PSTT/ETT tumors showed expression.[24]

PSTT exhibits a widespread expression of cytokeratin (AE1/3, Cam 5.2, and CK18), CD10, HLA-G, and GATA-3, which are findings consistent with its origin from the implantation site trophoblast. Most cells express human placental lactogen (hPL), MUC-4, and Mel-CAM, although occasionally, it may be positive for PLAP and p63. Expression of hCG and inhibin is limited to multinucleated (syncytiotrophoblast-like giant) cells. The proliferation index is usually low as compared to CC (10%–30%).[2]

The tumor cells of ETT express cytokeratin (CK18, AE1/3, and Cam 5.2), CD10, HLA-G, and GATA-3 in keeping with its trophoblast lineage. Expression of EMA, cyclin-E, p63, inhibin, and PLAP is usually diffuse, whereas Mel-CAM, hCG, and hPL expression are weak and focal. p63 is reliably positive in ETT and is a useful marker in the differential diagnosis with other malignant trophoblastic tumors. There is an increased expression of cyclin-E when compared with placental site nodule (PSN), but note that PSTT also shows cyclin-E positivity.[2]

Utility of Molecular Genotyping

Molecular genotyping can differentiate a gestational from nongestational tumors with overlapping histology. The presence of distinct paternal genetic complement not present in the patient's normal tissues definitively separates a gestational trophoblastic tumor from a nongestational neoplasm of either germ cell or somatic nature. Moreover, genotyping allows for precise identification of the index or causative pregnancy (HM, abortion, or term pregnancy). This is important for patients with CCA to accurately compute for the patient's prognostic score with respect to the causative or index pregnancy as well as the interval from the index pregnancy to the diagnosis of the disease.

The prognostic scoring system is not utilized in cases of PSTT and ETT. Nevertheless, genotyping may be used to differentiate PSTT and ETT from somatic tumors such as squamous cell carcinoma and epithelioid leiomyosarcoma. It must be remembered that genotyping has no role in the diagnostic separation between the various GTN and their reactive or preneoplastic

counterparts (PSTT vs. exaggerated placental site or ETT vs. atypical PSN vs. PSN) Furthermore, genotyping analysis does not have a prognostic value in cases of GTN.[8]

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Downloaded from http://journals.lww.com/pjog by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/28/2023

References

1. Genetics Home Reference. Available from: https://www.ghr.nlm.nih.gov/glossary=personalizedmedicine. [Last accessed on 2023 Jul 22].
2. Kaur B. Pathology of gestational trophoblastic disease (GTD). Best Pract Res Clin Obstet Gynaecol 2021;74:3-28.
3. Soper JT. Gestational trophoblastic disease: Current evaluation and management. Obstet Gynecol 2021;137:355-70.
4. Fukunaga M, Katabuchi H, Nagasaka T, Mikami Y, Minamiguchi S, Lage JM. Interobserver and intraobserver variability in the diagnosis of hydatidiform mole. Am J Surg Pathol 2005;29:942-7.
5. Howat AJ, Beck S, Fox H, Harris SC, Hill AS, Nicholson CM, *et al.* Can histopathologists reliably diagnose molar pregnancy? J Clin Pathol 1993;46:599-602.
6. Javey H, Borazjani G, Behmard S, Langley FA. Discrepancies in the histological diagnosis of hydatidiform mole. Br J Obstet Gynaecol 1979;86:480-3.
7. Messerli ML, Parmley T, Woodruff JD, Lilienfeld AM, Bevilacqua L, Rosenshein NB. Inter- and intra-pathologist variability in the diagnosis of gestational trophoblastic neoplasia. Obstet Gynecol 1987;69:622-6.
8. Buza N, Hui P. Genotyping diagnosis of gestational trophoblastic disease: Frontiers in precision medicine. Mod Pathol 2021;34:1658-72.
9. Philippine Society for the Study of Trophoblastic Diseases. Clinical Practice Guideline for Hydatidiform Mole in the Philippines, 2022.
10. Stevens FT, Katzorke N, Tempfer C, Kreimer U, Bizjak GI, Fleisch MC, *et al.* Gestational trophoblastic disorders: An update in 2015. Geburtshilfe Frauenheilkd 2015;75:1043-50.
11. Moein-Vaziri N, Fallahi J, Namavar-Jahromi B, Fardaei M, Momtahan M, Anvar Z. Clinical and genetic-epignetic aspects of recurrent hydatidiform mole: A review of literature. Taiwan J Obstet Gynecol 2018;57:1-6.
12. Hui P, Buza N, Murphy KM, Ronnett BM. Hydatidiform moles: Genetic basis and precision diagnosis. Annu Rev Pathol 2017;12:449-85.
13. Candelier JJ. The hydatidiform mole. Cell Adh Migr 2016;10:226-35.
14. Zheng XZ, Qin XY, Chen SW, Wang P, Zhan Y, Zhong PP, *et al.* Heterozygous/dispermic complete mole confers a significantly higher risk for post-molar gestational trophoblastic disease. Mod Pathol 2020;33:1979-88.
15. Nguyen NM, Slim R. Genetics and epigenetics of recurrent hydatidiform moles: Basic science and genetic counselling. Curr Obstet Gynecol Rep 2014;3:55-64.
16. Chilosi M, Piazzola E, Lestani M, Benedetti A, Guasparri I, Granchelli G, *et al.* Differential expression of p57kip2, a maternally imprinted cdk inhibitor, in normal human placenta and gestational trophoblastic disease. Lab Invest 1998;78:269-76.
17. Joyce CM, Fitzgerald B, McCarthy TV, Coulter J, O'Donoghue K. Advances in the diagnosis and early management of gestational trophoblastic disease. BMJ Med 2022;1:e000321.
18. Laban M, El-Swaify ST, Refaat MA, Ibrahim EA, Abdelrahman RM. Prediction of neoplastic transformation of hydatidiform mole: Current evidence. Reprod Sci 2021;28:3010-2.
19. St Laurent JD, Lin LH, Owen DM, Maestá I, Castaneda A, Hasselblatt KT, *et al.* Loss of selenoprotein iodothyronine deiodinase 3 expression correlates with progression of complete hydatidiform mole to gestational trophoblastic neoplasia. Reprod Sci 2021;28:3200-11.
20. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematol Oncol Clin North Am 2012;26:111-31.
21. Crum CP, Quick CM, Laury AR, Peters WA, Hirsch MS, editors. Gynecologic and Obstetric Pathology: High-Yield Pathology. Philadelphia, USA: Elsevier; 2016.
22. Shih IM, Kurman RJ. Ki-67 labeling index in the differential diagnosis of exaggerated placental site, placental site trophoblastic tumor, and choriocarcinoma: A double immunohistochemical staining technique using Ki-67 and Mel-CAM antibodies. Hum Pathol 1998;29:27-33.
23. Banet N, Gown AM, Shih IE, Kay Li Q, Roden RB, Nucci MR, *et al.* GATA-3 expression in trophoblastic tissues: An immunohistochemical study of 445 cases, including diagnostic utility. Am J Surg Pathol 2015;39:101-8.
24. Stichelbout M, Devisme L, Franquet-Ansart H, Massardier J, Vinatier D, Renaud F, *et al.* SALL4 expression in gestational trophoblastic tumors: A useful tool to distinguish choriocarcinoma from placental site trophoblastic tumor and epithelioid trophoblastic tumor. Hum Pathol 2016;54:121-6.