



Molar Pregnancy: Genetic, Histological, Clinical Features and the Risk for Gestational Trophoblastic Neoplasia



Sue Yazaki Sun¹, Marcia Marcelino de Souza Ishigai², Rosana Mercante Martinez³, Maria Teresa de Seixas Alves² and Andréa Cristina de Moraes Malinverni^{2,3*}

¹Department of Obstetrics, Universidade Federal de São Paulo - UNIFESP, Brazil

²Department of Pathology, Universidade Federal de São Paulo - UNIFESP, Brazil

³Laboratory of Molecular Pathology, Universidade Federal de São Paulo - UNIFESP, Brazil

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*Corresponding author: Andréa Cristina de Moraes Malinverni, Laboratory of Molecular Pathology, Department of Pathology, Universidade Federal de São Paulo - UNIFESP, Pedro de Toledo, 781, 5º andar, Vila Clementino, CEP: 04039-032, São Paulo, SP, Brazil, Tel: 5511-5576-4848; Email: andreamoraesmalinverni@gmail.com

Abstract

Hydatidiform mole (HM) is a complication of pregnancy, genetically abnormal, characterized by several degrees of trophoblastic proliferation and hydropic degeneration of chorionic villi with potential for malignant transformation. The HM is classified as complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM). The distinction between CHM and PHM and non-molar abortions (NM) is very important since the risk for the development of postmolar gestational trophoblastic neoplasia is higher in CHM. This article is a brief review of relevant topics about genetic, histological and clinical features of molar pregnancy.

Keywords: Molar pregnancy; Hydatidiform mole; Partial hydatidiform mole; Complete hydatidiform mole; Gestational trophoblastic neoplasia

Introduction

Molar pregnancy represents an obstetric complication of the first half of gestation in which the abnormal developmental of the placenta is characterized by excessive villous edema and the proliferation of the trophoblast [1]. The excessive villous stromal edema culminates with central cisterns formation, visible at macroscopic and ultrasonographic examination. Based on the morphological, genetic and clinical aspects, HM can be classified as complete (CHM) or partial (PHM) hydatidiform mole [1,2].

The CHM presents hydropic chorionic villi, trophoblastic hyperplasia and high levels of human chorionic gonadotropin hormone (β -hCG) [3]. However, in the PHM the placenta has normal and hydropic villi with the presence of fetal or embryonic elements, trophoblastic hyperplasia with pseudoinclusions, dual villous populations and lower levels of chorionic gonadotropin [1,4].

HM is considered the most frequent form of gestational trophoblastic disease (GTD), with estimated global incidence of 1 to 3 per 1000 pregnancies. The incidence in Asian countries and Latin America is higher than that reported in Europe and

North America. In Brazil there is no specific official record and it is estimated to occur in 1: 200-400 pregnancies, but this rate is based on data from reference centers for GTD which is quite high and probably does not reflect the population as a whole [5-7]. The risk for gestational trophoblastic neoplasia after the patient has had a CHM was observed in 10-30% and rarely occurs after PHM (0.5-5%) [1,5,8].

The distinction between CHM and PHM is very important because in CHM there is higher risk of progression of developing gestational trophoblastic neoplasia. Some cases of PHM have abnormal villous morphology that can be confused with NM. The clinical investigations and immunostaining with molecular studies are important to distinguish the diagnosis of PHM and NM.

Genetic aspects of hydatidiform mole

In the 70's some molecular investigations established the genetic bases of hydatidiform [9]. Genetically, CHM is diploid and 80% has 46XX karyotype in which all chromosomes are of paternal origin. This is because an enucleated egg without maternal genes

was fertilized by a haploid sperm (monospermia) followed by duplication forming a homozygous egg 46,XX. In the remaining 20% of CHM, the karyotype is 46,XY, due to the fertilization of an anucleated egg by two haploid sperm (dyspermia). In both cases we can say that CHM karyotype is androgenetic diploid [1,8,10].

Sometimes CHM can be related to mutations in the gene *NLRP7* with an increase the risk to recurrent hydatidiform mole [11]. In the first-trimester miscarriages, Triploidy is one of the most common chromosome abnormalities present in 18% of first-trimester miscarriages. [12,13]. The mechanism of genetic formation of the triploidy may result from fertilization of a normal haploid egg by two normal sperm or fertilization of a haploid egg by a diploid sperm. Another possibility is a fertilization of a diploid egg by normal haploid sperm. This is also true for PHM, which 70% of the cases has 69,XXY karyotype, but this finding can be different: 69,XXX or 69,XYY. The PHM has a maternal haploid component and two paternal (diandric triploidy) which differs genetically from non-molar triploidy [1,8,14].

Several genetic methodologies aid to improve the diagnosis of HM. The conventional karyotyping is the most used technique to identify the numerical and structural chromosomal abnormalities and confirms the presence of triploidy in PHM and diploidy in CHM. However, it cannot be used with formalin-fixed paraffin-embedded or alcohol tissues, only in fresh samples [12,13,15]. Flow cytometry is a method for analyzing ploidy in fresh and paraffin-embedded samples. It only allows the detection of polyploidy (triploidy) and does not detect trisomy and monosomy. Thus it separates a PHM from a CHM, but cannot distinguish between non-molar digynic triploid gestations and PHM [16-18]. Fluorescence in situ hybridization (FISH) is an indispensable technique in the study of the physical mapping of human genome because it allows a precise regional chromosomal location of single copy genes or repeated sequences of DNA. It can be used in paraffin-embedded samples, analyzes the ploidy and identifies the most common chromosomal abnormalities related to NM abortions according to the probes were used [12,19]. Molecular genotyping of microsatellites has been widely used in distinguishing HM. This technique can be performed with DNA from fresh or paraffin-embedded samples, allows analyzing alterations for ploidy and the parental origin of the genetic components present in the sample [20-23]. Each of these methods has their particularities, advantages and disadvantages [21,22,24,25].

Histological characteristics of HM

The diagnosis of HM is based on its morphology. In classical cases, around the 2nd trimester, the abnormally large villi have a vesicular or a grape-like appearance. Histologically, HM presents variable degrees of circumferential trophoblastic hyperplasia and epithelial atypia. Usually they are more pronounced on CHM. PHM displays irregular villous contours with geographic appearance becoming frequent epithelial pseudoinclusions into the villous stroma. Different from CHM, a compound of a

mixture of normal and abnormal villi, less number of vesicles and prominent stromal fibrosis. Cellular debris (stromal and vascular karyorrhexis) occurs in both types of HM, mainly in CHM [26]. The presence of membranes, fetal tissues or nucleated RBCs is uncommon in CHM unless it is twin pregnancy. This typical morphological pattern has changed over the years due to molar evacuation in early gestational age before the 11th week. [26,27]. At this stage the vesicles are less visible at macroscopy and cisterns are rare on histological examination. In early CHMs the villi has a typical "budding" arrangement, myxoid basophilic stroma with or without a collapsed vascular network. Some cases can be confused with non-molar abortion on pathology and US examination [28]. The p57 gene search by immunohistochemistry, allows for distinguishing CHM from PHM and non-molar abortions as the gene *CDKN1C* is maternally expressed and therefore, can be detected only in sample with maternal DNA. As expected, CHM is negative for p57 while non-molar and PHM present positivity in villous stroma and cytotrophoblast cells [29].

Clinical features of patients

The clinical features of CHM and PHM depend on the gestational age of diagnosis. Currently, due to an early detection of failed pregnancy by ultrasonography scan associated to high level of human chorionic gonadotropin the mean in the mean gestational age at diagnosis of HM has been decreasing. CHM has been diagnosed at 9 weeks and PHM at 12 weeks [6]. It contributes to a milder clinical presentation of HM resembling to miscarriage. Vaginal bleeding remains as the most common clinical feature occurring in 42% of cases of CHM and in 15% of cases of PHM [6]. Only 27.3% of PHM cases are diagnosed previously to evacuation and the diagnosis is made by the histopathological exam. Classical symptoms of HM as hyperemesis, preeclampsia, hyperthyroidism and theca-lutein cyst as well as respiratory distress are becoming less common. However, early diagnosis of CHM did not reduce the progression to gestational trophoblastic neoplasia [27]. Similar results were reported in Brazil [30].

Risk of gestational trophoblastic neoplasia

After the molar evacuation is recommended a weekly hCG measurement until three negatives values and after that, 6 monthly negative values in cases of CHM [31]. Some investigators have shortened the surveillance in cases of PHM to 2 negative values (<5mIU/mL). Besides the hCG surveillance it is important the use of an effective contraceptive method. The diagnosis of GTN is based on the FIGO 2000 criteria:

- Weekly hCG plateauing for at least 4 consecutive measurements for a period of at least 3 weeks (days 0,7,14,21),
- Weekly hCG rising for at least 3 consecutive measurements for a period of at least 2 weeks (days 0,7,14)
- Persistence of hCG more than 6 months after evacuation,

d. 95% of postmolar GTN are classified as low risk GTN (I to III, score 0-6) and the treatment is made with single chemotherapy agent, methotrexate or actinomycin D, reaching almost 100% of cure. High risk postmolar GTN (IV, score>7) is treated with EMA-CO and the survival in 5 years is of 8.2% [32-33].

Conclusion

CHM and PHM have been diagnosed in the first trimester of pregnancy resulting in a further decrease in some clinical classical presenting symptoms. The risk of development of post molar GTN has not been affected. After molar evacuation, the HM is usually classified based on morphological criteria and the use of immunohistochemical and molecular methods have improved the understanding of molar pregnancies. Further research about oncogenes and other immunomodulator molecules are important as prognostic markers.

Conflict of Interest

All contributors approved the submission to the Journal, and there is no conflict of interests.

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