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Review Article

Classification and etiologies of gestational trophoblastic disease

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ABSTRACT

Various forms of trophoblastic diseases were reported in the literature, including complete and partial of hydatidiform moles, gestational choriocarcinomas, placental-site and epitheloid trophoblastic tumors. Among patients who suffer from hydatidiform mole, gestational trophoblastic neoplasia can be easily diagnosed by using the levels of the human chorionic gonadotropin (hCG). Therefore, complex investigations are not usually necessary in measuring the levels of hCG, physical examination and assessments. In addition, patients' medical history can help the attending physicians to draw an adequate treatment plan for patients with gestational trophoblastic neoplasia. However, Pelvic Doppler ultrasonography might also be used for additional assessments, including the presence or absence of pregnancy, measurement of the uterine volume and size. Additionally, it determines the vasculature and spread of the neoplasm within the pelvic region. Furthermore, genetic analysis can be used to differentiate between the types of the disease. Moreover, among the reported staging and classification systems, the international federation of gynecology and obstetrics (FIGO) seems to be the best efficacious modality for the determination of the prognosis of the various types of the disease to properly choose the best treatment modality.

Keywords: Gestational trophoblastic disease, Hydatidiform mole, Prognosis, Staging, Classification

INTRODUCTION

The gestational trophoblastic disease was first linked to pregnancy at the end of the 19th century. It has been noticed an avascular, highly invasive, metastatic tumor is a result of major dysfunction in the regulatory mechanisms of the naturally-occurring trophoblasts. Malignant and benign types of the disease were reported, including the partial and complete hydatidiform mole, which is usually a benign condition. In addition, the invasive mole, choriocarcinomas, placental-site and epithelioid trophoblastic tumors, which pose a malignant characteristic, with metastatic features that need adequate management to intervene against serious morbidity and mortality.[1-3] In complete hydatidiform mole type, the case usually develops as an ovum is fertilized by a single sperm which leads to the routine duplication of its DNA. However, the fertilized ovum does not have maternal

chromosomes, resulting in an androgenic pattern of 46XX. The chromosomes of which are all patrilineal with no maternal characteristics, as reported with the majority of these cases.[4-6] In this study, we aim to conduct a literature review to formulate evidence regarding the etiology, staging and classification of gestational trophoblastic diseases.

METHODS

This literature review is based on an extensive literature search in Medline, Cochrane, and Embase databases which was performed on 19th June 2021 using the medical subject headings (MeSH) or a combination of all possible related terms. This was followed by the manual search for papers in Google Scholar while the reference lists of the initially included papers.[7,8] Papers discussing gestational trophoblastic diseases were screened for relevant information, with no limitation placed on date, language, age of participants, or publication type.

DISCUSSION

Causes of gestational trophoblastic disease

In complete moles, studies reported that around 10% of the cases usually result from fertilizing a single ovum with two sperms, resulting in an androgenic pattern of 46XY.[9] In such cases, it has been shown that the mitochondrial deoxyribonucleic acid (DNA) is usually maternal. Nevertheless, the nuclear DNA characteristics are paternally derived.[10] In another context, it was previously reported that a biparental molar can result as an atypical pattern in some cases with recurrent conditions that are not alike the usual androgenic disease, and can be sporadic or familial.[11] In such conditions, studies have shown that genetic involvement proceeds the condition in the affected families and the affected chromosomes include 19q13.3–13.4. Besides, genetic analysis showed that mutations from the NLRP7 type usually affect this location.[12,13] However, among the various studies in the literature, there is still no single evidence regarding the mechanisms of mutations and normal functions of the related genetic proteins that predispose the development of the disease.[14] On the other hand, it was reported that the NLRP7 region on the affected chromosomes usually comprises significant amounts of leucine, which has been noticed to be associated with significant amounts of mutations, indicating the vital role of this region in the normal functions and mutations that are important to the development of the disease.[15] Furthermore, mutations related to the NLRP7 region were also noticed with the hydatidiform moles. In addition, it also involves androgenic triploid and diploid moles. Nonetheless, evidence is yet to be confirmed by wider investigations.[16] Regarding the etiology of partial hydatidiform moles, most cases usually result from the fertilization of a healthy ovum with two sperms, resulting in a triploid disease.[17-19] Although some investigations reported the potential presence of diploid partial moles. These are usually misdiagnosed with complete moles.[20]

Classification and staging

Many classification systems have been proposed in the literature by various studies for the staging of gestational trophoblastic disease. However, not many of them were adequately validated. Therefore, these were not widely used in the clinical settings and were no longer reported among the different studies.[21] Various forms of the disease were reported in the literature, including complete and partial hydatidiform moles, gestational choriocarcinomas, placental-site and epithelioid trophoblastic tumors (Figure 1). Among patients who suffer from hydatidiform mole, gestational trophoblastic neoplasia can be easily diagnosed using the levels of the human chorionic gonadotropin (hCG). Therefore, complex investigations are not usually necessary in such situations. Measuring the levels of hCG, physical examination and assessments. Additionally, patients' medical history can help the attending physicians to draw an adequate treatment plan for these patients. Pelvic doppler ultrasonography might also be used for additional assessments, including the presence or absence of pregnancy, measurement of the uterine volume and size. In addition, it determines the vasculature and spread of the neoplasm within the pelvic region. Evidence in the literature shows that measuring the degree and extent of vasculature can significantly predict patients that might be subjected to the resistance of the treatment plans and disease severity.[22,23] It was also suggested that performing chest examination (eg: by using computed tomography (CT) of the chest) should also be indicated in such situations to adequately exclude the potential presence of metastasis, which is common with this disease.[24] However, it should be noted that simple chest radiographical approaches should be performed before conducting CT, which might not be necessary in some cases. Furthermore, micrometastasis is related to gestational trophoblastic neoplasia. However, the presence of these findings does not significantly affect the disease outcomes or prognosis.[25,26] In another context, if lesions were detected using chest radiographs, performing body CT and magnetic resonance imaging of the brain is recommended to exclude any potential spread of these metastases within the body, which might affect the functions of many organs, like the liver and brain. Therefore, the management plan would change based on these findings. A previous report by the international federation of gynecology and obstetrics (FIGO) has announced a scoring system for the classification and staging of gestational trophoblastic neoplasia and the determination of the prognosis and outcomes of the disease.[27] Many worldwide clinicians have accepted the scoring system and are being widely used since 2002. The main advantage of using this score is its ability to indicate the risk of developing resistance to dactinomycin or methotrexate monotherapy by estimating the cumulative prognostic score. An estimated score that is less than 7 is considered a low-risk disease while estimated scores that are 7 or more are considered high-risk scores. If a high-risk score was estimated, multi-drug chemotherapy should be planned as the efficacy of mono-chemotherapy is poor in such situations. Using the

anatomical classification systems does not add much to the management plan but helps physicians to compare their results with other centers. Furthermore, based on the FIGO guidelines, trophoblastic tumors occurring at the placenta should be staged and not given scores. Four stages for these tumors were reported including - stage I: which refers to the fact that the disease did not extend outside the uterus; stage II: the tumor outpassed the uterus and the genital tract; stage III: metastasis of the tumor was observed in the lung, irrespective of spreading to the genital tract or not; and stage IV: many metastases of the tumor were noticed at multiple sites including the liver, brain, kidneys and spleen. Estimates show that around 95% of patients with a hydatidiform mole of gestational trophoblastic disease tend to have a low risk of treatment resistance as estimated by the FIGO score. Although in stage I, the disease is confined to the uterus, evidence regarding the use of curettage and secondary dilatation, to decrease the need for chemotherapy administration, is controversial among the different studies in the literature.[28,29]

1) villous GTD	
Partial hydatidiform mole (PHM)	ICD-O: 9103/0
Complete hydatidiform mole (CHM)	ICD-O: 9100/0
Invasive mole (IM)	ICD-O: 9100/1
2) non-villous GTD	
Chorioncarcinoma (CC)	ICD-O: 9100/3
placental site trophoblastic tumor (PSTT)	ICD-O: 9104/1
epitheloid trophoblastic tumor (ETT)	
placental site nodule (PSN)	
exaggerated placental site (EPS)	SNOMED 79420

Figure 1: Proposed classification of gestational trophoblastic diseases by Horn and colleagues.[49]

As previously discussed, mono-chemotherapy for low-risk patients is the treatment of choice. Although previous studies have indicated that some treatment modalities might be associated with up to 90% efficacy, these were not randomized, and some of them were even retrospective.[30] On the other hand, some investigations reported that there is an urgent need to update the FIGO score, according to the results from their populations which showed that only 30% with 5-6 FIGO scores were not associated with mono-chemotherapy treatment resistance, while the rest, needed intensive therapy or other treatment modalities that are not usually indicated for the low-risk group.[31-34] It was also suggested using doppler pelvic ultrasonography might be useful in estimating the vasculature of the disease, which can help provide further data about the severity and staging of the disease.[22,23] In the high-risk population, patients usually present after the metastasis occurs in the different parts of their bodies after the initial gestational trophoblastic disease develops in months or years. According to the site of the metastasis, the clinical presentation of these patients develops.[35,36] However, it should be noted that irregular menstruation is not present in all of these patients, so the diagnosis of gestational trophoblastic disease should be thoroughly assessed in patients with multiple metastases, together with measuring the hCG levels in these patients. Brain imaging should also be considered to exclude the potential presence of metastasis and cerebrospinal fluid analysis should also be approached to exclude the presence of occult diseases with elevated hCG levels.[35,37] Taking a biopsy from the tumor can also aid in the diagnosis of the disease. However, it should be noted that some actions are not favorable in cases of highly vascular diseases, which subjects the patient to hemorrhage. It also demonstrated that DNA analysis for the patient can furtherly help in the diagnosis of trophoblastic placental-site tumors through conducting a comparison of the microsatellite polymorphisms within the tumor cells.[38] Furthermore, physicians should not depend on the morphology and phenotypic appearance of the tumor as many tumors might look alike as with the case of gestational carcinomas and choriocarcinomas.[38,39] In this context, a previous anatomical classification of gestational trophoblastic diseases as indicated by the FIGO. Nevertheless, it was no longer used later on because of the advanced reports about the significant involvement of clinical criteria in the diagnosis of the disease.[21,40,41] Studies have demonstrated that trophoblastic placental-site tumors are characterized by a slow growth pattern and a late metastasis that usually involved the lymph nodes.[42,43] The main difference between these tumors and choriocarcinomas is that they produce fewer levels of hCG. Therefore, it can be easily differentiated from them. However, as with the case with choriocarcinoma, these tumors usually develop after all the gestational trophoblastic diseases, even the partial mole.[44] Vaginal bleeding has been marked as the commonest clinical presentation.[45]

The diagnosis of the disease should not depend on the levels of the hCG, which might be relatively low as compared with the morphological size of the tumor. Accordingly, histological analysis is encouraged in such cases.[46,47] Many prognostic factors have been associated with trophoblastic placental-site tumors as the stage, the duration of the existence of the disease has been more than 4 years since the gestational trophoblastic disease was diagnosed, index of mitosis, and hCG levels. However, FIGO score was not reported as a significant predictor for the prognosis of these tumors.[42,43,48]

CONCLUSION

Various forms of the disease were reported in the literature, including complete and partial hydatidiform moles, gestational choriocarcinomas, and placental-site and epitheloid trophoblastic tumors. Among patients who suffer from hydatidiform mole, gestational trophoblastic neoplasia can be easily diagnosed using the levels of the hCG. Therefore, complex investigations are not usually necessary in such situations. Measuring the levels of hCG, physical examination, and assessments. In addition, patients' medical history can all help the attending physicians to draw an adequate treatment plan for these patients. Pelvic doppler ultrasonography might also be used for additional assessments, including the presence or absence of pregnancy, measurement of the uterine volume and size. Additionally, it determines the vasculature and spread of the neoplasm within the pelvic region. Further efforts are needed to establish proper scoring systems based on the various features of the disease.

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