

Case Report

Complete hydatidiform mole coexisting live fetus in a twin pregnancy

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Received March 4, 2018; Accepted December 5, 2018; Epub May 15, 2019; Published May 30, 2019

Abstract: Introduction: This study describes pathologic characteristics and clinical significance of a rare case of twin pregnancy, consisting of a complete hydatidiform mole and coexistent fetus (CHMF). In addition, a review of the literature was conducted. Case report: A complete hydatidiform mole and a coexisting fetus at 15 weeks gestation are reported. Ultrasound revealed a vital fetus alongside a normal placenta and a separate snow-storm cystic mass with features of a hydatidiform mole. The patient developed severe complications including excessive uterine size, anemia, preeclampsia, hyperthyroidism, and hypoproteinemia. Termination of pregnancy was chosen by the patient and performed thereafter. At 2 years follow up, there was no sign of persistent trophoblastic disease. Both the fetus and molar placenta had a 46, XY karyotype, which is rare in complete hydatidiform mole. Conclusion: Twin pregnancies consisting of a complete hydatidiform mole and coexistent fetus are rare. Individualized treatment of ongoing pregnancy with CHMF is crucial due to an increased risk of developing maternal complications. Close surveillance also in case of pregnancy termination is needed. Our case aimed to raise awareness among physicians of this rare but extremely mortal disease.

Keywords: Complete hydatidiform mole, CHMF, CHMCF, maternal complications, rare disease

Introduction

Complete hydatidiform mole (CHM) with a co-twin fetus is an extremely rare gestation, reportedly occurring in 1000-10000 pregnancies [1]. Despite significant progress in diagnostics, a correct differentiation between a singleton pregnancy consisting of a partial hydatidiform mole with an abnormal triploid fetus (which usually dies in utero during the first half of pregnancy (CHM)) and a twin gestation consisting of a complete hydatidiform mole along with a co-existing live fetus (CHMCF), is still challenging for clinicians [2]. The initial diagnosis is made when a combination molar-appearing placenta and co-twin fetus is seen. For clinical management, it is crucial to quickly differentiate further between the two entities in order to provide a rapid management in CHM. This is especially due to the high risk of development of a persis-

tent trophoblastic tumor [3]. Mastering an ultrasound scan can greatly facilitate the course of diagnostics until final pathological results are provided: in CHM, sonography identifies a fetal pole along an abnormal placenta [4].

In the rare case herein, a 28-year-old woman with CHMCF in the second-trimester, demonstrates the importance of distinguishing partial and CHM with coexisting live-fetus. The management and the sensitive discussion of termination versus continuation of pregnancy as well as the significance of a close long term (in our case 2 years) follow-up are discussed.

Case report

A 28-year-old gravida 2 para 1 (G2P1) presented in the emergency room at 15 weeks of pregnancy with vaginal bleeding, abdominal pain,



Figure 1. Twin pregnancy with a complete hydatidiform mole and co-existent fetus alongside a normal-looking placenta.

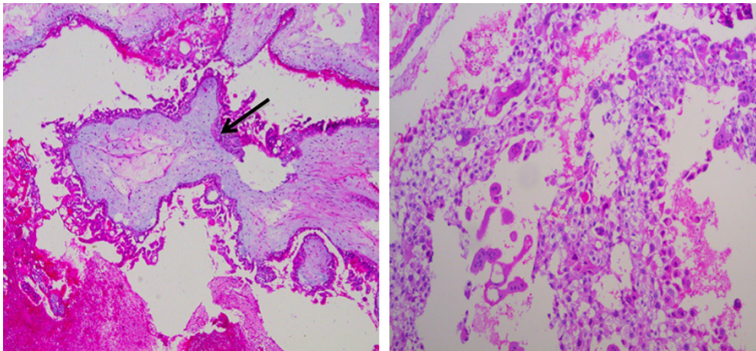


Figure 2. Microscopic appearance of the chorionic villi in complete hydatidiform mole with trophoblastic proliferation (hematoxylin and eosin, $\times 100$).

and general weakness. Despite awareness of her pregnancy, the patient had not consulted physicians before. The ultrasound scan showed a normal fetus with a regular placenta, which however had a cystic mass attached to a picture consistent with CHM. Both ovaries were enlarged, with theca lutein cysts (right 115 mm \times 102 mm in diameter, left 88 mm \times 89 mm), and were particularly painful on palpation. The serum level of human chorionic gonadotrophins (HCG) was very high (> 200000 mIU/ml). A chest X-ray showed pulmonary noduli, suggestive for lung metastases. Further suggestive clinical symptoms were seen in the diagnostic course: excessive uterine size, anemia, pre-eclampsia, hyperthyroidism and hypoproteinemia. The karyotype of the fetus was normal (46, XY) according to the examination of amniotic fluid cells.

An abortion was decided after an exhaustive discussion with the patient, who was made aware of the risks associated both with continuation and termination of the pregnancy, e.g. maternal pathology and potential medical complications at labor, such as trophoblastic embolization and severe bleeding. Vaginal delivery was induced with mifepristone, lasted for 9 hours and was accompanied with a severe bleeding. At 2 years' follow-up, there was no sign of persistent trophoblastic disease.

On gross examination, the placenta was very small (4 cm \times 3.5 cm), while the molar mass was 10 cm \times 6.5 cm, with typical grape-like vesicles (see **Figure 1**). Pathology findings revealed large chorionic villi with circumferential trophoblastic atypia (see **Figure 2**), p57 negative in immunohistochemistry, all of which are consistent with CHM. Both the fetus and molar placenta had a 46, XY karyotypes. The female fetus had no signs of chronic hypoxia.

Discussion

A complete mole is a diagnosis based on pathology. The exact etiology of CHM is still unknown. The literature output has a prevalently descriptive character. There are two types of CHM, distinguished by the type of zygosity [5]. Kajii and Ohama reported that all CHM are of paternal origin [6]. Several presumptive mechanisms of CHM have been demonstrated. One model proposed a fusion of an empty oocyte and a spermatid haploid genome, followed by duplication of the latter to obtain 46 chromosomes [7]. Another model proposed the fusion of an empty oocyte and two different spermatid genomes (dispermy) [8]. Marcorelles et al. analyzed DNA polymorphism in a series of moles, all of which indicated dispermy [9].

Cytogenetics and pathology revealed that hydatidiform mole (HM) has a variety of fertilization forms and a complex genetic background. CHM is divided into paternal origin moles (also named androgenetic CHM, AnCHM) and biparental hydatidiform moles (BiHM) [10]. AnCHM is usually diploid, arising from an ovum devoid of maternal nuclear genetic material that has been fertilized by one sperm and duplicates itself. About 20% of the forms arise from fertilization of two-sperm with empty ovum [11]. BiHM contains paternal and maternal chromosomes. With the classic pathological features of complete moles, it often manifests as recurrent and with life-long poor pregnancy outcome [12, 13].

The exact pathogenesis of hydatidiform mole is also vaguely understood. Bruchim et al. agreed that CHCF occurred after induction of ovulation by clomiphene or HMG/HCG therapy [14]. In 2006 mutations of NLRP7 or KHDC3L were found responsible for a disruption of the entire maternal imprinting gene expression and closely associated with the incidence of familial aggregation of hydatidiform moles [15]. As a member of NLRP family, NLRP7 participates in the development of HM through inflammatory pathways, which could be used as a new, targeted treatment [16-18].

Molar pregnancy can occur as a partial (PHM) or a complete one (CHM). They differ in various aspects, such as epidemiology (PHM > CHM), genetics (CHM: chromosomal material derived from the male, no fetal parts are identified; PHM: dispermy leading to a triploid fetus which ultimately dies), morphology (CHM all vesicular pattern, heterogeneous mass without embryonic or fetal structures, PHM has fetal parts.), histopathology, presentation, general risk, and occurrence of persistent gestational trophoblastic tumor (GTT) [19]. In contrast to CHM, the clinical presentation of PHM is less dramatic, mostly as an incomplete or missed abortion, accompanied with bleeding and low human chorionic gonadotropin HCG levels [20]. Vaginal bleeding in CHM patients is frequently severe, the trophoblastic growth is exuberant, the levels of (HCG) high [21-23]. Logically, CHM carries a number of complications, which can be fatal [24]. An immediate hysterectomy additionally reduces the risk of developing non-metastatic GTT, but consequently leads to infertility. Thus far, it is recommended that all molar pregnancies

are terminated upon a firm diagnosis. A regular further HCG monitoring is nevertheless obligatory because it is the most sensitive method for early GTT detection [25-28]. Immunohistochemistry for p57, the product of the maternally expressed gene CDKN1C, greatly facilitates the recognition of complete moles. Still, 20% to 30% of suspected molar cases are still incorrectly classified [29-31].

In our case, CHM was diagnosed in dizygotic twins. The patient was admitted to hospital with vaginal bleeding. Genetic amniocentesis revealed a normal 46XY karyotype. The ultrasound showed a normal placenta and a posterior separate mole. In 2017, our laboratory adapted an innovative genotyping method for suspected moles using DNA extracted from micro-dissected maternal and conceptus tissues from formalin fixed paraffin embedded tissues. This method was additionally used to confirm the diagnosis.

The choice of whether to continue or to terminate the pregnancy depends on mother's decision whether to take the risks of delivery and the strains of maternal complications and their management. Since CHMCF show some similarities to singleton molar pregnancies, a number of clinical criteria can be applied to assess the maternal risk: number of pregnancies, maternal age and parity, vaginal bleeding, uterine size vs. gestational age, β -HCG level, suggestive preeclampsia, and theca lutein ovarian cysts. In this case, the mother decided to terminate the pregnancy.

Twin pregnancies with CHCF frequently show an aggressive post-evacuation biological behavior with a persistent gestational trophoblastic disease in 20-33% of the cases [32]. Moreover, data report the incidence of live term births to be less than 50% [33]. A number of optimistic case reports have been published in the last years, which however are not representative for epidemiologic statistics [34-36]. Altogether, the knowledge and evidence-base of CHCF in twin pregnancies is very sparse, based mostly on single case descriptions [37-39].

Bristow et al. compared clinical features of CHM cases where fetus remained alive (viable group) vs. those where the pregnancy was terminated or ended in stillbirth (nonviable group,

evacuation at 18 weeks of gestation (GA) [40]. In the non-viable group, the peak serum level of HCG was high, while in molar disease, HCG is expected to peak at the beginning of the second trimester of pregnancy. If it is very high (~ 106 IU/l), there is a major risk of termination. On the other hand, if the peak is moderate and with a declining tendency, the outcome of the pregnancy might be a viable child. The serum b-HCG then usually continues to fall until the end of the pregnancy, as does the size of the molar part of the placenta on ultrasound scans [41-44]. While pre-eclampsia is indicative of a poor outcome, the elevated risk of severe bleedings and trophoblastic embolization, are hardly discussed in any of the reports [45]. Some authors described preventive methotrexate injections before inducing the termination in order to reduce the hemorrhage [46]. There are two types of molar pregnancy's evolution deduced by Marcorelles [9]: a quiescent mole, which allows the fetus to survive, and an extensively outgrowing mole, which ends in fetal death and leads to a number of complications for the mother. Twin pregnancies with hydatidiform mole are associated with a higher risk of persistent hydatidiform mole, as compared to singleton hydatidiform mole. Sebire and Niemann [47] however argue that an expectant treatment is better than an immediate termination of pregnancy.

The patient terminated the pregnancy and at 1 year follow up, there were no signs of PTD (FU with monthly β -HCG level measurement and ultrasound examinations). Therefore, management of such a specific pregnancy must be discussed individually with the expectant mother, who must be made aware of risks and possible medical complications. In the case of a normal fetal karyotype and the absence of serious signs of maternal pathology, a wait & watch strategy until fetal viability is achieved can be proposed.

Conclusion

Twin pregnancy with CHCF is a poorly investigated and not well-understood entity. Despite the presence of several established diagnostic criteria, there still is a misdiagnosis rate of 20-30%. Most CHMF gestations are still being terminated immediately following the diagnosis. However, increase in doctors' awareness and improvement of close surveillance detect-

ing potential early signs of maternal and fetal complications, will allow more pregnancies to be carried out viably. A detailed discussion and informed consent with the mother is compulsory and crucial. Specific communication and soft skills are fundamental. Regular, frequent follow-up of the mothers is mandatory as a preventative measure for PTG and GTT.

Acknowledgements

The present study was supported by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (grant no. 2015-311), the Shanghai Health and Family Planning Commission Project (grant nos. 20134298 and 201640253), the Shanghai Health and Family Planning Commission Fund for Qing Nian Yi Shi Training Project (grant no. 2014118), the Shanghai Yangpu District Science and Technology Commission Project (grant nos. 2016-2017, YP17ZM02), the Shanghai Yangpu District Health and Family Planning Commission Project (grant nos. 2011-2013 and 2016-2017, YP17ZM02), the Shanghai Yangpu District Health and Family Planning Commission Fund for Bai Yi Deng Gao Training Project (grant no. 2014-2016), the Shanghai Yangpu District Health and Family Planning Commission Fund for Hao Yi Shi Training Project (grant no. 201742), the Academic Leader in Climbing Program from Yangpu Center Hospital (grant no. Ye2201703), the Natural Science Foundation of Shanghai (grant no. 18ZR1436000). We thank all of the participants for their participation.

Disclosure of conflict of interest

None.

Abbreviations

GTT, gestational trophoblastic tumor; CHCF, Complete hydatidiform mole and a coexistent viable fetus; CHM, Complete hydatidiform mole; PHM, partial hydatidiform mole; CHMCF, co-existing live fetus; PTD, persistent trophoblastic disease; PTT, persistent trophoblastic tumor; BiHM, biparental hydatidiform moles; GTT, gestational trophoblastic tumor.

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