Placental Mosaicism in Multiple Gestation: Complete Hydatidiform Mole with Coexisting Twin Fetus

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ABSTRACT

Hydatidiform mole coexistent with a live fetus (CMCF) is a rare entity occurring in 1:20,000 to 1:100,000 pregnancies. Three mechanisms of this type are possible: (1) a singleton pregnancy consisting of partial mole with a triploid fetus, (2) a twin gestation consisting of an androgenic complete hydatidiform mole with a biparental diploid fetus, and (3) a twin gestation consisting of a biparental diploid fetus with a normal placenta and a partial hydatidiform mole (PHM) with a triploid fetus. The abnormal triploid fetus in a partial mole tends to die in the first trimester while the fetus coexisting with a complete or partial mole in the dizygotic twin pregnancy has a chance to survive. Early detection and diagnosis of a molar gestation with a viable fetus is needed to allow medical interventions, if available. Three cases of complete mole with a twin fetus (CMTF) that were diagnosed in the prenatal period by ultrasonography will be presented. This report will also discuss the indications for continuing the pregnancy, and review the literature on the recommended prenatal care, intrapartum management, and postpartum surveillance. This report aims to encourage others to document cases of CMTF in order to arrive at a consensus regarding its optimal management.

Keywords: twin pregnancy, hydatidiform mole, complete mole with a twin fetus

INTRODUCTION

Multiple gestations consisting of a complete mole and a co-existing normal fetus (CMCF) occur infrequently with a reported incidence of 1:20,000 to 1:100,000 pregnancies.[1] In the past, diagnosis is often made postpartum following histopathologic examination of an abnormal-looking placenta separate from a normal placenta that is attached to the fetus. However, recent advances in cytogenetics, molecular techniques, and ultrasonography now permit its detection antenatally. As a result, complications brought about by the condition can be anticipated leading to a better planned management scheme.

Between 2014 to 2018, 18.01 molar pregnancies occurred in every 1000 gestations in the national referral center for trophoblastic diseases in the Philippines.[2] Nationwide, the reported incidence of molar pregnancy was 2.4/1000 pregnancies.[3] However, a more accurate estimate of the incidence rate in the Philippines is difficult to determine since in most instances, only grossly abnormal abortuses are submitted for histologic examination. Data regarding the incidence of CMCF in the country is even more sparse and limited mostly to unpublished case reports from various institutions.

Three cases of CMCF that were diagnosed in the prenatal period by ultrasonography will be discussed. The first case is unique in that cytogenetic analysis was performed

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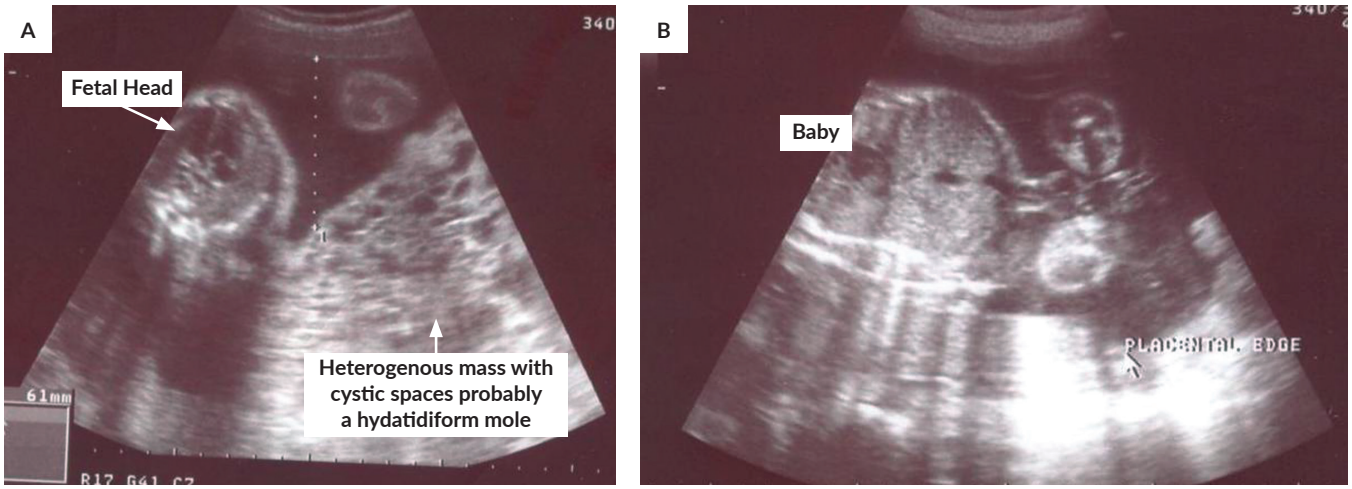

Figure 1. ***Ultrasound picture of Case 1.*** **(A)** Shows the proximity of the fetus to the molar mass; **(B)** Shows the placental edge of the normal fetus.

after delivery to confirm the diagnosis. The second case differs from other case reports of this nature in the country due to the route of delivery employed, and the third case presented an attempt at conservative management despite onset of maternal complications early in the pregnancy. This report will also discuss the indications for continuing the pregnancy, and review the literature on the recommended prenatal care, intrapartum management, and postpartum surveillance of such cases. It is hoped that this report will encourage others to better document cases of CMCF in order to establish guidelines for its optimal management.

CASE SERIES

Case 1

A 31-year-old, Gravida 5 Para 4 (4004) was admitted for vaginal spotting at 21 weeks and 2 days age of gestation (AOG). All previous pregnancies were carried to term and delivered vaginally without complications. For the current pregnancy, she had no prenatal check-ups. On admission, her vital signs were stable and she had normal systemic findings. Her abdomen was globular with a fundic height of 32 cm and an estimated fetal weight of 400-600 grams with good fetal heart tones. On speculum examination, there were no vaginal masses/nodularities and the cervix was smooth with bloody discharge per os. Internal examination revealed a smooth, parous vagina, and a cervix that was soft and closed. The uterus was larger than AOG with a boggy consistency at the isthmic portion. There was no adnexal mass or tenderness and the fornices were full. A transabdominal ultrasound showed a single, live intrauterine pregnancy in cephalic presentation with good cardiac and somatic activities, 22 weeks by biparietal diameter, and 21 weeks by femoral length with co-existent gestational trophoblastic disease probably complete hydatidiform mole, cannot totally rule out a partial mole. An intervening membrane measuring 0.3 cm between the hydatidiform mole and the fetus was seen. The placenta was 1.6 cm thick and 5.1 cm in length with homogenous echopattern. At its distal portion, and totally covering the cervical os was a heterogenous mass with multiple cystic spaces within measuring 1700 cc in volume (Figure 1). Initial serum β-human chorionic gonadotropin (hCG) was 533,167 mIU/mL.

The admitting diagnosis was pregnancy uterine, twin gestation with a normal fetus, 21 weeks and 2 days age of gestation, cephalic and a hydatidiform mole, in preterm labor, cannot totally rule out a partial hydatidiform mole (PHM). The plan was to bring the pregnancy as close to term as possible without compromising the health of the mother. Tocolysis was started using Nifedipine 30 mg/tab, 1 tablet as loading dose then 10mg/tablet, 1 tablet every 6 hours thereafter. Dexamethasone 6 mg was also given intramuscularly every 12 hours for four doses. The fetus was monitored through fetal movement counting and fetal heart tones monitoring every 4 hours daily. From the day of admission until her 26th hospital day, patient had intermittent episodes of either vaginal spotting or brownish vaginal discharge.

On her 27th hospital day (25 weeks and 1 day AOG), patient experienced regular uterine contractions with passage of vesicular materials. Since the hydatidiform mole was the presenting part, the plan was primary classical cesarean section with total hysterectomy under general anesthesia. Intraoperatively, the uterus was enlarged to 32 weeks age of gestation. The lower uterine segment was not formed. The surgeons then proceeded in performing a classical cesarean section. Upon opening the uterus, there was egress of vesicular material admixed with placental tissues. The molar tissue was totally covering the internal os, and superior and adjacent to it was the fetus contained within its own amniotic sac. Amniotomy was done and a live baby boy weighing 1200 grams, 29 weeks by pediatric aging with APGAR score of 4 becoming 9 was delivered (Figure 2). The baby

was immediately intubated after delivery due to intercostal retraction, but died after three days secondary to hyaline membrane disease.

The molar products were left within the uterus and a total hysterectomy with mole in situ was performed. The estimated blood loss was 1 liter for which she was transfused with two units of packed red blood cells. The patient received methotrexate prophylaxis at a dose of 0.4 mg/kg/day intramuscularly for five days and was discharged upon its completion. Patient was advised serial monitoring of her serum β-hCG but due to financial constraints, she was unable to follow up after achieving two normal serum β-hCG values.

On examination of the uterus, the vesicular materials were easily separated from the endometrium. The placenta looked grossly normal. All specimens were submitted for histopathologic examination which revealed a postpartum uterus, chronic cervicitis with squamous metaplasia and nabothian cysts, and complete hydatidiform mole. Histopathologic result for the placenta was premature singleton placenta with a non-remarkable three-vessel umbilical cord and extraplacental membrane (Figures 3-5).

Molar tissues placed in Carnoy's solution were submitted for karyotyping within 24 hours after collection at the National Institutes of Health. These were cultured in an amniovac. However, since molar tissues lack nucleated cells, the culture did not grow, hence karyotyping was not performed. The molar tissues as well as the blood of the parents and baby were sent for DNA profiling to the Natural Science and Research Institute at UP Diliman. The mole proved to be androgenic in origin while the fetal blood had a normal XY diploid karyotype.

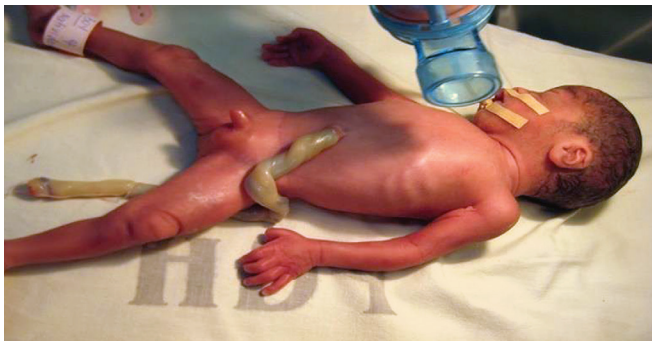

Figure 2. The baby from Case 1 who weighed 1200 g, 29 weeks by pediatric aging, APGAR 4,9. Intubation was done due to costal retractions.

Case 2

A 38-year-old, primigravid consulted due to elevated blood pressure at 22 weeks AOG. Her past medical history, family medical history, and personal and social histories were unremarkable. She had a previous ultrasound showing a live intrauterine pregnancy at 8 weeks AOG. During this time, she was admitted due to intractable nausea and vomiting, as well as vaginal spotting. She was given anti-emetics, hydration, and oral isoxsuprine. A repeat ultrasound was performed showing placenta previa. She was discharged after a week, still with vomiting but with cessation of spotting. She was advised complete bed rest and continued intake of folic acid, isoxuprine, and dydrogesterone. Over the succeeding weeks, her nausea and vomiting persisted prompting her to consult a different obstetrician gynecologist at 21 weeks age of gestation. On consult, she was noted to have an elevated blood pressure and was advised intake of Methyldopa

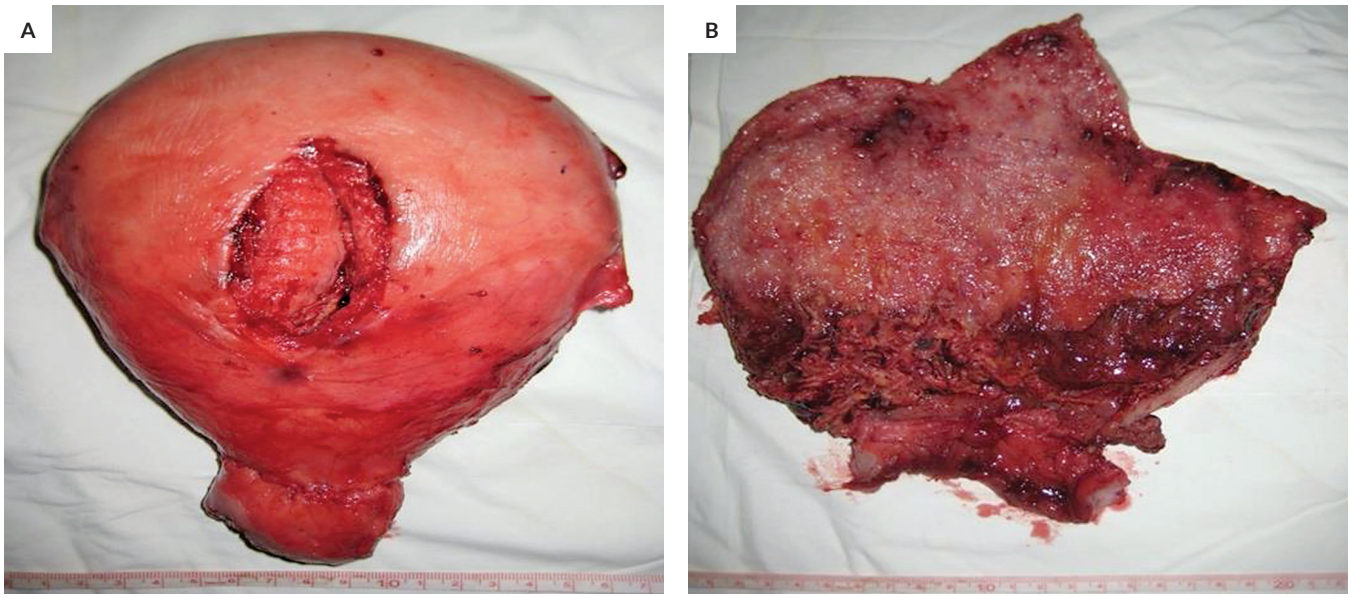

Figure 3. ***Uterus from Case 1.*** **(A)** Uterus showing the primary classical cesarean section. It measured 17 x 9 x 5.5 cm with smooth serosa; **(B)** Uterus on cut section. Notice that there was no invasion of the mole into the myometrium.

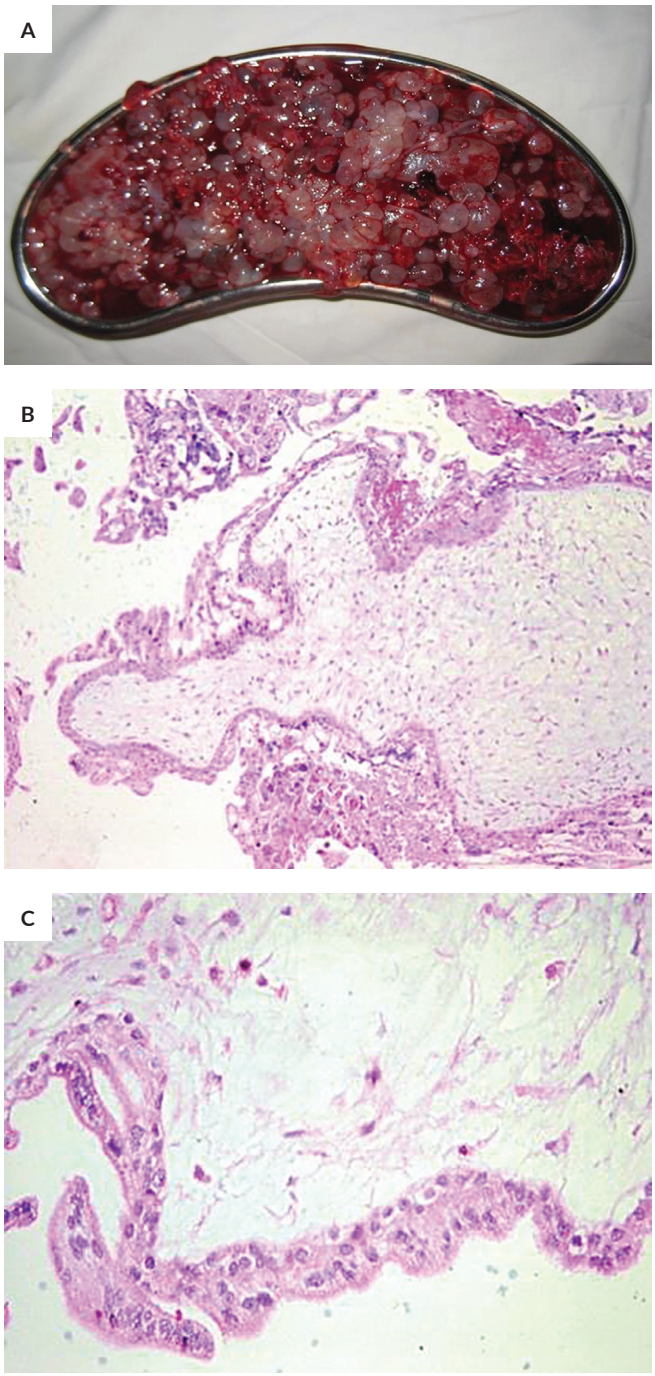

Figure 4. ***The hydatidiform mole.*** **(A)** Vesicular products that were easily detached from the underlying endometrium; **(B)** Photomicrograph of the vesicular products on 40x magnification shows chorionic villi with edematous hypocellular myxoid stroma. The outlines are scalloped with trophoblastic proliferation; **(C)** At 400x magnification, the hydropic villi have hypocellular stroma and two-layered trophoblastic covering: cytotrophoblasts in the inner layer and syncytiotrophoblasts in the outer layer.

500 mg three times a day. A repeat ultrasound was done revealing a single, live intrauterine pregnancy, cephalic in presentation with good cardiac and somatic activities, 21 weeks and 4 days by biparietal diameter, and 21 weeks and 5 days by femoral length with co-existent gestational trophoblastic disease probably complete hydatidiform mole, cannot totally rule out a partial mole. She was then referred to a trophoblastic disease specialist for further management.

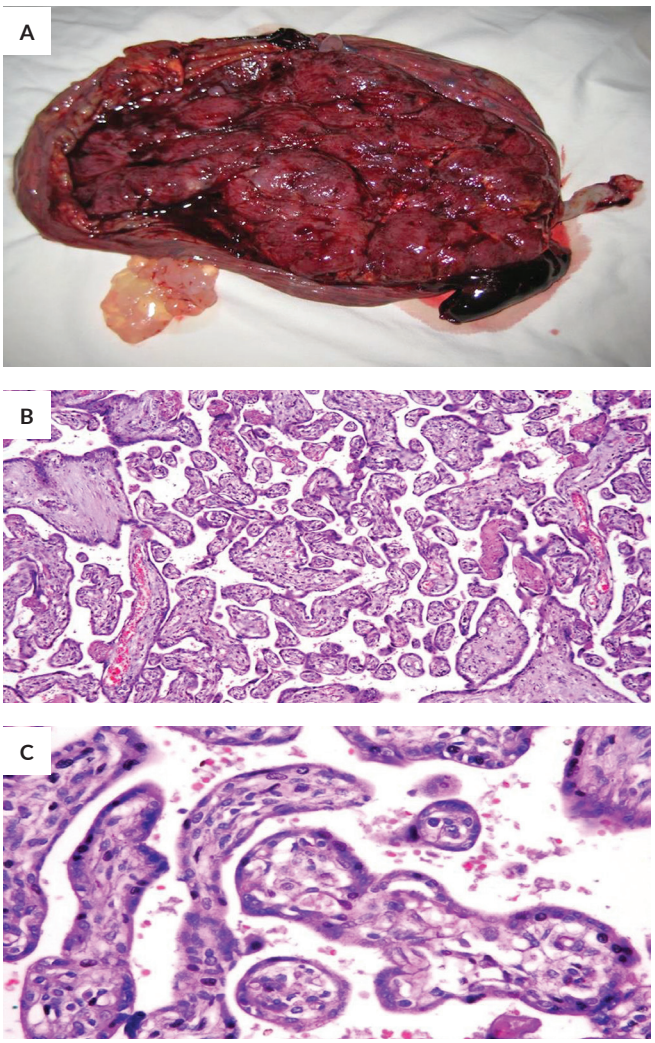

Figure 5. ***The placenta.*** **(A)** The placenta which weighed 220 g. It measured 14.5 x 11 x 2 cm with an attached 11 cm umbilical cord. The fetal surface was smooth. The maternal surface was also smooth with minimal amount of vesicular pale brown tissues adhering on its surface; **(B)** Photomicrograph of the placenta taken at 100x magnification shows immature placental villi with minimal peri-villous fibrin; **(C)** Photomicrograph of the placenta taken at 400x magnification shows small, non-edematous chorionic villi that have a single layer of trophoblastic lining (syncytiotrophoblast) with 3-4 peripherally located, RBC containing capillaries.

On consult with the specialist, blood pressure was elevated to 160/100 mmHg, full minute heart rate was 120 beats per minute, respiratory rate was 24 cycles per minute, and her body temperature was 37.8°C. She also had a grade 3 bipedal edema. Her abdomen was globular with a fundic height of 25 cm. Her uterus was boggy and no fetal heart tones could be appreciated. A transabdominal ultrasound was done which revealed molar tissues totally covering the os and a fetal death in utero. Baseline β-hCG was 801,800 mIU/ml and urine albumin was plus 4. Thyroid function test revealed hyperthyroidism (FT4 = 3.2 ng/dL and TSH = 0.02 mIU/L). Patient was admitted with an impression of twin gestation consisting of a complete hydatidiform mole and an intrauterine fetal demise, pre-eclampsia severe, to consider hyperthyroidism secondary to molar gestation. She was loaded with magnesium sulfate ($MgSO_4$) 4 grams intravenously and 6 grams intramuscularly on both buttocks with succeeding doses given every 6 hours intramuscularly for four doses. Internal examination was done revealing normal external genitalia, smooth, nulliparous vagina, cervix closed, posterior, uterus was enlarged to 24-26 weeks size, boggy in character, no adnexal mass or tenderness noted. Baseline hemoglobin was 92. She was then transfused with one unit of packed RBC pre-operatively. To address the hyperthyroidism, she was started on propranolol 10 mg three times a day and propylthiouracil (PTU) 50 mg/tab, 12 tablets per rectum. Laminaria was inserted into the cervical canal. Patient's blood pressure and heart rate were controlled after 12 hours of admission. She eventually underwent suction curettage of the molar products under ultrasound guidance followed by spontaneous vaginal delivery of a macerated fetus weighing 500 grams. Total blood loss was 1.5 liters. She was transfused with another three units of packed RBC. Vesicular tissues and fetal placenta were sent for biopsy. Histopathologic result revealed a complete hydatidiform mole and an unremarkable immature placenta with a three-vessel umbilical cord. She was not given methotrexate chemoprophylaxis due to elevated liver enzymes and serum creatinine but was advised close β-hCG monitoring. Beta-hCG taken one week after evacuation of the products of conception revealed a value of 4,797.4 mIU/ml. There was a continuous drop in the β-hCG levels until an increase was noted after the fourth determination following her curettage, from 199.4 mIU/ml to 260.9 mIU/ml. Transvaginal ultrasound revealed normal results and metastatic work-up was negative. Diagnosis at this point was persistent trophoblastic disease. She then received methotrexate, administered intramuscularly at a dose of 0.4 mg/kg/day for 5 days given every 10 days. She achieved remission after receiving four cycles of chemotherapy (inclusive of two consolidation treatment). No toxicity was experienced during treatment and she has remained asymptomatic with normal β-hCG titers. She was likewise started on oral contraceptive pills and advised to continue this for at least a year following remission.

Case 3

A 28-year-old G2P1 (1001) was admitted at 12 weeks and 5 days AOG due to vaginal bleeding. She had no prior prenatal consults or ultrasound examination and her medical history was unremarkable. Her first pregnancy was a livebirth delivered vaginally six months ago. Upon admission, she had stable vital signs. Except for pale conjunctivae, she had essentially normal systemic findings. On speculum examination, the cervix was smooth, with blood clots per cervical os. On internal examination, the cervix was closed and the corpus was enlarged to 16-18 weeks AOG.

Baseline ultrasound showed a live fetus with good cardiac and somatic activity, 11 weeks and 6 days AOG. Seen inferior to the fundally located gestational sac was an irregular mass with cystic spaces (volume = 238 cc), consider a hydatidiform mole. The fundally located gestational sac was separated from the live fetus by a thin intervening membrane (Figure 6).

Pertinent laboratory results included a serum β-hCG of 737,905 mIU/ml, elevated thyroid function tests (FT4 21.99 pmol/L, FT3 8.71 pmol/L), and hemoglobin of 91 g/L. Her chest radiograph, renal, and liver functions tests were normal. The admitting impression was hydatidiform mole with co-existing live fetus (11 6/7 weeks); hyperthyroidism from GTD, not in storm; anemia secondary to acute blood loss. Despite the presence of maternal complications, the plan was for expectant management due to the presence of the live fetus. The hyperthyroidism was controlled with propylthiouracil and propranolol. The anemia was corrected with blood transfusion. On the third hospital day, the patient developed elevated blood pressure (160/100 mmHg) and proteinuria, prompting a diagnosis of severe preeclampsia. She was given magnesium sulfate for seizure prophylaxis and amlodipine. On her 2nd week of admission, she developed two episodes of moderate vaginal bleeding. During both times, the fetus remained healthy so expectant management was continued. Repeat serum β-hCG on the 13th hospital day (2,917,462.37 mIU/ml) showed significant increase.

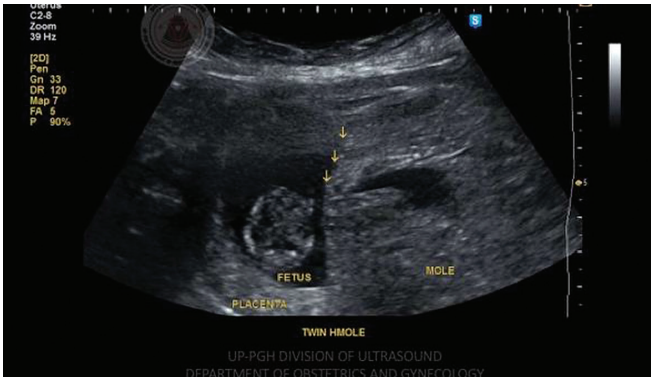

Figure 6. Sonographic picture of the relationship of the fetus, placenta, and molar tissue. A thin intervening membrane can be seen separating the normal fetus from the hydatidiform mole *(yellow arrows)*.

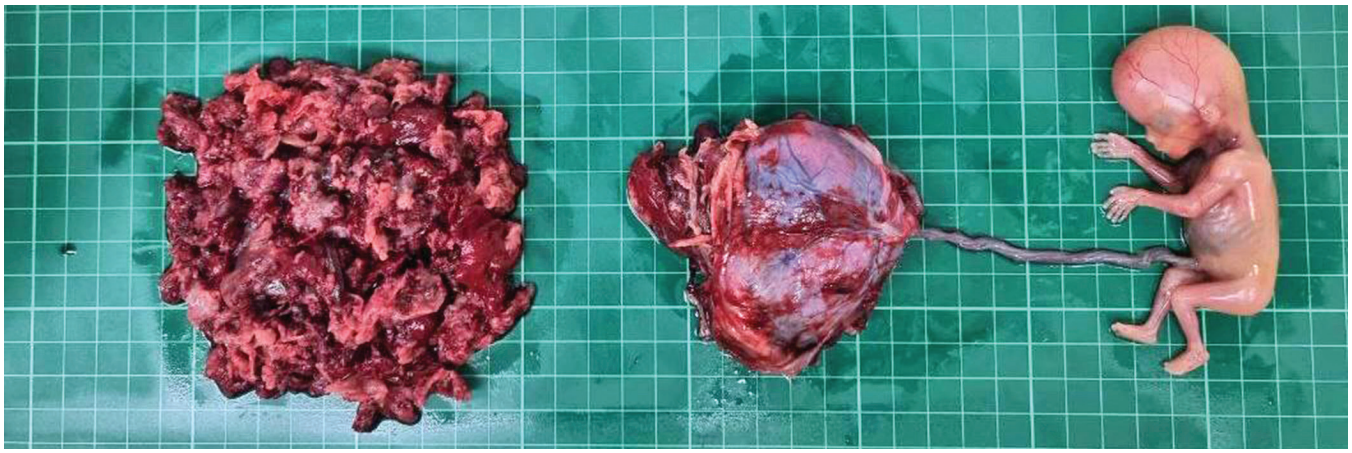

Figure 7. Gross specimen of molar tissue (left) and the normal fetus with its placenta (right).

On the 13th hospital day, the patient developed profuse vaginal bleeding with passage of vesicular tissue, followed by passage of the fetus (Figure 7).

Ultrasound-guided suction curettage was then performed and 800 cc of vesicular tissue was obtained. Patient was transfused with two units packed RBC, was given Methotrexate chemoprophylaxis and was discharged improved. Histopathologic examination revealed hydatidiform mole and an immature singleton placenta. Her serum β-hCG one week post-chemoprophylaxis was 564.20 mIU/ml. She was started on combined oral contraceptive pills and advised diligent β-hCG monitoring. Unfortunately, she was lost to follow-up after the 2nd post-evacuation β-hCG (57.22 mIU/ml).

DISCUSSION

Compared to other forms of pregnancy, hydatidiform mole has a relatively rare occurrence, with an estimated incidence of 0.57-2.0 per 1,000 pregnancies.[4] Pregnancies involving a hydatidiform mole with a coexisting fetus are even rarer with an incidence of 1:20,000 to 1:100,000 pregnancies.[1] Worldwide, only about 229 cases have been reported.[5] In the Philippines, only five cases have been reported in literature. Villar reported a case of hydatidiform mole with coexisting fetus delivered at 33 weeks of gestation.[6] In 2000, Dy-Meguizo reported two additional cases of complete mole with co-existing fetus, both of which did not go beyond the first half of pregnancy due to maternal complications.[7] Lagare reported a case of twin molar pregnancy in a 27/G2P1 (1001) who underwent primary cesarean section at 31 weeks.[8] Lastly, Kintanar reported a case of hydatidiform mole with coexisting fetus which was complicated by preterm labor, preeclampsia, HELLP syndrome, hyperthyroidism, anemia, and postpartum hemorrhage.[9] In a country known for its high incidence of hydatidiform mole, it is highly doubtful that these are the only cases of CMCF. Unreliable national data regarding this condition may be due to the following: (1) a number of pregnancies in the Philippines take place without the benefit of prenatal care, (2) histologic examination of placenta is not practiced in all institutions, (3) unaccountable home or non-institutional deliveries, and (4) absence of a national registry for gestational trophoblastic diseases (GTD).

When dealing with a hydatidiform mole with a coexisting fetus, three conditions must be considered: (1) a singleton pregnancy consisting of partial mole with a triploid fetus, (2) a twin gestation consisting of a complete hydatidiform mole with a diploid fetus, and (3) a twin gestation consisting of a diploid fetus with a normal placenta and a triploid fetus whose placenta has hydropic changes. The first condition results from the fertilization of a haploid egg by two haploid sperms, giving rise to a triploid fetus which tends to die in the first trimester. In contrast, the second and third conditions represent a form of dizygotic twinning in which fertilization results in a hydatidiform mole in one twin and a normal fetus in the other.[10] Differentiation between the three conditions is important due to differences in fetal survival, risk of maternal complications and development of Gestational Trophoblastic Neoplasia (GTN). Other differential diagnoses for CMCF include placental mesenchymal dysplasia (PMD), chorangioma, placental cysts, subchorionic hematoma, and placenta accreta spectrum (PAS) disorders.[1] Markedly elevated serum β-hCG is particularly useful in differentiating CMCF from these conditions.

The diagnosis of CMCF is based on the patient's clinical signs and symptoms, physical examination findings, sonographic picture, abnormal biochemical data, and cytogenetic studies. Case 1 presented with vaginal spotting at 21 weeks AOG and a fundic height that was much larger for her AOG. The uterus was likewise boggy particularly at the lower uterine segment, although fetal heart tones were appreciated on auscultation. Based on these physical examination findings, a twin gestation was suspected. However, the patient's markedly elevated serum β-hCG (533,167 mIU/mL) pointed to a Gestational Trophoblastic

Disease (GTD). The diagnosis of CMCF was confirmed when an ultrasound revealed a single intrauterine pregnancy with co-existent GTD. On the other hand, the second case presented with hyperemesis gravidarum and threatened abortion followed by development of elevated blood pressure and signs of hyperthyroidism. On examination, the uterus was boggy and larger than the age of gestation, with absent fetal heart tones. At this time, a diagnosis of hydatidiform mole was made. Findings on physical examination such as elevated blood pressure, tachycardia, tachypnea, and grade 3 bipedal edema were attributed to the maternal complications of molar pregnancy. CMCF was diagnosed based on sonographic results and serum β-hCG value of 801,800 mIU/ml. Case 3 presented with vaginal bleeding, hyperthyroidism, and anemia at 11 6/7 weeks AOG. With a corpus size of 16-18 weeks, the uterus was significantly larger than that expected of her AOG. The diagnosis of CMCF was clinched due to the markedly elevated serum β-hCG (737,905 mIU/ml) and the ultrasound finding of a live fetus and irregular cystic mass in two separate gestational sacs.

Approximately 68% of CMCF are detected via ultrasound, usually between the 12th and 14th weeks of gestation.[11] Detection of a multi-cystic placenta that is distinct from a normal-looking one, as seen in the cases presented, is pathognomonic for CMTF.[10] Magnetic resonance imaging (MRI) has also been used to delineate the relationship between a fetus, a normal placenta, and hydatidiform mole.[12,13] Demonstration of a heterogeneous, markedly hyperintense mass on T2-weighted images that is contained in a sac that is separate from a fetus and normal placenta leads to a precise diagnosis of CMCF and rules out a partial hydatidiform mole.[14]

In situations in which the diagnosis of CMCF is uncertain, prenatal invasive testing through karyotyping of the coexistent fetus obtained by chorionic villous sampling, amniocentesis or fetal blood sample will be of much help in establishing the diagnosis.[15] A triploid fetus or placenta is suggestive of a partial hydatidiform mole, which is not compatible with life. Patients should however be counselled that in approximately 40% of invasive procedures, there may be insufficient sample or no growth of the sample.[1] Antenatal karyotyping was not done in Case 1 and Case 3 due to the invasiveness of the procedure along with the increased risk of further pushing the patient into preterm labor. Prenatal karyotyping in the second case was no longer indicated since the fetus was dead upon admission.

Whether or not CMCF is diagnosed during the antenatal period, the type of CMCF must be confirmed after molar evacuation and delivery of the fetus. Careful examination of the placenta is warranted and all suspicious placenta should be submitted for pathologic evaluation so that microscopic molar changes can be accurately defined and reported. Examination of hematoxylin sections complemented by immunohistochemical staining using p57 can also be done. P57, which is the protein product of the paternally imprinted, maternally expressed *CDKN1C* gene, is absent in androgenetic conceptuses (complete mole). On the other hand, it is expressed in biparental conceptuses such as in a normal pregnancy, abortion, and partial mole.[16] Routine hematoxylin staining of specimens derived from both our patients revealed a complete hydatidiform mole and a normal placenta. Unfortunately, staining with p57 was not done in the first two cases due to its unavailability in the country at that time. Karyotyping of molar products after evacuation may also be done to establish the diagnosis. This was attempted in the first case, but no cell grew from the culture. Lack of cell growth was explained as due to the absence of nucleated cells in the materials submitted. Since complete hydatidiform mole lack nucleated fetal cells, the result was an indirect proof that the tissues submitted were from a complete hydatidiform mole.

Karyotyping alone would not be able to differentiate CMCF from placental mesenchymal dysplasia and the rare diploid PHM, since all have a diploid karyotype. In these cases, molecular genotyping using short tandem repeat (STR) polymorphisms can be used to identify parental contribution and ploidy number.[17] STRs are segments of deoxyribonucleic acid (DNA) that contain repetitive tandems of base pairs, the number of which usually varies per individual. DNA may be obtained from formalin-fixed, paraffin-embedded products of conception (POC) and amplified using polymerase chain reaction (PCR). The DNA from the POC may then be compared to maternal and paternal DNA at specific target STR loci.[16] A balanced biallelic profile showing both paternal and maternal contributions will be seen in the normal placenta of the co-existing twin in CMCF and in cases of PMD. In contrast, a complete hydatidiform mole will have alleles that were of purely paternal origin.[17] Rarely, the fetus in a PHM can have a diploid genome, which is theorized to be a result of post-zygotic diploidization of a triploid fetus. In such a case, the diploid fetus was shown to share all its alleles with the biparental triploid molar tissue.[18] Additionally, molecular genotyping is also used to differentiate between the triploid PHM and the diploid non-molar abortuses, since these cannot be differentiated using p57 immunostaining.[16] In the first patient presented, molecular genotyping was done and it was confirmed that the molar component was androgenic in origin whereas the fetus had an XY diploid karyotype.

Detailed information regarding the outcome of CMCF is poorly understood because of its rarity. In a systematic review of 244 cases of CMCF, 62 (25.4%) underwent elective termination and 182 (74.6%) underwent expectant management. Among those who decided to continue with the pregnancy, 50% had live births and 40.1% ended in intrauterine fetal demise. Among the livebirths, 78% were delivered prematurely.[19] No major congenital anomalies have been reported among livebirths.[20] In the Philippines, 50% of the reported cases resulted in livebirths, all of which were delivered before term. Approximately 80.8% of cases of CMCF present with antenatal maternal complications. The

most common complication was vaginal bleeding (70.5%), followed by hyperthyroidism (23.2%), and preeclampsia (14.3%).[19] The presence of theca lutein cysts, maternal respiratory distress, intrauterine fetal death, and even maternal death have also been reported.[21] All of our reported cases were complicated by vaginal bleeding, while the second and third cases also suffered from hyperthyroidism and preeclampsia.

Once the diagnosis of CMCF is suspected, referral to a maternal-fetal medicine specialist and trophoblastic specialist should be done. If the diagnosis of CMCF is unsure, invasive prenatal testing for fetal karyotype should be done to rule out a PHM with a triploid fetus. The woman should also be counselled regarding the risks of maternal complications and adverse fetal outcome.[15] If the woman does not wish to continue with the pregnancy, elective termination may be offered. The elective termination rate of CMCF ranges from 11.7% – 33% in literature. If the woman chooses to continue with the pregnancy, expectant management under close observation is reasonable.[21]

In the Philippines where therapeutic abortion is not allowed, management of a patient with CMCF seems straightforward. Despite early diagnosis, we allow the pregnancy to continue, intervening only when obstetrically indicated. The patient as well as the family members should be properly educated regarding the course and prognosis of the pregnancy. She must also be cautioned about the risks of developing serious maternal complications and of developing GTN. In the first case presented, the plan was to carry the pregnancy as close to term as possible and control of preterm labor was attempted. It was unfortunate that she eventually passed out vesicular products after 27 days in the hospital, necessitating an emergency abdominal delivery. In the third case presented, the plan was for expectant management despite the numerous maternal complications, since she had a live fetus.

There is no recommended route of delivery for CMCF, but abdominal delivery seems to be more common than vaginal delivery. The risks and benefits of each method should be considered and the plan should be individualized. If abdominal delivery is chosen, curettage is recommended at the time of cesarean section. The route of delivery does not seem to affect the risk of developing GTN.[13] A primary classical cesarean section was done for the first case because the hydatidiform mole was the presenting part and the baby could die from the blood loss incurred during curettage. Contrary to the first case, a suction curettage followed by spontaneous vaginal delivery of the fetus was done in the second case. This route was chosen because the baby was already dead and the patient was a primigravid. Since there was spontaneous passage of the fetus in the third case, the mode of delivery for the molar tissue was straightforward.

Approximately 20% of patients with complete hydatidiform mole develop GTN. This risk appears to be significantly higher in CMCF. A review of 244 cases of CMCF found that 34% of the patients subsequently developed GTN.[19] Other reported rates of malignant degeneration ranged from 19% to 63%. The length of gestation did not seem to influence the risk of developing GTN. However, high β-hCG level, presence of maternal complications, and lower fetal viability rate have been linked to higher rate of GTN.[21] Administration of chemotherapy after molar evacuation to prevent GTN remains to be a controversial issue. While some studies have shown a decrease in the incidence of GTN among patients given chemoprophylaxis, other authors have discouraged its use due to toxicities and the potential of developing chemoresistance should GTN develop. The Philippine Society for the Study of Trophoblastic Diseases recommends the administration of chemoprophylaxis to patients with CMCF.[4] Chemoprophylaxis was given to the first case and she did not develop GTN. The second case did not receive chemoprophylaxis despite the presence of high-risk factors due to elevated liver enzymes and serum creatinine levels. She eventually developed GTN and she went into remission after four cycles of methotrexate. The third case was given chemoprophylaxis but she was lost to follow-up. Because of the potential for malignant degeneration, patients with CMCF should be counseled on the importance of β-hCG monitoring, even after receiving chemoprophylaxis. It should also be emphasized that a successful subsequent pregnancy is possible after developing CMCF.

CONCLUSIONS

The cases presented demonstrate a clear pathological scenario of CMCF, distinct from either partial hydatidiform mole or placental mesenchymal dysplasia as confirmed by the genetic analysis of the androgenic mole and normal fetal cell lines for the first case and histopathologic diagnosis for the second case. Most important in the management of these cases is a thorough discussion with the expectant mother and her family regarding the complications that may arise as a result of the condition, the possibility of immediate termination of the pregnancy, and the risk for developing GTN. Due to the increased risk associated with such pregnancies and because of the diversity in their behavior, it is important to continue to report clinical experiences with CMCF in order to evaluate their natural history and to determine their optimal management.

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Author Disclosure

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