Looks Can Be Deceiving: A Case of Placental Mesenchymal Dysplasia With Concomitant Cytomegalovirus Infection

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ABSTRACT

Pregnancy with placental mesenchymal dysplasia (PMD), with concomitant cytomegalovirus (CMV) infection, and with coexistent normal viable fetus is very rare. An 18 year old, Gravida 2 Para 0 (0-0-1-0), was referred to our institution at 24 weeks age of gestation, with impression of molar pregnancy with a live twin fetus. Subsequent ultrasound revealed placentomegaly with placental features similar to hydatidiform mole. Her pregnancy was complicated with intrauterine growth restriction (IUGR) and oligohydramnios. TORCH panel at 25 weeks age of gestation revealed positive for CMV IgG. She had normal serum β-HCG, with elevated maternal serum alpha feto protein (msAFP). A caesarean section was done at 37 weeks age of gestation for placenta previa marginalis in haemorrhage. She delivered a live baby girl, APGAR score of 9,9, maturity testing of 37 weeks, small for gestational age. The baby was also positive for CMV IgG. Gross examination of the placenta revealed tortuous vessels and multiple cystic spaces. Histopathologically, there were hydropic stem villi with no trophoblastic proliferation. Immunohistochemically, placental mesenchymal dysplasia was confirmed.

Keywords: Placental mesenchymal dysplasia, PMD, Cytomegalovirus, CMV, placental mesenchymal dysplasia with cytomegalovirus, PMD with CMV

INTRODUCTION

First described by Moscoso et al in 1991, placental mesenchymal dysplasia (PMD) is a rare placental abnormality characterized by placentomegaly and with features resembling molar pregnancy on ultrasonography. Prenatal diagnosis is difficult, and final diagnosis is achieved by postpartum histologic examination of the placenta. Both placental mesenchymal dysplasia and cytomegalovirus are associated with adverse pregnancy outcome, and the fetus is at an increased risk for IUGR, intrauterine fetal demise (IUFD) or perinatal death, and Beckwith-Wiedemann syndrome.

Our case is an 18 year old Gravida 2 Para 1 (0-0-1-0), with prenatal diagnosis of molar pregnancy with a live twin fetus and CMV infection, complicated by IUGR and oligohydramios. She delivered a live healthy baby girl, who was positive for CMV IgG. PMD was then confirmed during postnatal evaluation, which included gross, histologic, and immunohistochemical examination of the placenta.

This paper aims to increase awareness of clinicians regarding PMD, and that it should be considered in the differential diagnosis of every placental abnormality, especially in specific sonologic findings of enlarged cystic placenta.

CASE REPORT

The patient is an 18-year old Gravida 2 Para 0 (0-0-1-0), referred to our institution at 24 weeks age of gestation by a clinic in Guam, with their impression of molar pregnancy with a live twin fetus, rule out partial mole.

She had no known illnesses, with family history of diabetes and hypertension. Patient is an American citizen, single, unemployed, and previous marijuana user. Patient had spontaneous abortion last February 2013, with no dilatation and curettage done.

Patient was on a regular follow up with her obstetrician in Guam. An ultrasound done on her 14 weeks and 2 days age of gestation revealed "Single live intrauterine fetus, mean sonographic age of 14 weeks, with a large "mass" with cystic spaces in the lower uterine segment completely covering the os." The primary consideration was molar pregnancy with a live twin fetus, rule out partial mole. Option for induced abortion was offered, but the patient opted to continue pregnancy. Repeat ultrasound done at 16 weeks and 3 days age of gestation revealed similar findings. At 17 weeks age of gestation, quantitative serum β-HCG was elevated at 339,217 mIU/ml. She was referred to our institution for further evaluation and management. The patient consulted our institution at 24 weeks and 1 day age of gestation. Ultrasound was done, revealed "Pregnancy uterine 23 weeks and 1 day by average fetal biometry, live singleton in cephalic presentation; Sonologic findings of molar changes in the placenta suggestive of complete hydatidiform mole (Figure 1), To consider complete hydatidiform mole with coexistent live twin fetus

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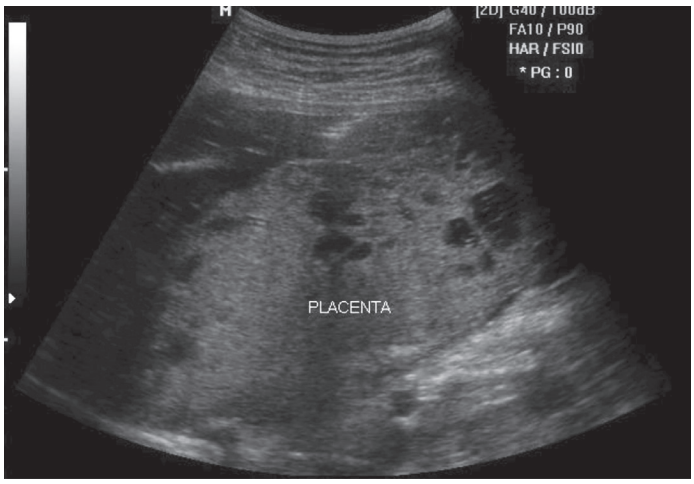

Figure 1. Ultrasound at 24 weeks and 1 day age of gestation: Molar changes in the placenta suggestive of complete hydatidiform mole.

(CHMTF); Oligohydramnios, with an amniotic fluid index (AFI) of 5.28 cm". The patient was advised to increase fluid intake of 3 liters per day, prenatal milk formula, high protein-caloric diet, aspirin tablet, calcium tablet, and fish oil capsule. She was referred to a perinatologist.

The patient was seen by the perinatologist at 25 weeks age of gestation, wherein a congenital anomaly scan and Doppler velocimetry were performed. Significant findings were "Placentomegaly and placenta previa totalis; Oligohydramnios, with an AFI of 4.75 cm; To consider intrauterine growth restriction (IUGR), with an estimated fetal weight below the 10th percentile (622 grams). Congenital anomaly scan showed dolicocephaly which may be due to fetal position; Consider a partial mole, rule out twin gestation with a singleton fetus and hydatidiform mole (Figure 2); All doppler indices are normal except for occasional bilateral uterine artery notching indicative of abnormal subendothelial trophoblastic invasion of the spiral arterioles predictive of possible development of hypertension later in pregnancy." TORCH panel was also done, which showed positive for cytomegalovirus (CMV) IgG. The possible effects of CMV infection on her pregnancy and fetus, including oligohydramnios, intrauterine growth restriction and neurodevelopmental sequelae, were discussed with the patient.

At 26 weeks and 3 days age of gestation, repeat ultrasound and Doppler velocimetry were done and showed fetal weight gain, now in the 10th percentile (772 grams), oligohydramnios at 5.39 cm, with normal maternal and fetal doppler indices. The patient was admitted for hydration.

During her admission, she underwent non stress test once daily, all of which were reactive. Amniotic fluid index (AFI) monitoring was done every two days, all of which revealed normohydramnios, with AFI upon discharge of 8.08 cm (low normal). She was for amniocentesis by the perinatologist for karyotyping and CMV-DNA PCR, however

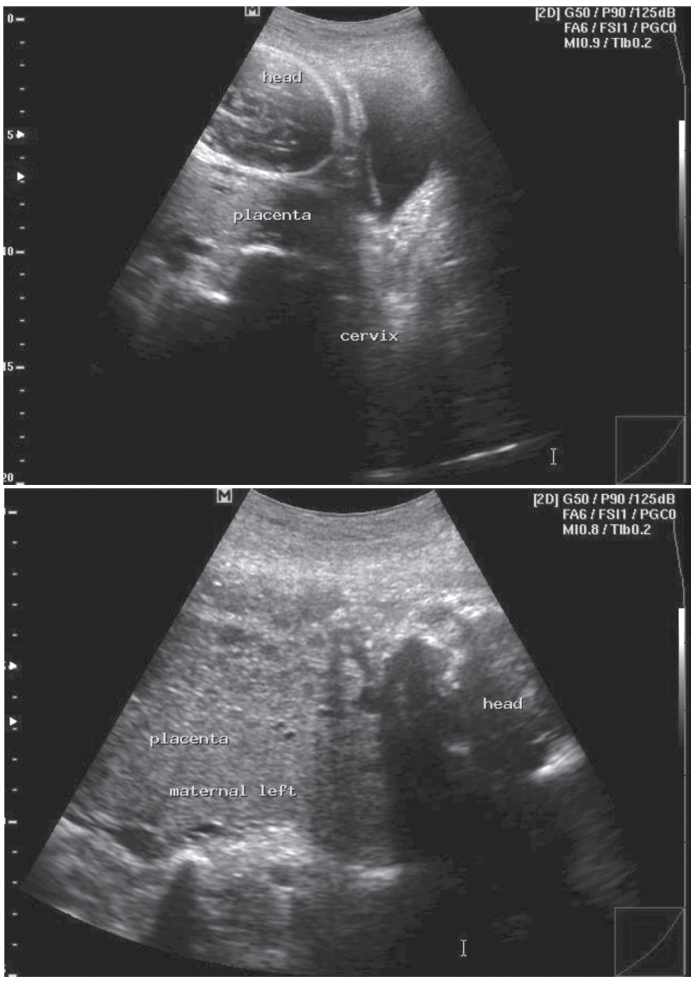

Figure 2. Ultrasound at 25 weeks age of gestation: Placentomegaly and placental previa Totalis; Consider a partial mole, rule out twin gestation with a singleton fetus and hydatidiform mole.

were eventually deferred due to financial constraints. Quantitative serum β-HCG was requested during this time, which was already within normal limits for her age of gestation at 33,510 mIU/ml. However, her maternal serum alpha feto protein (msAFP) was elevated at 450.6 ng/ml. Patient was discharged stable at 27 weeks and 2 days age of gestation, with instructions of AFI monitoring twice per week, Doppler velocimetry studies weekly, and fetal growth monitoring every two to three weeks. Patient was advised to continue her prenatal medications. The plan of prolonging the gestation was discussed with the patient, and that intervention in the form of abdominal delivery was considered in the case of deteriorating fetal status and/or haemorrhage.

Follow-up amniotic fluid monitoring was done at 28 weeks and 1 day age of gestation, which revealed 5.82 cm (below the 5th percentile for age of gestation). Patient was readmitted for hydration. She was given steroids for fetal lung maturity. Pelvic ultrasound was done on the second hospital day, which revealed an enlarged placenta with multiple cystic spaces totally covering the os (Figure 3), amniotic fluid below the 5th percentile for age of

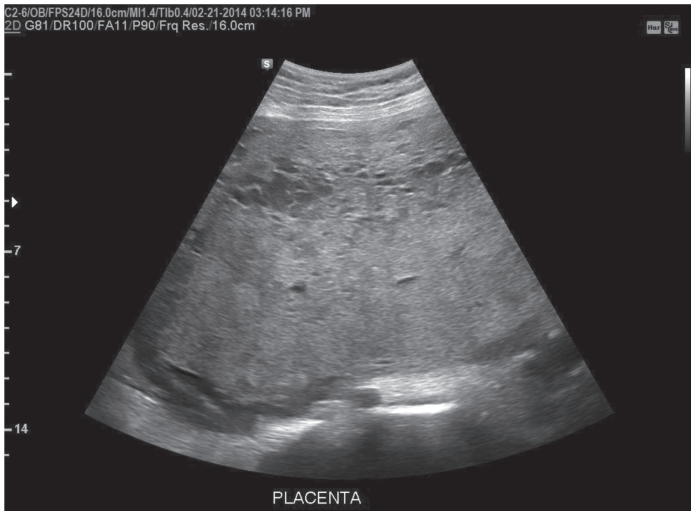

Figure 3. Ultrasound at 28 weeks and 2 days age of gestation: Enlarged placenta with multiple cystic spaces totally covering the os.

gestation (AFI of 6.4 cm), and estimated fetal weight of 995 grams, appropriate for gestational age. All Doppler indices, maternal and fetal, were normal. Non stress test done twice daily were all reactive. After three days of intravenous hydration, she was discharged with improved amniotic fluid of 9.4 cm. Patient was advised to increase oral fluid intake of 3 to 5 liters per day, regular sonographic monitoring, and possible readmission for repeated intravenous hydration.

During the interim, patient had been on regular follow up. She had stable vital signs, no febrile episodes, no blood pressure elevations, and with good fetal movement. Serial ultrasound results still showed placentomegaly and placenta previa, with the cystic changes in the placenta proportionately less than what were previously appreciated during the first two trimesters. Her latest ultrasound at 36 weeks age of gestation revealed "Placenta posterolateral grade III with hydropic changes (Figure 4), consider placenta previa marginalis; Normohydramnios (AFI of 13.5 cm); Estimated fetal weight appropriate for gestational age (2,196 grams); Biophysical profile score of 8/8."

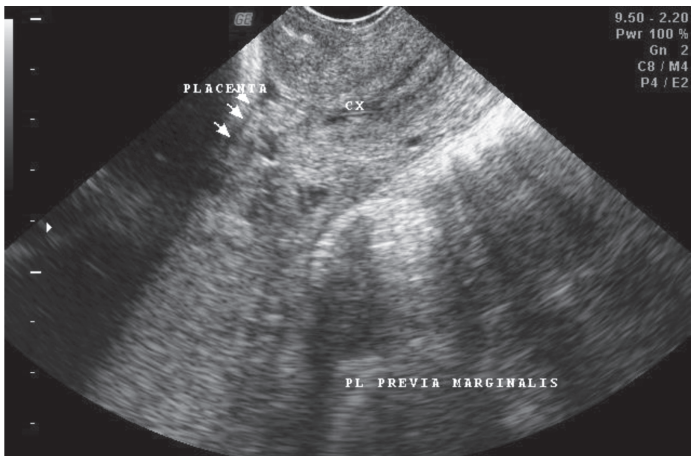

Figure 4. Ultrasound at 36 weeks age of gestation: Placenta posterolateral grade III with hydropic changes, consider placenta previa marginalis.

However, at 36 weeks and 1 day age of gestation, patient was admitted due to vaginal bleeding. Upon admission, she had stable vital signs, with good fetal heart tones, with minimal bleeding per os, and with a reactive non stress test. Admitting impression was "Gravida 2 Para 0 (0-0-1-0) Placenta previa marginalis in haemorrhage; Singleton pregnancy with placentomegaly versus complete hydatidiform mole with coexistent live twin fetus". Complete blood count and urinalysis were requested, both revealed normal results. Patient was given oral tocolytic and prophylactic antibiotic. During the hospital stay, she had minimal brownish to pinkish vaginal spotting, with occasional mild contractions, with reactive non stress test. Medications were continued.

The patient eventually underwent low transverse caesarean section I for placenta previa marginalis in haemorrhage at 37 weeks age of gestation. Post-operative impression was "Gravida 2 Para 1 (1-0-1-1) Pregnancy uterine cephalic delivered live term baby girl, APGAR score of 9,9, birthweight of 2010 grams, maturity testing of 37 weeks, small for gestational age; Placentomegaly; Placenta previa marginalis in hemorrhage". Intra-operatively, the placenta was noted to be enlarged, implanted anteriorly covering 4/5 of the uterine cavity, with the edge partially covering the anterior lower uterine segment. It had enlarged varicosities, with a three-vessel umbilical cord (Figure 5). The placenta was sent for histopathology. There were no post-operative complications, and the patient was discharged stable from the hospital on the third post-operative day.

The official histopathology report stated that the placenta weighed 1,024 grams and measured 20.0 x 19.0 x 6.0 cm (Figure 6). Cut sections of the placenta revealed multiple tan white cystic spaces filled with light

Figure 5. Intra-operative finding: Placenta was noted to be enlarged, implanted anteriorly covering 4/5 of the uterine cavity, with the edge partially covering the anterior lower uterine segment. It had enlarged varicosities, with a three-vessel umbilical cord.

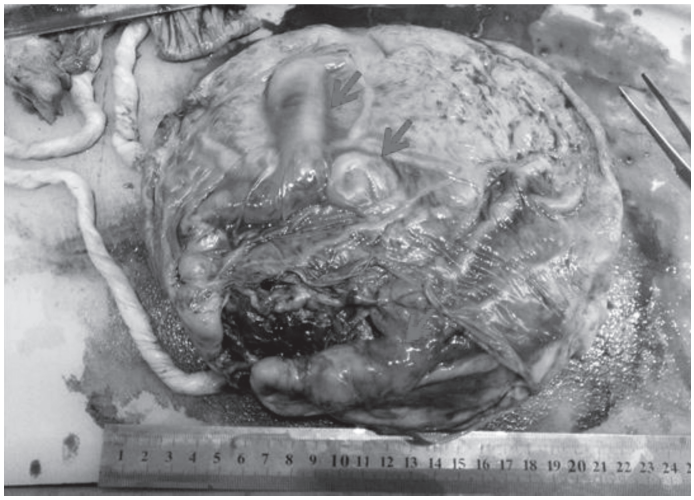

Figure 6. Grossly, enlarged placenta with cirsoid (dilated) chorionic vessels (red arrows) seen on the fetal side and eccentrically inserted umbilical cord.

yellow watery fluid (0.2 to 3.2 cm in widest diameter) with a smooth shiny lining (Figure 7). The placental side had tortuous blood vessels. Microscopically, there were dilated chorionic vessels, large hydropic stem villi with myxomatous stroma, dilated thick-walled vessels without trophoblastic proliferations and stromal inclusions (Figures 8 and 9), and villous chorangiosis (Figure 10).

Immunohistochemical study was further done on the placenta (Figure 11, 12, 13), which revealed: "Positive for desmin, Negative for SMA and Ki-67: Consistent with placental mesenchymal dysplasia (PMD)"

Figure 7. Cut section of the placenta on the maternal side showing multiple cystic spaces/vesicles (arrows).

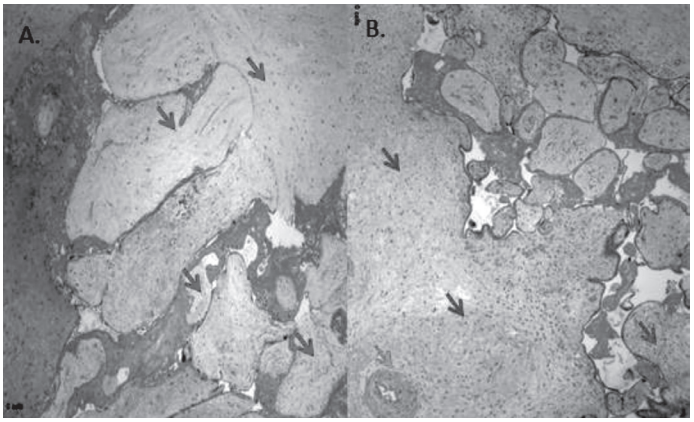

Figure 8. A. Large hydropic villli (red arrows) with no trophoblastic proliferation. B. Large villi with fibrotic stroma (blue arrows) and central vessels with muscular sclerosis (green arrow).

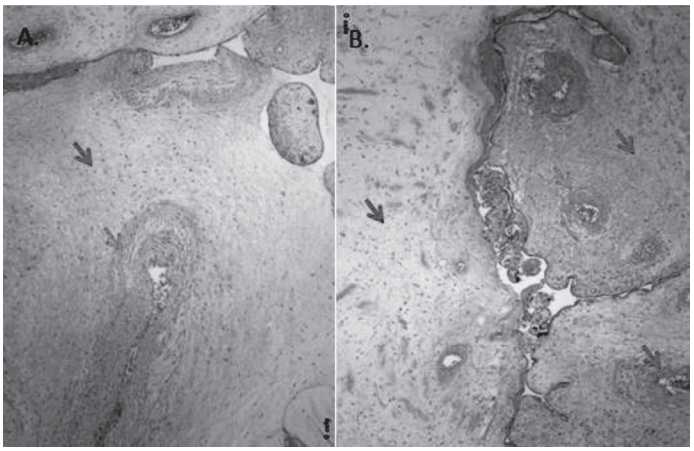

Figure 9. A and B. Large villli with fibrotic stroma (red arrows) and central vessels with muscular sclerosis (green arrows).

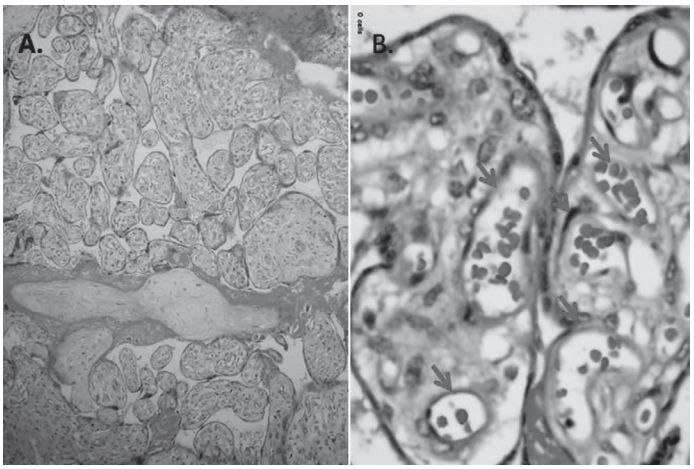

Figure 10. A. Mature villli with chorangiosis on scanner view. B. Chorangiosis, multiple dilated capillaries (red arrows) on high-power objective view.

The patient's baby, on the other hand, was admitted at the neonatal intensive care unit for workup. She had unremarkable complete blood count and blood culture results, however, she was positive for CMV IgG. The baby had neonatal pneumonia, and was given amikacin and ampicillin as antibiotics. Phototherapy was also done for 24 hours to address the jaundice on the chest and thigh. At the eighth day of life, the baby was discharged stable.

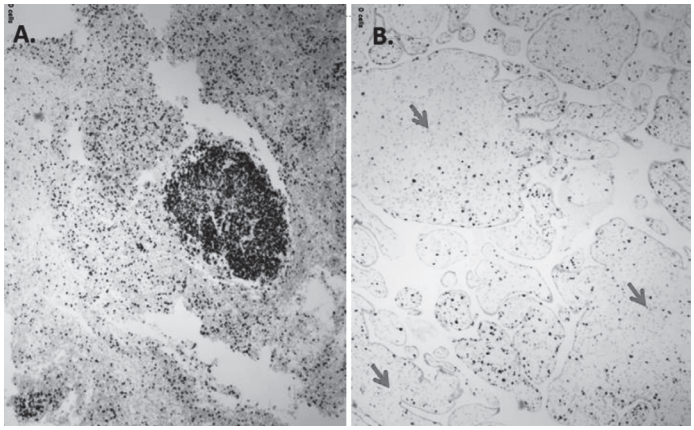

Figure 11. A. Positive control for Ki-67 on scanner view. B. Patient: Negative in hydropic villi, abnormal villi (red arrows) on scanner view.

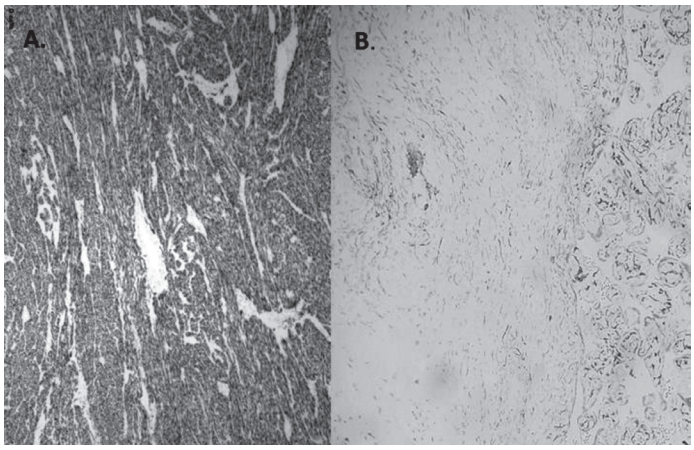

Figure 12. A. Positive control for Desmin on scanner view. B. Patient: Strongly positive in all villi.

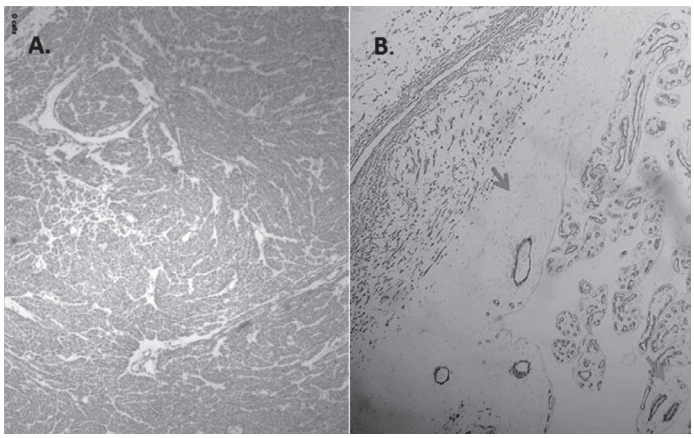

Figure 13. A. Positive control for Smooth Muscle Actin on scanner view. B. Patient: Negative in abnormal villi (red arrows) on scanner view.

DISCUSSION

Our patient was referred to us by a clinic in Guam, with impression of molar pregnancy with a live twin fetus, rule out partial mole. Her initial β-HCG at 17 weeks age of gestation was elevated. Subsequent ultrasound scans done in our institution showed placentomegaly with features similar to hydatidiform mole, i.e. hydropic changes, multiple cystic spaces. Two different mechanisms of the formation of hydatidiform mole with a live twin fetus are possible: (1) A complete hydatidiform mole (46 chromosomes; all paternal in origin) coexistent with a live twin fetus (46 chromosomes; 23 maternal and 23 paternal), and (2) A partial mole with an abnormal triploid fetus (both having 69 chromosomes of maternal and paternal origin). [1]

Fetal karyotype is important in the prognosis of pregnancy. In partial mole, the fetus is triploid and severely malformed, hence, the indication for termination of pregnancy is evident, or, the fetus may die in the first trimester. In complete hydatidiform mole with coexistent live twin fetus (CHMTF), the fetus may be normal and continuation of pregnancy may be done with risk of possible maternal complications such as preeclampsia, anemia, hyperthyroidism, hyperemesis gravidarum, respiratory distress due to trophoblastic embolization to the lungs, persistent trophoblastic disease [2, 3]. Our patient first consulted our institution during her second trimester with a normal viable fetus, and with unremarkable fetal well-being monitoring done subsequently. Even in the absence of fetal karyotyping, partial molar pregnancy was ruled out based on these findings. CHMTF was hence considered, with close monitoring of the possible complications associated with it. Our patient remained asymptomatic throughout her pregnancy, with no blood pressure elevations.

A pertinent finding in our case is that our patient was positive for cytomegalovirus (CMV) IgG, negative for CMV IgM. Our patient is an American citizen from Guam, and approximately 50 to 80 percent of adult women in the United States have serologic evidence of past CMV infection. IgM titers reflect primary, recurrent, or reactivation infections. It usually declines rapidly over a period of 30 to 60 days, but they can still remain elevated for many months. Hence, measurement of IgG avidity is valuable in confirming primary CMV infection, but this was not done on our patient [5]. Her test result raises that possibility of either a latent CMV infection, or a primary infection that occurred during the first trimester.

Our patient's pregnancy was complicated with IUGR and oligohydramnios, with persistent sonologic finding of placentomegaly. It is undisputed that placentomegaly is observed in CMV infection. A study done by La Torre and co-workers (2006)[6] concluded that at each sonographic measurement between 16 and 36 weeks of gestation, women with primary CMV infection who had a fetus or newborn with CMV disease had placentas that were significantly thicker. Oligohydramnios and IUGR, on the other hand, occur during symptomatic—apparent—CMV infection. Pereira and co-workers (2014)[7] found that primary infection impairs placental development and

leads to IUGR.

Vertical transmission of CMV may occur as a result of transplacental infection, which is more likely during the first half of pregnancy. Primary maternal CMV infection is transmitted to the fetus in about 40 percent of cases and can cause severe morbidity [4, 5]. In contrast, recurrent maternal infection infects the fetus in only 0.15 to 1 percent of cases [5]. CMV nucleic acid amplification testing of amnionic fluid is the gold standard for diagnosing fetal infection [5]. This was not done on our case. Our patient delivered a live, healthy baby girl, who was also positive for CMV IgG, negative for CMV IgM. This led to two hypotheses. First, the baby may have had CMV infection during the first trimester. Second, the test result could be reflective of the passive immunity of the baby to CMV. In a study done by Chen and co-workers (2012)[8], they demonstrated that maternal anti-CMV IgG was effectively transferred to her newborn, and that maternal anti-CMV IgG in the majority of newborns is higher than that in their mothers. Transplacental transfer of maternal IgG to the fetal bloodstream is mediated by neonatal Fc receptor in syncytiotrophoblasts of the placenta and contributes to the passive immunity of newborns to pathogens.

Meanwhile, the histological hallmarks of CMV infection in the placenta, i.e. chronic lymphoplasmacytic villitis, thrombosis of villous capillaries, adjacent hemosiderin deposits, necrosis of villous tissue and trophoblast, and inclusion-bearing cytomegalic cells ("owl-eye" cells) [9], were not evident in our case. However, Muhlemann and co-workers (1992) [10] did an immunocytochemical study on six CMV-infected placenta. They suggested that histologic features are often inconclusive, and they found inclusion bodies in only one of six cases. Immunocytochemistry, on the other hand, revealed viral antigen in five of the six placenta. Since immunocytochemistry was not done in our case, we cannot totally rule out transplacental CMV infection.

In our patient, given the sonologic finding of placentomegaly with molar features, elevated msAFP, with latest β-HCG within normal limits for age of gestation, and with placental morphologic finding of large hydropic stem villi but no trophoblastic proliferation, we considered placental mesenchymal dysplasia.

Placental mesenchymal dysplasia (PMD) is a rare placental anomaly. It was initially described by Moscoso and co-workers in 1991 [11] as placentomegaly which gives the image of partial hydatidiform mole with elevated level of alpha feto-protein (AFP). Various terms have been used, such as "mesenchymal hyperplasia", "mesenchymal stem villous hyperplasia," and "pseudo-partial mole." Approximately 100 cases have been reported. True incidence is not known but it has been estimated at 0.02%. Maternal age range from 16 to 38 years, and majority of the fetuses were female, with a male to female ratio of 1:8. [12]

The exact etiology of PMD is not yet established, however, there are multiple theories which include congenital malformation of the mesoderm, molecular disruption of the imprinting genes of chromosome 11p15.5 associated with Beckwith-Weidemann syndrome (BWS), and androgenetic/biparental mosaicism [12].

Nayeri and co-workers (2012) reviewed 64 cases and reported that sonographically, 50% of the placentas were enlarged or thickened, 80% were cystic with hypoechoic areas, and 16% had dilated chorionic vessels. Oligohydramnios were also observed on isolated cases [13]. In our case, oligohydramnios was evident and serial sonology results showed placentomegaly with features similar to hydatidiform mole. The gross features of PMD include placentomegaly, dilatation of chorionic vessels, and large areas of cystic villous changes along with areas of normal placenta[14]. Grossly, the placenta in our case weighed 1,024 grams, which is above the 95th percentile of weight for age of gestation [15]. It had tortuous blood vessels, and cut sections revealed multiple tan white cystic spaces filled with light yellow watery fluid. The histologic findings of PMD consist of enlarged stem-cell villi with varying degrees of edema which contain abnormal thick-walled fetal blood vessels, which in some cases were thrombosed. Trophoblastic proliferation and stromal inclusions, both characteristic of molar pregnancies, are notably absent. Villous chorangiosis (hypercapillarization), defined as more than 10 terminal villi showing 10 or more capillaries per villus, have been identified on cases of PMD[16]. All these histologic findings were present on our case.

Pham and co-workers (2006) did an immunohistochemical study on placentas of PMD. The study concluded that dysplastic villi in PMD were immunoreactive for desmin, but negative for smooth muscle actin (SMA) and Ki-67. Immunohistochemical study was likewise done in our case (Figures 11, 12, 13), which revealed: "Positive for desmin, Negative for SMA and Ki-67: Consistent with placental mesenchymal dysplasia (PMD)"

At this point it is important to discuss the difference between PMD and molar pregnancy, because PMD is most often mistaken for molar pregnancy based on similar sonographic findings of enlarged, thickened placenta with cystic spaces. Although β-HCG level is increased in 38% of PMD cases, β-HCG is always elevated in molar pregnancies. Also, PMD is more likely associated with elevated msAFP levels (70%) [12]. This is true for our patient, who had elevated msAFP and with latest β-HCG within normal limits. Partial molar pregnancies demonstrate triploidy, which is exceedingly rare in PMD. Karyotyping via amniocentesis should be done to exclude partial molar

pregnancy, and Cohen and co-workers reported that karyotype was normal in 32/36 (89%) of PMD cases[17]. Lastly, the characteristic feature of PMD is the absence of trophoblastic proliferation, which is a hallmark of gestational trophoblastic disease. In our case, there was no trophoblastic proliferation.

Pregnancy outcomes for PMD range from healthy, uncomplicated pregnancies to adverse maternal and/or neonatal complications. As mentioned, our patient's pregnancy was complicated with IUGR and oligohydramnios. She delivered a live term baby girl, with APGAR score of 9,9, maturity testing of 37 weeks, small for gestational age. Approximately 23% of the cases of PMD are associated with Beckwith-Weidemann syndrome (BWS), which is characterized by macrosomia, exomphalos, macroglossia, omphalocele[18]. 52% of pregnancies with PMD had preterm deliveries. Intrauterine growth restriction (IUGR) occurred in 33%, while intrauterine fetal demise (IUFD) occurred in 13% of cases [12]. Pham and co-workers (2006) [16] proposed that IUGR and IUFD may occur because of obstructive vascular thrombosis and decreased maternal-fetal gas exchange owing to a reduction in the normal amount of chorionic villi. These also explain the placental remodelling seen in PMD cases as adaptive mechanisms, such as hypervascularity (chorangiosis), which is evident on our case. At this time, there is paucity of literature on PMD, and most publications consist of case reports or series. Management of PMD at present is focused mainly on heightened surveillance. Sonographic findings of PMD warrant careful evaluation of the fetus to rule out abnormalities associated with BWS, and to address complications such as oligohydramnios. There is no evidence to suggest that Doppler velocimetry would help to recognize cases of PMD, but it may play a role in cases of IUGR.

CONCLUSION

In conclusion, placental mesenchymal dysplasia (PMD) is a rare and clinically significant anomaly that should be considered in the differential diagnosis of every placental abnormality, especially in findings of enlarged cystic placenta with dilated chorionic vessels. Elevated msAFP further support the diagnosis. Karyotype should be obtained to exclude molar pregnancy in order to avoid unnecessary termination of pregnancy. The placenta should be sent for histopathologic evaluation for confirmation of PMD.

Cytomegalovirus (CMV) is the most common perinatal infection in the developed world, and evidence of fetal infection is found in 0.2 to 2 percent of all neonates. Primary maternal CMV infection is transmitted to the fetus in about 40 percent of cases and can cause severe morbidity. Because of this, CMV nucleic acid amplification testing of amnionic fluid should be done to confirm congenital CMV infection.

PMD and CMV are associated with adverse pregnancy outcome. Patients should be counselled regarding complications. Heightened surveillance with assessment of fetal well-being should be always be considered. A detailed histologic, immunohistochemical and also genetic analyses are essential for accurate diagnosis.

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