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Placental Mesenchymal Dysplasia Associated with Beckwith–Wiedemann Syndrome

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Introduction and Literature Review

Placental mesenchymal dysplasia (PMD) is a rare benign disorder of the placenta characterized by placentomegaly and grapelike vesicles that can resemble at ultrasound examination with a molar pregnancy. (1) PMD was described initially by Moscoso et al (2) as stem villous hyperplasia with elevated maternal serum alpha- fetoprotein and enlarged placentas with ultrasound features that are suggestive of partial mole.

This condition may resemble a partial hydatidiform mole (PHM), however in contrast to partial mole trophoblastic proliferation is absent, the disorder being characterized by aneurysmal dilatation of vessels on the fetal surface of the placenta with dilated stem villi. Although there are some papers that report an incidence around 0.02% of pregnancies,(3) the true incidence of PMD is unknown because it has been previously reported under a variety of names such as “placenta- megaly with massive hydrops of placental stem villi” and “pseudo-partial moles.(4,5) More in the female than male (3.6:1).

Moreover, placental mesenchymal dysplasia is associated with fetal growth restriction (IUGR) in the majority of the cases and in approximately one quarter of the reported cases with Beckwith–Wiedemann syndrome (BWS) (4,6) or intrauterine fetal demise (IUFD) but can also be associated with normal appearing fetuses.

This case report intends to highlight the salient features of PMD and the importance of distinguishing PMD from its differential, the most important of which is a partial mole. Placental mesenchymal dysplasia is associated with Beckwith-Wiedemann syndrome (BWS) and fetal growth restriction in the majority of the cases but can also be associated with normal-appearing fetuses.

Pathogenesis

The understanding of the etiology and pathogenesis of PMD has advanced in recent years, and paternal uniparental disomy(UPD) for the Beckwith–Wiedemann syndrome (BWS) locus on chromosome 11p15.5, often as a consequence of androgenetic biparental mosaicism (ABM), has been shown to underlie most cases of PMD.

While PMD is known to be associated with a diploid karyotype, distinguishing it from the triploid karyotype of PHM, recent genotyping studies have shown the phenotypic and immunohistochemical features of PMD are associated with androgenetic biparental mosaicism (ABM) (7, 8–9). ABM in PMD is characterized by a mixture of two cells lines: an androgenetic cell line in the chorionic mesenchyme and a biparental cell line found in the villous cytotrophoblast and amnion.(7)ABM arises either from a single zygote (mosaicism) by a mitotic error or fusion of two zygotes (chimera).

Although most PMD cases are diploid, there are reports of cases with PMD morphology and immunohistochemical staining pattern with lack of trophoblastic hyperplasia which show a hyper-diploid component (triploid/tetraploid) in the cytotrophoblast cells. (7, 11, 10)

However, a recent case of PMD in a dichorionic twin gestation demonstrated that there may be early embryonic death and no recognizable fetal tissue later in gestation in PMD,(10) stressing that there may be a spectrum of the phenotypic expression of ABM which depends on the quantity and distribution of the diploid androgenetic cell line.

PMD may be considered to fall within the range of genetic possibilities between a completely biparental conceptus (normal) and a completely androgenetic conceptus.

The reported cases of PMD range from 30 % to 100 % involvement of the placenta. (10–12) It is possible that in some placentas with even smaller percentages of involvement, the cystic changes may be overlooked while those with 100 % involvement may not develop a fetus. (10)

Rare cases with gross and histologic features of PMD have been found to be uniformly biparental without androgenetic allelic imbalance, suggesting that not all cases with PMD morphology are secondary to ABM.(12) Some of these cases may result from ABM below the threshold that can be detected by molecular genetic techniques.

However, several case reports suggest that PMD occurs with mosaic paternal UPD or other forms of loss of heterozygosity confined to the 11p15.5 region,(13,12, 14) some cases associated with BWS,(12, 14) and aberrant expression of genes CDKN1C and/or IGF2 located within this imprinted region of chromosome. Therefore, the villous stromal overgrowth seen in PMD is likely secondary to genes within this region alone, particularly, overexpression of the IGF2 gene, which is primarily expressed from the paternal allele. (5, 12)

The immunohistochemical expression pattern of p57KIP2 in PMD is abnormal. P57KIP2 is a cyclin-dependent kinase inhibitor nuclear gene product (CDKN1C) encoded on 11p15.5 that is maternally expressed but paternally silenced, and therefore has become a useful indirect marker of an androgenetic genotype. (15)

Histopathology

Gross examination: PMD placentas are large for gestational age with aneurysmally dilated chorionic plate vessels with fibromuscular hyperplasia and normal placental parenchyma. Cystically dilated vesicles are present, which are similar to those seen in molar pregnancies.

Histopathology features

- Absence of trophoblastic proliferation in PMD placentas is the main histological difference from partial moles.
- Mixture of normal and abnormal villi.
- Enlarged proximal stem villi with edematous/myxomatous stroma with cistern formation and thick- walled peripheral blood vessels.
- Distal villi have increased capillaries, chorioangiomata, chorioangiosis, and increased nucleated fetal erythrocytes.
- Normal villous trophoblast unlike molar pregnancy which has hyperplasia of trophoblast.
- Fetal thrombotic vasculopathy (FTV) - thrombi within the large, dilated chorionic vessels, vaso-obliterative changes in stem villous vessels, and avascular villi or villous stromal vascular karyorrhexis in the distal villi.
- Abnormal immunohistochemical expression, P57 KIP2.

- Vascular anomalies, such as cirsoid chorionic vessels, thrombosis, thickening of vessel wall, vascular stenosis.

There have also been reports of umbilical cords abnormalities, including tortuous, marked twisted cords, and excessively long cords. (16, 17)

Clinical presentation

Clinically, PMD presents on antenatal ultrasonography as a thickened placenta with hypoechoic areas and absent or low velocity blood flow early in pregnancy. (17)

Later in the pregnancy, the patient usually presents with intrauterine growth restriction or fetal demise. Patients may also present with polyhydramnios if the fetus has swallowing difficulty as part of BWS.

Many cases are asymptomatic and are diagnosed postpartum because of delivery of an abnormally large placenta. The sonographic features of PMD are very similar to those of partial moles. (18)

The most common abnormal laboratory test includes increased level of maternal serum alpha fetoprotein, which is thought to be of fetal origin. It is speculated that the increase in the surface transfer area because of increased placental volume and increased vessels within the stem villi may lead to increased transfer of alpha fetoprotein into the maternal circulation.(18) The level of -human chorionic gonadotropin is normal to slightly increased but returns to normal levels soon after delivery.(19,20)

U/S Findings

As PMD is a relatively newly described entity, the predominance of cases has been diagnosed after pathology examination; however, with increasing awareness of the lesion, PMD is becoming recognized prenatally by antenatal imaging techniques. By conventional ultrasound methods, the placenta in PMD is typically described as large and thickened with multi-cystic, hypoechoic areas. A few small anechoic spaces can be present in the placental tissue without any clinical significance. (21) However, if the process is diffuse, close monitoring of the pregnancy is required.

Color Doppler has recently become a tool to help distinguish PMD from a molar gestation. (22, 23) PMD is reported to show a “stained-glass” appearance suggesting abundant blood flow in PMD while complete hydatidiform mole (CHM) shows little to no blood flow. (23) The large cystic parenchymal spaces in PMD are typically devoid of blood flow as they represent cystic change within the villous stroma.

However, blood flow seen in PMD may be related to the dilated chorionic vessels and/or the thickened vessels within the dilated stem villi. The absence of color Doppler signal may not exclude PMD as the degree of flow may vary from patient to patient (24) and vary with gestational age. (25)

Niaux et al (26) evaluated 6 suspected cases of PMD with serial prenatal ultrasonography and Doppler imaging that showed cystic spaces located deep in the placental parenchyma and increased placental thickness early in gestation. As the pregnancy advanced, the cystic spaces moved toward the chorionic plate. The chorionic plate vessels, including both the arteries and veins, became progressively dilated and aneurysmal. No abnormal chorionic vessels were seen before mid- gestation.

MRI

Recently, magnetic resonance imaging (MRI) has also been described as a method to distinguish CHM with twin co-existent fetuses from PMD. (22) MRI may, more accurately, discern the location of the cystic placental tissue as within or outside the fetal "sac" (CHM outside, PMD within), and aid in the distinction of these two entities. (22) With continued recognition of cystic placental changes by advanced imaging techniques, it is likely that obstetricians will consider PMD in the differential diagnosis, more frequently.

Beckwith Wiedemann Syndrome (BWS)

There is a definite association of PMD with BWS, approximately one-third to one- fourth of cases of PMD are associated with BWS. Paternal uniparental disomy (UPD) at 11p15.5 (involving IGF2 and CDKN1C), either as an isolated chromosomal defect or as part of pan genomic paternal UPD in ABM, could be the genetic factor linking PMD and BWS. (27)

BWS has an estimated incidence of one in 13,700; about 300 children with BWS are born each year in the United States. (28) The exact incidence of BWS is unknown because of the marked variability in the syndrome's presentation and difficulties with diagnosis.

The number of reported infants born with BWS is most likely low because many are born with BWS but have clinical features that are less prominent and therefore missed. BWS has been documented in a variety of ethnic groups and occurs equally in males and females.

Children conceived through In vitro fertilization have a three to four-fold increased chance of developing BWS. It is thought that this is due to genes being turned on or off by the IVF procedures. (29,30)

Beckwith-Wiedemann syndrome, which can be due to uniparental disomy of 11p15, is associated with the sonographic findings of macroglossia, macrosomia, organomegaly, abdominal wall defects, and placentomegaly. (31)

It is generally accepted that diagnosis of BWS requires at least 3 clinical findings including at least 2 major findings:

Major clinical findings: Macroglossia (present in more than 95% of patients), macrosomia or overgrowth, defined as pre- and-/-or postnatal growth greater than the 97th percentile (present in about 80% of patients). The trend to increased size continues through early childhood but becomes less dramatic with increasing age, abdominal wall defects (exomphalos, umbilical hernia, diastasis recti; 65% of patients), organomegaly involving principally abdominal organs: kidneys, liver, spleen, pancreas and adrenal glands (present in 50% of patients).

Minor clinical findings: Hypoglycemia in the neonatal period (occurs in about 40% of patients), mostly mild and transient, renal abnormalities: malformations, medullary dysplasia, ear creases and pits (30% of patients), facial nevus flammeus (30% of patients), Hemi-hyperplasia (30-35% of patients), embryonal tumors: about 7.5% of BWS patients develop tumors (Wilms' tumor, neuroblastoma, adrenal carcinoma, hepatoblastoma, rhabdomyosarcoma), most commonly in the first 6 years of life, polyhydramnios.

Also, some premature newborns with BWS do not have macroglossia until closer to their anticipated delivery date. (32)

Fetuses diagnosed with BWS may have favorable outcomes if they survive the neonatal period, although they may have difficulty with feeding or breathing due to macroglossia. Mental status may be normal or slightly reduced, other possible long- term complications include development of seizures, hypoglycemia, and embryonal tumors such as neuroblastoma and hepatoblastoma. (31)

While most children with BWS do not develop cancer, children with BWS do have a significantly increased risk of cancer. Children with BWS are most at risk during early childhood and should receive cancer screening during this time. (33)

Differential Diagnosis

It is important to distinguish PMD from molar pregnancy because it may avoid unnecessary termination of pregnancy especially if prenatal ultrasonographic examination shows features suggestive of molar pregnancy in the presence of a normal-appearing fetus.

The main differential diagnoses of PMD, both clinically and pathologically, are partial hydatidiform moles, a twin gestation with complete mole, spontaneous abortion with hydropic changes, confined placental mosaicism, chorioangioma, intervillous hematoma, and infarct or nonspecific hydropic changes.

Unlike partial hydatid moles (PHM), the placenta in PMD is almost always diploid (except in rare instances), and histologically the villi do not show proliferation of trophoblasts or stromal trophoblastic inclusions. For this reason, in PMD, levels of maternal serum Beta HCG are normal or slightly increased throughout

gestation, (17) in fact PMD is associated with elevated maternal alpha fetoprotein. The triploid fetus associated with a partial mole shows growth restriction with a variety of external and internal defects and can be excluded by further genetic work up.

In twin gestations with complete moles, the abnormal fetal vessels in the stem villi characteristic of PMD are absent even though the fetus may have a diploid karyotype.

The placenta of a complete mole with co-twin and partial molar pregnancy look heterogeneous, with partially solid and cystic areas.

In contrast complete hydatidiform moles may also exhibit high levels of IGF-II expression and loss of expression of p57KIP2, but these are purely androgenetic, and the entire genome is paternally derived. (34)

Additionally, there is no known risk of persistent gestational trophoblastic disease with PMD.

Spontaneous abortion with hydropic change may have vesicle formation and can be confused with early PMD. The vesicles in hydropic spontaneous abortion, if present, are usually small and are not diffuse. Second, the histology of spontaneous abortions shows degenerative changes without the classic histopathologic features of PMD.

Cases of confined placental mosaicism involving trisomy 16 have been reported to have cystic villi on ultrasonography, but these cases can be diagnosed accurately by karyotyping both the newborn and the placenta. (35)

Chorioangioma has different echogenicity sonographically than the rest of the placenta and is located on the fetal placental surface. (36,37)

Complications

Placental mesenchymal dysplasia is a rare disease entity, and it is difficult to determine whether the complications faced by these fetuses are true complications of this disease process or merely coincidental findings.

Some of the complications seen in fetuses born with PMD are secondary to BWS without fully developed phenotypic features, for example, hyper-insulinemic hypoglycemia seen in neonates with PMD is secondary to islet cell hyperplasia of the pancreas, which is a frequent finding in BWS. (38)

The common fetal complications reported in phenotypically normal fetuses associated with PMD are prematurity, intrauterine growth restriction, and intrauterine fetal demise. (39,40) Severe intrauterine growth restriction may be related to diversion of fetal blood within the vascular malformations or stem

villi blood vessel thrombosis resulting in hypoperfusion and hypoxia that ultimately leads to intrauterine growth restriction. (39)

Although many obstetrical complications such as polyhydramnios, fetal hydrops, gestational diabetes, and preeclampsia may be associated with a large placenta, placentomegaly in PMD, in and of itself, is thought not to be the cause of fetal complications.(26) No direct association of placental weight and fetal or maternal complications have been identified.

Rather, the complications are thought to be related to the degree of vascularity and excessive vascular shunting into the Chorangiomatous areas.(26) Cases associated with chorangiomas are thought to be associated with a higher rate of fetal complications including anemia and thrombocytopenia, which in turn are thought to be secondary to microangiopathic hemolytic anemia because of abnormal shunting of the blood.(41,42)

Chromosomal abnormalities may be found in a few fetuses, but most are karyotypically and phenotypically normal females. Rare cases of fetal congenital adrenal hyperplasia, vascular hamartoma, and hepatic mesenchymal hamartoma have been described. (43–44) Phenotypically normal newborns with PMD should be followed up for development of BWS features or other mesenchymal tumors.

Follow-up of most of the normal-appearing infants has shown no developmental problems.

Maternal complications associated with PMD are comparatively rare. Gestational protein-uric hypertension has been reported, but it is believed that hypertension in these cases is probably a coincidental finding rather than any specific association with PMD. (45) Although, some authors suggest that the degree of vascularity and shunting in the placenta may lead to complications to fetus (fetal growth restriction or intrauterine fetal death) and to the mother (hypertension). (1)

Nayeri et al in a systematic review data base from 1991 to 2011 have reported following associations with PMD cystic placenta 80%, enlarged thick placenta 50%, dilated chorionic vessels 16%, increased βhCG 38%, increased AFP 70%, fetal anomalies 38%, BWD syndrome 19%, neonatal hepatic tumor 17%, neonatal anemia and or thrombocytopenia 5%, IUGR 33%, IUFD 13%, preterm delivery 52%, preeclampsia, eclampsia, HELLP, and gestational hypertension 9%.13 Pregnancy was uncomplicated only in 9% of cases.

Management

Management aim for accurate diagnosis, close monitoring, anticipation and treatment of complications and proper postnatal follow up.

Antenatally, serial ultrasound for suspected placenta, detailed anomalies scan, fetal growth monitoring and Doppler is recommended.

Keeping in mind the differential diagnosis of large cystic placenta during antenatal ultra-sound scan, serum Beta human chorionic gonadotrophins (βhCG), serum alpha fetoproteins (AFP), venereal disease research laboratory (VDRL), Toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus (TORCH IgG and IgM) and amniocentesis for fetal karyotyping - Fluorescence in situ hybridization (FISH) and culture must be done.

The place of histological evaluation of chorionic villus biopsy specimens in the diagnosis of PMD is yet to be established. (46)

The patient should be counseled on the potential associations of Beckwith- Wiedemann syndrome with prematurity, fetal growth restriction, or intrauterine fetal death. (47) Other possible fetal complications must be discussed.

Also, should be counseled about the increased risk of preeclampsia (27%), (48) persistent gestational trophoblastic disease (GTD;45%), (5) fetal loss (62%), (48) and maternal morbidity. (48)

Close follow-up evaluation is needed for preterm labor, hypertensive disorders of pregnancy and intra-partum monitoring as high-risk patient is mandatory.

Postnatally placental pathologic examination and further genetic and immunochemistry work up are paramount to confirm the diagnosis, follow up with βhCG like a molar pregnancy is not recommended in case of PMD, as βhCG becomes normal within few weeks of delivery.

Prognosis

A 5-year follow up of mothers with PMD showed no sign of trophoblastic disease or recurrence of PMD in subsequent pregnancies.(49) However, it should be noted that 15% of BWS cases are familial, and theoretically there is a small increased chance of having recurrence of PMD in such families.

Case Report

28 years old female, Gravida 3 Para 1 Abortion 1 at 30 weeks + 6 days of gestational age, previous normal vaginal delivery presented to our Hospital in established preterm labor and pre-eclampsia, she had antenatal care in private Hospital, ultrasound report suggested hypo-echoic placental lesions and fetal skeletal dysplasia, normal fetal karyotype, tri-ploidy was excluded by amniocentesis, however placental mosaicism cannot be ruled out. Cytomegalo- virus and Parvo B19 were Negative.

Ultra-sound Scan done on admission showed: single, viable fetus, BPD: 6.90 cm<2.3, HC:25.9 cm <2.3% (Figure 4), AC:26.3 cm: 35.5%, FL:4.56 cm<2.3%

(Figure 7), EFW = 1.215 kg (16.2%). Brain? absent CSP, ventricles prominent, heart? cardiomegaly with minimal pericardial effusion (Figure 8), bowel echogenic, dilated bowel loops 1.58cm (Figure 9), anterior abdominal wall intact, fetal limbs showed short long bones, placental Localization: anterior high thickened measured 7.89 cm, bulky placenta with some cystic spaces(Figure 3).

Doppler study normal for Umbilical artery doppler- diastolic notch present, MCA diastolic notching present. She was planned for FMU scan, but patient progressed in labor and was taken for emergency lower segment cesarean section for pathological CTG within 6 hours from admission, intra-partum placenta noticed to be large multi-cystic structures and tortuous dilated blood vessels (Figure 10,11,12).

Maternal post-natal period was uneventful, partial molar pregnancy was suspected, hence, BHCG level checked normal and chest x ray image also normal.

Fetal Outcome

Baby female, APGAR 7,8,9, weight 1.255 kg (16th centile), Length 37 cm (5th), Head Circumference 26 cm (3rd), placenta weight:1.455 kg measures 23x20x4 cm, and with large multi-cystic structures and tortuous dilated blood vessels, after thorough examination and investigations, the following complications were identified during the first 2 weeks of neonatal life, including: respiratory insufficiency, fetal anemia at birth hemoglobin of 7.3 g/dl, coagulopathy, thrombocytopenia, hyperkalemia, acute kidney injury with oliguria, cardiomegaly, mild mitral regurgitation, moderate to severe tricuspid regurgitation, large PDA with left to right shunt, mild pulmonary hypertension, hepatosplenomegaly, persistent hypo-glycaemia and small bowel obstruction. (due to immature ganglion).

Ultra-sound abdomen showed dilated large bowel loops with evidence of minimal Ascites, mild dilatation of the left renal pelvis with otherwise normal both kidneys size and echo pattern, ultra-sound brain was normal.

Screening for TORCH and Parvo B19 Ig G and Ig M were negative and karyotype showed normal 46, XX.

Baby underwent multiple resuscitative procedures but fail to thrive and died at 2 weeks of life.

Placental histopathology result showed

Gross Description: The placenta weighs 1.380 kg and measures 23 x 20 x 4 cm, the umbilical cord is eccentrically attached and measures 60 cm in length x 1.5 cm in diameter, it shows 3 blood vessels and the cord shows a single true knot 43 cm away from the insertion.

The membrane is translucent and complete. The fetal surface shows very prominent thick-walled bluish blood vessels which appear dilated on cut surface (Figure 10,11). The maternal surface is irregular and ragged (Figure 12).

On sectioning, the placental parenchyma is mostly spongy & reddish admixed with multiple small brownish to yellowish cysts and vesicles containing clear fluid & gelatinous material.

Microscopic Description: Sections reveal placenta showing normal third trimester chorionic villi admixed with dilated & enlarged villi showing mesenchymal core composed of proliferating spindly loose fibroblastic cells & stellate cells. Central thick-walled blood vessels are present. Stromal hydropic degeneration and central cistern formation is also seen in few of these villi. However, no trophoblastic hyperplasia is seen, villi showing chorangiomatosis-like changes are noted, few of them showing hemorrhage with presence of nucleated red blood cells.

There is no evidence of cytological atypia or increased mitotic activity in the sections examined, membranes show normal histology, no chorioamnionitis. Umbilical cord shows three blood vessels, no funisitis.

Immunohistochemistry (IHC) done for p57 shows intact nuclear staining in both normal & enlarged villi and the Ki-67 proliferation index in lining trophoblastic cells is appears low 3-5%. IHC for Desmin done shows positivity in stromal cells in both normal & enlarged villi.

Comment

The antenatal history & radiology scans were referred from the clinical charts. Clinical history noted, the overall features favor Placental Mesenchymal Dysplasia (PMD).

Genetic Interpretation

We detected genome-wide mosaic loss-of-heterozygosity, which was confirmed by UPD testing for 11p15 and UPD was shown to be of paternal origin, the result is consistent with a genetic diagnosis of mosaic genome-wide uniparental disomy (GW-UPD).

Recommendations

Considerate medical check-up, especially regarding malignancies, is recommended.

WES analysis is recommended to evaluate the nature of the detected genomic aberration.

Genetic counselling is recommended to explain and discuss the result.

Variant interpretation

The mosaic GW-UPD phenotype is extremely rare and has been described as associated with extensive clinical heterogeneity, much of which is attributable to varying levels of tissue mosaicism.

Mosaicism for genome-wide paternal uniparental disomy (patUPD), attributed to androgenetic/biparental mosaicism, has been shown to underlie placental mesenchymal dysplasia (PMD), a distinctive cystic placental phenotype.

Manifestations of Beckwith–Wiedemann syndrome (BWS) have been observed in approximately one-third of fetuses or live born infants from pregnancies complicated by PMD. There are very few reports describing live born individuals with proven mosaicism for genome-wide patUPD in somatic tissues.

Two further children were reported with complex phenotypes including some findings of BWS, congenital hyper-insulinemic hypoglycemia, prolonged feeding difficulty and failure to thrive in infancy. The first developed short stature, bilateral pheochromocytomas and progressive arterial stenoses, and the second had congenital adrenal cysts, and later developed hepatoblastoma and patchy hyperpigmentation.

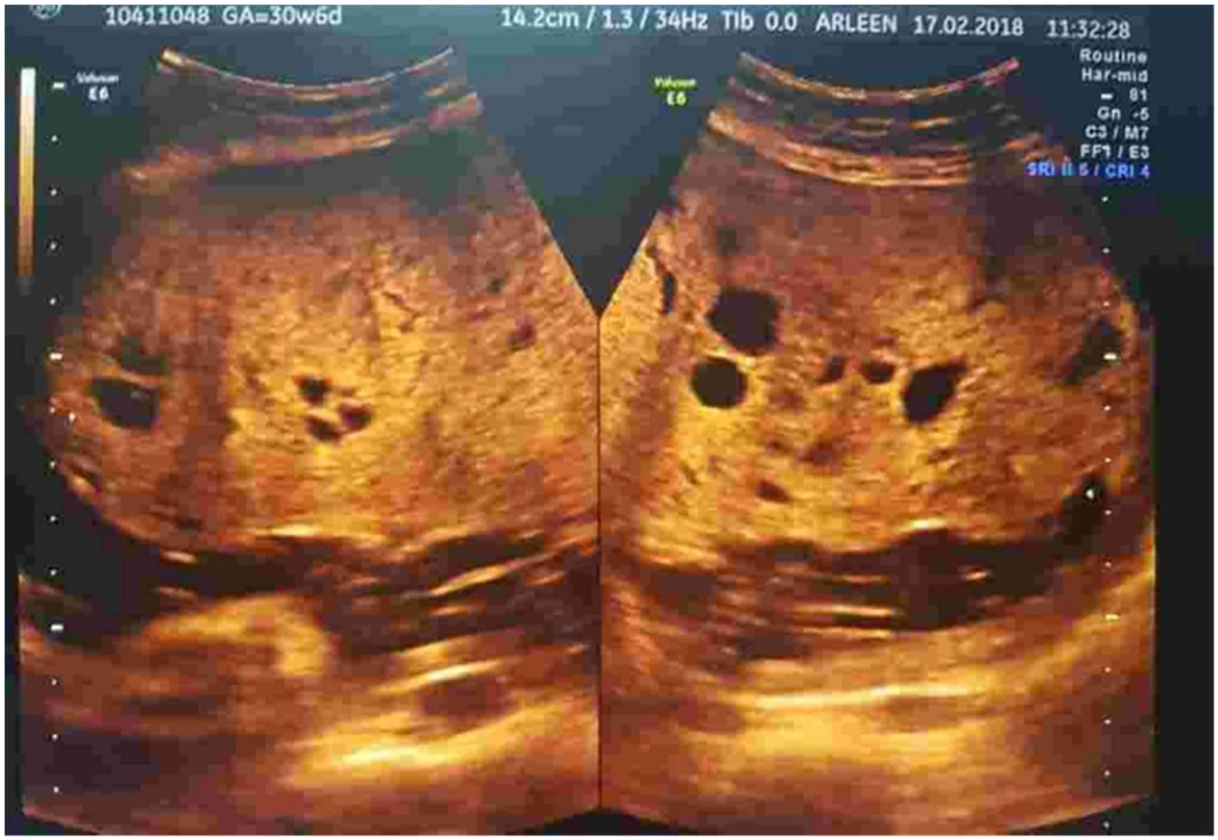

Figure 1: 2D U/S image showing aspect large multi-cystic placenta.

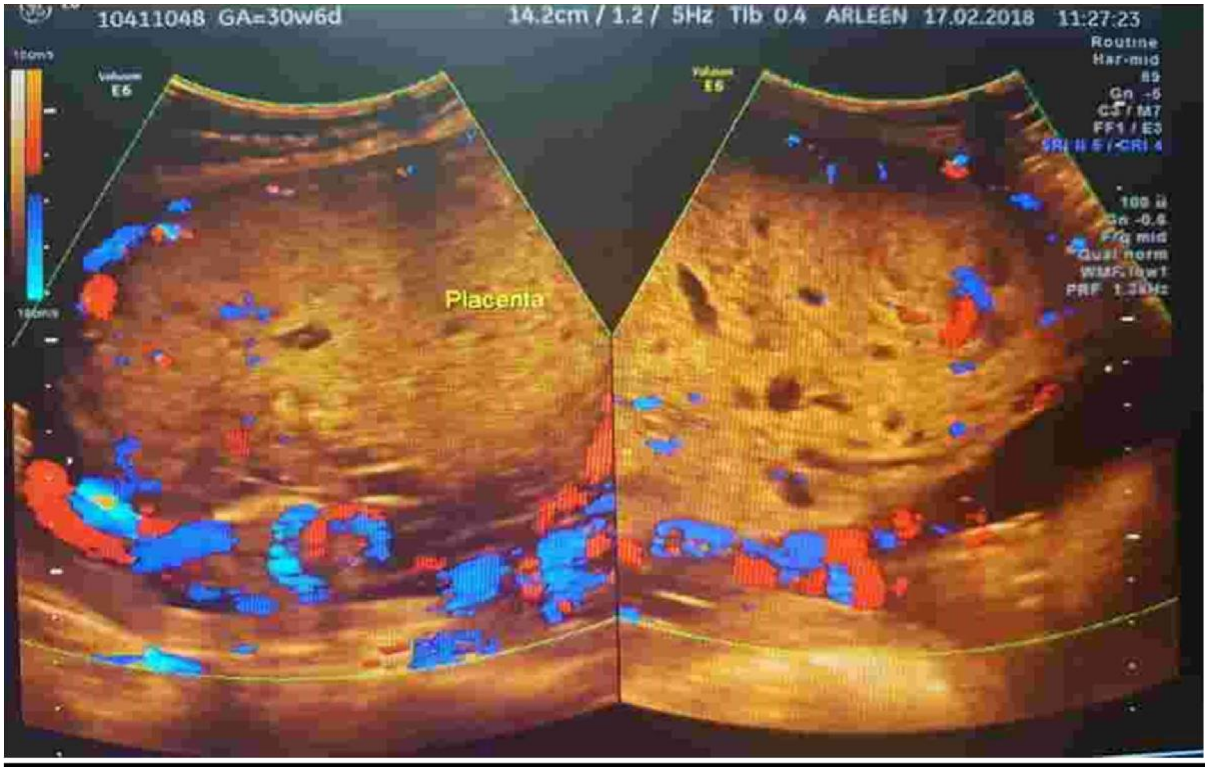

Figure 2: 2D U/S image showing aspect of large multi-cystic placenta with color Doppler.

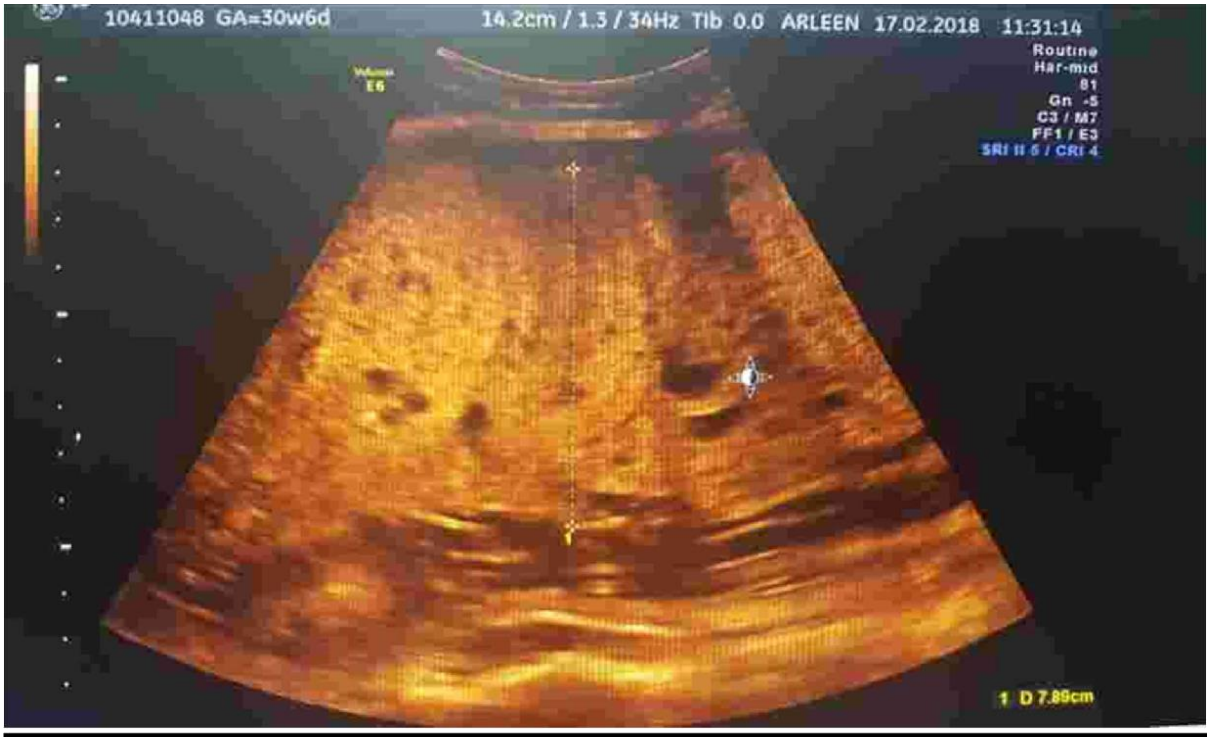

Figure 3: 2D U/S image, showing aspect of large multi-cystic placenta, placenta thickness measures 7.89 cm.

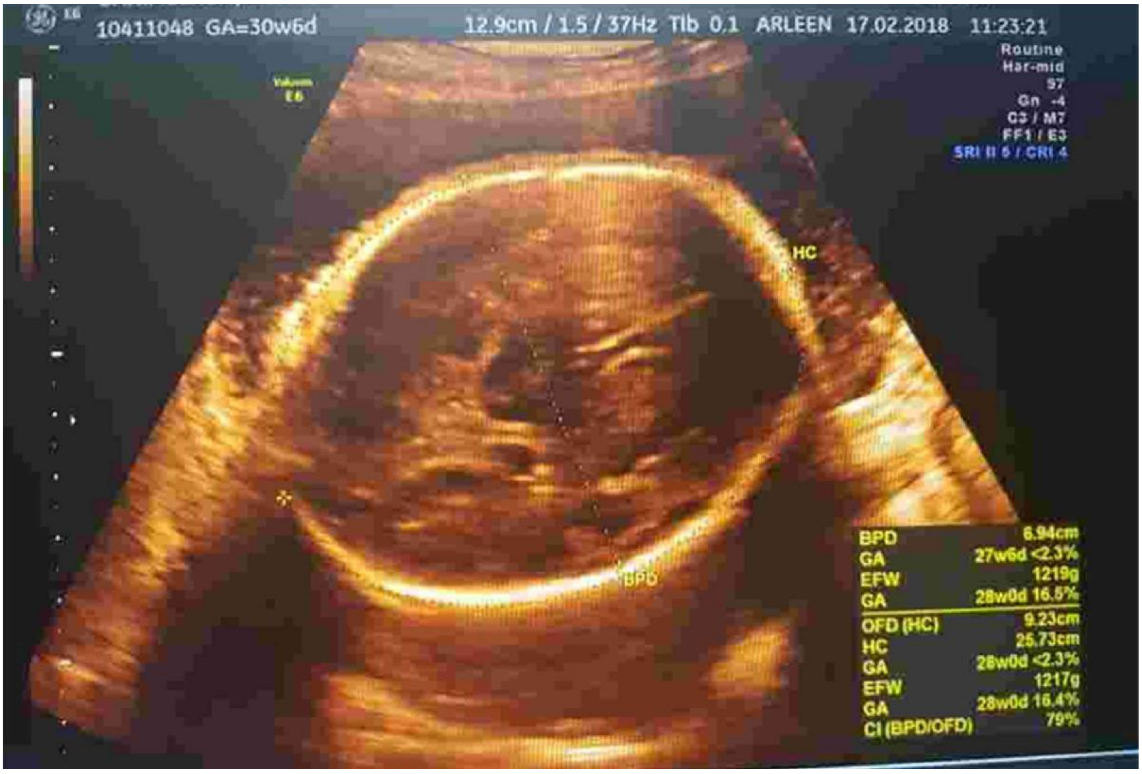

Figure 4: 2D U/S image, showing axial view of the head, BPD & HC<2.3%.

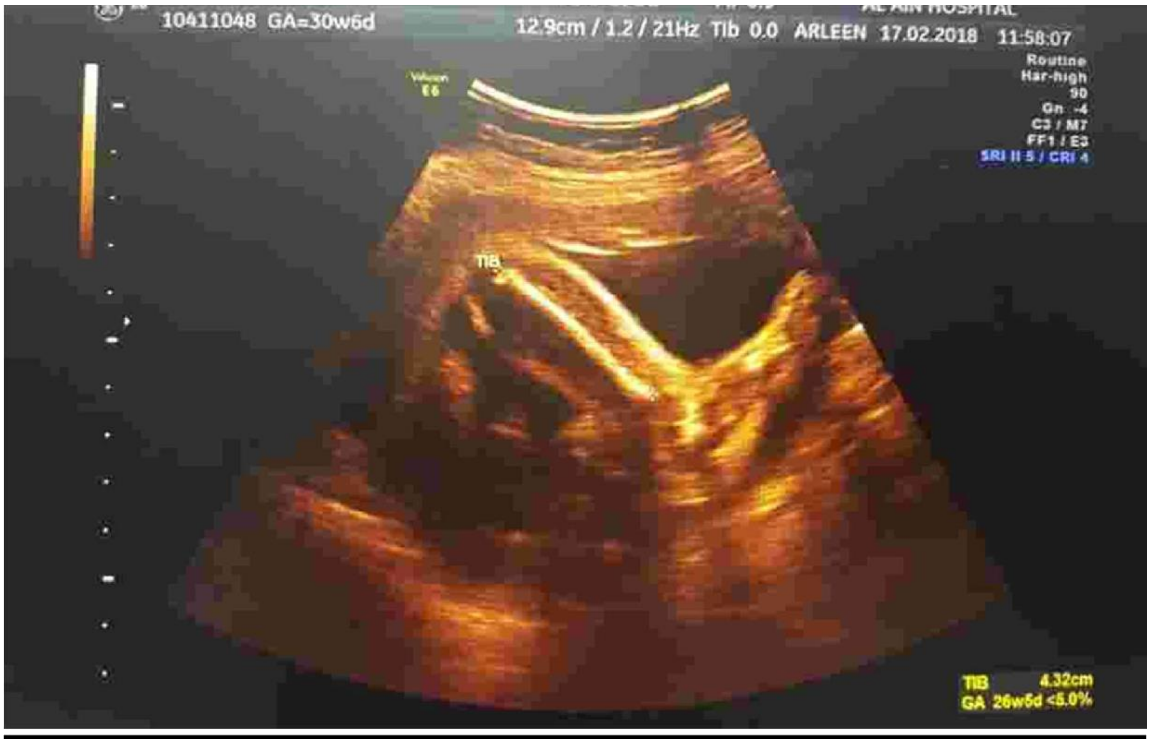

Figure 5: showing 2D U/S image, sagittal view of Tibia measurement<5.0%.

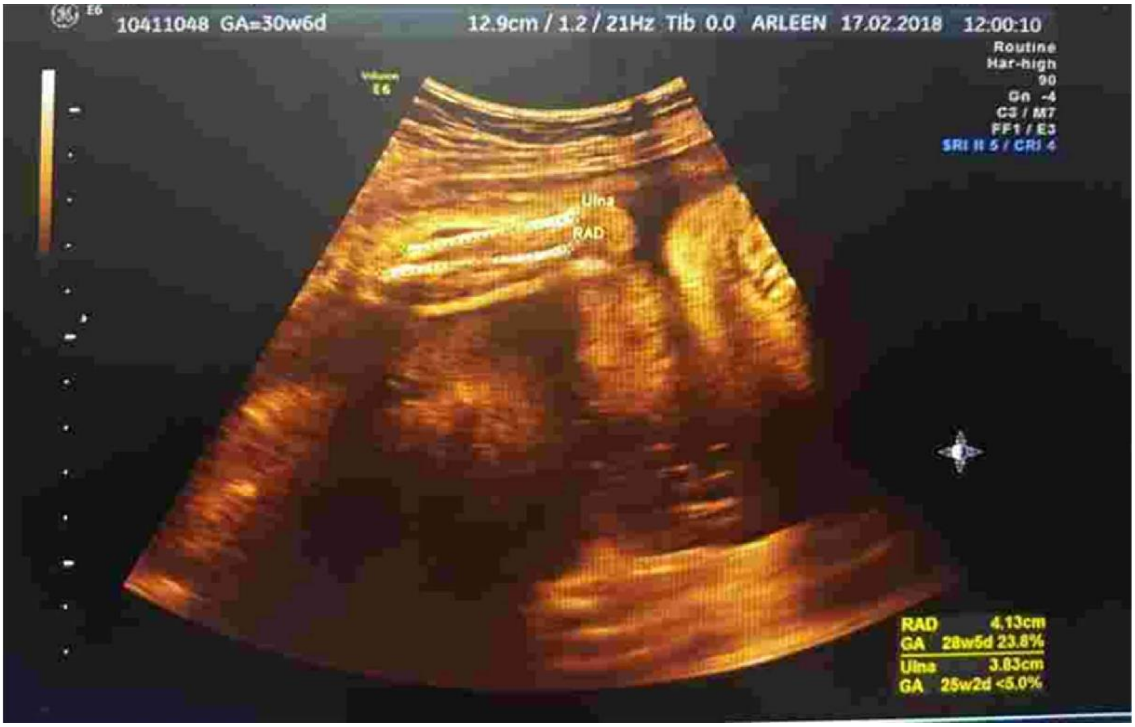

Figure 6:2D U/S image, showing sagittal view of Ulna<5.0% and Radius at 23.8%.

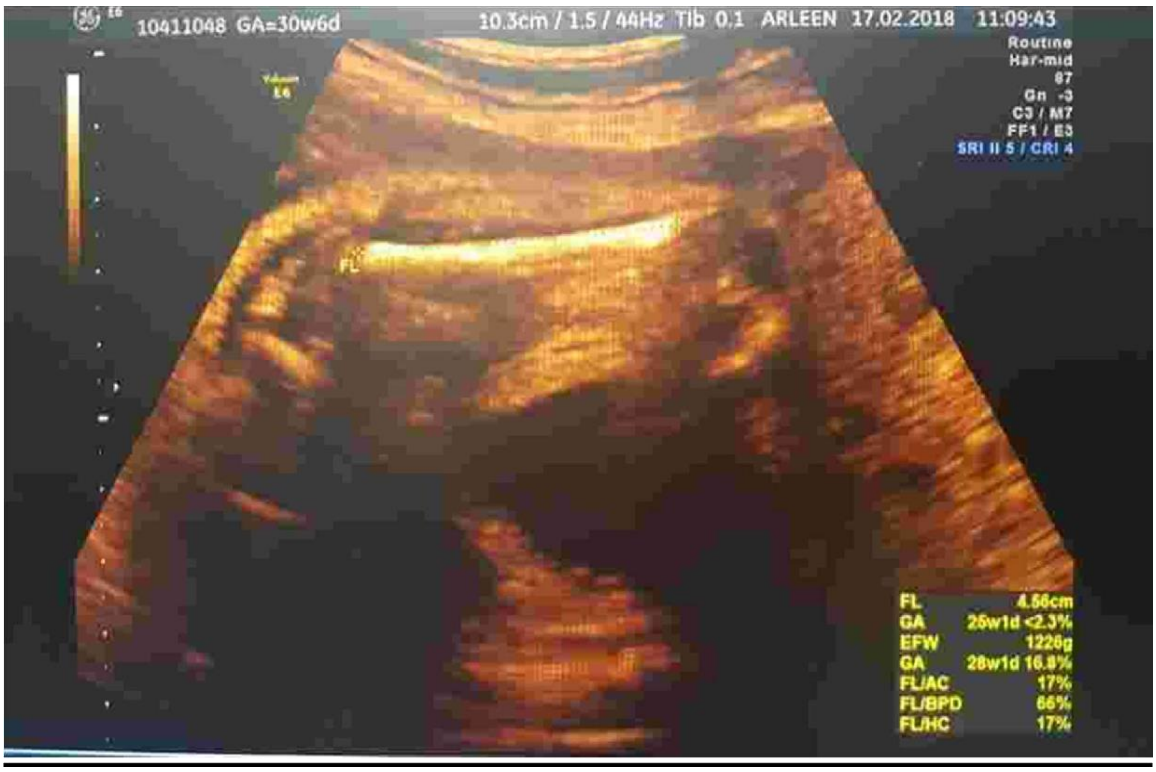

Figure 7: 2D U/S image, showing sagittal view of the femur measure<2.3%.

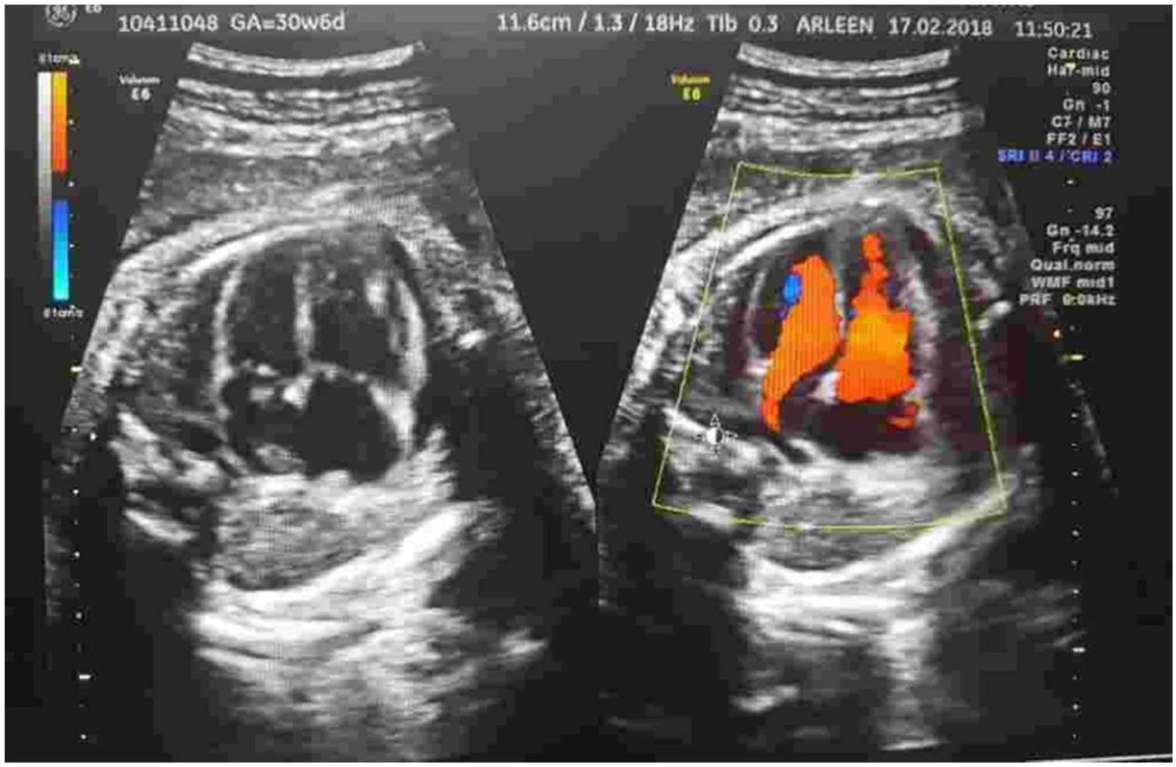

Figure 8: 2D U/S image, four chamber view showing cardiomegaly and mild pericardial effusion.

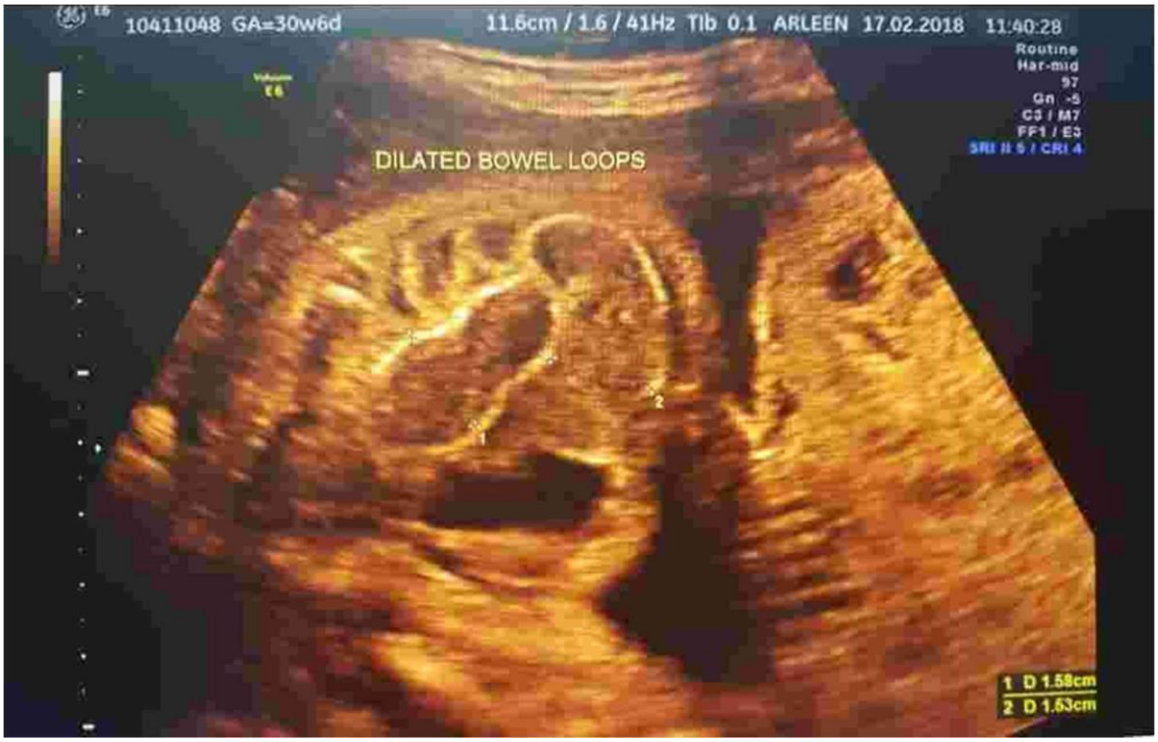

Figure 9: 2D U/S image, showing aspect of Dilated bowel loops.

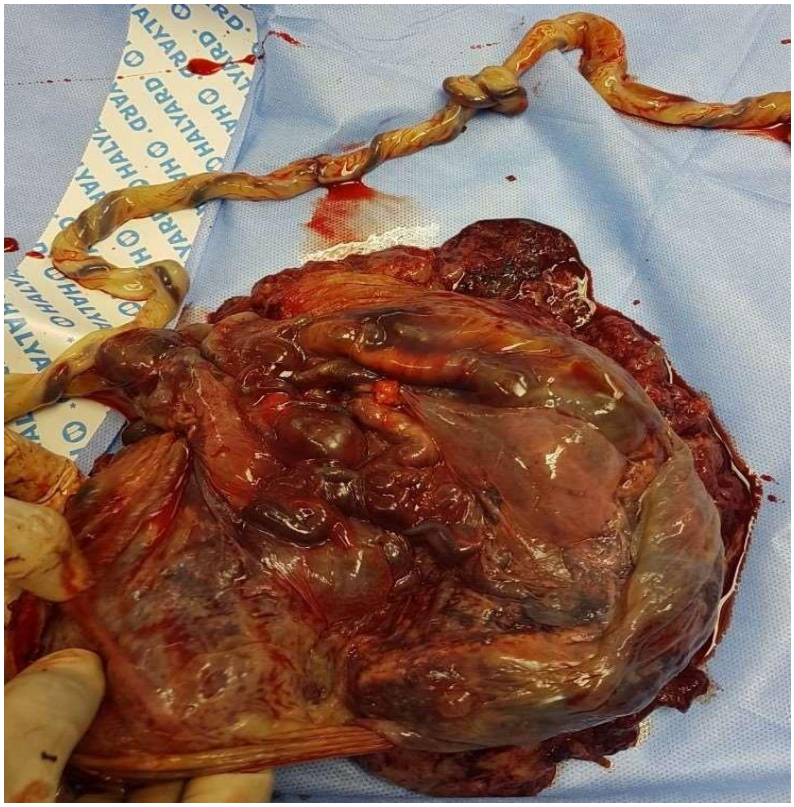

Figure 10: Image of fetal surface of the placenta, showing dilated tortuous sub-chorionic vessels characteristically seen in placental mesenchymal dysplasia and true cord knot.

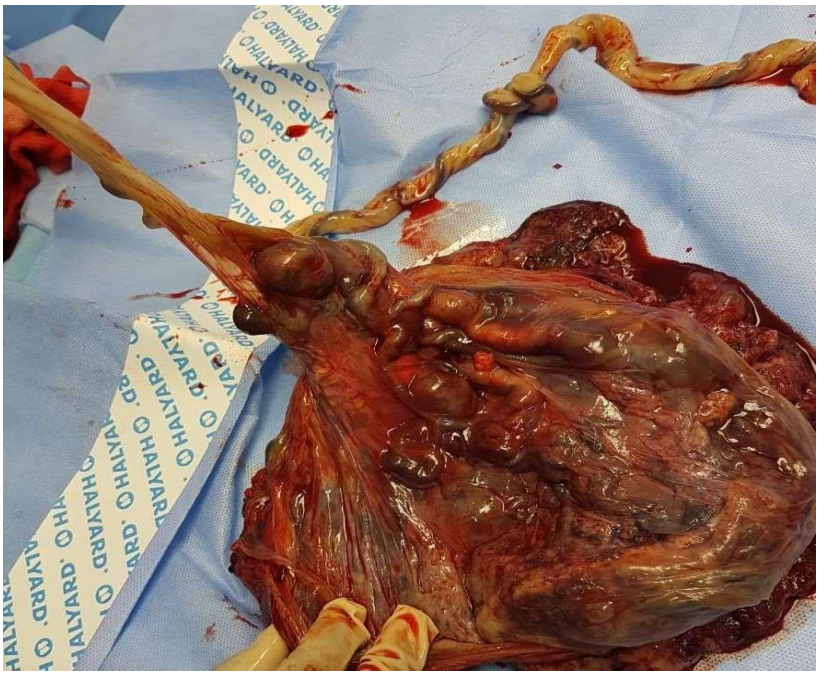

Figure 11: Image of fetal surface of the placenta, showing dilated tortuous sub- chorionic vessels and eccentric cord insertion.

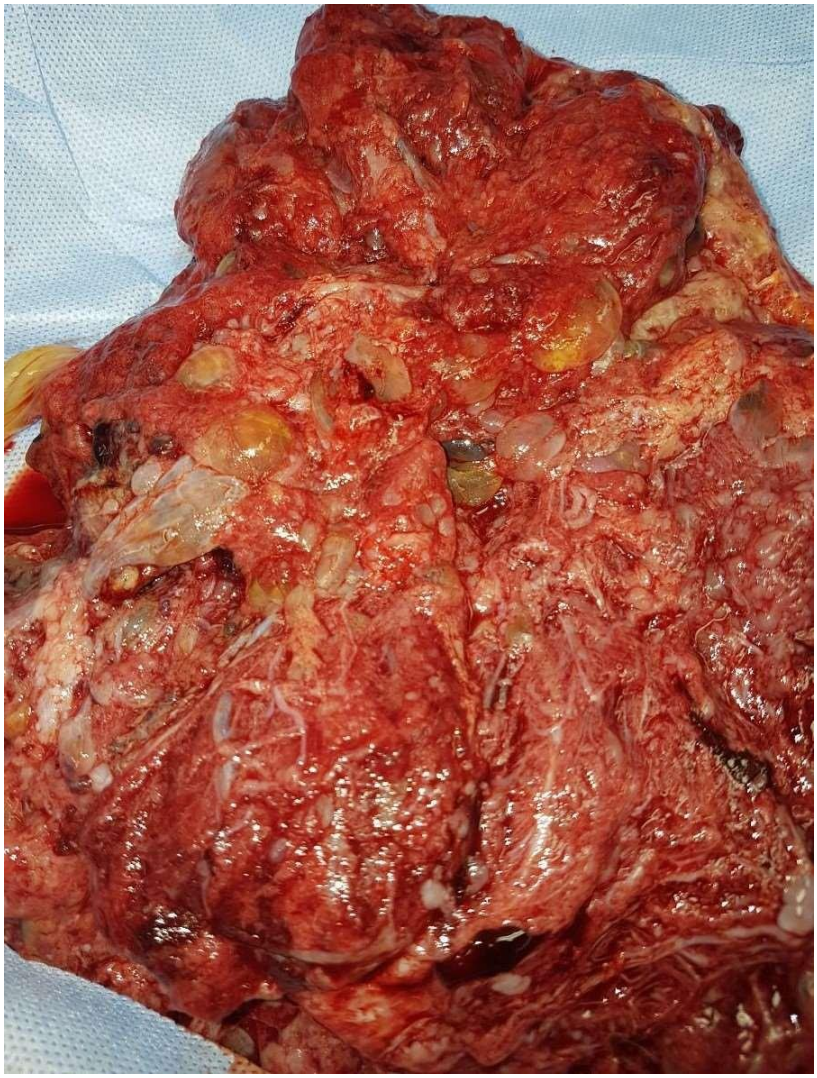

Figure 12: image of placental maternal surface showing multiple vesicles.

Discussion

Based on the clinical presentation, ultrasound features, fetal outcome and associated findings, placental histopathological findings and genetic work up, the diagnosis of this case is PMD most likely associated with Beckwith Wiedemann syndrome.

Antenatal ultrasound findings of large placenta and multi-cystic lesions should raise the possibility of PMD, and it is differential diagnosis mainly gestational trophoblastic disease, the other differential diagnoses of these ultrasonographic findings include confined placental mosaicism, chorioangiomas and sub-chorionic hematomas. However, these findings are not as common as in PMD, in this case

histopathology confirmed the presence of chorioangioma, which can explain the fetal anemia and coagulopathy.

PMD must be part of differential diagnosis of placental cystic lesions and differentiated from molar pregnancy as PMD can coexist with normal fetuses, hence, prevent unnecessary termination of the pregnancy.

Therefore, the work up including BHCG level, alpha fetoprotein, CVS and amniocentesis for fetal karyotype, fetal infections screening, close antenatal follow up and ultrasound monitoring are mandatory to establish a definitive diagnosis, which will affect the plan of management in the current and future pregnancies.

The fetuses with PMD are prone to fetal growth restriction, features of overgrowth, sudden IUFD, structural congenital malformations, rare chromosomal abnormalities and association with Beckwith Wiedemann, therefore, close attention must be paid to fetal morphology and growth for early recognition of complications and to reduce fetal morbidity and mortality.

In this case, GTD was excluded antenatally by normal levels of BHCG and Diploid karyotype, but PMD was not suspected till diagnosed postnatally by placental histopathology.

This patient presented to our Hospital late with preeclampsia, preterm delivery, which have been associated with PMD according to the literature without proven mechanism, importantly histopathological examination of the placenta confirmed the diagnosis of PMD, on the other hand, due to heterogenicity in fetal malformations, the definitive diagnosis was difficult antenatally and postnatally, the fetus diagnosed antenatally by ultra-sound as case of skeletal dysplasia with brain and cardiac anomalies, during the neonatal period the following findings were confirmed: fetal short stature, microcephaly, normal birth weight, persistent hypoglycemia, cardiac anomalies, hepatosplenomegaly, fetal anemia, thrombocytopenia, acute renal failure in early neonatal period, and dilated small bowl with obstruction. Some of these findings suggest the Beckwith-Wiedemann syndrome (hepatosplenomegaly, fetal anemia, thrombocytopenia, neonatal hypoglycemia), which was supported by genetic study showed genome-wide mosaic loss-of-heterozygosity, confirmed by UPD testing for 11p15, UPD was shown to be of paternal origin. This result was consistent with a genetic diagnosis of mosaic genome-wide uniparental disomy (GW-UPD). It is attributed to androgenetic/biparental mosaicism, which has been shown to underlie placental mesenchymal dysplasia (PMD), immune-histochemistry (IHC) done for p57 shows intact nuclear staining in both normal & enlarged villi, which reflect the presence and distribution of both maternal and paternal cell lines in this case.

Genetic lab interpretation in our Hospital report that mosaic GW-UPD phenotype is extremely rare and has been described as associated with extensive clinical heterogeneity, much of which is attributable to

varying levels of tissue mosaicism, there are very few reports describing live born individuals with proven mosaicism for genome-wide patUPD in somatic tissues.

Two further children were reported with complex phenotypes including some findings of BWS, congenital hyper-insulinemic hypoglycemia, prolonged feeding difficulty and failure to thrive in infancy. The first developed short stature, bilateral pheochromocytomas and progressive arterial stenoses, and the second had congenital adrenal cysts, and later developed hepatoblastoma and patchy hyperpigmentation.

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