Placental mesenchymal dysplasia (PMD) is a rare placental abnormality characterised by placentalomegaly and grape-like vesicles resembling partial mole by ultrasonography, but in contrast to partial mole can co-exist with a viable fetus. Although the karyotype is normal, the fetus is at increased risk for intrauterine growth restriction, intrauterine fetal demise or perinatal death and Beckwith–Wiedemann syndrome. Prenatal diagnosis is difficult and the final diagnosis is usually achieved by postpartum histological examination of the placenta.

Case report 2
A 2nd trimester triple screen at 16 weeks 5 days' gestation in a 22-year-old woman showed elevated MSAFP (5.24 MoM) and hCG (3.14 MoM). Ultrasound examination did not reveal any fetal anomalies, however the placenta was thickened with multiple large cystic areas. Prenatal diagnosis was thought to be a partial mole or a twin pregnancy with a molar placenta co-existing with a normal fetus. For further analysis, an amnioncentesis was offered but declined by the patient. Serial ultrasonographic evaluation was performed at 2-week intervals. At 20 weeks' gestation, as well as the development of clinically severe pre-eclampsia, the fetus demonstrated hepatosplenomegaly and early hydropic changes. Specifically, the placenta was thickened, contained multiple anechoic vesicles and showed a large subchorionic haemorrhage (Figure 1). Thus, termination of pregnancy was planned by hysterotomy. Autopsy findings following termination of pregnancy was correlated with ultrasound, additionally overlapping fingers detected in the female fetus, weighed 370 g. The placenta was partially fragmented, markedly enlarged and weighed 270 g. On the maternal plate, there were numerous grape-like cystic vesicles.

Introduction
Placental mesenchymal dysplasia (PMD) is an uncommon disorder of the placenta, characterised by placentalomegaly with diffuse hydropic stem villous, aneuerysmally dilated vessels and lack of trophoblastic proliferation. Generalised vesicular lesions on ultrasonographic examination and gross appearance of placenta usually suggest a partial mole. Unlike partial moles, characterised by absent or malformed fetus, PMD can co-exist with a viable fetus. The common fetal complications reported in phenotypically normal fetuses associated with PMD are intrauterine growth restriction, intrauterine fetal demise or neonatal death (Truc et al. 2006). Additionally, approximately one-quarter of cases of PMD are associated with fetal Beckwith–Wiedemann syndrome (BWS). The exact aetiology of PMD is unknown but increasing evidence suggests that PMD may be originated from androgenetic/biparental mosaicism, confined predominantly to the placenta (Kaiser-Rogers et al. 2006).

Case report 1
A 37-year-old woman was admitted in her fifth pregnancy at 30 weeks' gestation, with persistent uterine contractions and pre-term rupture of membranes. The gestational age was confirmed by previous ultrasonographic determination of crown-rump length at 8 weeks' gestation. Ultrasound examination revealed a single fetus that demonstrated reduced growth parameters (< 5th percentile), normal amniotic fluid and generalised vesicular lesions affecting the whole placenta. Serum β-hCG level was 34.320 IU/ml. The fetal heart rate pattern was previously normal, but 22 hours later, fetal tachycardia with mild variable decelerations was observed. Emergency caesarean delivery was performed and a female infant, weighing 915 g was delivered. The Apgar scores were 4 and 6 at 1 and 5 min, respectively. Physical examination after birth revealed structurally normal, asymmetric fetal growth retardation and respiratory distress syndrome (RDS). Surfactant therapy and intermittent positive pressure ventilation was applied but the infant died after 19 days of life, due to RDS. Peripheral blood karyotyping of the neonate revealed a 46,XX karyotype.

The placenta measured 17 cm in diameter, 5 cm in thickness and weighed 630 g. The cord was eccentrically inserted and had three vessels. The fetal surface of the placenta showed dilated and tortuous chorionic vessels penetrating into the maternal side. Numerous clusters of grape-like fluid filled vesicles were scattered throughout the placenta.

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Microscopic examination of both placental specimens revealed enlarged and hydropic stem villi containing cistern formation. Most of these hydropic villi had peripherally located thick-walled vessels and surrounding normal appearing tertiary villi. Some terminal villi contained increased numbers of stromal capillaries (chorangiosis). Abnormal trophoblastic proliferation and trophoblastic inclusions were not observed in any of the sections examined. Immunohistochemistry study revealed that endothelial cells in capillaries were positive for CD31. The cisternae did not show evidence of CD31 immunostaining unlike neighbouring blood vessels. Immunohistochemical studies for p57KIP2, a paternally imprinted maternally expressed cyclin-dependent kinase inhibitor, demonstrated two distinct patterns of immunoreactivity in villous tissue from both placentas. Some enlarged villi with irregular contours, oedematous stroma or central cisterns showed complete absence of nuclear staining, with antibody directed against p57KIP2 in villous cytotrophoblast and villous mesenchyme. On the contrary, other enlarged villi with regular contours and all the smaller villi showed strong positive immunostaining of villous cytrophoblast and stromal nuclei. Therefore, these pathological findings and mosaic pattern of villous population led to a diagnosis of PMD (Figure 2).

In case 2, flow cytometric analysis of paraffin-embedded, fixed placental tissues revealed a diploid DNA content. Also, quantitative PCR was performed and only one genetic marker locus (D3S1358) was successfully amplified and gave an informative result as a diploid state. Identical heterozygous biallelic genetic composition in the chorionic villi of the placenta and renal tissue achieved from fetus 2 are shown in Figure 3. No comment could be made about the parental origin of the D3S1358 alleles, because parental DNA was not available.

**Discussion**

PMD is a potentially misdiagnosed entity and has not yet gained wide recognition. The incidence of PMD is 0.02% (Arisawa and Nakayama 2002) with a definite preponderance of females (about 1 in 500 cases referred for probable molar change) (Paradinas et al. 2001). The main differential diagnoses of PMD, both clinically and pathologically, are twin pregnancy with a molar placenta co-existing with a normal fetus and partial mole. In twin gestation with complete mole, the fetus has a diploid karyotype and a chance of surviving. In this condition, molar placenta with fluid filled vesicles is attached to normal placenta. In partial mole, the fetus and molar part generally result from dispermy and reveal a triploid karyotype. The fetus associated with partial mole is typically growth restricted, shows a wide variety of external and major internal defect and tends to die in the 1st trimester. In contrast with a partial hydatidiform mole, the fetus associated with PMD is either structurally normal or shows features of BWS. Also, PMD is almost always associated with a diploid karyotype, although Cohen et al. (2005) described three cases of PMD associated with fetal aneuploidy.

Although most of the fetuses associated with PMD are phenotypically normal, fetal complications such as prematurity, IUGR and intrauterine fetal death (IUFD) are not rare. Pham et al. (2006) collected 11 new PMD cases and reviewed a meta-analysis of the associated IUGR and fetal death rates. Among all cases without BWS, 50% had IUGR and 43% had IUFD or neonatal death, as a result of complications of prematurity. Truc et al. (2006) posulated that the IUFD seen in these patients may be explained by a potentially chronic hypoxia secondary to obstructive fetal vascular thrombosis and a decrease in maternal–fetal gas exchange as a result of an insufficient amount of normal chorionic villi and the shunting of blood from the exchange surface in chorionangiomas and dysplastic villi. Maternal complications such as the gestational proteinuric hypertension relationship with PMD are relatively rare, especially compared with known specific associated with molar pregnancy. Gestational proteinuric hypertension has been reported in four cases, and interestingly, all the fetuses showed features of BWS (Chan and Sampson 2003).

Recently, Kaiser-Rogers et al. (2006) reported that a mosaic pattern of normal and androgenetic cell types is the only recognized aetiology for PMD and suggested that the phenotype of androgenetic mosaicism can presumably range from mild PMD,
which may not even be diagnosed, to the typical findings of a complete hydatidiform mole, depending on the extent and distribution of the androgenetic lineage. The authors hypothesized that such mosaicism arose as the result of failure of the maternal genome to duplicate before the first cleavage with normal duplication and segregation of the paternal genome, resulting in two daughter cells; one with normal biparental genes and one with only paternal genes. Such failed division would produce a diploid/haploid mosaic embryo and endoreduplication of the haploid paternal-only daughter cell could then occur to produce the diploid androgenetic lineage, while the female and male haploid complements would merge to form a daughter cell with normal biparental inheritance. Indeed, this novel hypothesis also may account for the marked female predominance in PMD because an androgenic 46,YY cell line presumably is non-viable. The abnormal androgenetic cells would be confined to the chorionic mesoderm, membranes and vessels, whereas the trophoblastic cells would be normal with no evidence of androgenetic cells. This feature would explain the absence of trophoblast overgrowth in PMD in contrast to complete moles, in which androgenetic cells are identified in the trophoblastic cell layer.

Immunohistochemistry using antibodies against products of paternal imprinting genes such as the antibody against p57KIP2 protein is a potential marker that may prove helpful in distinguishing PMD from molar pregnancy (Umazume et al. 2011). The villous cytotrophoblastic cells of complete hydatidiform mole lack the maternal genome, which is why they reveal negative immunostaining for p57KIP2. On the contrary, in villous cytotrophoblastic cells of PHM and hydropic abortion, immunohistochemical staining for this marker is positive. The immunohistochemical detection of androgenetic/biparental mosaicism in stromal cells suggests to a diagnosis of PMD, because this mosaicism is unusual in molar pregnancies.

At the present time, only one reported case of PMD showed signs of persistent trophoblastic disease (Surti et al. 2006). In this report, the authors presented a case of a dichorionic/diamniotic twin pregnancy in which one twin presented with ultrasound findings suggestive of molar changes in the placenta. After dilatation and curettage for inevitable abortion, the patient developed and was treated for persistent gestational trophoblastic disease. Histological and genetic evaluation of the fetus and the placenta determined that this twin was a chimera with an androgenetic XY cell line and a biparental XX cell line. Thus, the authors concluded that the androgenetic cell line that resulted in placental abnormalities also later gave rise to persistent gestational disease.

Although trophoblastic differentiation appears normal in PMD, the important placental overgrowth could explain the increased maternal serum β-hCG concentration found in one case in this study. Additionally, the most common abnormal laboratory test includes increased level of maternal serum alpha-fetoprotein (MSAFP). The cause of the raised MSAFP is debatable. It is speculated that the increased surface-transfer area because of increased placental volume and the thin walled vessels in stem villi may lead to increased transfer of AFP in to the maternal circulation (Moscoso et al. 1991).

Placental mesenchymal dysplasia and BWS appear to form a spectrum of phenotype ranging from isolated placental features of stem vessel hydrops, through to classic placental and fetal features of BWS (Parveen et al. 2007). There are no consensus diagnostic criteria for BWS. It is accepted that this diagnosis based on the presence of at least three major (anterior abdominal wall defect, macroglossia, pre- or postnatal overgrowth) or two major and one minor finding (ear creases on the lobes or post-auricular pits, prominent facial nevus flammeus, hypoglycaemia, nephromegaly or hemihyperplasia) (Elliot et al. 1994). In the present study, both fetuses do not have classical diagnostic features of BWS. However, in case 2, we consider that the diagnosis may be compatible with BWS because the fetus had hepatosplenomegaly, which is a characteristic feature of BWS.

In conclusion, PMD is a rare and clinically significant lesion with high rates of IUGR, IUFD and neonatal death. It is important to recognize the detailed gross and histopathological features of this rare disease entity and be able to differentiate this condition from cases presenting as possible partial hydatidiform moles. Prenatal recognition of PMD during early as well as late gestation could prevent unnecessary termination of pregnancy. Ultrasoundographic

findings suggestive of a molar pregnancy because of hypoechoic spaces in the placenta in the presence of an apparently normal fetus, a fetus with growth restriction, or a fetus with features of overgrowth should raise the possibility of PMD.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**

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