The challenging trisomy 16: a case report

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Summary

Background: Trisomy 16 is a very frequent autosomal anomaly accounting for about 2% of first trimester abortions. In most pregnancies the chromosomal genome found in the fetus is also present in the placenta. Confined placental mosaicism is frequently detected in the placental region along with a structurally normal fetus. *Case:* We present the case of a 39-year-old primigravida with confined placental mosaicism diagnosed with chorionic villus sampling. Amniocentesis showed a normal karyotype (46, XX). Detailed scanning revealed no structural fetal anomalies, but severe oligohydramnios. *Conclusion:* Diagnosis of trisomy 16 does not necessarily mean that the newborn has anatomical abnormalities.

Key words: Confined placental mosaicism and fetal anatomy; Triploidy; Trisomy 16; Mosaicism; Oligohydramnios; Chromosome 16.

Introduction

The identification of two or more cell lines with different genomes is called chromosomal mosaicism. All cell lines are derived from a single zygote. Mosaicism may involve both fetal tissues and extraembryonic membranes. This case report demonstrates our concerns about possible anatomical abnormalities and pregnancy outcome due to the restricted ability of the fetus to move freely in the uterus and the positioning of the skeleton and extremities during intrauterine life due to severe oligohydramnios.

Case Report

A 39-year-old primigravida woman visited the clinic at 12 weeks of gestation. She was rhesus positive, a non-smoker with a pre-pregnancy weight of 56 kg, and no allergies or co-morbidities reported. Maternal serum biochemistry (free beta hCG: 2,42 MoM, PAPP-A: 0,13MoM) gave her an increased risk for Down's syndrome (1 in 19). After an informed discussion with the woman and her husband, they requested invasive testing; an uncomplicated transabdominal chorionic villus sampling was performed at 13 weeks of gestation. The results of karyotyping reported trisomy 16 within the chorionic villi. The couple agreed to have an amniocentesis in order to establish whether it was confined to placental mosaicism. Amniocentesis was performed at 16 weeks and showed a normal karyotype (46, XX). Detailed sonography at 20 weeks showed no obvious structural abnormalities (Figure 1), but severe oligohydramnios (AFI~6 cm, amniotic fluid index), with a large placental mass (width 45 mm) with multiple "cysts", covering a large posterior surface of the uterus (Figure 2). Doppler assessment of the uterine, umbilical, and middle cerebral arteries was normal. Fetal growth velocity slowed down in the abdominal circumference. In view of raised human chorionic gonadotropin (β-hCG) and a diagnosis of confined placental mosaicism (CPM) the fetus was monitored for growth due to risk of early onset of intrauterine growth restriction (IUGR). Caesarean section was performed due to fetal distress at 33 weeks and a female neonate of 2000 g was born with an Apgar score of 1 at 1 min and 2 at 5 min. The newborn breathed normally later on and growth improved in the first four months.

Trisomy 16 diagnosed prenatally is common and associated with variable pregnancy outcomes making counselling challenging.

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Diagnosis of CPM does not necessarily mean the presence of birth defects; children identified prenatally with CPM function in a similar way compared to normal children [1]. CPM diagnosed in the non-mosaic state can be lethal and not compatible with normal fetal development [2]. The detection of trisomy 16 cells in the amniotic fluid increases the risk of fetal abnormalities [3].

Discussion

Trisomy 16 is a chromosomal abnormality in which there are three copies of chromosome 16 rather than two. It is the most common cause of miscarriage during the first trimester of pregnancy.

Mosaicism occurs when two or more different genomes are expressed in one individual developing from a single fertilized egg. Mosaicism can occur in different fetal tissues and affect various stages of embryonic development. Mosaicism may result from a mutation during development which is propagated to only a subset of adult cells. Mosaicism may be present in the fetal and extra embryonic tissues (cytotrophoblast, villous stroma), or it may be present in the placental unit only.

In CPM there is a discrepancy between the fetus karyotype and the placenta; the mosaic cells are strictly limited to within the placental area.

In CPM, the cell can be trisomic; the chromosome can be of either paternal or maternal uniparental disomy (UPD), or of unknown origin [4]. It seems that maternal UPD 16 exerts a stronger influence on the prevalence of IUGR and fetal anomalies [5].

CPM may be found in the placental tissue along with a normal fetus [6].

It has been observed in spontaneous abortions, with trisomy of chromosomes 7, 16, 18, being the most common [7].

Trisomy 16 mosaicism is associated with IUGR, preterm delivery, fetal death and fetal anomalies, i.e., two-vessel cord, clinodactyly, congenital diaphragmatic hernias [8].

Confined placental mosaicism occurs in about 1% of pregnancies, where there is a mixture of cells with different karyotypes located in the placental regions [9]. In

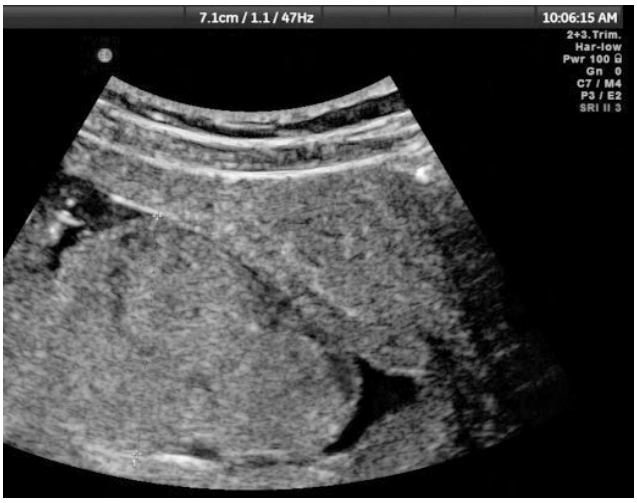

Figure 1. — Large placental mass and reduced amniotic fluid.

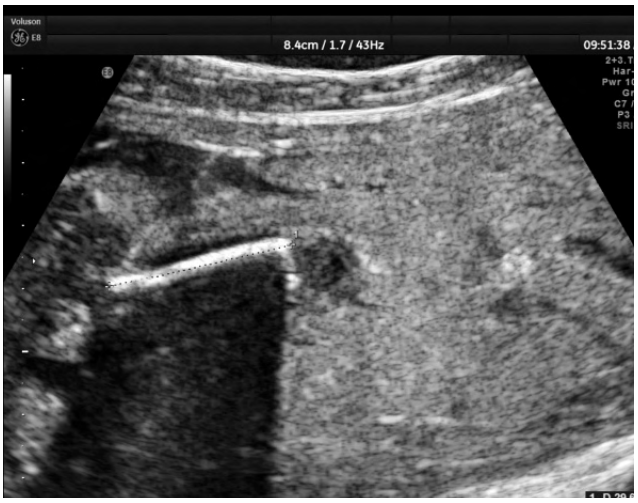

Figure 2. — Humerus.

90% of these, the fetus has a normal karyotype, while in the remainder the fetus is also a mosaic with variable phenotypic results [10].

Some studies showed that there is no clear correlation between IUGR and CPM [11].

The phenotypic effects of mosaicism may be dramatic, however not all cases are serious. In about 20% of cases, pregnancy outcome is absolutely normal [12].

It is not possible for a child to be born with an extra copy of chromosome 16 present in all cells (full trisomy 16). It is however possible to be born with the mosaic form [12].

Examination of multiple tissues is highly recommended before determining the actual identity of CPM. The first step is the performance of a chorionic villus sample (CVS). A follow-up amniocentesis shows the euploid cell line on the fetus in contrast to the placenta mosaic cells. Chorionic villi illustrate a much higher proportion of mosaic cells compared to fetal tissue. Mosaicism should be confirmed by amniocentesis before any clinical decisions are made. CPM detected through invasive testing is not a benign finding (the findings always depend on the chromosome involved), it is associated with abnormal outcomes, most commonly IUGR, cardiac defects, congenital diaphragmatic hernias, hypospadias, and global developmental delay [6, 12]. A very rare finding in trisomy 16 mosaicism is fetal artery stenosis [13].

Elevated titres of maternal hCG and alpha fetoprotein characterize the syndrome, indicate possible placental dysfunction, and should be markers for fetal echocardiography and serial scanning evaluation [14].

Prenatally diagnosed CPM can cause IUGR and preeclampsia. Pregnant women suspected of trisomy 16 mosaicism should be offered testing for preeclampsia since they are at increased risk for severe preeclampsia [15].

References

[1] Amor D.J., Neo W.T., Waters E., Heussler H., Pertile M., Halliday J.: "Health and developmental outcome of children following prenatal diagnosis of confined placental mosaicism". *Prenat. Diagn.,* 2006, *26,* 443.

[2] Astner A., Schwinger E., Caliebe A., Jonat W., Gembruch U.: "Sonographically detected fetal and placental abnormalities associated with trisomy 16 confined to the placenta. A case report and review of the literature". *Prenat. Diagn.,* 1998, *18,* 1308.

[3] Benn P.: "Trisomy 16 and trisomy 16 mosaicism: a review". *Am. J. Med. Genet.,* 1998, *79*, 121.

[4] Yong P.J., Barrett I.J., Kalousek D.K., Robinson W.P.: "Clinical aspects, prenatal diagnosis, and pathogenesis of trisomy 16 mosaicism". *J. Med. Genet.*, 2003, *40,* 175.

[5] Eggermann T., Curtis M., Zerres K., Hughes H.E.: "Maternal uniparental disomy 16 and genetic counselling: new case and survey of published cases". *Genet. Couns.*, 2004, *15,* 183.

[6] Johnson P., Duncan K., Blunt S., Bell G., Ali Z., Cox P. *et al.*: "Apparent confined placental mosaicism of trisomy 16 and multiple fetal anomalies: case report". *Prenat. Diagn.,* 2000, *20,* 417.

[7] Kalousek D.K., Barrett I.: "Confined placental mosaicism and stillbirth". *Pediatr. Pathol.,* 1994, *14,* 151.

[8] Chen C.P., Shih J.C., Chern S.R., Lee C.C., Wang W.: "Prenatal diagnosis of mosaic trisomy 16 associated with congenital diaphragmatic hernia and elevated maternal serum alpha-fetoprotein and human chorionic gonadotrophin". *Prenat. Diagn.,* 2004, *24*, 63.

[9] Wilikins-Haug L., Quade B., Morton C.C.: "Confined placental mosaicism as a risk factor among newborns with fetal growth restriction". *Prenat. Diagn.*, 2006, *26,* 428.

[10] Miura K., Yoshiura K., Miura S., Kondoh T., Harada N., Yamasaki K. *et al.*: "Clinical outcome of infants with confined placental mosaicism and intrauterine growth restriction of unknown cause". *Am. J. Med. Genet.,* 2006, *140A,* 1827.

[11] Yong PJ, Langlois S, Von Dadelszen P, Robinson W. The association between preeclampsia and placental trisomy 16 mosaicism". *Prenat. Diagn.*, 2006, *26,* 956.

[12] Neiswanger K., Hohler P.M., Hively-Thomas L.B., McPherson E.W., Allen Hogge W., Surti U.: "Variable outcomes in mosaic trisomy 16: five case reports and literature analysis". *Prenat. Diagn.*, 2006, *26,* 454.

[13] Hidaka N., Yamamoto N., Tsukimori K., Hojo S., Suzuki S.O., Wake N.: "Prenatal diagnosis of trisomy 16 mosaicism manifested as pulmonary artery stenosis". *J. Clin. Ultrasound,* 2009, *37,* 107.

[14] Tantravahi U., Matsumoto C., Delach J., Craffey A., Smeltzer J., Benn P.: "Trisomy 16 mosaicism in amniotic fluid cell cultures". *Prenat. Diagn.,* 1996, *16,* 749.

[15] Robinson W.P., Penaherrera M.S., Jiang R., Avila L., Sloan J., McFadden D.E. *et al.*: "Assessing the role of placental trisomy in preeclampsia and intrauterine growth restriction". *Prenat. Diagn.,* 2010, *30,* 1.

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