Intrauterine growth restriction (IUGR) associated with confined placental mosaicism of ring chromosome 15

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The present report describes a case that showed a normal fetal karyotype in an antenatal genetic study but an abnormal placental karyotype of 46,XX,r (15) on postnatal examination. The pregnancy was complicated by fetal nuchal translucency in the first trimester and intrauterine growth restriction in the second and third trimesters. A 1780 gm female baby was born after 40 weeks of gestation, but died of respiratory distress and sepsis on the 10th day of life. Our case was unique in that the placental chromosomal aberration was a structural abnormality instead of a numerical aberration that is seen in most reported cases of confined placental mosaicism.

Keywords : Intrauterine growth restriction, confined placental mosaicism, ring chromosome 15, nuchal translucency

INTRODUCTION

One of the prevailing beliefs in the interpretation of pathogenesis of abnormal intrauterine fetal development is that there is always a genetic identity between fetus and placenta. In fact, close to 2% of human fetuses are supported in utero by placentas which carry different genetic information from that of the fetus (Leadbetter *et al.*, 1992; Wang *et al.*, 1993). This genetic inconsistency within conceptus is known as confined placental mosaicism (CPM) (Kalousek and Dill, 1983; Kalousek, 1990). It was first described in 2 cases of term pregnancy with unexplained intrauterine fetal growth restriction (IUGR) (Kalousek and Dill, 1983). We report a case of IUGR who revealed postnatal abnormal placental karyotype of 46,XX,r (15) in the presence of normal karyotype of 46,XX by amniocentesis.

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CASE REPORT

A 32-year-old woman, gravida 4, para 1, and abortion 2, visited our department for antenatal care. Her obstetric history revealed a birth of a healthy male baby followed by two spontaneous abortions. Initial obstetric ultrasonogram taken at 10.5 weeks of gestation revealed a viable fetus with a nuchal translucency of 3 mm wide and crown-rump length of 38 mm (Fig. 1). Follow-up ultrasonogram taken at 12.5 weeks demonstrated a viable fetus with nuchal translucency of now 6 mm. The amniocentesis at 13 weeks and 5 days showed a normal karyotype of 46,XX from analysis of more than 30 cells. On detailed ultrasonogram taken at 24 weeks, the fetus showed severe IUGR with the head and abdominal circumferences below the third percentile of normal. However, the fetus was structurally normal. The pregnancy was carried on with close fetal monitoring. The nonstress test at 37 weeks showed poor variability. The S/D ratio of the umbilical artery was higher than 90 percentile. At 38 weeks, chemical analysis of amniotic fluid suggested inadequate fetal lung maturation. Fetal monitoring at 40 weeks showed distress with late deceleration, necessitating an emergency cesarean section delivering a 1780 gm cyanotic female baby. The Apgar scores at 1 and 5 min were 1 and 3, respectively. The baby and placenta were stained with thick meconium. The

general appearance of the baby was normal except minor digital anomalies including defective middle phalanx of the left 5th finger and short 5th toe with digital overlapping of the left foot. In spite of extensive postnatal management and resuscitation, the baby succumbed 10 days after birth due to respiratory distress and sepsis. The lymphocyte culture of the cord blood showed a normal female chromosome complement in all 20 cells. The karyotyping of the central and peripheral placental villi showed 46,XX,r (15) in 15 metaphases (Fig. 2). The parents refused autopsy. The pathologic examination of the placenta showed a mature placenta with 5th percentile of weight, multiple decidual arteriopathy, diffuse nonspecific chronic villitis and chorangiosis (Fig. 3).

DISCUSSION

Szabo and Gallen (1990) first described an association between a thickened sonolucent region in the nape of the fetus in the first trimester and chromosomal defects. In the fetus with a nuchal translucency greater than 3 mm in thickness, the detection rate of aneuploidy varied from 30 to 80 percent, with the false positive rate of 2.5-9.9 percent (van Zalen-Sprock *et al.*, 1992; Nicolaides *et al.*, 1992;

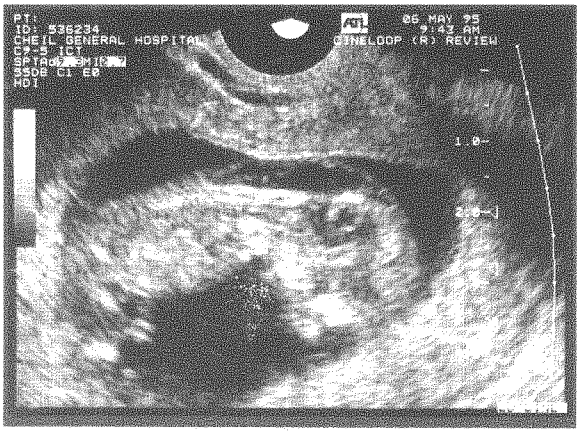

Fig. 1. Ultrasonographic finding of nuchal translucency at 11 weeks of gestation.

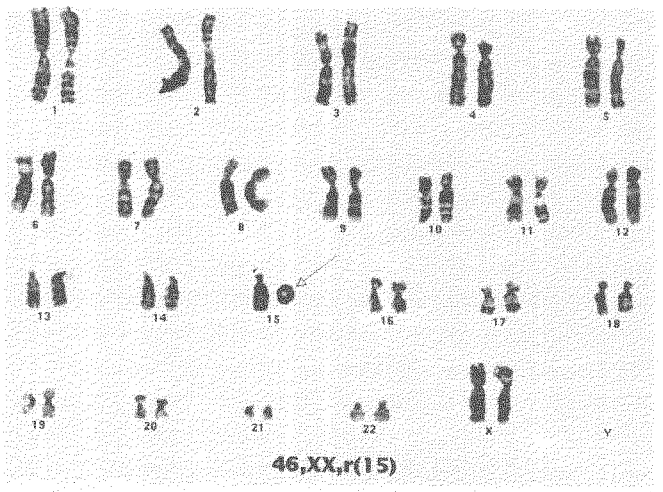

Fig. 2. Postnatal placental karyotype.

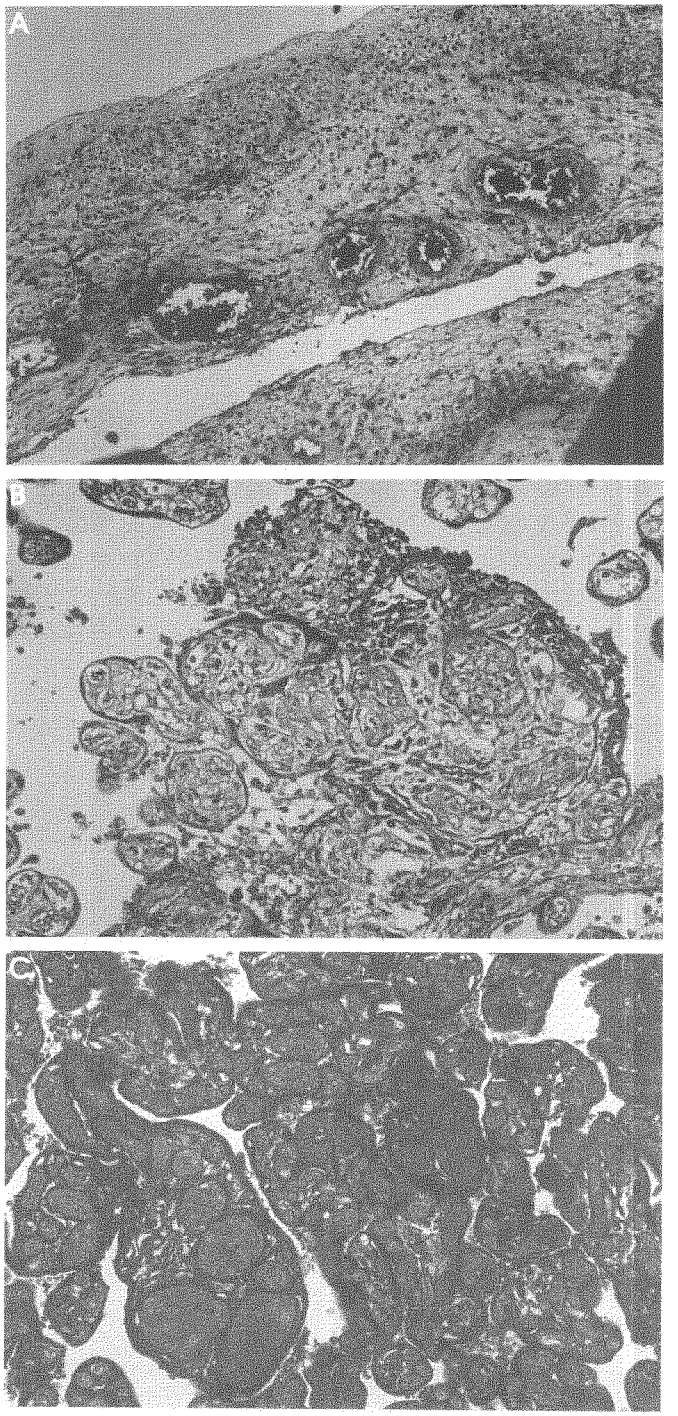

Fig. 3. Placental pathology. **A**, Decidual vasculopathy; **B**, Nonspecific chronic villitis; **C**, Chorangiosis.

Roberts *et al.*, 1995; Comas *et al.*, 1995; Pandya *et al.*, 1995). In our case, in spite of nuchal translucency, fetal karyotype by amniocentesis was normal, 46,XX. But, little information is available with regard to the prognosis of euploid fetuses with nuchal translucency. Trauffer *et al* (1994) reported that normal karyotype fetuses with a first trimester nuchal translucency greater than 3 mm have an excellent prognosis and that normal outcome was seen in 80% of pregnancies carried to the third trimester. In the present case, the fetus showed severe IUGR in the second trimester of pregnancy. We tried to figure out the cause (s) of IUGR in this karyotypically normal fetus. Among others, fetal infection, maternal disease and constitutional factor were given consideration. Recently, a number of institutes have been interested in placental pathology or CPM as a potential cause.

CPM is characterized by a discrepancy between the chromosomal constitution of embryo/fetus and the placenta (Ford, 1969; Kalousek and Drill, 1983). CPM has been reported in about 1%-2% of viable pregnancies in the studies based on the chorionic villus sampling (CVS) analysis of the cytotrophoblast or mesenchymal stroma at 9-12 weeks of gestational age. Kalousek and Drill (1983) found two cases of placental mosaicism among nine conceptuses with IUGR in their retrospective study. In these two cases, they failed to document other reasons for IUGR and suggested that IUGR represented a clinical manifestation of abnormal placental function related to the chromosome aberrations. Various mechanisms responsible for aneuploidy confined to the placenta have been proposed. Theoretically, postzygotic mitotic errors that occur in an extraembryonic cell might confine the aneuploidy to the chorionic villi. Since the precursor cells of fetus proper are relatively few in number and may not be the direct descendants of this aneuploid cell line, the newborn may possess a diploid complement (Crane and Cheung, 1988). Alternatively, an originally trisomic conceptus may selectively lose aneuploid chromosome in some cells but not in all. Selection may favor continuation of those pregnancies with a resulting diploid complement in the fetus (Kalousek *et al*, 1993).

The clinical significance of confined placental mosaicism either during the first trimester or at term continues to be debated. Increased incidence of pregnancy loss and IUGR have been documented in some but not all clinical studies of the first trimester CVS mosaicisms (Wapner *et al.*, 1992; Vejerslev and Mikkelsen, 1989; Johnson *et al.*, 1990). Wilkins-Haug *et al* (1995) analysed the karyotypes of placenta from 12 infants with normal karyotypes and unexplained IUGR and 24 appropriately grown control infants. Placental mosaicism was found not only in 3/12 (25%) of IUGR cases but also in 2/24 (8.3%) of controls.

The mechanism by which an abnormal cell line may alter placental function is unknown (Johnson *et al.*, 1990). Histologic findings in the placentas of spontaneous abortuses with cytogenetic abnormalities included villus arrest and dysmaturity (Oberweis *et al.*, 1983). It was postulated that such changes may lead to the disruption of vascular supply, induce intrauterine hypoxia with fetal compromise, or involve some as yet undetermined mechanism (Johnson *et al.*, 1990). In our case, the small placenta revealed multiple decidual arteriopathy, diffuse nonspecific chronic villitis, and chorangiosis. The placenta was small, which is a reflection than a cause of IUGR, but other pathologic feature of the placenta are considered to be responsible for high S/D ratio of the umbilical artery and also IUGR. Regrettably, there is not yet any direct correlation with placental phenotype, e.g., pathologic feature, in the various types of CPM (Benirschke, 1995). The chromosomally abnormal areas of villous biopsied show structural pathologic features but have not further elaborated (Delozier-Blanchet *et al.*, 1993).

Most of reported cases of CPM showed numerical aberration. In our case, however, the placental chromosomal aberration was a structural abnormality in nature which was a ring chromosome 15. The ring chromosome 15 syndrome has been known to usually be sporadic, due to *de novo* ring chromosome formation with rare familial occurrence (Horigome *et al.*, 1992). These children may have variable characteristics including IUGR, different degrees of postnatal growth failure, triangular facies, fifth finger clinodactyly, and occasionally cafe-au-lait spots and discrepancy in the leg length (Fryns *et al.*, 1979, 1986) with variable developmental and speech delay (Kitatani *et al.*, 1990). The phenotype needs to be correlated with the amount of deleted euchromatin and the degree of mosaicism with other cell lines. Peoples *et al* (1995) reported that growth failure in the ring chromosome 15 syndrome has been related to hemizygocity at the insulin-like growth factor 1 receptor (IGF 1R) locus.

We were not able to perform the chromosomal study of the skin or other tissues in this fetus. Hence, it is not known wether the fetus had a mosaicism. The mechanism of IUGR was not clear either, but the placenta has abnormal components of ring chromosome 15, and placental pathology revealed decidual vasculopathy, nonspecific diffuse chronic villitis and chorangiosis. These findings suggested that the function of the placenta was inadequate in utero, causing a chronic hypoxia and neonatal death.

REFERENCES

Benirschke, K. and Kaufmann, P. (1995) Pathology of the human placenta, 3rd edition, p. 639, Springer-Verlag, New York

Comas, C., Martinea, J., Ojuel, J., Casals, E., Puerto, B., Borrell, A. and Ortuny, A. (1995) First trimester nuchal edema as a marker of aneuploidy, *Ultrasound Obstet Gynaecol* 5: 26-29

Crane, J. P. and Cheung S. W. (1988) An embryogenic model to explain cytogenetic inconsistencies observed in chorionic villus versus fetal tissue. *Prenat Diagn* 8: 119-29

Delozier-Blanchet, C., Francipane, L., Ebener, J., Coxx, J. and Extermann, P. (1993) Cytogenetic discrepancies between fetus and placenta; a frequenct cause of reproductive pathologies?. *Placenta* 14: A14

Ford, C. E. (1969) Mosaicism and chimaeras. *Br Med Bull* 25: 104-109

Fryns, J. P., Kleczkowska, A., Buttiens, M., Jonckheere, P., Brouckmans-Buttiens, K. and van den Berghe, H. (1986) Ring chromosome 15 syndrome: further delineation of the adult phenotye. *Annals Genet* 29: 45-48

Fryns, J. P., Timmermans, J., D'Hondt, F., Francois, B., Emmery, L. and van den Berghe, H. (1979) Ring chromosome 15 syndrome. *Hum Genet* 51: 43-48

Furlanetto, R. W., DiCarlo, J. N. and Wisehart, C. (1987) The type II insulin-like growth factor receptor does not mediate deoxyribonucleic acid synthesis in human fibroblasts. *J Clin Endocrin Metab* 64: 1142-1149

Horigome, Y., Kondo, I., Kuwajima, K. and Suzuki, T. (1992) Familial occurrence of ring chromosome 15. *Clin Genet* 41: 178-180

Johnson, A., Wapner, R. J., Davis, G. H. and Jackson, L. G. (1990) Mosaicism in chorionic villous sampling: an association with poor perinatal outcome. *Obstet Gynecol* 75: 573-577

Kalousek, D. K. (1990) Confined placental mosaicism and intrauterine development. *Pediatric Pathology* 10: 69-77

Kalousek, D. K. and Dill, F. J. (1983) Chromosomal mosaicism confined to the placenta in human conceptions. *Science* 221: 665-667

Kalousek, D. K., Langlois, S., Barrett, I., *et al.* (1993) Uniparental disomy for chromosome 16 in humans. *Am J Hum Genet* 52: 8-16

Kitatani, M., Takahashi, H., Ozaki, M., Okino, E. and Naruoka, T. (1990) A case of ring chromosome 15 accompanied by almost normal intelligence. *Hum Genet* 85: 138-139

Leadbetter, D. H., Zachery, J. M., Simpson, J. L., *et al.* (1992) Cytogenetic results from the US collaborative study on CVS. *Prenat Diagn* 12: 317-354

Nicolaides, K., Azar, G., Byrne, D., Mansur, C. and Marks, K. (1992) Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *Br Med J* 304: 867-869

Oberweis, D., Gillerot, Y. and Koulischer, L. (1983) Le placenta des trisomies dans le dernier de la gestation. *J Gynecol Obstet Biol Reprod* 12: 345-9

Pandya, P., Goldberg, H., Walton, B., Riddle, A., Shelley, S., Snijers, R. and Nicolaides, K. (1995) The implementation of first trimester scanning at 10-13 weeks' gestation and the measurement of fetal nuchal translucency thickness in two maternity units, *Ultrasound Obstet Gynaecol* 5: 20-25

Roberts, L., Bewley, S., Mackinson, A. and Rodeck, C. (1995) First trimester fetal nuchal translucency. *Br J Obstet Gynaecol* 102, 381-385

Szabo, J. and Gallen, J. (1990) Nuchal fluid accumulation in trisomy 21 detected by vaginosonography in the first trimester (Letter). *Lancet* 336: 1133

Trauffer, P.M.L., Anderson, C.E., Johnson A., *et al.* (1994) The natural history of euploid pregnancies with first trimester cystic hygroma. *Am J Obstet Gynecol* 170: 1279-84

Vejerslev, L. O. and Mikkelsen, M. (1989) The European collaborative study on mosaicism in chorionic villus sampling: data from 1986 to 1987. *Prenat diagn* 9: 575-88

Wang, B. T., Rubin, C. H. and Williams, J. III. (1993) Mosaicism in chorionic villus sampling: an analysis of incidence and chromosomes involved in 2612 consecutive cases, *Prenat Diagn* 13: 179-190

Wapner R. J., Simpson, J. L., Golbus, M. S., *et al.* (1992) Chorionic mosaicism: association with fetal loss but not with adverse perinatal outcome. *Prenat Diagn* 12: 347-55

Wilkins-Haug, L., Roberts, D.J., Morton, C.C. (1992) Confined placental mosaicism and intrauterine growth retardation: an analysis of 12 cases and 24 matched controls. *Am J Hum Genet* 51: 11

van Zalen-Sprock, M., van Vugt, J. and van Geijn, H. (1992) Non-echogenic nuchal oedema as a marker in trisomy 21 screening (Letter). *Lancet* 339: 1480-1481