Prenatal diagnosis of a de novo ring chromosome 11

[1]Laboratory of Medical Genetics, Medical Research Institute,
Cheil General Hospital and Women's Healthcare Center, Seoul, Korea
[2]Department of Obstetrics and Gynecology, Kwandong University College of Medicine, Seoul, Korea

Ju-Yeon Park[1] · Moon-Hee Lee[1] · Bom-Yi Lee[1]
Yeon-Woo Lee[1] · Hyun-Mee Ryu[1,2] · So-Yeon Park[1]

A 36-year-old pregnant woman was referred for amniocentesis at 19.5 weeks gestation because of advanced maternal age and evidence of increased risk for Edward syndrome in the maternal serum screening test. Cytogenetic analysis of the cultured amniotic fluid cells revealed mosaicism for ring chromosome 11: 46,XX,r(11)[65]/45,XX,-11[16]/46,XX[34]. Parental karyotypes were normal. A targeted ultrasound showed intrauterine growth restriction (IUGR). Cordocentesis was performed to characterize the ring chromosome and to rule out tissue specific mosaicism. Karyotype was confirmed as 46,XX,r(11)(p15.5q24.2)[229]/45,XX,-11[15]. And a few new form of ring were detected in this culture. The deletion of subtelomeric regions in the ring chromosome were detected by fluorescent in situ hybridization (FISH). The pregnancy was terminated. The fetal autopsy showed a growth-retarded female fetus with rocker bottom feet. We report a case of prenatally detected a de novo ring chromosome 11.

Key Words : Ring chromosome 11, Intrauterine growth restriction (IUGR), Ring formation, Ring instability, Prenatal

INTRODUCTION

Ring chromosomes are uncommon chromosomal abnormalities found in prenatal diagnoses. Estimated frequency of a ring chromosome is approximately 1 in 2,500 newborn and prenatal diagnoses[1]. About 99% of ring chromosomes arise sporadically[2]. Ring chromosomes have been reported for all chromosomes, and nearly half of them occur in acrocentric chromosomes[3]. Ring chromosome 11 is a very rare abnormality first described in 1977[4]. Clinical features of ring chromosome 11 vary from subtle minor anomalies to multiple major anomalies such as growth retardation, heart defects, convulsions and pancytopenia.

Corresponding author : So-Yeon Park, Ph.D.
Laboratory of Medical Genetics, Cheil General Hospital & Women's Healthcare Center,1-19 Mukjeong-dong, Jung-gu, Seoul 100-300, Korea
Tel : +82-2-2000-7680, Fax : +82-2-2278-4574

CASE REPORT

A 36-year-old, gravida 4, para 1 woman was referred for amniocentesis at 19.5 weeks gestation due to advanced maternal age and evidence of increased risk for Edward syndrome in the maternal serum screening test. Cytogenetic analyses were performed on amniotic fluid cells using an in-situ culture method and flask culture method. A total of 115 metaphases were analyzed with GTG banding. Cytogenetic analysis of the cultured amniotic fluid cells revealed mosaicism with ring chromosome 11. The karyotype was 46,XX,r(11)[65]/45,XX,-11[16]/46,XX[34]. Both parents showed unremarkable medical history and normal karyotypes. A targeted fetal ultrasound at 20 weeks of gestation showed no significant abnormalities

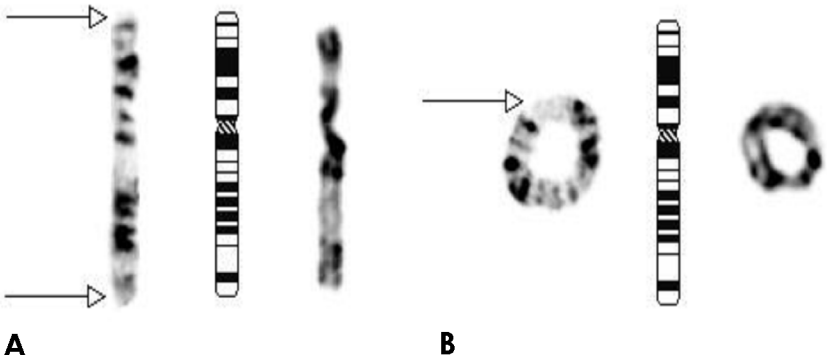

Fig. 1. Partial karyotype of chromosome 11 (A) and ring chromosome 11 (B). Chromosome spreads were processed for high-resolution GTG-, RBG-banding with cord blood lymphocytes. There was no detectable deletion region of ring chromosome 11 by conventional cytogenetic investigations.

other than intrauterine growth restriction (IUGR). Cordocentesis was performed at 22 weeks of gestation to characterize the ring chromosome by high resolution and reverse banding. The karyotype was 46,XX,r(11)(p15.5q24.2)[229]/45,XX,-11[15] (Fig. 1). In this culture, a few dicentric rings and double-sized new ring structures were observed. There was no normal cell line. The ring chromosome 11 was characterized by FISH using two subtelomeric chromosome 11p and 11q probes (Vysis, USA). Metaphase slide were generated from a cord blood culture. FISH showed that deletions of both signals for 11p and 11q were detected on the ring chromosome 11 (Fig. 2) Follow up ultrasound at 24 weeks showed no significant IUGR which is 370 g, 0.05 percentile of gestation age. After genetic counseling, the parents did not want to continue the pregnancy. The pregnancy was terminated at 24 weeks of gestation. The autopsy revealed a growth-retarded female fetus with rocker bottom feet. However, the internal organs were unremarkable.

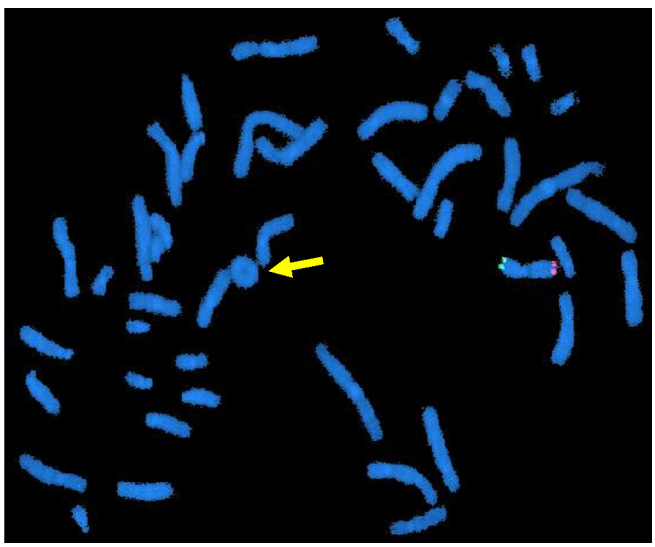

Fig. 2. FISH using the probes for short and long arms of chromosome 11. Normal chromosome 11 showed a green signal and a red signal for both the 11p and 11q, whereas ring 11 showed no hybridization signals. These results suggest that the subtelomeric regions for 11p and 11q in the ring 11 were deleted. The arrow indicates ring chromosome 11.

DISCUSSION

Ring chromosome formation is due to breaks in both arms of the chromosome and subsequent fusion of the ends of the distal segments in most cases. An additional hypothesis involves telomere to telomere fusion of a chromosome ends without loss of chromosomal material [4-6]. In this case, we could not identify deletion of chromosomal materials in conventional cytogenetic investigations. However, subsequent FISH analysis indicated that the breakpoints on the both arms of chromosome 11 were located subtelomeric regions and the fetus had a partial monosomy for the terminal regions of short and long arms.

Clinical features of patients with a ring chromosome are various. Clinical phenotype variations could be related to the amount of missing genetic materials. Patients with partially deleted rings have clinical abnormalities asso-

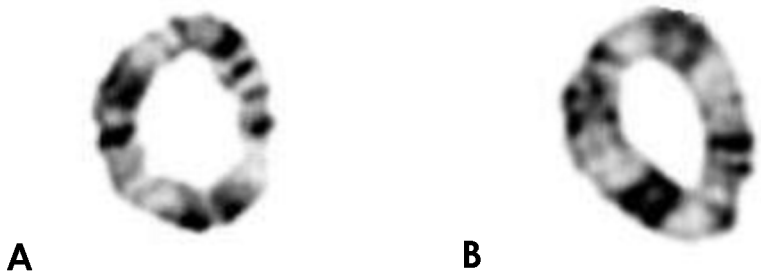

Fig. 3. Ring chromosome instability leads to double-sized new ring structures (A) and dicentric rings (B) in cord blood culture.

ciated with partial monosomies[5, 6, 9, 10]. In some cases with a ring chromosome 11, patients share typical features of the 11q- syndrome[7, 8]. Although terminal deletions on 11p and 11q were detected, there was no significant clinical anomaly except for IUGR. The 'ring syndrome' was proposed to describe a phenotype of primordial growth failure without major malformations[11, 12].

The proportion of cells with or without ring chromosome depends on the stability of the ring chromosome during mitosis[13]. Generally, larger ring chromosomes are more instable than smaller ring chromosomes[3]. Larger ring chromosomes offer more opportunities for sister chromatid exchanges to occur than with smaller ring chromosomes. Ring chromosome instability also leads to double-sized dicentric rings, interlocking rings, or a complete loss of the ring chromosome in subsequent cellular generation. Chromosome 11 is belongs relatively large chromosome. The ring chromosome instability was observed in our case. In repeated cytogenetic analysis at 22 weeks of gestation, we observed a dicentric ring chromosome and double-sized new ring structures (Fig. 3) and the proportion of the ring chromosome increased as compared with first cytogenetic analysis at 19.5 weeks gestation. This is a result of a process termed "dynamic mosaicism". This case showed prenatally detected a de novo ring chromosome 11 with dynamic mosaicism.

한글요약

고리염색체(Ring chromosome)는 매우 낮은 빈도로 발견되는 염색체 이상으로 모든 번호에서 보고되고 있으며 특히 끝곁 매듭 염색체(acrocentric chromosome)에서 빈번하게 관찰 된다. 본 증례는 ring chromosome(고리염색체)11의 산전진단에 관한 것이다.

산모는 36세의 여성으로 모체혈청검사에서 에드워드 증후군의 표시인자가 증가되어, 태아의 염색체 검사를 위해 임신 19.5주에 양수천자술을 시행하였다. 결과는 46,XX,r(11)[65]/45,XX,-11[16]/46,XX[34]로 고리염색체(ring chromosome) 11이 mosaic으로 관찰되었다. 혈액을 이용한 부모 염색체 검사는 모두 정상이었다. 임신 20주에 실시된 정밀초음파 검사에서는 자궁내성장장애(IUGR) 소견을 보였다. 모자익시즘의 확인을 위해 임신 22주에 재대 혈액을 이용한 두번째 염색체 검사 결과는 46,XX,r(11)(p15.5q24.2)[229]/45,XX,-11 [15]이었으며 첫번째 검사에서 관찰되지 않았던 다양한 형태의 고리염색체(ring chromosome)가 소수의 세포에서 관찰되었다. 고리염색체(ring chromosome)11에 대한 FISH 검사에서는 11 염색체의 장완과 11 염색체의 단완의 subtelomeric 부위가 결실되어 있었다.

REFERENCES

1) Wyandt HE. Ring autosomes: identifcation, familial transmission, causes of phenotypic effects and in vito mosaicism. In: Daniel A, editor. The cytogenetics of mammalian autosomal rearrangements. New York: Alan R Liss 1988;667-96.
2) Kosztolanyi G, Mehes K, Hook E. Inherited ring chromosomes: an analysis of published cases. Hum Genet 1991;87:320-4.
3) Kosztolanyi G. Does "ring syndrome" exist? An analysis of 207case reports on patients with a ring autosome. Hum Genet 1987;75:174-9.
4) Cote G.B, Katsantoni A, Deligeorgis D. The cytogenetic and clinical implications of a ring chromosome 2. Ann

Genet 1981;24;231-5.
5) Kosztolanyi G. Ring chromosome 4: Wolf syndrome and unspecifc developmental anomalies. Acta Paediatr Hung 1985;26:157-64.
6) Sawyer JR, Lukacs JL, Hassed SJ, Arnold GL, Mitchell HF, Muenke M. Subband deletion of 7q36.3 in a patient with ring chromosome 7: association with holoprosencephaly. Am J Med Genet 1996;65:113-6.
7) Niikawa N, Jinno Y, Tomiyasu T, Fukushima Y, Kudo K. Ring chromosome 11 [46,XX,r(11)(p15q25)]. Associated with clinical features of the 11q- syndrome. Ann Genet (Paris) 1981;24;172-5.
8) Scott-Emuakpor AB, Cousineau AJ, Higgins J, Mody G. Ring chromosome11: phenotype-karyotype correlation with the 11q- syndrome. Am J Hum Genet 1981;33:121-5.
9) Suerinck E, Noel B, Rethore MO. Ring chromosome 5 in two malformed boys with cri du chat syndrome. Clin Genet 1978;14:125-9.
10) Rodriguez L, Sanchis A, Villa A, Canovas A, Peris S, Estivalis M, et al. Ring chromosome 7 and sacral agenesis. Am J Med Genet 2000;94:52-8.
11) Scribanu N, McCullars EB, Baumiller RC, Colon AR. The syndrome of ring chromosome 12. Am J Med Genet 1980; 5:165-70.
12) Zuffardi O, Danesino C, Poloni L, Pavesi F, Bianchi C, Gargantini L. Ring chromosome 12 and latent centromeres. Cytogent Cell Genet 1980;28;151-7.
13) Hoo JJ, Obermann U, Cramer H. The behavior of ring chromosome 13. Humangenetik 1974;24;161-71.