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Case Report

Prenatal diagnosis of a *de novo* 9p terminal chromosomal deletion in a fetus with major congenital anomalies

Wen-Chien Hou [a], Chih-Ping Chen [a, b, c, d, e, f, g], Kwei-Shuai Hwang [a], Ying-Chieh Chen [h], Yu-Ju Lai [a], Chau-Yang Tien [a], Her-Young Su [a, *]

[a] *Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[h] *Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

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ABSTRACT

Objective: We describe a prenatal ultrasonography diagnosis of omphalocele and symbrachydactyly in a fetus and review the literature on prenatal diagnosis of 9p terminal chromosomal deletions.
Case report: A 31-year-old woman (gravida 3, para 1) was referred for genetic counseling because a fetal omphalocele had been detected. Prenatal ultrasonography at 17+ weeks of gestational age revealed a singleton female fetus with biometry equivalent to 18 weeks with an omphalocele. In addition, symbrachydactyly was also noted in the right arm; the wrist bones as well as the metacarpals were missing. A chromosomal study was arranged for a congenital anomaly involving omphalocele. We obtained Giemsa-banded chromosomes from fetal tissue cells, and an abnormal male karyotype with a terminal deletion of the short arm of chromosome 9 at band 9p13 was noted. After delivery, the fetus showed omphalocele, symbrachydactyly, trigonocephaly, sex reversal, a long philtrum, low-set ears, telecanthus, and a frontal prominence.
Conclusion: Prenatal diagnosis of abnormal ultrasound findings with omphalocele and symbrachydactyly should include the differential diagnosis of a chromosome 9p deletion.

Introduction

Deletion 9p syndrome is a well-known chromosomal disorder. It is characterized by craniofacial dysmorphisms, such as craniostenosis with trigonocephaly, a prominent forehead with a metopic ridge, midfacial hypoplasia, a flat nasal bridge, anteverted nares, low-set poorly formed ears, a long philtrum, developmental delay, mental retardation, seizures and impaired learning ability, abnormal digits, cardiovascular defects, and gonadal abnormalities as well as short arms and an umbilical hernia [1–11]. Marked developmental delay with attention deficit hyperactivity disorder and peripheral myopathy involving intentional tremor and myoclonic jerking are associated with the 9p13 interstitial deletion [12].

Isolated omphalocele is a rare congenital deformity, occurring in approximately two to three per 10,000 live births [13]. Omphaloceles occur sporadically, and about 56% of the affected patients show karyotypic anomalies, including trisomies 13, 15, 16, and 18 and Beckwith-Wiedemann syndrome [14–16].

As for right upper limb deformities, symbrachydactyly was first named by Blauth and Gekeler in 1973. This is regarded as a transverse deficiency, caused by bony dysplasia, graded by its severity into four categories [17]. The common clinical features are unilateral and some cases are associated with anomalies in the pectoral muscle (Poland syndrome) [18]. The prevalence of skeletal dysplasia is 2.14 per 10,000 deliveries [19]. In our case, all digits were absent, although some rudimental fingers were observed. According to the Blauth and Gekeler classification, this fetus

* Corresponding author. Department of Obstetrics and Gynecology, Tri-Service General Hospital, 325, Section 2, Chenggong Road, Neihu District, Taipei, Taiwan.
E-mail address: su108868@gmail.com (H.-Y. Su).

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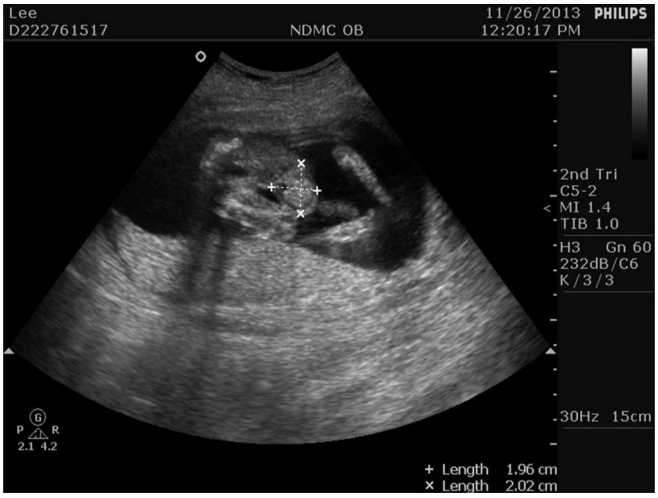

Fig. 1. Prenatal ultrasonography at 17+ weeks of gestational age revealed a 2.02 × 1.96 cm isolated omphalocele.

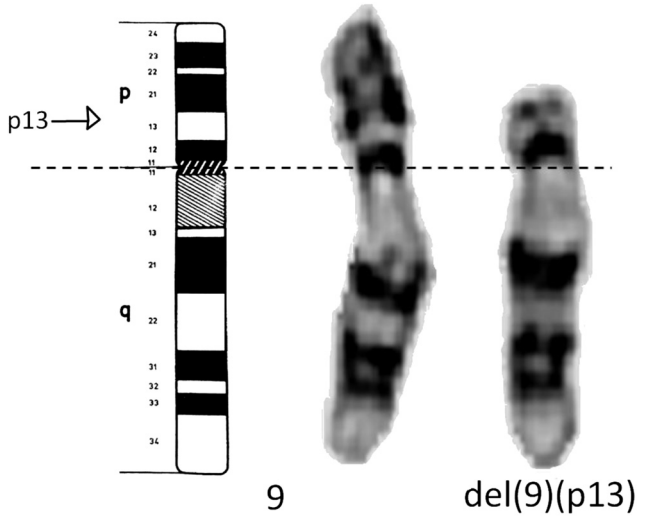

Fig. 3. Karyotype of the fetus revealed 46,XY,del(9)(p13), and the breakpoint is marked by the arrow.

belonged to Grade 4, the peromelia type. However, the genetic cause has not been established [17].

Here, we present a case of chromosome 9p deletion with the typical symptoms mentioned above and two other rare symptoms: omphalocele and symbrachydactyly.

Case report

A 31-year-old woman (gravida 3, para 1) was referred to our hospital for genetic counseling after an omphalocele was detected in the fetus. The woman was Taiwanese and not obese. Neither she nor her husband showed any substance abuse. There was no family history of congenital malformations. Maternal serum screening showed that the levels of α-fetoprotein, unconjugated estriol, total β-human chorionic gonadotropin, and inhibin-A were 0.78, 0.82, 1.27, and 1.63 multiples of median, respectively. Risk evaluation results were calculated as a probability of 1/335 of having Down syndrome, 1/5,5900 of having an open neural tube defect, and 1/32,200 of having trisomy 18. Prenatal ultrasound was arranged at 17 2/7 weeks gestational age and showed a 188-g singleton fetus with biometry equivalent to 18 weeks of gestation, a normal amount of amniotic fluid, and a 2.02 × 1.96 cm isolated omphalocele (Fig. 1). In addition, symbrachydactyly was observed over the

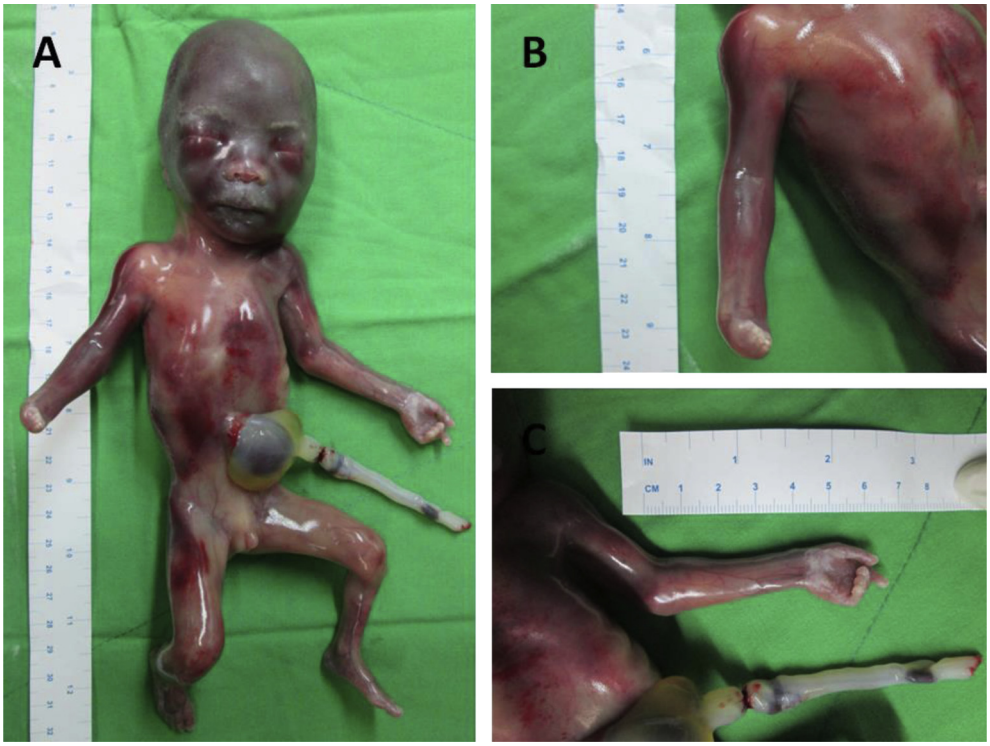

Fig. 2. (A) Photograph of a fetus showing metopic prominence, telecanthus, long philtrum, low-set ears, omphalocele, midfacial hypoplasia, and omphalocele. (B, C) Shortened right upper extremities and symbrachydactyly are shown.

left upper arm with few nubbins, absence of bony formation in the pulmar region, and a shortened forearm and upper arm. The woman underwent medical termination of the pregnancy because of these fetal malformations, and a chromosomal study was arranged, including Giemsa-banded karyotypes of the fetus and parents. The 350-g ostensibly female fetus was delivered at 19 6/7 weeks of gestational age and showed omphalocele, symbrachydactyly, trigonocephaly, a long philtrum, low-set ears, telecanthus, a metopic prominence, and sex reversal (Fig. 2). Chromosome culture and karyotyping was performed on fetal tissue cells. Nineteen metaphase spreads were analyzed using Giemsa banding. The maximum resolution achieved was 400 bands. The metaphases from the fetus revealed terminal deletion of the short arm of chromosome 9. The karyotype was 46,XY,del(9)(p13) (Fig. 3), confirming a sex reversal phenotype. Parental peripheral blood chromosomal analyses were normal. Hence, a *de novo* 9p deletion was diagnosed.

Discussion

Chromosomal abnormalities, including the 9p deletion syndrome, can be detected in early pregnancy by evaluating maternal serum biochemistry [20–25]. In our case, the serum studies were normal and the relative risk of Down syndrome 1/335. High-resolution mapping techniques, such as fluorescence *in situ* hybridization and microarray-based comparative genomic hybridization, might be able to detect the precise region of the deletion and eliminate other chromosomal anomalies, but such techniques had not been established for this case.

The current case was associated with a chromosomal 9p terminal deletion with a breakpoint at p13. This 9p terminal deletion produces haploinsufficiencies of the *DOCK8*, *DMRT1*, *DMRT2*, and *DMRT3* genes [21]. Genomic aberrations of *DOCK8* are associated with the failed organization of filamentous actin of adult and fetal brains, subsequently resulting in mental retardation [26]. The *DMRT* clusters are known as candidate genes for sex determination and differentiation in mammals, involved in suppressing female differentiation and maintaining mammalian testis determination [27,28].

For trigonocephaly, a critical region has been discovered strongly associated with genomic regions from D9S912 to RP11-439I6 [29]. The *CER1* gene was hypothesized to be one of the critical genes, but two other studies disproved it [5,30].

In fact, fetuses with 9p deletion syndrome might survive. In some cases, they have even lived as long as 4 decades. Nevertheless, developmental delay, including motor and speech disorder, should be monitored closely as well as behavioral problems and valvular heart diseases [5]. Other phenotypes include pulmonary hypoplasia, cardiovascular defects, craniofacial dysmorphism with trigonocephaly and forehead prominence, midfacial dysplasia with anteverted nares, a long philtrum, gonadal dysgenesis with sex reversal, hypospadias, cryptorchidism, and malformed external genitalia, etc. Precise links between genotype and phenotype have not yet been established because the phenotype varies extraordinarily widely. Some 9p deletion cases with major congenital anomalies can be observed by prenatal examinations, as in this case. Therefore, cytogenetic analysis is beneficial for early diagnosis and subsequent genetic counseling. In our case, after discussion, the parents decided to undergo medical termination because of the severe limb deformities in the fetus.

In conclusion, we carried out an analysis of chromosome 9, with a breakpoint associated with omphalocele and symbrachydactyly. Further genetic work on breakpoints in regions 13–22 might be necessary to identify the genetic causes of these developmental anomalies.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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