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Achondrogenesis Type II (Langer-Saldino Achondrogenesis) : A Case Report

Achondrogenesis is a lethal form of congenital chondrodystrophy characterized by extreme micromelia. We describe a case of achondrogenesis type II (Langer-Saldino achondrogenesis) detected by prenatal ultrasonography at 20-week gestation. A dwarfed fetus with large head, short neck and chest, prominent abdomen and short limbs was terminated transvaginally. Radiologic and histopathologic examination revealed features of mild form of achondrogenesis type II. Although the case had no known risk factor and the phenotypic abnormality was mild, modern development in prenatal screening made the early detection possible.

Key Words: *Achondroplasia; Achondrogenesis Type II; Lethal Skeletal Dysplasia; Ultrasonography, Prenatal*

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INTRODUCTION

Achondrogenesis, which occurs in approximately 1 in 40,000 births (1), belongs to lethal forms of chondrodysplasia. Clinically it is characterized by a severe short-limbed dwarfism, and affected infants die in utero or shortly after birth. Achondrogenesis has been subclassified into type IA, IB and type II, based mainly on clinical and radiological criteria such as pattern of ossification deficiency and deformities of the ribs (2).

Achondrogenesis type II was initially described by Langer et al. (3) and Saldino (4); the disorder is also called Langer-Saldino achondrogenesis. The clinicopathologic features of this lethal dwarfism has recently been more completely delineated by others (5, 6), and the major clinical features include short trunk with prominent abdomen, striking micromelia and hydropic appearance. The basic radiographic findings are severe underossification of the vertebral bodies, a typical configuration of the iliac bones with concave medial and inferior borders, and nonossification of the ischial and pubic bones. The tubular bones are short, and the metaphyses are splayed and cupped, with irregular ends and spur formation (3-6).

Achondrogenesis type II and hypochondrogenesis has similar radiologic features, but were previously thought to be distinct disorders. It has been described that in hypochondrogenesis, ossification of the vertebral bodies is less severely retarded, the ilia are larger, and the tubular bones are longer with less severe splaying of their ends when compared with achondrogenesis type II (7). But recent data indicate that these two disorders represent a spectrum of the same disorder, with marked phenotypic variability (6, 8, 9). According to the international classification of osteochondrodysplasias, achondrogenesis type II, hypochondrogenesis, and spondyloepiphyseal dysplasia congenita are placed together in the same group (10).

We report an autopsy case of a fetus that was terminated at 22-week gestation. Abnormal shortening of femur was detected by prenatal sonography and the autopsy findings were compatible with those of achondrogenesis type II.

CASE REPORT

A female fetus was delivered transvaginally at 22-week gestation and died shortly after birth. Pregnancy had been uneventful until week 20 of gestation, when an ultrasound scan showed significantly shortened femur for the gestational age and nuchal edema (Fig. 1). Amniocentesis for chromosome analysis was performed and yielded a normal female karyotype. The baby was the first for the 26 year-old mother and 30 year-old father. Family history was unremarkable, and there had been no known teratogen exposure.

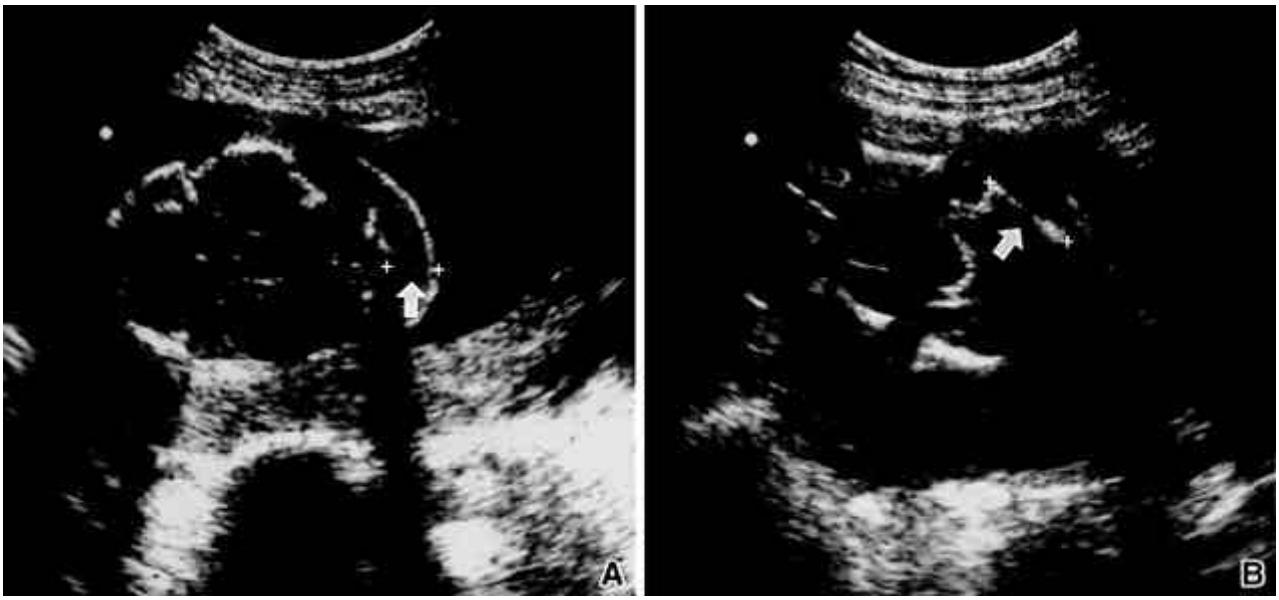

Fig. 1. Ultrasonography at 22-week gestation shows nuchal edema (A) and markedly shortened femur (B). (observed femur length/ expected femur length : 2.31 / 3.2 = 0.72)

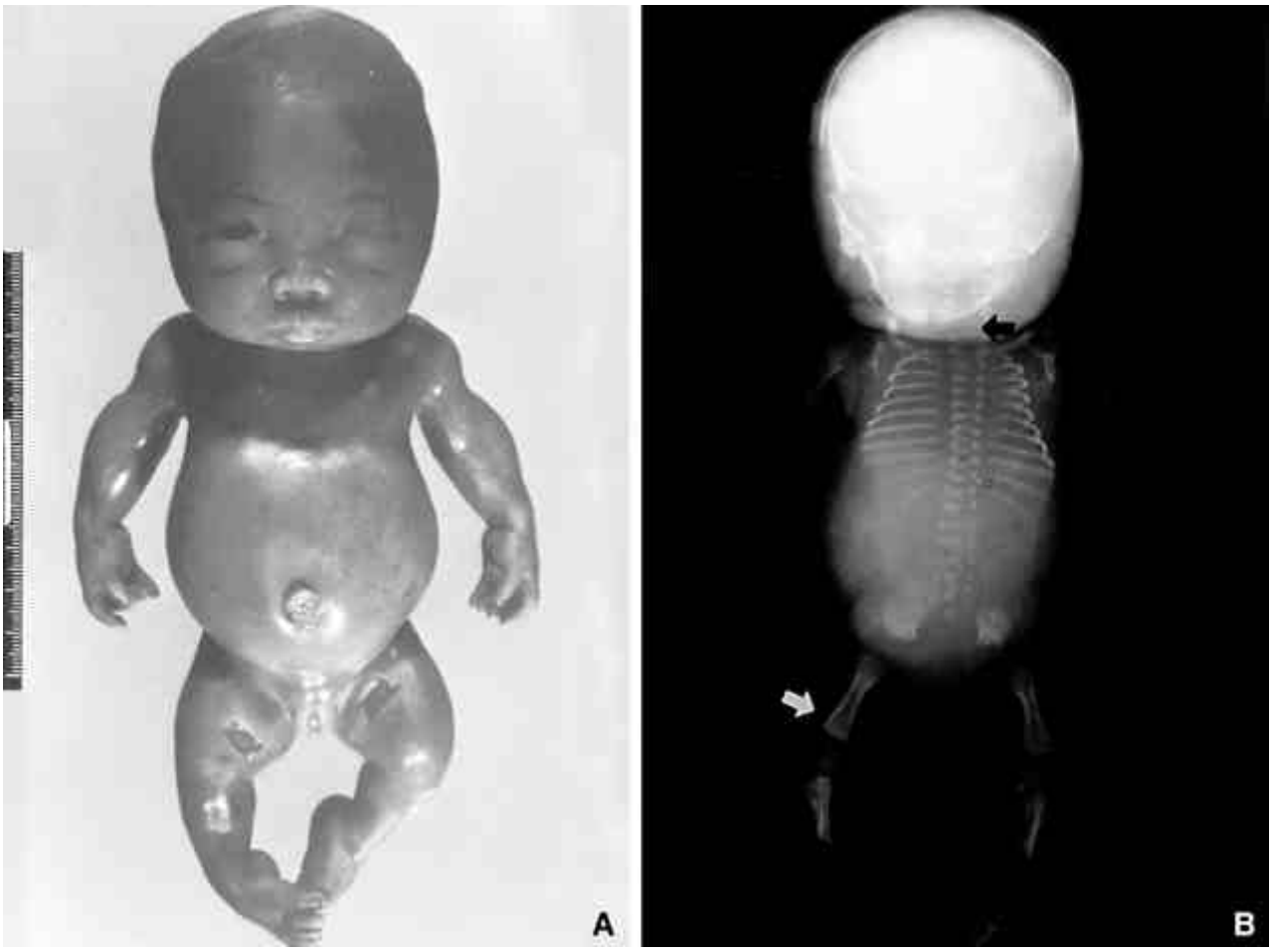

Fig. 2. Photography and radiography of fetus at postmortem examination. (A) The fetus has craniofacial anomaly, short neck and chest, distended abdomen and severe micromelia. (B) Radiography show short tubular bone, widened metaphyses and non-ossified cervical vertebrae.

The fetus was small for gestational age (weight: 490 g, CR length: 17.3 cm). She had craniofacial anomaly including relatively large calvarium (head circumference: 22.3 cm, biparietal diameter: 6.15 cm), micrognathia, small mouth, hypertrophied tongue, flat nose and hypertelorism. The neck was very short and the thorax was short with antero-posterior flattening. The abdomen was large and distended. There was severe shortness of upper and lower limbs, especially of the rhizomelic segments. The extremities were also bowed and bilateral club foot was noted (Fig. 2A).

Radiologic examination of the skeleton confirmed the shortness of limbs. The tubular bones were short and broad, and the metaphyses were widened with irregular ends and lateral spurs. The calvaria were relatively well-ossified. The ribs were horizontal without fracture. The vertebral bodies were insufficiently ossified, predominantly in the cervical spine. The iliac wings were square with a horizontal acetabular angle and a concave internal edge. Both ischial and pubic bones were nonossified (Fig. 2B).

Histopathologic examination of the chondro-osseous tissues revealed hypervascularity of cartilage. Cellular density was high and the matrix was reduced (Fig. 3A). The cells were large, often starred, and their lacunae were enlarged (Fig. 3B). In the growth zone, the cells showed irregular columns that ended in hypertrophic cells placed irregularly. Vascular penetration was irregular in the ossification line. The primary trabeculae were thickened, irregular and uneven. The gross and microscopic examination of other organ revealed appropriate growth and development for gestational age and no significant anomaly. On the basis of clinical, radiological and microscopic findings, this case was diagnosed as a mild form of achondrogenesis type II (Langer-Saldino).

DISCUSSION

Achondrogenesis type II is a very rare and lethal skeletal dysplasia, especially in Korea, and the present case would be the second case reported in Korea (15). Affected infants die in utero or in the neonatal period. Therefore, the majority of previous reports dealt with cases of stillborn or immediate postnatal death (3-6). When compared with the cases delivered at later gestational age, our case showed milder degree of limb shortness and absence of other anomalies (15). The case reported by Kim et al. (15) was a fetus at 29-week gestational age which had about one third of the expected length of lower limb (the length of the case was 5.5 cm and the expected length for body weight was 14 cm), while in our case it reached about a half of the expected length (5 cm and 10 cm).

Because making a radiological differential diagnosis between mild achondrogenesis type II and severe hypochondrogenesis is very difficult, several studies performed a clinical, radiographic and morphologic analysis in an attempt to distinguish between heterogeneity and clinical variability (6, 8, 9). These reports suggested that hypochondrogenesis and achondrogenesis type II represent a spectrum of the same disease with marked phenotypic

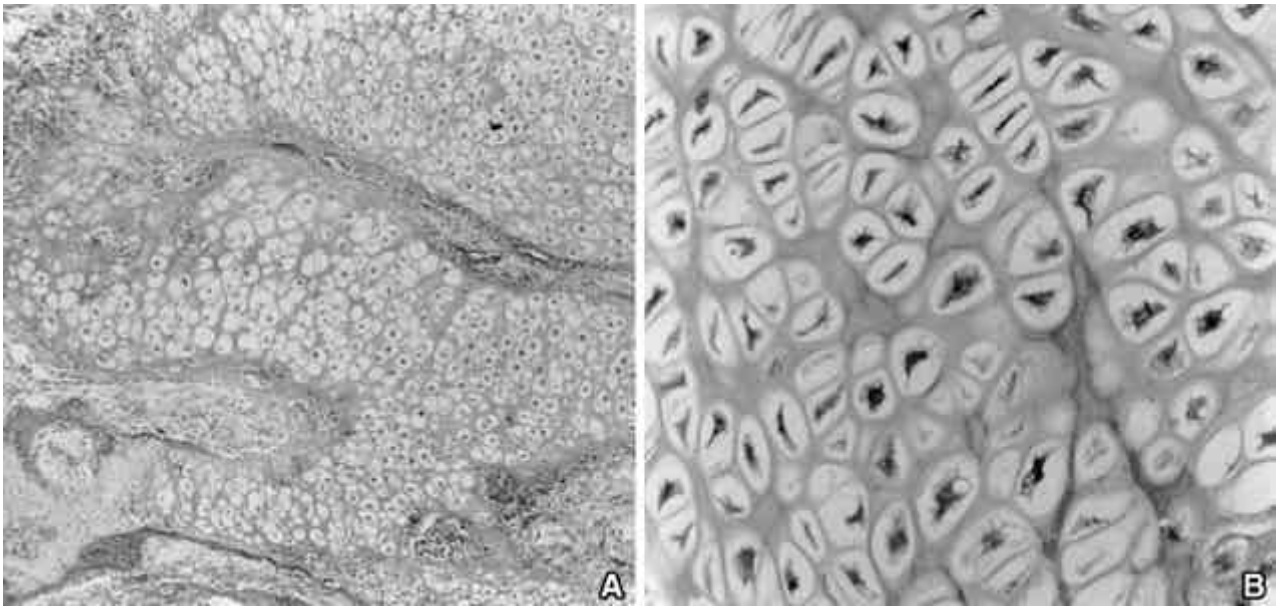

Fig. 3. Light microscopy of costochondral junction shows higher cellularity and reduced matrix (**A**, H&E, ×100). The cells and their lacunae are enlarged (**B**, H&E, ×400).

variability. Achondrogenesis type II, hypochondrogenesis and spondyloepiphyseal dysplasia congenita are placed together in the same group according to the International Classification of Osteochondrodysplasias (10). The present case belongs to mild form of achondrogenesis type II with overlapping features of hypochondrogenesis (6, 8), which supports the relevance of the current classification (Table 1).

Recent development in prenatal ultrasonography made it possible for the early detection of various skeletal dysplasias. Both types of achondrogenesis have been diagnosed prenatally by demonstrating poor limb growth as early as 15-19 weeks of gestation in cases known to be at risk because of a previously affected individual (1). Other abnormalities including polyhydramnios, subcutaneous edema, hydrops, cystic hygroma, and cleft soft palate are also helpful markers that can be detected by ultrasonography (1, 4, 5). Subcutaneous edema, polyhydramnios, and cystic hygroma, especially, are easily detected during early gestational period (1, 14) although shortness of limb is not prominent. In this case, prenatal ultrasound identified shortness of femur and nuchal edema. Other routine prenatal examination and amniocentesis for chromosome analysis were normal. No known risk factors were detected.

The common metabolic defect of achondrogenesis type II-hypochondrogenesis seems to be a lack of expression of type II collagen (11, 12). Since type II collagen is mainly found in hyaline cartilage and vitreous humour, its deficiency results in the association of spinal, epiphyseal and ocular abnormalities. Type II collagen consists of three identical polypeptide chains which are coded by the *COL2A1* gene located on chromosome 12 (7). Chromosome 12 is a putative site for a small deletion in patients with achondrogenesis type II-hypochondrogenesis (11). Another site could be the distal part of the short arm of chromosome 4, where the genes responsible for lethal osteochondrodysplasia were proposed to be clustered (13). Although no chromosome anomaly was detected in our case, the possible presence of such a small deletion cannot be excluded.

In addition to skeletal abnormalities, severe pulmonary hypoplasia was also suggested to be directly related to the underlying pathology in collagen expression (11). In severe forms, respiratory distress is seen early after birth; in some cases, despite therapy, it leads to death within the first hours or days of life. In other cases it is less severe (14). Our case revealed neither pulmonary abnormality nor other associated anomalies such as cleft soft palate and aortic hypoplasia (1). It seems that the defects

Table 1. Radiological and chondro-osseous morphological features of achondrogenesis type II and hypochondrogenesis (6, 8)

	Achondrogenesis type II	Hypochondrogenesis	The present case
Radiology			
Long bones	Short and bowed with metaphyseal flaring and cupping	Less bowed and shortened with irregular or smooth metaphyses	Had metaphyseal flaring and cupping
Spine	Variable pattern of ossified or unossified vertebral bodies and pedicles	Thoracic and upper lumbar vertebral bodies ossified, cervical and lower lumbar bodies unossified	Thoracic and upper lumbar vertebral bodies ossified, cervical and lower lumbar bodies unossified
Pelvis	Halberd-like iliac bones, with unossified ischial and pubic bones	Near normal developed iliac bones with partial ossification of ischial bones and unossified pubic bones	Unossified ischial and pubic bones
Thorax	Short and barrel or bell-shaped with short unfractured ribs	Near normal but shallow cage with short unfractured ribs	Short and barrel-shaped with unfractured ribs
FCI*	2.0-4.7	5.1-10.7	7.3
Histology			
Epiphyseal chondrocytes	Densely packed with dilated lacunae	Densely packed with dilated lacunae	Densely packed with dilated lacunae
Growth plate	Fully disorganized	Focally some columnization of chondrocytes	Fully disorganized
Bony trabeculae	Plump and disorderly arranged	Some longitudinal arrangement	Some longitudinal arrangement

*FCI: Femoral cylinder index (maximum length/midshaft width)

of collagen type II affect the skeleton more profoundly.

In summary, we report a very rare autopsy case of a mild form of achondrogenesis type II detected by prenatal ultrasound examination. The case raises the need for more careful prenatal routine examination, and also for meticulous radiologic and histologic examination during autopsy to identify fetuses affected by skeletal dysplasia in early pregnancy as the clinicopathological features may not be prominent.

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