Prenatal Sonographic Features of Fetal Atelosteogenesis Type 1

Suchaya Luewan, MD, Kornkanok Sukpan, MD, Piyarat Udomwan, MD, Theera Tongsong, MD

Atelosteogenesis is a lethal chondrodysplastic disorder characterized by severe micromelia and spinal abnormalities, including a heterogeneous group of disorders with overlapping phenotypic features.[1,2] Three subtypes have been described on the basis of radiologic and pathologic findings. Type 1 has pathologically unique giant cell chondrodysplasia. Type 2 has similar humeral and femoral bone shapes but typically has a hitchhiker thumb or toe and distinctive chondro-osseous histopathologic features caused by the diastrophic dysplasia sulfate transporter gene, whereas types 1 and 2 are caused by the filamin B gene. Type 3 has less dysmorphic facial features and well-ossified but disharmonious short tubular bones. Atelosteogenesis type 1, a synonym for spondylohumerofemoral hypoplasia, is a rare chondrodysplastic disorder caused by mutations in filamin B located at 3p14.[3,4] This gene has an important role in vertebral segmentation, joint formation, and endochondral ossification. It is characterized by severe rhizomelia with bowing of the limbs, especially the humeri, femurs, proximal and middle phalanges, and fibulas, with distal tapering and delay in ossification of vertebrae.[1,5] Other clinical hallmarks of the disorder include midface hypoplasia, micrognathia with a cleft palate, and a narrow thorax, leading to pulmonary hypoplasia and laryngeal stenosis, attributable to the lethality.[1,5,6] Histopathologic findings are hypocellular and acellular areas and occasional giant cells in the resting cartilage, similar to boomerang dysplasia.[1,5,7]

Because atelosteogenesis type 1 is usually lethal, prenatal diagnosis is desirable for proper management. To our best knowledge, only 4 cases have been prenatally diagnosed and reported in the literature.[6,8–10] Here we present the prenatal sonographic features of atelosteogenesis to add to the number of cases, which may be helpful in diagnosis when skeletal dysplasia is encountered.

Received March 25, 2009, from the Departments of Obstetrics and Gynecology (S.L., P.U., T.T.) and Pathology (K.S.), Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Revision requested April 7, 2009. Revised manuscript accepted for publication April 14, 2009.

Address correspondence to Theera Tongsong, MD, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

E-mail: ttongson@mail.med.cmu.ac.th

Case Report

A 28-year-old pregnant woman, gravida 2, para 0010, underwent antenatal care at 17 weeks' gestation. The pregnancy had been uneventful with no history of exposure to any potential teratogens. Her medical and familial histories were unremarkable. Her husband was healthy, and the couple denied consanguinity.

She received a routine second-trimester sonographic scan for fetal anomalies. Sonography revealed a fetus with appropriate biometric measurements of the head and abdomen as well as a normal amniotic fluid index, but the fetus had severe shortening of all extremities (less than the fifth percentile for the gestational week) with marked rhizomelia and an abnormal posture (Figures 1 and 2), a small chest, hypoechoic anterior bodies of the spine (Figure 3), and micrognathia (Figure 4) with a flattened nasal bone. Very poorly ossified femurs and humeri but no fractures or abnormal curvature of the long bones were shown.

On the basis of the sonographic findings, the fetus had a diagnosis of lethal skeletal dysplasia, probably atelosteogenesis type 1, Robert syndrome, or achondrogenesis, and elective termination of the pregnancy was done with misoprostol, resulting in a female abortus weighing 132 g. The general appearance showed extremely short limbs with froglike leg postures, a short trunk with a small thorax, a depressed nasal bridge, hypertelorism, micrognathia, a cleft palate, and low-set ears with subcutaneous edema (Figure 5A).

Radiographically, the skeletal system showed an unossified humerus, femur, radius, and fibula bilaterally and bilateral angulation of the ulna and tibia with shortening of the fingers (Figure 5B). There was incomplete ossification of the cervical, upper thoracic, lower lumbar, and sacral vertebrae. Postabortion radiography revealed multiple abnormalities of the long bones. The thorax was small. The spine showed mild scoliosis. The vertebral bodies were underossified, and platyspondyly of the spine was present. Histopathologic examination showed that the physeal growth zones of the ulna and tibia were moderately disorganized, and the chondrocytes in these areas were separated into groups by septa of acellular matrix. Giant chondrocytes were occasionally observed in the resting cartilage of the long bones of the upper and lower extremities (Figure 6). The final diagnosis of this case was atelosteogenesis type 1.

Discussion

Skeletal dysplasia consisting of a large number of disorders affecting the growth and development of the musculoskeletal system is often difficult to diagnose correctly with sonography diagnosis because many of these disorders have similar findings. For example, in cases of severely shortened and hypoechoic long bones, many disorders must be taken into consideration, such as thanatophoric dysplasia, achondrogenesis, Robert syndrome, diastrophic dysplasia, and rare cases of atelosteogenesis. However, thanatophoric dys-

Figure 1. Sonograms of upper limbs showing a relatively normal-size hand, an absent radius, and a very poorly ossified humerus.

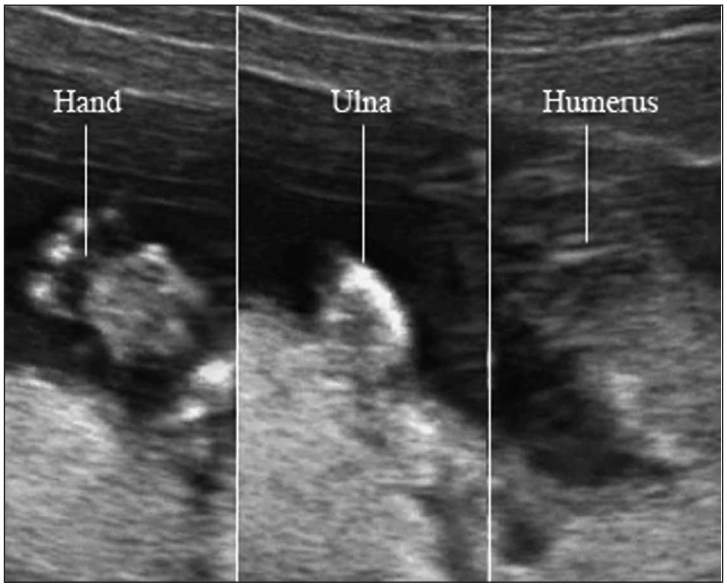
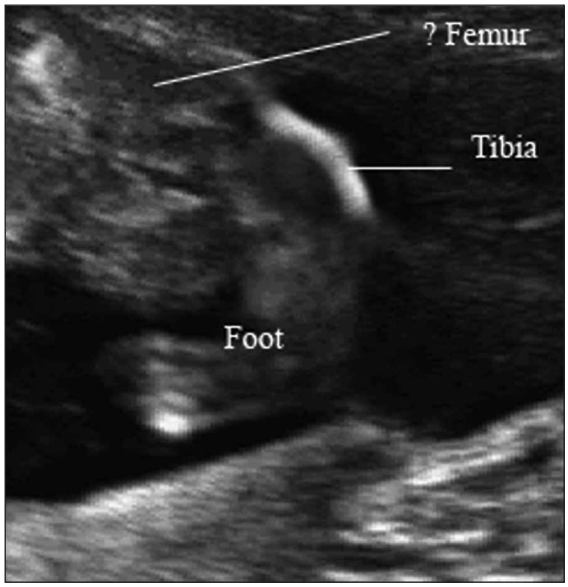


Figure 2. Sonogram of a lower limb showing a bowing tibia and an absent femur and fibula.



plasia and diastrophic dysplasia could be readily excluded because of their normal ossification. Atelosteogenesis, achondrogenesis, and Robert syndrome are very similar because all have severe short limbs, spine abnormalities, and a facial cleft. Achondrogenesis has been characterized by poor ossification of the skull and long bones as well as the spine, especially anterior bodies, as in this case. Robert syndrome is associated with tetraphocomelia in most cases, but ossification of other bones is usually normal, unlike in this case. Visualization of micrognathia, severe rhizomelia with bowing of the limbs, and a hypoechoic spine in this case was highly suggestive of atelosteogenesis.

The sonographic diagnosis in this case was mainly based on the identification of severely abnormal tubular bones, very poor ossification of anterior bodies of the spine, humeri, and radii, resulting in severe rhizomelia, and less severity in the ulnas and fibulas as well as other abnormalities, including micrognathia, a flattened nasal bridge, and a small chest.

The definite diagnosis in this case was based on both postabortion radiography and autopsy findings and was confirmed by demonstration of focal areas of hypocellularity and matrix degeneration in the growth plate and giant cell chondrodysplasia. The typical radiologic findings of this disorder comprise deficient ossification of the vertebrae, particularly the midthoracic spine, distally tapered or occasionally absent humeri and femurs, bowed radii, ulnas, and tibias, hypoplastic fibulas, and distinctly deficient ossification of the metacarpals, proximal phalanges, and middle phalanges together with short, wide, well-ossified distal phalanges.

On the basis of the sonographic findings in this case and a literature review,[6,8–10] the consistent helpful sonographic findings in fetuses with atelosteogenesis type 1 include severe limb shortening and deficient ossification of the long bones, especially the femurs, humeri, and anterior bodies of the spine. Markedly foreshortened or absent humeri and femurs and proximal flaring of the humeri and femurs, resulting in rhizomelic, in particular, or micromelic dwarfism, are strongly suggestive. Other abnormalities detectable by sonography that are helpful in the diagnosis of this disorder include a depressed

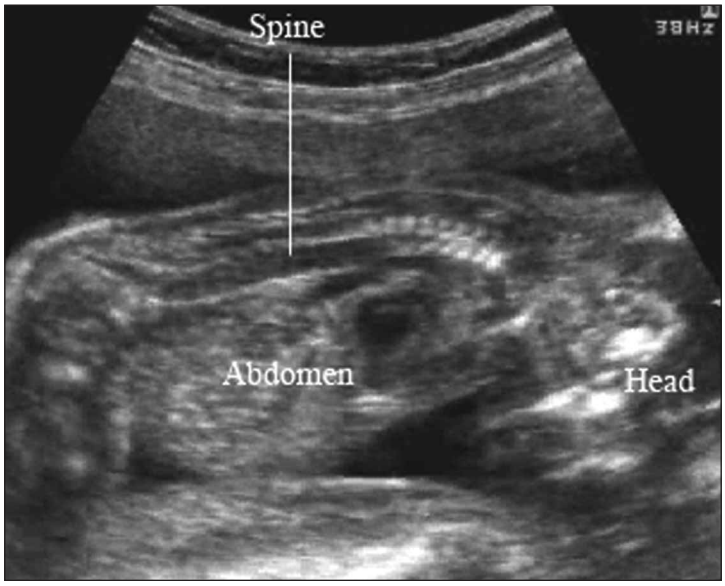
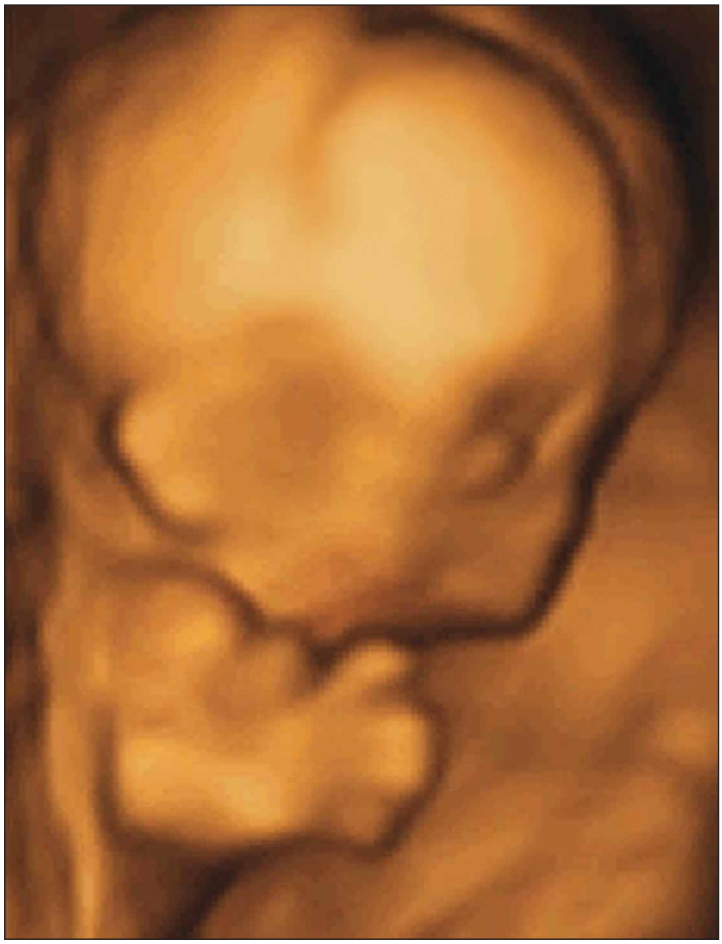


Figure 3. Sagittal sonogram of the spine showing markedly hypoechoic anterior bodies of the vertebrae.

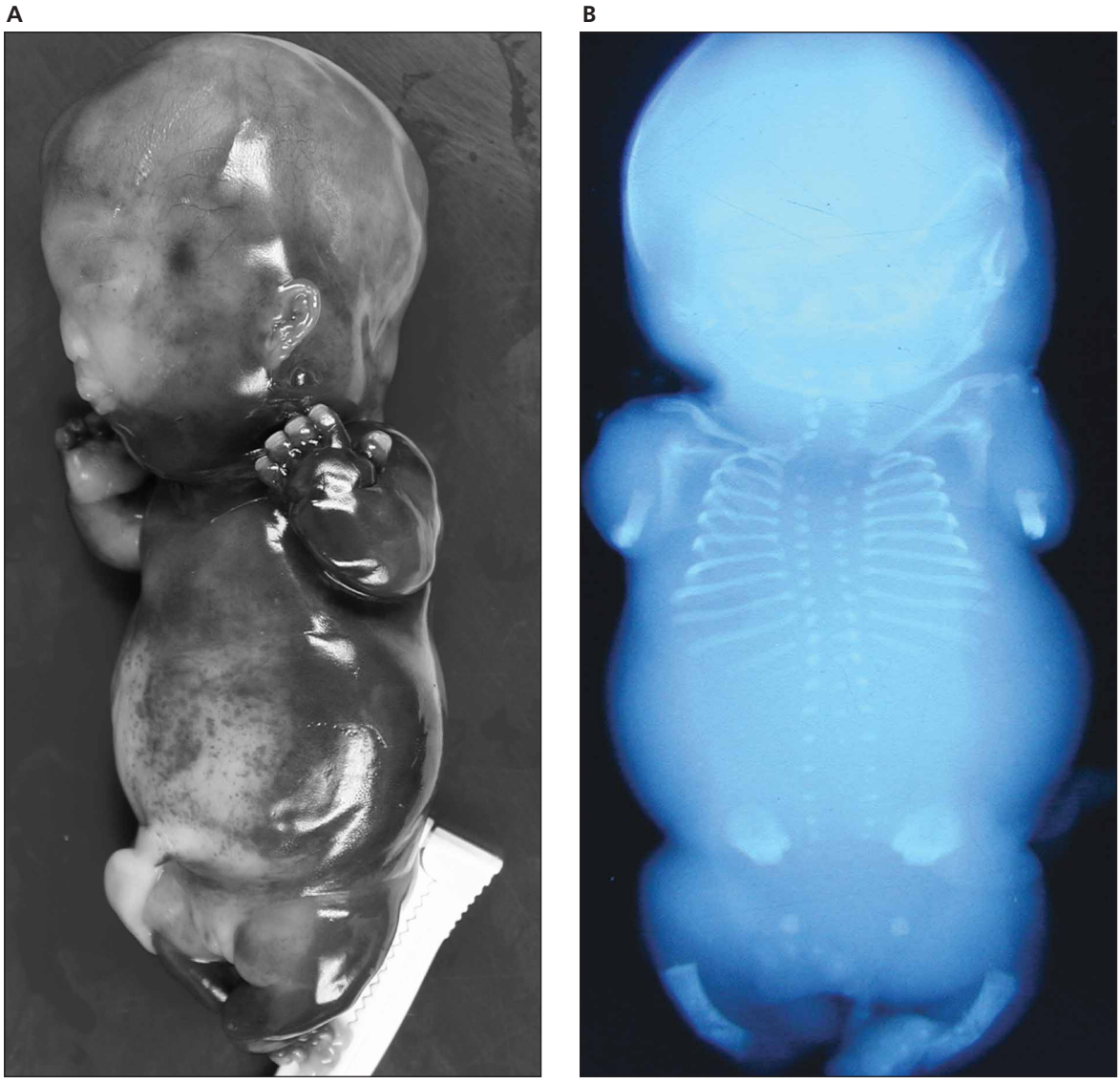
Figure 4. Three-dimensional sonogram of the fetal head showing marked micrognathia.

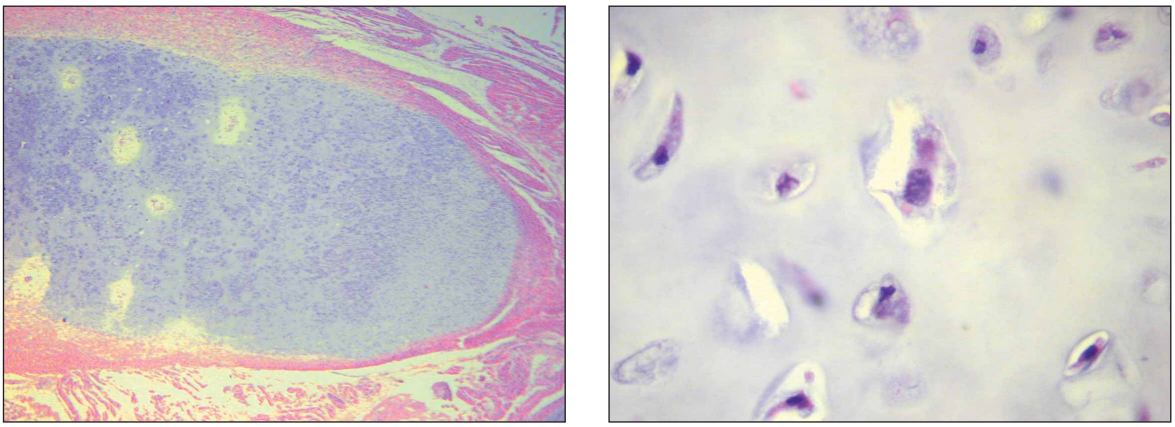


nasal bridge, hypertelorism, micrognathia, abnormal vertebral bodies, thoracic platyspondyly with coronal clefts, a narrow thoracic cage, gross shortening of all limbs, bowed radii, ulnas, and tibias, absent fibulas, clubfeet, and polyhydramnios. The major differential diagnoses include (1) other skeletal dysplasias associated with micromelia and reduced ossification, such as achondrogenesis, hypophosphatasia, and osteogenesis imperfecta, and (2) other skeletal dysplasias associated with similar limb shortening, such as camptomelic dysplasia, Ellis-van Creveld syndrome, homozygous achondroplasia, metatropic dysplasia, Robert syndrome, short rib–polydactyly syndrome, and thanatophoric dysplasia.

The typical diagnostic sonographic findings may be apparent in mid pregnancy, as in this case, or as early as 15 weeks' gestation.[6] Because of its lethal nature due to a combination of pulmonary hypoplasia and tracheobronchomalacia, correct early prenatal diagnosis of this disorder is essential for early intervention. Whereas DNA analysis and other forms of prenatal diagnosis are not widely available, sonographic examination plays an important role in early detection of this skeletal dysplasia.

Figure 5. Postabortion findings. **A**, Flattened nasal bridge, micrognathia, an apparently protuberant abdomen, and severe micromelia. **B**, Radiograph showing a narrow thoracic cage, absent bilateral humerus, femur, radius, and fibula, and incomplete calcification of the vertebrae, especially anterior bodies, with platyspondyly.





A **B**

Figure 6. Microscopic findings of a section of the ulna (hematoxylin-eosin). **A**, Hypocellular area in the physeal zone of cartilage (original magnification ×40). **B**, Chondrocyte pleomorphism with giant chondrocytes (original magnification ×270).

The pattern of inheritance for this disorder is thought to be autosomal dominant, with all cases being new mutations.[3,4] Therefore, the recurrence risk in subsequent pregnancies for this patient should be very rare.

References

1. Sillence D, Worthington S, Dixon J, Osborn R, Kozlowski K. Atelosteogenesis syndromes: a review, with comments on their pathogenesis. Pediatr Radiol 1997; 27:388–396.
2. Sillence DO, Kozlowski K, Rogers JG, Sprague PL, Cullity GJ, Osborn RA. Atelosteogenesis: evidence for heterogeneity. Pediatr Radiol 1987; 17:112–118.
3. Krakow D, Robertson SP, King LM, et al. Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. Nat Genet 2004; 36: 405–410.
4. Farrington-Rock C, Firestein MH, Bicknell LS, et al. Mutations in two regions of FLNB result in atelosteogenesis I and III. Hum Mutat 2006; 27:705–710.
5. Maroteaux P, Spranger J, Stanescu V, et al. Atelosteogenesis. Am J Med Genet 1982; 13:15–25.
6. Bejjani BA, Oberg KC, Wilkins I, et al. Prenatal ultrasonographic description and postnatal pathological findings in atelosteogenesis type 1. Am J Med Genet 1998; 79:392–395.
7. Hunter AG, Carpenter BF. Atelosteogenesis I and boomerang dysplasia: a question of nosology. Clin Genet 1991; 39:471–480.
8. Chervenak FA, Isaacson G, Rosenberg JC, Kardon NB. Antenatal diagnosis of frontal cephalocele in a fetus with atelosteogenesis. J Ultrasound Med 1986; 5:111–113.
9. Greally MT, Jewett T, Smith WL Jr, Penick GD, Williamson RA. Lethal bone dysplasia in a fetus with manifestations of atelosteogenesis I and boomerang dysplasia. Am J Med Genet 1993; 47:1086–1091.
10. Ueno K, Tanaka M, Miyakoshi K, et al. Prenatal diagnosis of atelosteogenesis type I at 21 weeks' gestation. Prenat Diagn 2002; 22:1071–1075.