NEW SYNDROME

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Ultrasound Diagnosis of Severe Mesomelic Dysplasia in Two Fetuses, Associated With Increased Neck Translucency and Tetralogy of Fallot in One and Cystic Hygroma in the Other

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Two stillborn male sibling fetuses born to the same parents had severe mesomelic dysplasia documented at ultrasound and confirmed by radiography and autopsy. The 17-week-old fetus with increased neck translucency had additional heart and great vessel anomalies consistent with tetralogy of Fallot. The 15-week-old fetus had a nuchal cystic hygroma. We posit that these sibs have a distinct, previously unreported skeletal dysplasia. The mode of genetic transmission could be autosomal recessive or X-linked recessive. © 2010 Wiley-Liss, Inc.

Key words: bone dysplasia; mesomelic dysplasia; increased neck translucency; hygroma colli; tetralogy of Fallot; lung hypoplasia

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INTRODUCTION

The mesomelic dysplasias are a group of well-recognized skeletal disorders characterized by mesomelic shortening of the extremities. Increased neck translucency (INT) and nuchal cystic hygroma (NCH) is the most frequent fetal neck pathology, and is secondary to abnormal lymphatic fluid dranage. Similar explanations have been suggested for the development of some common defects of the heart and great vessels [Tanriverdi et al., 2005]. The INT, NCH, and the tetralogy of Fallot can occur as single anomalies or in association with other malformations.

Severe fetal mesomelic dysplasia associated with INT and tetralogy of Fallot (Case 1) or NCH (Case 2) has not previously been reported.

CLINICAL REPORT

Fetus 1

The propositus was a stillborn male fetus delivered at 22–23 weeks of gestation after an induced labor. The 24-year-old mother and the 27-year-old father were healthy and unrelated. There were no previous offspring and no family history of birth defects or heritable disorders.

The pregnancy was uneventful but the routine ultrasound examination at 17 weeks, demonstrated a single fetus in breech presentation, with significant shortening of all extremities, consistent with a bone dysplasia. There was also suggestion of INT and congenital heart disease. The placenta was normal and the amniotic volume was appropriate. Amniocentesis for chromosome analysis revealed a normal 46XY karyotype.

At autopsy, the fetus was consistent with 22–23 weeks gestation with marked (50%) shortening of the forearms and the legs with manus vara bilaterally. No other phenotypic abnormalities were noted (Fig. 1A,B). The fetal weight at 275 g was more consistent with 19–20 weeks gestation, with length 20 cm and crown-buttock length 15 cm consistent with 17 weeks gestation. The head circumference at18.5 cm was consistent with 21+ weeks gestation. The heart weight was 1.46 g was consistent with 19 weeks gestation. The heart and the great vessels showed a complex malformation pattern consistent with tetralogy of Fallot. The lungs were small but microscopic

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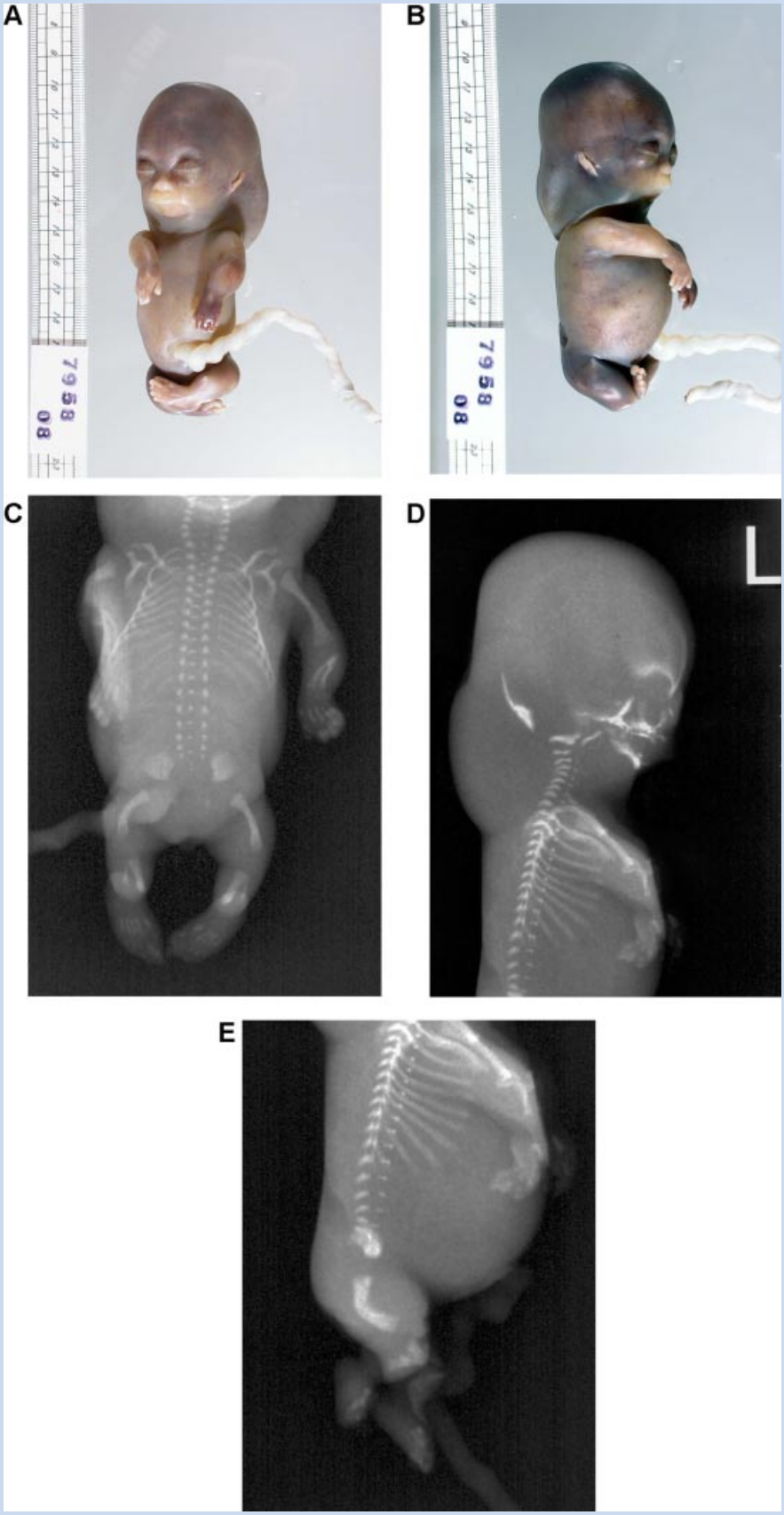

FIG. 1. Fetus 1. Mesomelic dysplasia, increased nuchal translucency, tetralogy of Fallot. A,B: Photographs of the 17-week-old fetus show short forearms and legs. C–E: Radiographs show severe hypoplastic/dysplastic forearm and leg bones with bowed femora. There is platyspondyly in the lower thoracic and the lumbar spine. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

examination showed normal fetal histology. Other organs and the placenta were unremarkable. Postmortem skeletal survey documented severe mesomelic dysplasia. Both the forearm and leg bones were hypoplastic/dysplastic but well ossified. The femora were bowed and there is platyspondyly in the lower thoracic and the lumbar spine. No other skeletal abnormality was present (Fig. 1C–E).

Fetus 2

In the subsequent pregnancy, the same mother was referred at 15 weeks gestation for ultrasound examination because of the abnormal first pregnancy (Case 1). Similar bone changes to those seen in the first fetus were documented, in association with NCH. The length of the upper extremity was 4 cm (forearm 1 cm), the length of the lower extremity 2.5 cm (legs 0.7 cm). Amniocentesis revealed a normal 46XY karyotype. A stillborn male was delivered vaginally after induced labour at 16–17 weeks gestation.

At autopsy, the NCH and marked (50%) shortening of the forearms and legs with manus vara was confirmed. The ears were low set, small, and angulated. No other phenotypic abnormalities were noted (Fig. 2A). The weight was 105 g consistent with 14–15 weeks gestation; crown heel 12.5 cm, and crown rump length 9.5 cm were consistent with 12–13 weeks gestation. The head circumference 12 cm, and thorax circumference 10 cm, were consistent with 16 weeks gestation. The neck circumference was 9.5 cm. The umbilical cord at 11 cm was short (normal for 16 weeks gestation is 16.1 cm), and inserted more laterally. The skin of the extremities was stretched and the subcutaneous edema was present. Both lungs were bilobar and very small—left 0.36 g and right 0.37 g (normal combined for 16 weeks gestation 2.5–5.5 g). Microscopic examination of the lungs showed normal fetal histology. Other organs and placenta were unremarkable. Postmortem skeletal survey showed similar changes to Case 1 (Fig. 2B).

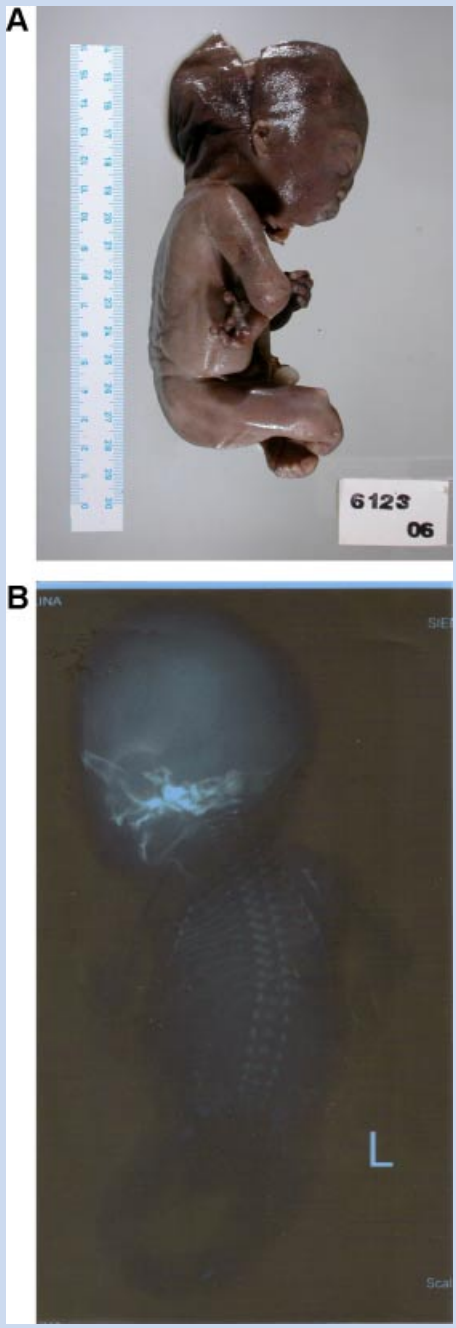

FIG. 2. Fetus 2. Mesomelic dysplasia, hygroma colli. A: Photograph of the 15-week-old fetus shows shortening of the forearms and legs, and large hygroma colli. B: Babygram shows shortening of the forearms and legs with hypoplastic/dysplastic forearm and leg bones. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

The remarkable feature present in both fetuses is the severe mesomelic dysplasia. The differential diagnosis of the severe hypoplastic/dysplastic bony abnormality of the forearms and legs is with other mesomelic dysplasias. Only the Nievergelt [Young and Wood, 1974] and Langer types [Kunze and Klemm, 1980], show such severe middle segment involvement. Rhomboid tibiae are a diagnostic radiographic feature of Nievergelt syndrome. The appearances of the forearm and leg bones of Langer dysplasia are similar to those of the fetuses, which we studied. These fetuses also had marked bowing of the femora—a feature absent in the Langer form of mesomelic dysplasia. The unique feature of this homozygous entity is that both heterozygous parents have dyschondrosteosis. The parents of our fetuses were normal, and not related, but came from the same geographical area.

In Fetus 1, there was an associated INT and heart anomaly and in Fetus 2 NCH found. Although some associations between heart defects and bony abnormalities are well recognized, such as the Holt–Oram syndrome [Basson et al., 1994] and Ellis–van Creveld syndrome [McKusick et al., 1964], no consistent pattern of bony malformation in patients with tetralogy of Fallot has been recognized. In fetuses with NCH and abnormal karyotype, limb abnormalities are more common than in fetuses whose karyotype is normal, but no constant relationship has been perceived [Trauffer et al., 1994; Tanriverdi et al., 2005]. Achondrogenesis 2 type II [Wenstrom et al., 1989] is a very severe lethal bone dysplasia in which associated NCH has been described.

No examples of severe mesomelic dysplasia with INT and tetralogy of Fallot or NCH have previously been reported. It is not known how the mesomelic abnormalities would have progressed if the pregnancies had continued, but it is unlikely that the bony changes would have stabilized or regressed.

We suggest that our cases represent a new form of mesomelic dysplasia associated with lymphatic fluid obstruction sequence—INT, NCH, tetralogy of Fallot, and hypoplastic lungs.

The mode of inheritance could be autosomal recessive or X-linked recessive.

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