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CASE REPORT

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A new type of a lethal osteochondrodysplasia with angel-shaped brachyphalangy

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Abstract A hydropic stillborn female fetus of 22 weeks' gestation with shortlimbed skeletal dysplasia and brachyphalangy is described. The markedly shortened phalanges of both hands had a most unusual angel-like configuration radiologically. Histological examination and comparison with a normal hand of the same gestational age revealed this appearance to be due to disturbed enchondral ossification with premature calcification of epiphyseal cartilage and thickening and outfolding of diaphyseal bone as wing-shaped appositions. Magnetic resonance imaging of the fetus demonstrated marked hyperplasia of cartilage, most impressive in the pelvis. This new type of lethal bone dysplasia may be placed in the group of metatropic dysplasias and similar disorders.

Key words Lethal osteochondrodysplasia
Dwarfism · Acrodysplasia · Magnetic resonance imaging · Molecular biology

Introduction

The list of osteochondrodysplasias (OCD), in particular the subdivision of the lethal types, is growing rapidly. Spranger and Maroteaux (1990) have published an updated classification. The best known and most frequent lethal lesions are achondrogenesis type I and thanatophoric dysplasia, the former published first by Parenti (1936), the latter by Maroteaux et al. (1967). The diagnosis and classification of OCD is made on radiological criteria. Particular histological findings may be helpful. In this report a particular radiological finding, the angel-shaped phalanx, has for the first time been examined by pathological-anatomical methods, thus enabling a precise correlation of radiology, magnetic resonance imaging (MRI) and morphology.

Most OCD seem to be inborn errors of metabolism. In a steadily increasing number, a metabolic defect is shown to be responsible for the disorder (Spranger 1992). The defects include mutations in the collagen genes, mainly of type I in the osteogenesis imperfecta group and type II in the spondyloepiphyseal dysplasia congenita and Kniest-Stickler dysplasia groups (Byers 1989; Lee et al. 1989; Pool et al. 1988; Tiller et al. 1990); others may be due to deficiencies in lysosomal enzymes, resulting in storage disease such as mucopolysaccharidoses (Hopwood and Morris 1990).

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Clinical history

A 20-year-old primigravida had an induced abortion at 22 weeks' gestation for sonographic findings of a hydropic fetus, which then was stillborn. The parents were unrelated.

Materials and methods

Before dissection of the body, radiographs of the entire fetus (antero-posterior and lateral) were taken. After removal of the internal organs, an examination by MRI was performed. Extensive sampling of the bones then followed. The tissue was fixed in 4% buffered formaldehyde, decalcified in 5% nitric acid and embedded in paraffin. Tinctorial stains included haematoxylin and eosin, elastin-van Gieson's, periodic acid-Schiff and alcian blue stains.

Results

Radiologically, the small disproportioned fetus presented with large head, short trunk and very short long

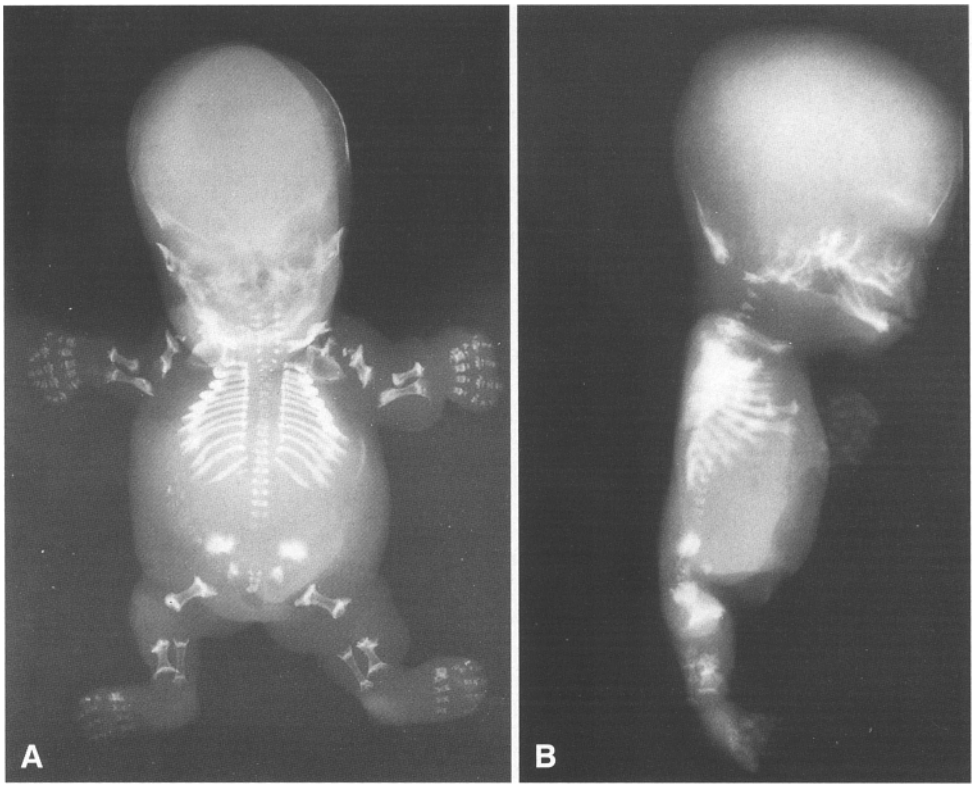

Fig. 1 Radiograph of the fetus; antero-posterior (**A**) and lateral (**B**)

bones (Fig. 1). The calvarium was slightly underossified, the mandibular angle obtuse. The calcification of the vertebral bodies in the cervical, upper thoracic, lower lumbar and sacral region was diminished or completely lacking, but the tail-like coccyx was markedly developed. The ribs were short with fork-like flaring at the anterior ends. Fractures were not seen. The ilia were diminished in height, the acetabular roof was trident, the incisura ischiadica major narrow and the ischium ossified. The long bones were shortened with flaring, partially cup-shaped and strongly calcified metaphyses. The humeral heads were calcified. The short tubular bones were markedly shortened. All metacarpal epiphyses were calcified. The phalanges were composed of a proximal and distal calcified fragment. With the exception of the thumb, calcified wing-like structures extended in symmetrical pairs laterally, originating between the two fragments of most of the basal and middle phalanges – suggesting the metaphoric term of "angel-shaped" phalanges (Fig. 2). The feet showed similar changes in the short tubular bones, without however, the angel-shaped extensions. There were calcified spots over the abdomen, presumably due to peritoneal calcifications.

At autopsy the female fetus was severely macerated, small and underweight for date in spite of fetal hydrops (body weight 117.5 g; normal 398 ± 117 g). There was micromelic shortening of both arms and legs and bilateral club feet. The hands resembled paws, the head was turricephalic with wide open fontanelles and a flat face (Fig. 3). The total body length was reduced (crown-heel length 14 cm; normal 27.4 ± 2.5 cm). Dissection of the long bones confirmed severe shortening with broadened epiphyses (Fig. 4). The cartilage was markedly hypertrophic throughout the body.

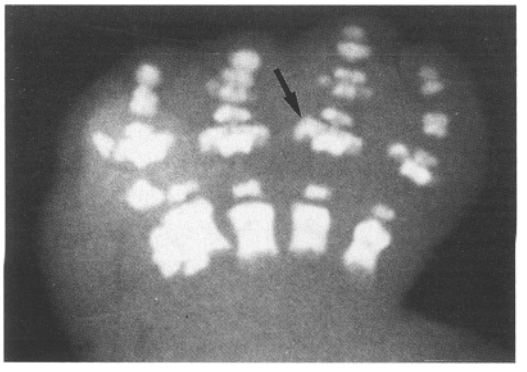

Fig. 2 Radiograph of the right hand. Basal and middle phalanges show wing-like calcified structures (*arrow*). The proximal and distal fragments of all phalanges are calcified

On MRI the hypertrophy of the cartilage of the pelvis, of the lower part of the spinal column and of the head of the right femur was clearly seen as hyperintense structures (T1-weighted MRI). A correlation between radiology, MRI and autopsy is presented in Fig. 5.

Histologically the long tubular bones showed identical histological findings. In the epiphyses and metaphyses the hypertrophic cartilage contained focal areas of necrosis, capillary growth, fibrosis and pseudocysts. No normal zones of proliferating and hypertrophic carti-

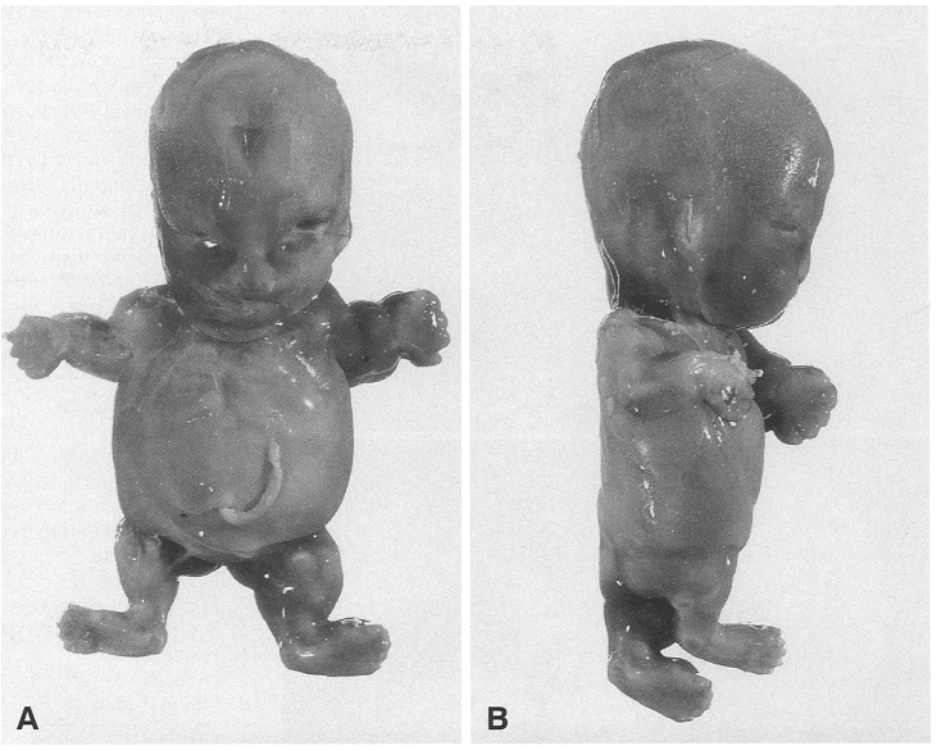

Fig. 3 Frontal (**A**) and lateral (**B**) view of the hydropic stillborn female fetus. Beside the extreme shortening of the arms and legs the left clumsy hand is very conspicuous

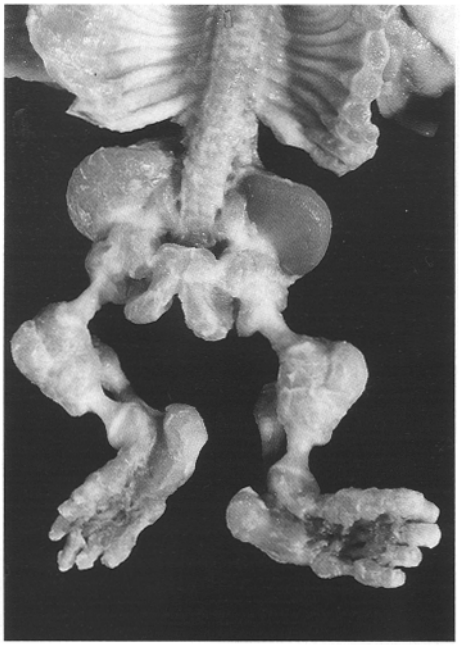

Fig. 4 The pelvis, knees and feet demonstrate hypertrophy of the cartilage

lage were present; the formation of columns was absent. There was only resting and degenerating, hypertrophic cartilage. The latter displayed band-like, cup-shaped, precocious calcification at the chondro-osseous junction (Fig. 6A, B). The primary bony trabeculae were sparse, short and thickened. Precocious calcification was also seen in the resting cartilage. The changes of disturbed enchondral ossification were minor in the ribs, metacarpal and metatarsal bones, but essentially similar to those in the long tubular bones.

The angel-shaped lesions were only present in the basal and middle phalanges of the hands (Fig. 7) and to a mild degree in the feet. These bones are extremely short. Primary bone marrow was not seen. The proximal epiphysis and the distal pseudoepiphysis also displayed precocious calcification in large areas. The calcification in the proximal epiphysis corresponded to the body and that in the distal pseudoepiphysis to the head of a little angel. The cortical bone of the diaphysis was severely shortened and extremely broadened, thus forming the wings of the angel (Fig. 8A, B).

Discussion

Lethal and non-lethal OCD are classified by radiological criteria. Spranger (1992) has recently published an updated list. The lethal OCD have recently been put in a useful nosological order by Spranger and Maroteaux (1990), consisting of 11 main groups (Table 1). Each group contains well-known entities as well as single case reports. Our patient may be placed in subgroup 7, the lethal metatropic dysplasias and similar disorders (Table 2). It is quite similar to an isolated case described as type 7.6, but there the angel-shaped phalanges are lacking.

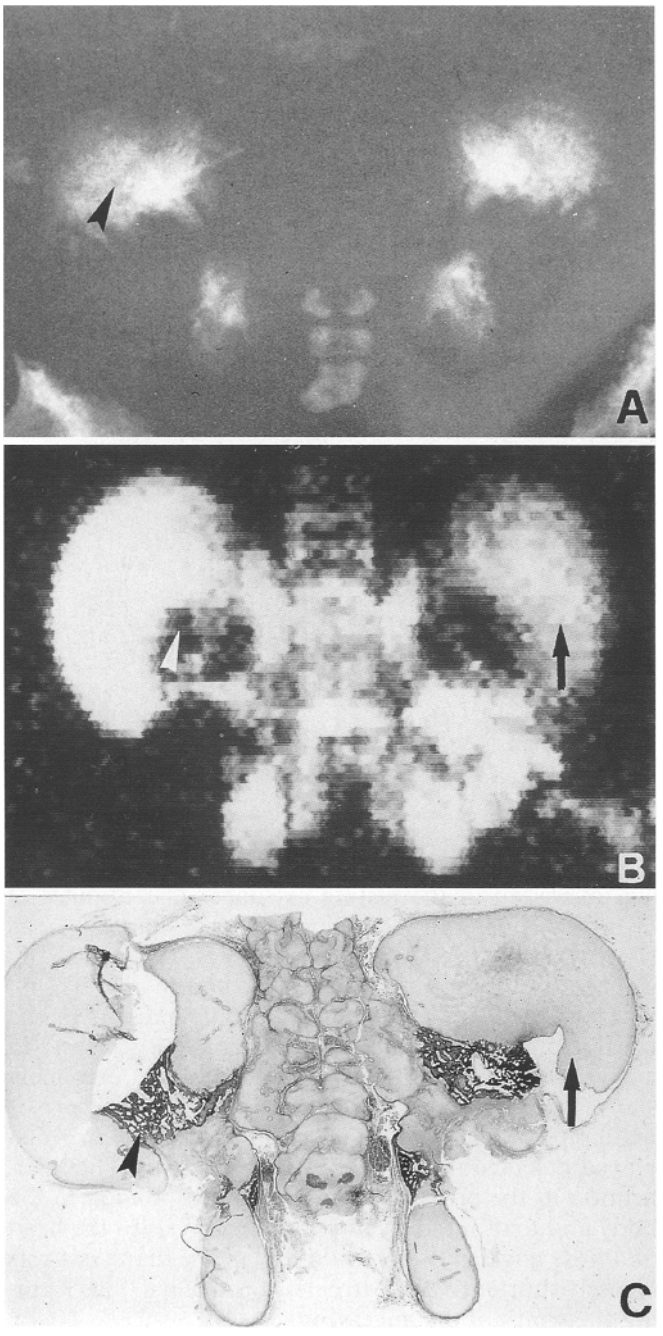

Fig. 5 Comparison between conventional radiology (**A**), magnetic resonance imaging (MRI; **B**) and histology (**C**). The correlation of the hypertrophy of the cartilage by MRI and histology is excellent. The hyperintense structures correspond to cartilage (*arrows*), the hypointense structures to primary bone (*arrow-heads*)

Stoess et al. (1991) reported a child with possible osteoglophonic dysplasia. The radiographic appearance of the basal and middle phalanges was somewhat similar to the findings of our patient and described as a Maltese cross. The other radiological findings and the histology were completely different to our patient. The enchondral ossification was normal and the process in the long tubular bones resembled fibrous dysplasia. The

Table 1 Nosology of lethal osteochondrodysplasias (Spranger and Maroteaux 1990)

1. Hypophosphatasia and morphologically similar disorders
2. Chondrodysplasia punctata and similar disorders
3. Achondrogenesis and similar disorders
4. Thanatophoric dysplasia and similar disorders
5. Platyspondylic lethal chondrodysplasias
6. Short-rib (polydactyly) syndromes
7. Lethal metatropic dysplasia and similar disorders
8. Kniest-like disorders
9. Lethal osteochondrodysplasias with pronounced diaphyseal abnormalities
10. Osteogenesis imperfecta and similar disorders
11. Lethal disorders with gracile bones

Table 2 Subgroups of lethal metatropic dysplasia and similar disorders (Spranger and Maroteaux 1990)

1. Lethal metatropic dysplasia (hyperchondrogenesis)
2. Isolated case
3. Isolated case
4. Fibrochondrogenesis
5. Schneckenbecken dysplasia
6. Isolated case
7. Isolated case
8. Isolated case

histological features of the Maltese cross (the angel-shaped lesions) were not described.

Angel-shaped phalanges as a genetic radiological bone marker of non-lethal OCD have been discussed recently by Giedion et al. (1993), who reported the autosomal dominant angel-shaped phalangoepiphyseal dysplasia.

The angel-shaped structures in our patient were restricted to the diaphyses of the basal and middle phalanges of the hands and feet. The other tubular bones, including the metacarpal and metatarsal bones, were spared. The "wings" of the "angels" correspond to massively shortened, but extremely thickened cortical bone with circular outfolding. The "head" and "body" or "skirt" of the angels, however, do not consist of bone but of a massive, irregular calcification in the proliferating and hypertrophic zones of the epiphyseal phalangeal cartilage. The shorter the tubular bone of our fetus, the less the bone marrow, but the more the precocious calcified hyaline cartilage is generally seen. The abnormality of enchondral ossification is probably most severe in the shortest tubular bones (the phalanges) where the bone marrow develops later. Because of the severe maceration, sampling of well-preserved tissue and/or material sampling for electron microscopic or molecular biological studies was not possible.

Nevertheless the autopsy and histological findings allow us to define the lesion clearly as a qualitative change in the hyaline cartilage with widely abnormal enchondral ossification, resulting in abnormal skeletal growth. Most importantly it also affects the cartilage elsewhere in the body as demonstrated in larynx, trachea and bronchi.

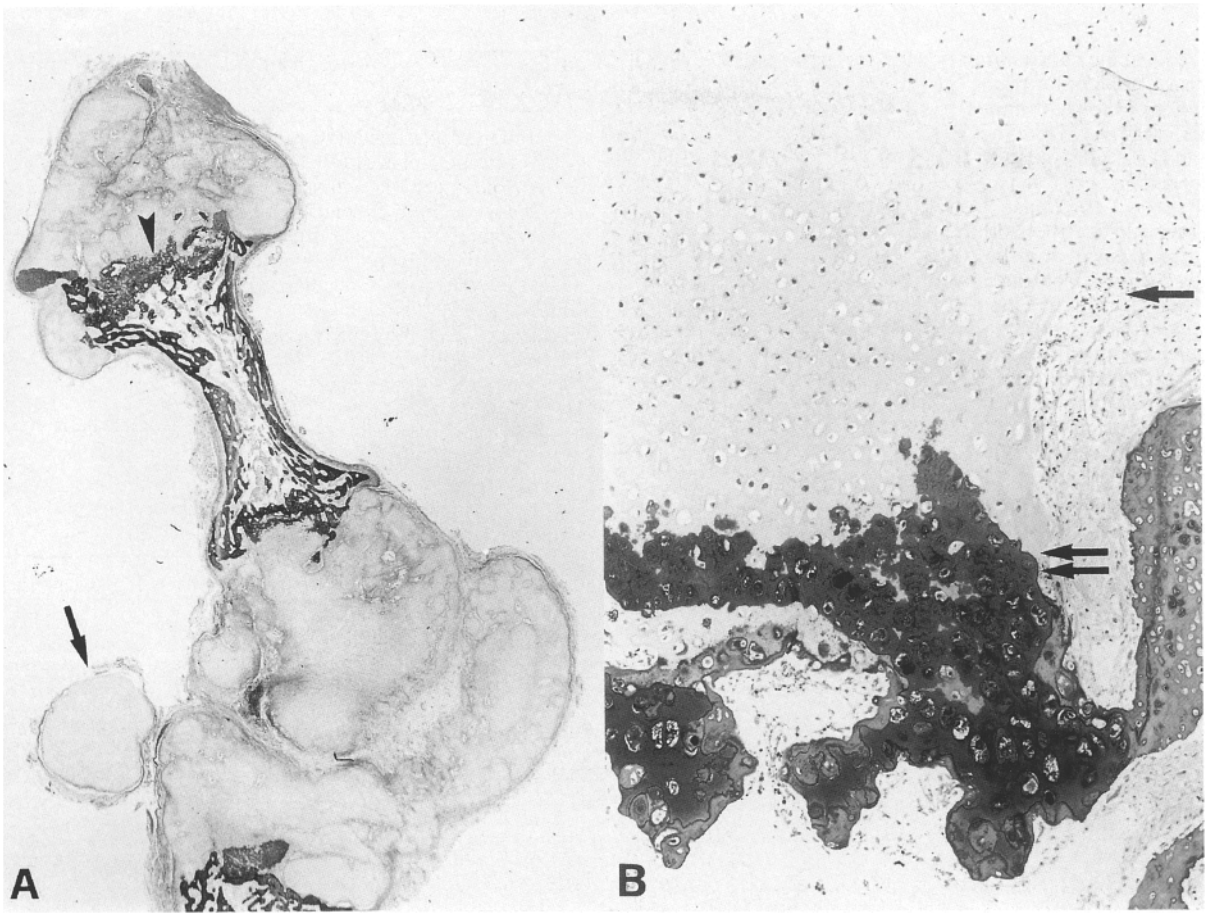

Fig. 6 **a** Entire femur with patella (*arrow*). In spite of a proliferating and hypertrophic cartilage column a broad band-like calcification is seen at the chondro-osseous junction (*arrowhead*). **b** Severely altered enchondral ossification in long tubular bones (femur). Fibrous tissue (*arrow*) dissects the zone of proliferating cartilage and a band of precocious calcification (*double arrow*) is present in the hypertrophic zone which shows no column formation. Primary bony trabeculae are irregular and short. ×80

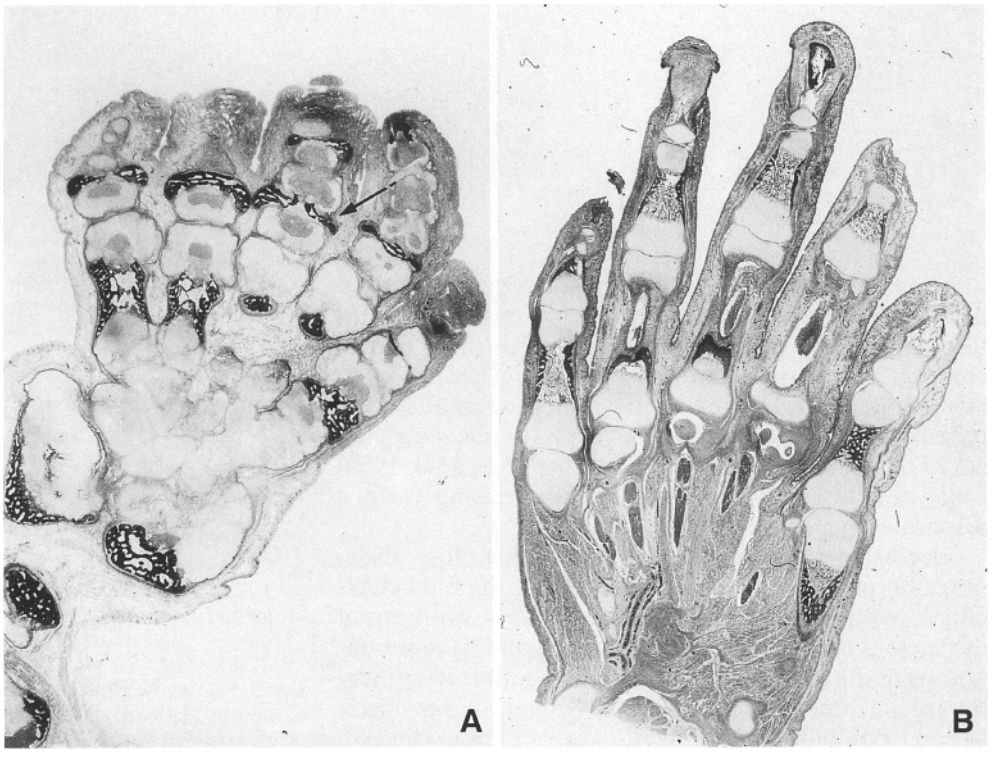

Fig. 7 **A** Abnormally developed hand with angel-shaped structures (*arrow*) at the diaphyses of the basal and middle phalanges. **B** For comparison a normal hand of a fetus with same gestational age

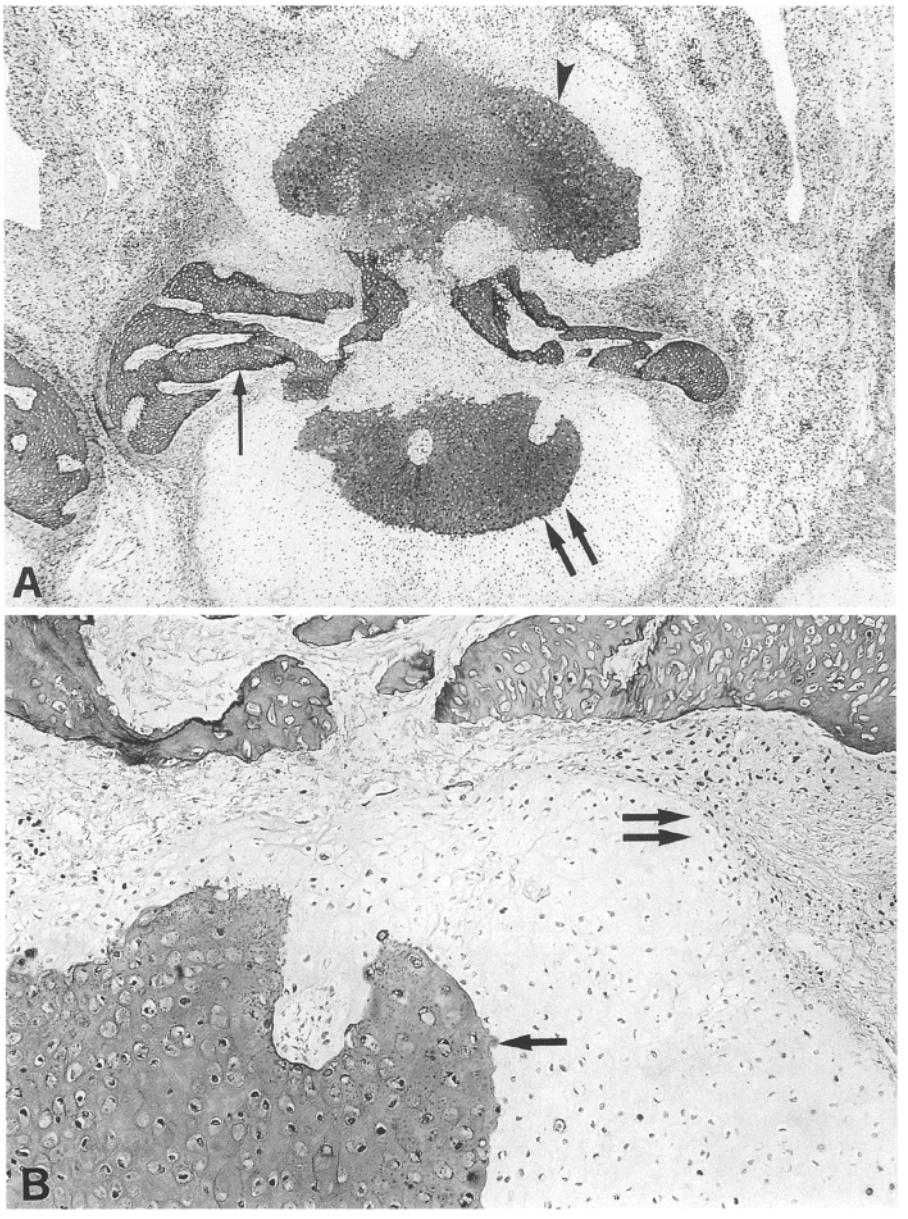

Fig. 8 **A** Extreme shortening of the basal phalanx of the third finger of the right hand. No bone marrow exists. The broadened outfolded cortical bone corresponds to the "wings" (*arrow*), the upper precocious calcification to the "head" (*arrow head*) and the lower precocious calcification to the "body" or "skirt" (*double arrow*) of the angel, ×35. **B** Higher magnification showing precocious calcification (*arrow*) of hypertrophic cartilage. Column formation is absent and there is a rim of fibrous tissue (*double arrow*) separating cartilage from cortical bone. ×125

Even though OCD are a highly heterogeneous group of disorders, many defects may be the result of mutations affecting the structural integrity of cartilage matrix components or the regulatory pathways of chondrogenesis (Rimoin and Lachmann 1983). Some recent studies refer to alterations in type I and type II collagen genes, i.e. COL1A1 and COL2A1 (Byers 1989; Lee et al. 1989; Tiller et al. 1990; Vissing et al. 1989), causing various disparate phenotypes.

The exact clinical, radiological and histological description of an OCD is still the basis for the final elucidation by the detection of aberrations in the synthesis of the various components of the skeleton and its representations in the genome. Hopefully, the possible identification of a distinct bone marker, the "angel" in our observation, is helpful in this direction.

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