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Bone growth, modeling and remodeling in a supernumerary metatarsal bone associated with segmental gigantism in cutis marmorata telangiectatica congenita

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Summary. Skeletal structure and processes of bone growth, modeling and remodeling were studied in a supernumerary metatarsal surgically removed from a 3-year-old boy affected by Cutis Marmorata Telangiectatica Congenita (CMTC), associated with hypertrophy of the right upper and lower limbs and postaxial hexadactylism of the homolateral hand and foot. No other anomalies were observed. The excess of periosteal growth, due to congenital anomaly, induced an abnormal development of both modeling and remodeling processes. In bone modeling, osteoblast activity on the periosteal surface was not paralleled by osteoclast resorption along the wall of the medullary canal, and this enormously increased the cortical thickness. In bone remodeling, osteoclastic resorption cavities were not refilled by secondary Haversian systems, thus inducing a severe bone loss. While the alteration of bone growth and modeling can be ascribed to the congenital disease, the unbalanced bone remodeling appears mainly to depend on mechanical disuse of the supernumerary metatarsal.

Key words: Supernumerary metatarsal, Bone growth, Bone modeling, Bone remodeling, Cutis marmorata telangiectatica congenita

Introduction

Cutis marmorata telangiectatica congenita (CMTC), a congenital vascular anomaly described for the first time by Van Lohuizen in 1922, is characterized by persistent cutis marmorata, telangiectasia and phlebectasia with occasional atrophy and ulcerations of the involved skin. The cutaneous phenomenon may be diffused to one or both sides of the body, or localized to circumscribed areas (Moore et al., 1997; Amitai et al., 2000; Gerritsen et al., 2000). The course of the disease is generally benign and the appearance of the skin tends to improve with age (Moore et al., 1997; Amitai et al., 2000; Gerritsen et al., 2000). Vascular anomalies and body asymmetry are so frequent that they can be considered as part of the expression of the CMTC itself (Amitai et al., 2000). Body aymmetry is characterized by either hyperplasia or hypoplasia of upper and/or lower limbs (Moore et al., 1997; Amitai et al., 2000; Gerritsen et al., 2000).

Polydactyly appears to be a very rare event in CMTC-associated segmental gigantism. To our knowledge very few cases have been reported in the literature (Franceschini et al., 2000; Yano and Watanabe, 2001). Because of such uncommon association of CMTC with polydactyly and considering that no microscopical analyses have so far been performed in the skeleton of such supernumerary digits, this paper, besides providing a brief description of a case of CMTC, mainly refers to the bone structure and processes of growth, modeling and remodeling in a post-axial hexadactyly metatarsal bone surgically removed from the right foot of a young boy affected by CMTC.

Materials and methods

The supernumerary metatarsal bone soon after surgical excision was cleaned from the surrounding soft tissues and processed for light microscopy, polarized light and microradiography analyses, and for transmission electron microscopy observations.

Light microscopy (LM), Polarized light microscopy (PLM), Microradiography (MR)

Undecalcified cross sections 2 mm thick, cut with a

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saw from various levels of the shaft, were ground to a uniform thickness (50 μm) and perfectly polished. Microradiographs were made with an Italstructures Microradiograph (1.7 Kw, 18 mA). Analyses were performed by light microscope under transmitted light and polarized light on unstained sections and their microradiographs.

Transmission electron microscope (TEM)

Undecalcified cross-sections 2 mm thick, cut with an indented blade from the mid-diaphyseal level of the supernumerary metatarsal bone, were fixed with 4% paraformaldehyde (0.1 M cacodylate buffer, pH 7.4) for 2 hours, postfixed with 1% osmium tetroxide (0.1 M cacodylate buffer), dehydrated in graded ethanol, and embedded in epoxy resin (Durcupan ACM). To better visualize ultrastructural cellular details, some specimens were decalcified in EDTA 4% (0.1 cacodylate buffer). The specimens were sectioned with a diamond knife mounted in an Ultracut-Reichert microtome. Ultrathin sections (70-80nm) were mounted on Formvar-coated and carbon-coated copper grids, stained with 1% uranylacetate and lead citrate, and examined under TEM (Zeiss EM 109).

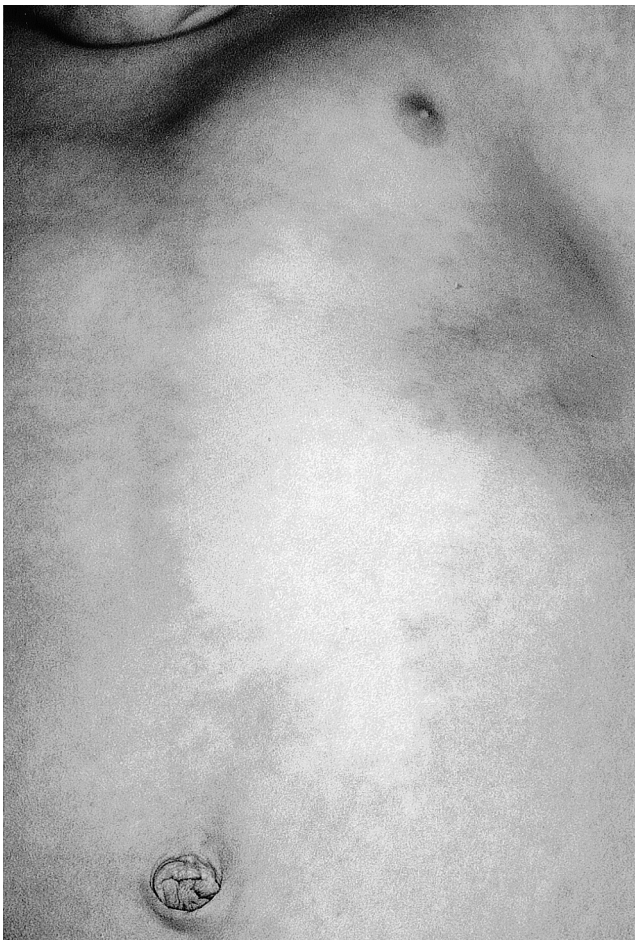

Fig. 1. Diffuse cutaneous telangiectasia of the trunk at age 3 years.

Results

Case report

The following description refers to a boy, affected by CMTC, who was born at full term by Cesarean section for cephalopelvic disproportion following a physiologic pregnancy from healthy nonconsanguineous Caucasian parents. There was no family history of congenital or vascular anomalies, nor was there any evidence of exogenous factors during pregnancy.

At birth his weight was 4.880 Kg (>97th percentile), height 59 cm (>97th percentile) and head circumference 39 cm (>97th percentile). The skin showed deep purple reticular appearance with diffuse angiomatosis on the right side of the body and on the face. The skin of the left side was involved only in some areas of the trunk and limbs. Hypertrophy of the right upper and lower limbs with post-axial hexadactylism of both right foot and hand were also observed. The post-axial hexadactylism of the right hand was constituted of only soft tissue and was removed soon after birth through ligation. The genitals were male (karyotype = 46 XY), with cryptorchidism and hydrocele of the right testis. Tongue and jaws were normal.

At age 3 years, physical examination showed persistent cutis marmorata that gradually faded with time, leaving a pale pink diffused and in some areas reticular pattern (Fig. 1). Height and weight were between the 90th and 97th percentile. Hypertrophy of the right upper and lower limbs persisted and, on radiological examination, the disproportions in length between the right and left limbs, observed at 2 mo, were increased (right upper +1.5 cm, right lower +2 cm) and the soft tissues of the right lower limb still showed a considerable hypertrophy with respect to the contralateral side (Fig. 2). Magnetic resonance imaging (MRI) of the abdomen and lower limbs confirmed hypertrophy of the soft and bone tissues on the right lower limb and revealed that the diameter of the right iliac artery was enlarged. Abdomen echogram and total-body computed tomography (CT) showed no dimensional or structural malformations of the internal organs. Echo-doppler examinations of the lower and upper limbs showed normal vessel patency and blood flow speed, and no signs of arteriovenous fistulas up to age of 3 years.

At 3 years of age, the post-axial hexadactyly metatarsal bone of the right foot was surgically removed (Fig. 3) for both psychological and functional reasons and the parents of the boy authorized the histopathological study of the excised supernumerary bone.

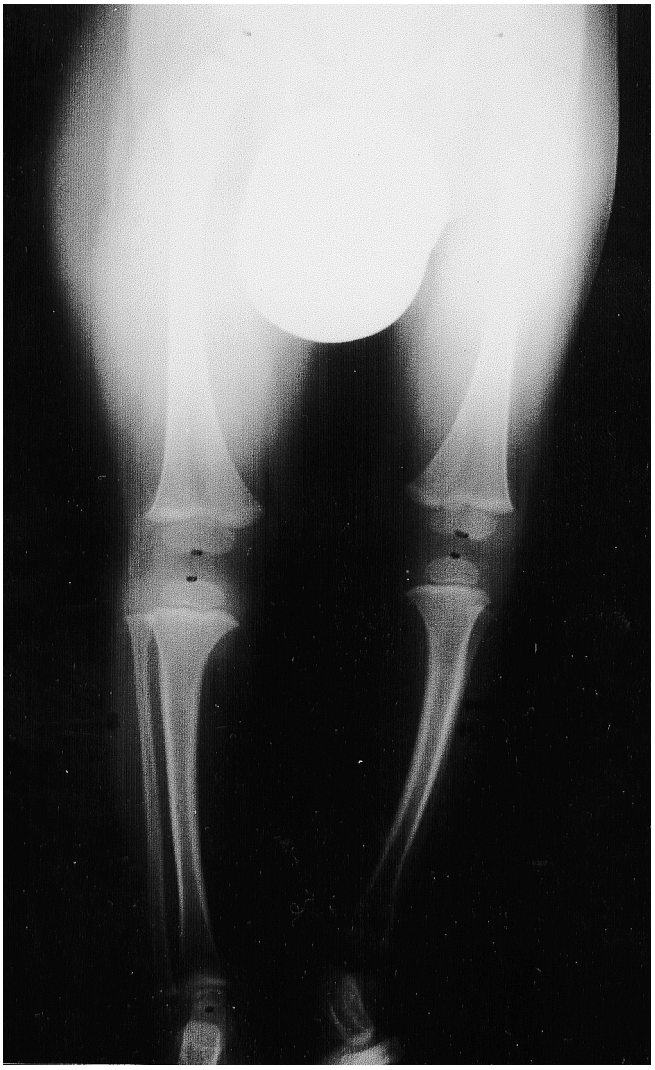

Fig. 2. X-ray of lower limbs at age 3 years showing the increased length of the right femur and tibia as compared with that of the opposite limb. Also note the remarkable hypertrophy of soft tissues in the right tight.

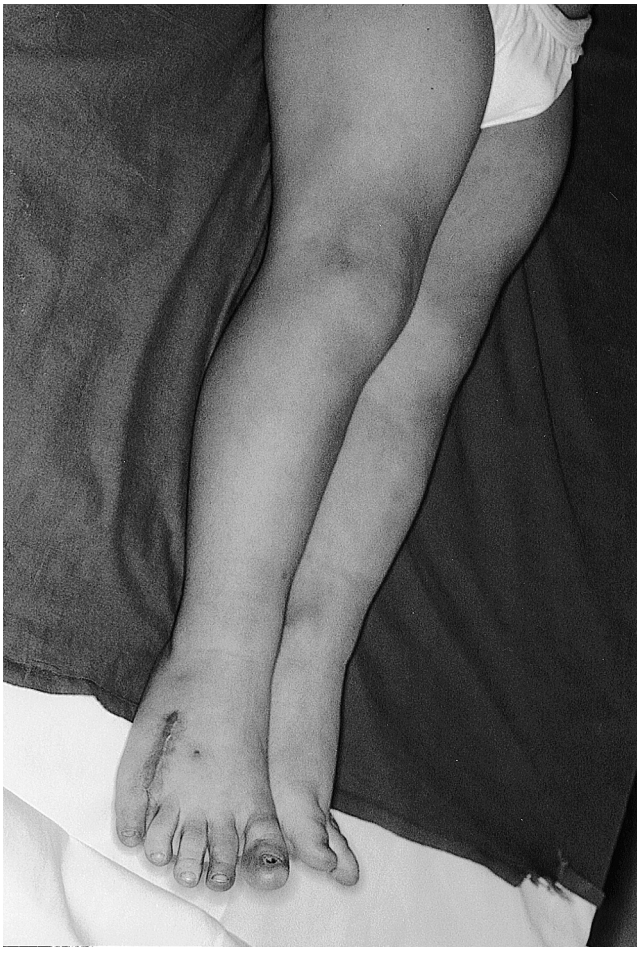

Fig. 3. The right foot after the surgical excision of the postaxial hexadactyly metatarsal bone.

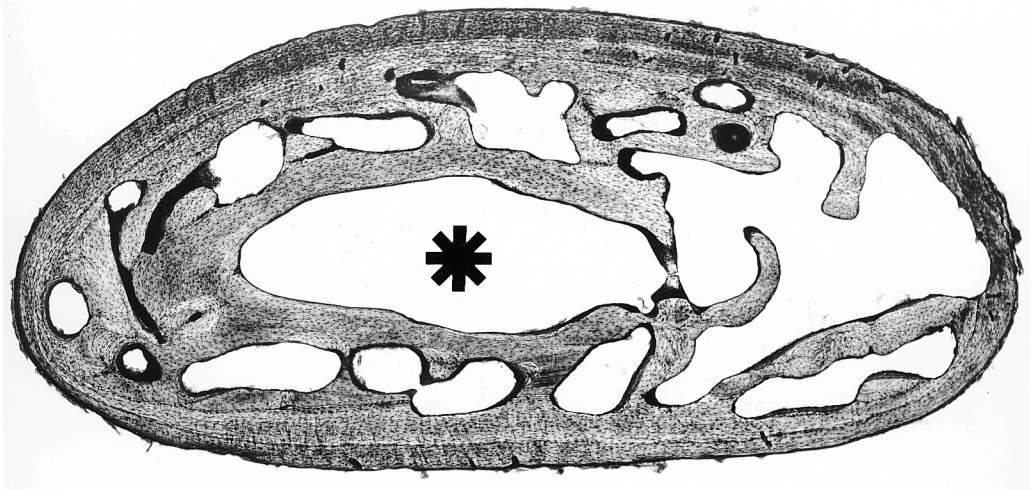

Fig. 4. . LM micrograph of a cross-section at the mid-diaphyseal level of the supernumerary metatarsal bone. The narrow medullary canal (asterisk) displays a smooth surface, indicating that no osteoclastic resorption occurs along its wall. Abnormally enhanced osteoclastic activity occurs inside the cortex with the formation of uniformly distributed enormous cavities which impart compact bone a spongy architecture. x 23

Bone histopathology

Analyses of cross sections through the cortex of the diaphysis of the supernumerary metatarsal bone showed the existence of several resorption cavities, which imparts cortical bone an abnormal trabecular-like architecture. Such resorption cavities have an exceptional enormous size and appear rather uniformly

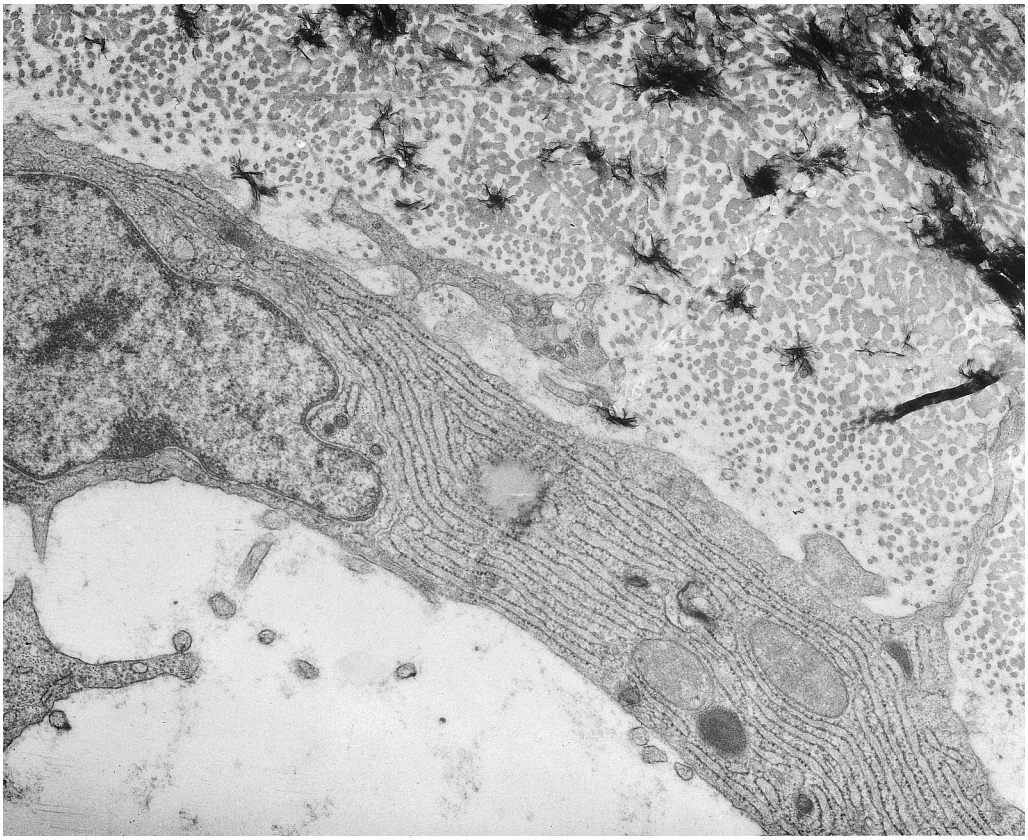

Fig. 5. TEM micrograph of a very active osteoblast (note the abundant rough endoplasmic reticulum) in the inner layer of the periosteum. x 24,000

Fig. 6. PLM micrograph of part of the cross section in Fig. 4 showing the woven-fibered texture of periosteal bone (arrows). x 45

distributed throughout the cortex (Fig. 4). An intense bone apposition was found to occur along the periosteal surface, accounting for the external hypertrophy of the shaft; accordingly very active osteoblastic laminae were observed by TEM in the inner layer of the periosteum (Fig. 5). As shown by PLM, such periosteal primary bone has a typical woven texture (Fig. 6).

Notwithstanding the larger external size of the supernumerary metatarsal and its osteopenic appearance, the overall thickness of its cortex appears greater than normal because of the small calibre of the medullary canal. In fact no signs of bone resorption were found along the surface of the medullary canal, as also shown by its smooth profile (Fig. 4). On the contrary osteoclastic bone resorption appeared to be very active inside the cortex, where several active osteoclasts within the abnormally large resorption cavities were observed by TEM (Fig. 7). The indented profile of these resorption cavities indicates they are still enlarging and, in fact, neither osteoblasts nor osteoid seams were found along their surface. Secondary osteons (Fig. 8) as the result of bone formation inside resorption cavities are very rare.

Microradiographic analysis showed a normal pattern of bone mineralization: as usual periosteal primary woven-bone appeared to be less radiotransparent, thus more mineralized, than the areas of secondary lamellar bone (Fig. 8B).

Discussion

CMTC is a rare congenital disorder marking the skin with a typical reticular pattern similar to the physiologic functional cutis marmorata but, in CMTC, the vessel ectasia does not depend upon environmental influences such as temperature (Moore et al., 1997; Amitai et al., 2000; Gerritsen et al., 2000). In most cases, the skin pattern fades with age (Moore et al., 1997; Amitai et al.,

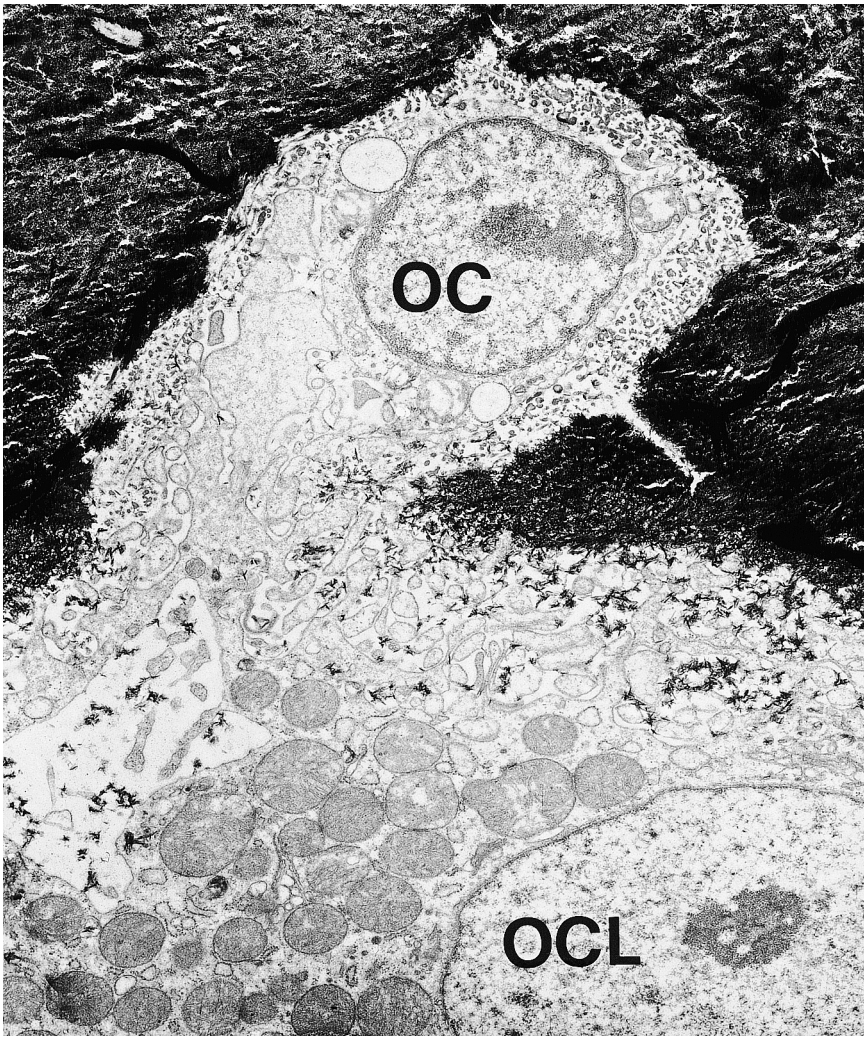

Fig. 7. TEM micrograph of an osteoclast (OCL) inside a resorption cavity of the cortex. An osteocyte (OC) is going to be destroyed by the osteoclast. x 14, 000

2000; Gerritsen et al., 2000). The boy who came to our observation showed the typical cutaneous signs of CMTC. The reticular, deep-purple pattern of cutis marmorata, present during the first months of life, was replaced by a more homogeneous pale pink appearance that progressively faded during the 3 years of life.

Several anomalies associated with CMTC have been reported, among which body asymmetry either as hypertrophy or hypotrophy is quite common (Amitai et al., 2000; Gerritsen et al., 2000). Polydactyly appears to be a rare associated anomaly: only few cases have been reported so far, always combined with macrocephaly (Franceschini et al., 2000). Our case was affected since birth by segmental gigantism of the upper and lower limbs of the right side, involving hypertrophy mainly of soft tissues but also of skeletal segments, with postaxial hexadactyly of both right hand and foot. No other anomalies were observed.

The main target of the present investigation was to provide original findings about bone growth, modeling and remodeling in supernumerary skeletal segments. Several cases of polydactyly have been reported in the

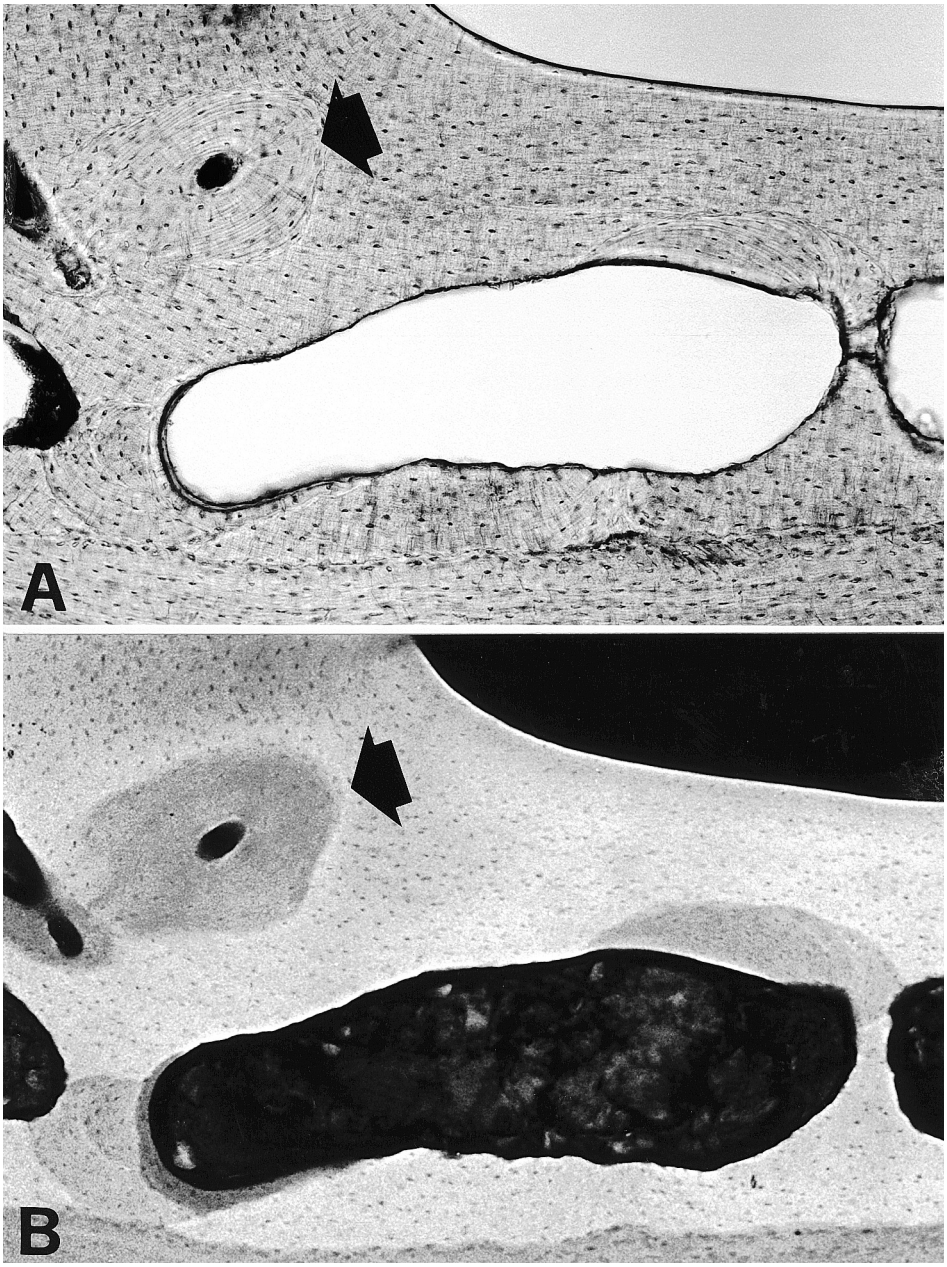

Fig. 8. LM **(A)** and MR **(B)** micrographs of a secondary lamellar osteon (arrows). Note in B, the less radiotransparency of the osteon as compared with the surrounding woven primary bone. x 100

literature and associated with different congenital anomalies, but, to our knowledge, microscopic structure and ultrastructure of bone in such supernumerary digits were never analyzed.

During somatic growth, skeletal segments increase in size and simultaneously undergo two main processes: bone modeling and bone remodeling. Long bones elongate mainly by extension of endochondral ossification into the epiphyseal cartilages, whereas their outer circumference increases at the shaft level by periosteal bone apposition; only the latter bone growth was taken into account in the diaphysis of the supernumerary metatarsal here investigated.

As generally admitted, bone modeling at the shaft level implies that periosteal bone is added externally and eroded internally; by this mechanism the shaft expand in transverse diameter and, at the same time, the medullary canal enlarges. But such simultaneous processes of periosteal bone formation and endosteal bone resorption did not take place at the shaft level of the supernumerary metatarsal. The former process (i.e., periosteal bone apposition) resulted in being more intense than normal; this fact, also evidenced by magnetic resonance, appears to be in line with the hypertrophy of the right lower limb, and thus might be ascribed to the congenital anomaly (CMTC). The latter process (i.e., endosteal bone resorption) did not occur at all according to our microscopic observation, at least at the time of the surgical excision. As a consequence, the cortex of the supernumerary metatarsal was found to be incomparably thicker than normal. This fact, too, appears to be in line with the limb hypertrophy.

Also the process of bone remodeling - i.e., the formation of osteoclastic resorption cavities followed by their refilling with secondary Haversian systems (osteons) laid down by osteoblasts – was found to be unbalanced. In fact, the first stage of bone remodeling (i.e. bone resorption) not only took place in an abnormal overwhelming manner but was not followed by osteon deposition. As a result, the cortex of the supernumerary metatarsal achieved a trabecular osteoporotic microarchitecture. The uniform distribution of resorption cavities throughout the cortex is pathognomonic of bone unloading, i.e. disuse osteoporosis. Clinical evidences and experimental studies showed that bone resorption takes place according to a pattern which differs in disuse osteoporosis from biochemical and other osteoporoses: in the former, bone resorption occurs uniformly throughout the skeletal segments (Lozupone and Favia, 1982; Bagi and Miller, 1994), in the latter bone resorption was found to occur in the central part of long bones (Lozupone and Favia, 1988; Bagi and Miller, 1994), namely in the region less subjected to mechanical loading. It has been rightly argued that such different patterns of bone resorption are mainly dictated by mechanical loads; they also provide a further demonstration of the precise mechanism by which bone cells regulate skeletal homeostasis, namely the adaptation of bone mass and structure to actual mechanical demands [see also the Mechanostat Setpoint Theory and the Utah Paradigm (Frost, 1987, 2000, 2001; Jee, 2000).

In conclusion, the present structural and ultrastructural investigation shows that both processes of bone modeling and bone remodeling took place in an abnormal manner in the supernumerary metatarsus. In bone modeling osteoblast activity on the periosteal surface was not paralleled by osteoclast resorption along the wall of the medullary canal, whereas in bone remodeling osteoclastic resorption was not followed by osteon formation. However of these two processes only the impairment of bone modeling can be ascribed to the congenital disease, whereas the alteration of bone remodeling, which determined a high degree of bone loss, seems mainly to depend on the fact that the supernumerary metatarsal was under a partial unloading condition. In other words, because of the impaired bone modeling the bone mass of the cortex of the supernumerary metatarsal not only would have exceeded physiological mechanical demands even if it were located in a normal foot but, in addition, it likely was partially unloaded owing to its supernumerary anatomical condition. Thus skeletal homeostasis seems to have followed a normal course in the supernumerary metatarsal.

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