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An Unusual Case of Metaphyseal Chondrodysplasia with an Abnormal Perilacunar Matrix Associated with Agranulocytosis and Hypoplasia of the Thymus

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Summary. We report herein an unusual skeletal dysplasia in a 6-month-old boy characterized by metaphyseal dysplasia associated with agranulocytosis and hypoplasia of the thymus. A radiological survey revealed generalized metaphyseal abnormalities showing widening and increased density. Pathological changes in the chondro-osseous tissues were unusual and distinctive. There was widespread evidence of abnormal chondrocytes with an abnormal perilacunar matrix containing a PAS-positive, diastase resistant substance. Chondrocyte maturation and regular columnar arrangement were absent in most growth plates with only scattered ball-like nests of chondrocytes showing incomplete maturation. This case is a newly described form of osteochondrodysplasia.

Key words: Bone disease, developmental – Dwarfism – Metaphyseal chondrodysplasia – Agranulocytosis – Hypoplasia of the thymus

Introduction

Skeletal dysplasias are a heterogenous group of disorders in which over eighty distinct types have been distinguished (Rimoin 1978). Further heterogeneity has been documented (Horton et al. 1979), and other conditions remain to be delineated and classified. Pathological changes may be characteristic and pathognomonic in some and in others the clinical, genetic or radiologic findings may be diagnostic without characteristic morphological changes.

We describe herein findings of metaphyseal chondrodysplasia related to unusual and distinctive pathological changes associated with agranulocytosis and hypoplasia of the thymus.

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Case Report

Clinical History

A 6-month-old Japanese boy was born following a 39-week gestation period and a spontaneous delivery. He weighed 2,400 g and was the only child of healthy parents. There was no history of dwarfism or other skeletal abnormalities in the family. The mother had not been exposed to potential teratogenic agents. At the age of 4 days, his body length was 42.0 cm (normal, 50.2 cm for age), weight 2.18 kg (normal, 3.2 kg for age), chest circumference 30.0 cm (normal, 32.8 cm for age), and head circumference 31.0 cm (normal, 32.5 cm for age). He had coarse Hurler's syndrome-like features (broad forehead, flat nasal bridge, broad nasal tip with wide nostrils, heavy eyebrows, large and patulous lips, large tongue, and micrognathia), short neck, stiff joints with claw-hand deformity, thoracic deformity, widely spaced nipples, short extremities, and hepatosplenomegaly (Fig. 1).

A radiological survey revealed generalized abnormality of metaphyseal ends which were widened and slightly irregular with increased density (Figs. 2–4). The long bones were generally short and the femora were dumbbell-shaped (Fig. 3). The metacarpals and phalanges were also generally wide and short (Fig. 4). The iliac wings were shortened longitudinally with small iliac and acetabular angles. The distance between the acetabular roofs and the upper ends of the femora was reduced suggesting dysplastic femoral epiphyses. Interestingly, small ossification centers of the tuberosity of the ischium were evident at the age of 1 month, and the rami of the pubis and ischium were already fused irregularly at the age of 4 months. The vertebral bodies appeared slightly shortened in their vertical height, particularly in the thoracic region. The thorax was short with transverse ribs and narrowed intercostal spaces (Fig. 2). The costochondral junctions were widened and cupped. The size and shape of the skull appeared normal. A thymic shadow was not evident on chest roentgenogram.

Laboratory examinations revealed: haemoglobin level 17.5 g/100 ml, total leukocyte count 1,800/mm^3 with 5% neutrophils, 9% lymphocytes, 82% monocytes, 2% eosinophils, and 1% basophils. Myelogram showed the myeloid-erythroid ratio to be 4.2/1, and there was a marked left shift (so-called maturation arrest). Colony formation in the in vitro bone marrow culture was markedly reduced. Lymphocyte surface markers revealed an E-rosette formation of 58%, while the EAC formation was 45%. The serum calcium level was 4.8 mEq/l and alkaline phosphatase was 5.9 Bodansky units. Serum immunoglobulin levels were IgG 960 mg/100 ml, IgA 0 mg/100 ml, and IgM 5 mg/100 ml. Duodenal aspiration showed the trypsin and lipase activities to be normal. Karyotypic analysis revealed 46 chromosomes with long Y. The baby died at the age of 6 months following aspiration pneumonia.

Results

Autopsy Findings (Autopsy Number, 1117)

The body was that of a 6-month-old male infant. The height was 60 cm (under 3 percentile) and the weight 6.5 kg (under 3 percentile). Gross, visible abnormalities were as described in the clinical history.

Grossly, chondro-osseous tissues were unremarkable and had a normal consistency. Representative specimens containing endochondral growth plate and resting cartilage from a long tubular bone (femur), flat bones (ribs, sternum, and ilium), cuboidal bone (vertebrae), and cartilages (larynx, epiglottis, trachea, and bronchi) were studied. For *comparison,* 5 autopsy cases of the same age group with no skeletal abnormalities were studied simultaneously. These included a 7-month-old girl (lobar pneumonia), a 6-month-old girl (bronchopneumonia), a 4-month-old girl (congenital heart disease), an 11-month-old boy (biliary atresia), and a 3-month-old girl (congenital heart disease).

Representative specimens were fixed in 10% buffered neutral formalin and decalcified with 2.5% solution of EDTA (ethylenediaminetetraacetic acid) or 7% trichloroacetic acid, except for

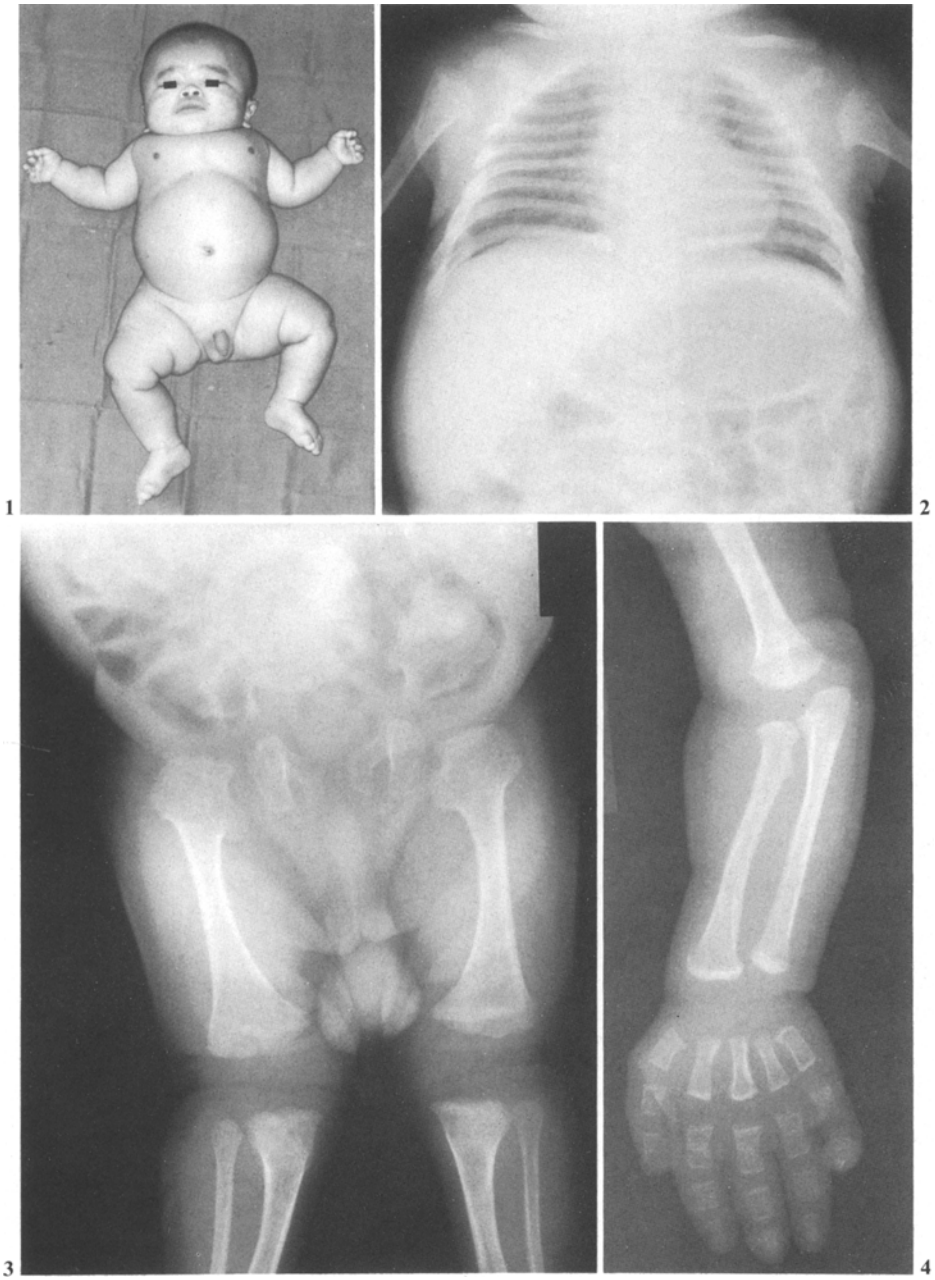

Fig. 1. Appearance of the 6-month-old patient. Characteristic facial features, short neck and extremities and thoracic deformity are evident

Fig. 2. Antero-posterior chest roentgenogram at the age of 2 months showing short thorax with transverse ribs and narrowed intercostal spaces. The vertebral bodies look shortened, particularly in thoracic region. A thymic shadow is not evident

Fig. 3. Roentgenogram of the pelvis and lower extremities at the same age as in Fig. 2 showing widening and increased density in the metaphyseal ends of the knees and hips. Small ossification centers of the tuberosity of the ischium are evident

Fig. 4. Roentgenogram of the right upper extremities at the same age as in Fig. 2 showing metaphyseal changes of the elbow and wrist similar to those seen in Fig. 3

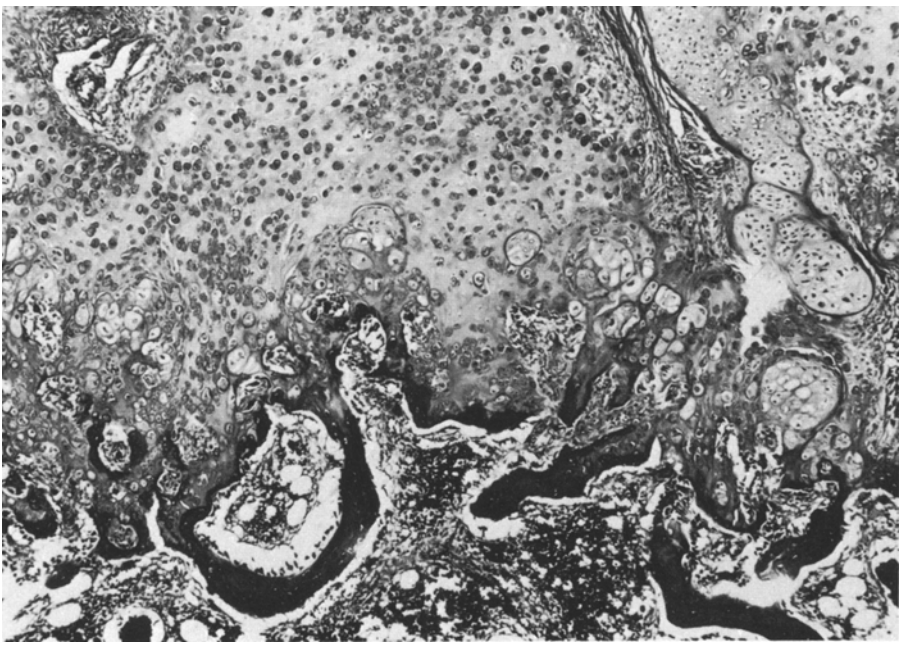

Fig. 5. Histological appearance of the growth plate and adjacent metaphysis of the head of the femur. The growth plate is irregular and there is no columnar arrangement. (H-E, × 53)

small pieces of bones and cartilages which were sectioned without decalcification for calcium staining. After embedding in paraffin, 5 micron sections were cut. In addition, small pieces of bones and cartilages were embedded in glycol methacrylate and 1 micron sections were cut with a glass knife. The sections were stained with a haematoxylin and eosin (H-E), Hale's colloidal iron, alcian blue, periodic acid-Schiff reaction (PAS) with diastase control, Best's carmine, Mayer's mucicarmine, Weigert's method for elastic fibers, Watanabe's silver impregnation method for reticulin, Heidenhain's method for collagen, and Kossa's method for calcium.

For electron microscopy, the specimens fixed in 10% buffered neutral formalin and decalcified with EDTA were postfixed in 1% sodium tetroxide. Some were processed without decalcification. Epon embedded specimens were sectioned with glass or diamond knives. Ultrathin sections were stained with uranyl acetate and lead citrate and were examined under a Hitachi H-500 electron microscope.

Light Microscopic Findings

Growth Plate. There is a marked disruption in the head of the femur, vertebrae, ribs, sternum and ilium. Lines of the growth plates are distorted and irregular and there is no orderly parallel columnar arrangement of chondrocytes (Fig. 5). Instead, there are scattered chondrocytes with an abnormal perilacunar matrix in most areas (Figs. 5, 6A, 7, 8). They have relatively large round- or oval-shaped nuclei with granular chromatin pattern and occasional nucleoli. The cytoplasm is moderate in amount and round or polygonal in shape. The glycogen content is markedly diminished. The lacunar spaces are indistinct. Characteristically, the perilacunar matrix stains strongly with eosin and appears to be enlarged cytoplasm of chondrocytes when observed under low magnification. This matrix

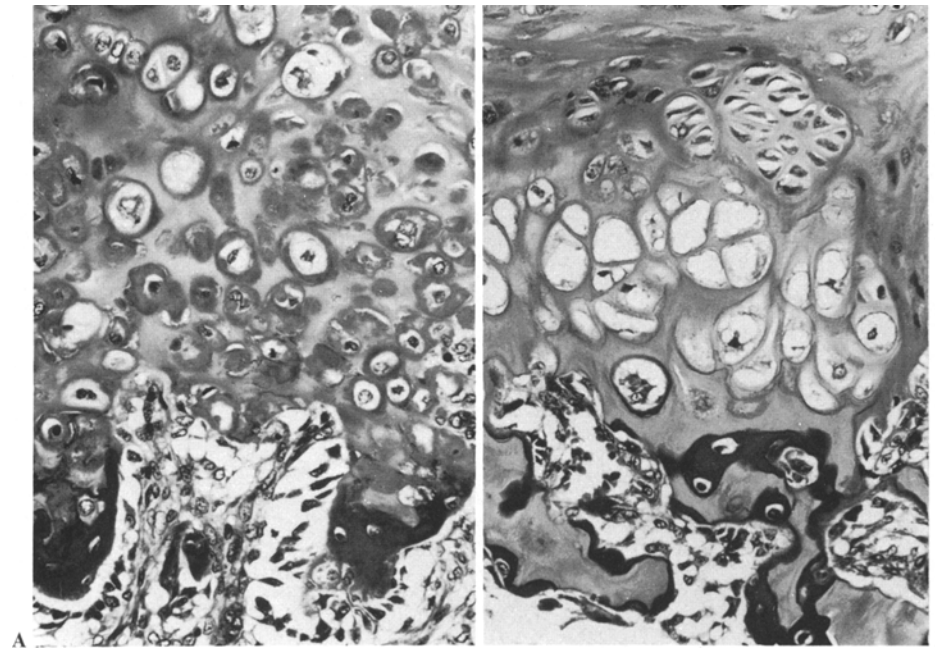

Fig. 6. A High power view of the growth plate of the head of the femur. The columnar arrangement has been completely replaced by abnormal cartilage showing abnormal chondrocytes and perilacunar matrix. Note the scattered individual cells with vacuolar degeneration. (H-E, ×185). **B** Another field of the growth plate of the head of the femur. Ball-like nests of chondrocytes with incomplete columnar arrangement are evident. (H-E, ×185)

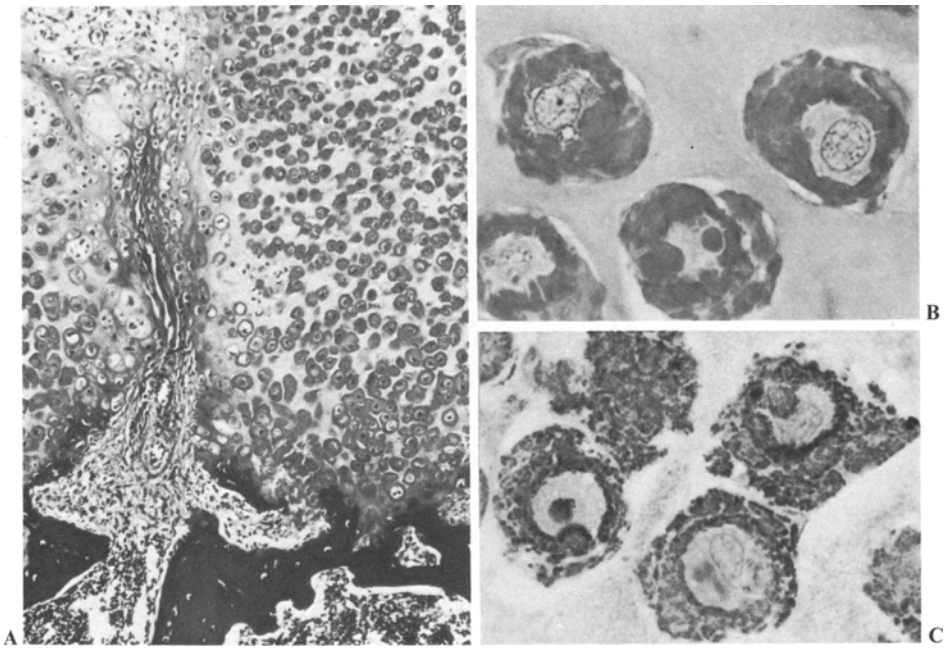

Fig. 7. A Histological appearance of the growth plate of the superior aspect of the lumbar vertebra. The area is replaced completely by abnormal cartilage with abnormal chondrocytes and perilacunar matrix. Note the blood vessel penetrating deeply into the cartilage. (H-E, ×70). **B** Semi-thin section of the lumbar vertebra showing chondrocytes surrounded by a dark staining PAS-positive perilacunar matrix. The matrix is resistant to diastase digestion. (PAS, ×930, embedded in glycol methacrylate). **C** A section similar to that of B. showing granular perilacunar matrix. (Watanabe's silver impregnation, ×930, embedded in glycol methacrylate)

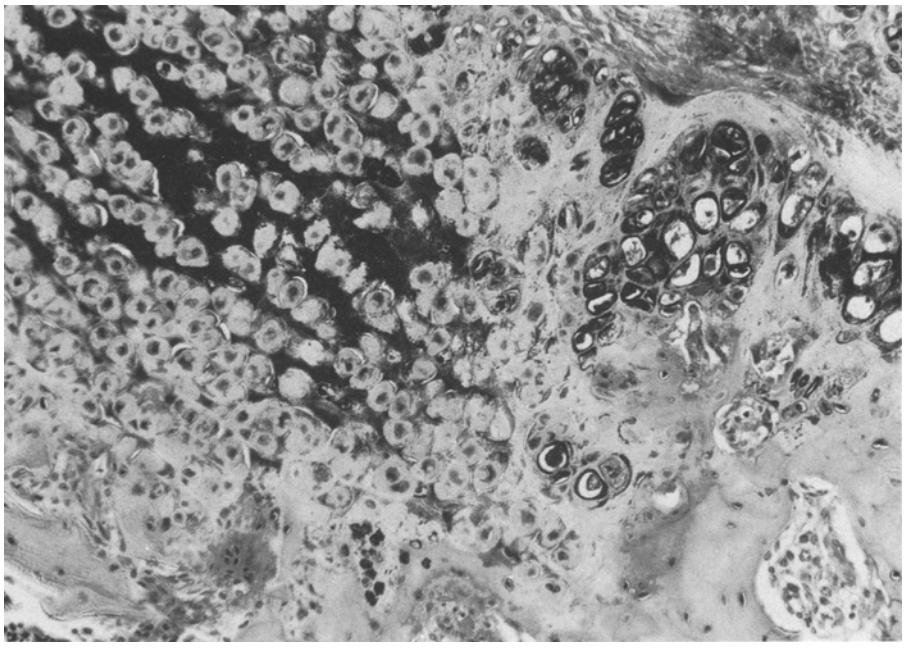

Fig. 8. Histological appearance of the lumbar vertebra stained for acid mucopolysaccharide. A positive interlacunar matrix is seen in contrast with a negative perilacunar matrix on the left. Nests of chondrocytes with strongly positive territorial matrix are seen on the right. (Hale's colloidal iron, ×130)

also stains strongly with PAS and is resistant to diastase digestion. Therefore, there is a sharp contrast between the perilacunar matrix and the cytoplasm of chondrocytes or the interlacunar matrix, since the latter stain weakly with PAS and are digested by diastase. The perilacunar matrix is generally negative with alcian blue or colloidal iron stain with only a small granular or fibrillar positive areas, whereas the cytoplasm of chondrocytes or the interlacunar matrix is generally positive (Fig. 8). The perilacunar matrix stains either red or blue using the Heidenhain's method for collagen and shows a black granularity with Watanabe's silver impregnation method (Fig. 7C). Only small parts of the matrix stain red with mucicarmine, but the matrix is negative with Best's carmine stain. Because the abnormal chondrocytes are distributed haphazardly, a condensation known as territorial or capsular matrix is not identified. Though the interlacunar matrix generally stains positively with alcian blue or colloidal iron stain, the staining varies in places (Fig. 8). In many areas, the color is a homogeneously light blue in contrast to granular dark blue in the controls. Because of lack of normal chondrocyte maturation, open lacunae invaded by capillary loops are rarely evident. Instead, there are a small number of blood vessels accompanying mesenchymal cells which penetrate deeply at irregular intervals into the abnormal cartilage (Fig. 7A). Calcification and ossification seem to occur at the border between these blood vessels and the abnormal

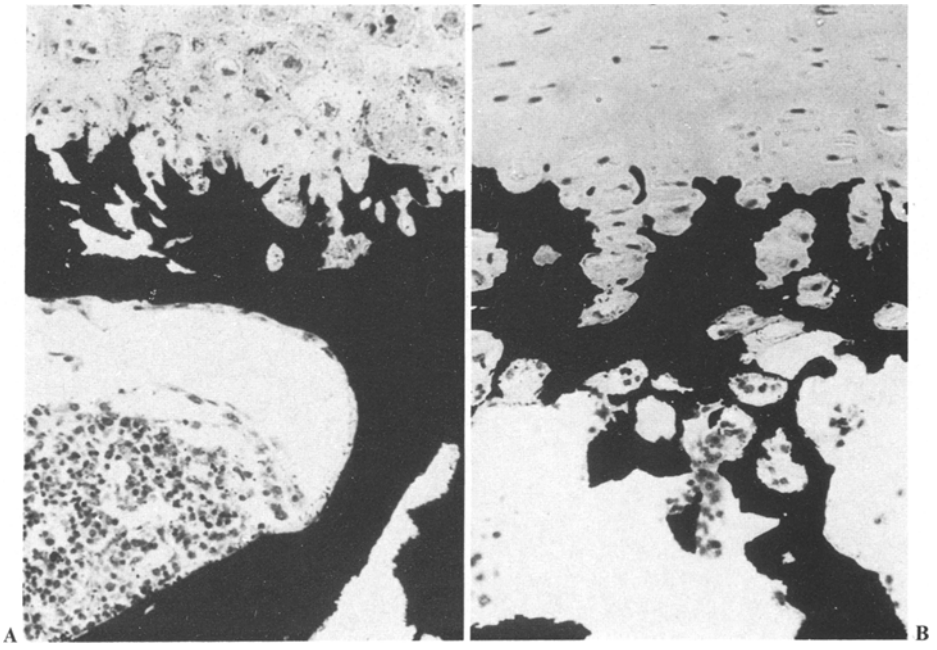

Fig. 9. A Histiological appearance of the growth plate of the lumbar vertebra stained for calcium. The zone of provisional calcification is indistinct and thin with abrupt thick bone trabeculae. (Kossa's stain for calcium, ×150). **B** Normal control for comparison showing normal pattern of calcification in the zone of provisional calcification. (Kossa's stain for calcium, ×150)

cartilage and resulting in irregular lines of the chondro-osseous junction. In addition, there are scattered single cells with a distended vacuolar cytoplasm similar to vacuolated cells seen in the normal cartilage column (Fig. 6A), or ball-like nests of chondrocytes of various size (Fig. 6B). In these nests, the chondrocytes have an incomplete parallel arrangement and a gradual maturation resembling normal cartilage column. The cytoplasm of these chondrocytes is strongly PAS positive and digested by diastase, thereby suggesting a practically normal glycogen content. Territorial and interterritorial matrix is identified in these regions and show a minimal deviation in stainability from that of the controls (Fig. 8). It seems that ossification occurs in similar fashion to that of the normal growth plate in these particular areas. Zones of provisional calcification are indistinct and thin in many places (Fig. 9). The extent of changes described above is seen to be most marked in the sternum followed by the femur, vertebrae, ilium, and ribs.

Epiphysis. The epiphysis of the head of the femur is almost entirely replaced by abnormal cartilage continuous with the chondro-osseous junction. Only the articular cartilage appears normal.

Metaphysis and Diaphysis. In most areas adjacent to the abnormal cartilage of the growth plates where there is no columnar arrangement, transition from

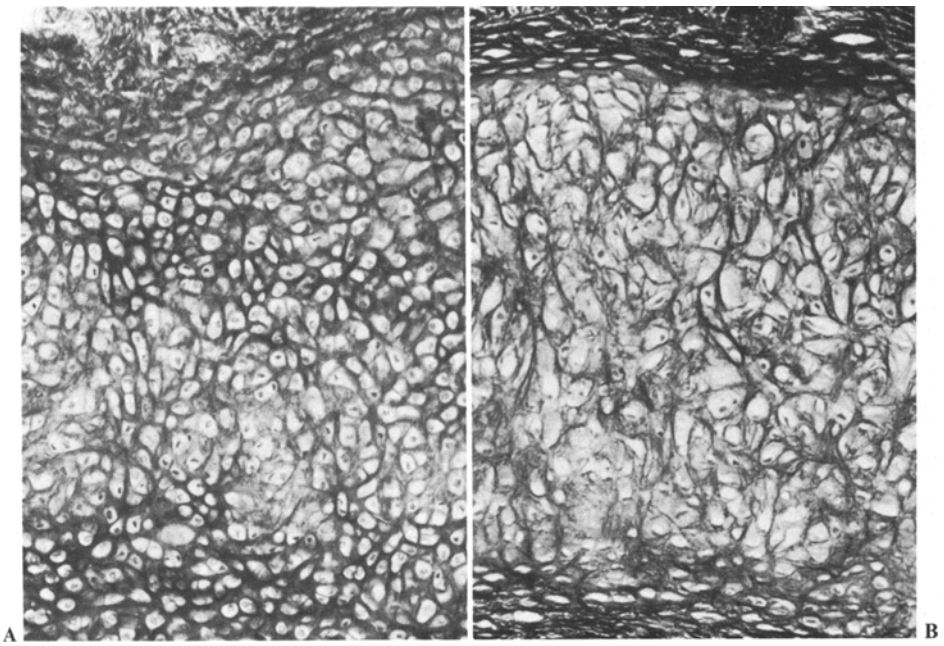

Fig. 10. A Histological appearance of the elastic cartilage of the epiglottis. Cellularity of chondrocytes is more extensive than in the control. (Weigert's method for elastic fibers, ×130). **B** Normal control for comparison. (Weigert's method for elastic fibers, ×130)

cartilage into bone appears to be fairly abrupt forming mainly transverse bone plates with little longitudinal bone trabeculae (Fig. 5). In areas where ossification occurs from the nests of chondrocytes, there are longitudinally oriented bone trabeculae (Fig. 5). Only in these areas is there a persistence of cartilaginous cores in bone trabeculae (Fig. 6B) which are commonly seen for fairly long distance into the metaphysis. The number and appearance of osteocytes, osteoblasts or osteoclasts seem normal. There is no osteoid formation and periosteal ossification in the diaphysis also appears to be normal.

Other Hyaline Cartilages. Hyaline cartilage other than that of the growth plates or epiphysis is almost entirely replaced by abnormal cartilage similar to that described above. In the cartilage of the larynx, trachea, and bronchus, only the peripheral portions of the cartilage are abnormal. Abnormal cartilage is not evident in small bronchi.

Elastic Cartilage. The epiglottis has a normal thickness. The size of the chondrocytes is much the same as in controls, but the degree of cellularity is higher (Fig. 10). The glycogen content of the chondrocyte appears normal. Additionally, a small number of abnormal chondrocytes with abnormal perilacunar matrix are observed in the peripheral areas. The matrix of these cells, however, is not so enlarged as in hyaline cartilage and appears in the form of a thin rim surrounding the chondrocytes. The arrangement of elastic fibers is somewhat distorted and the matrix stains irregularly with stains for acid mucopolysaccharides.

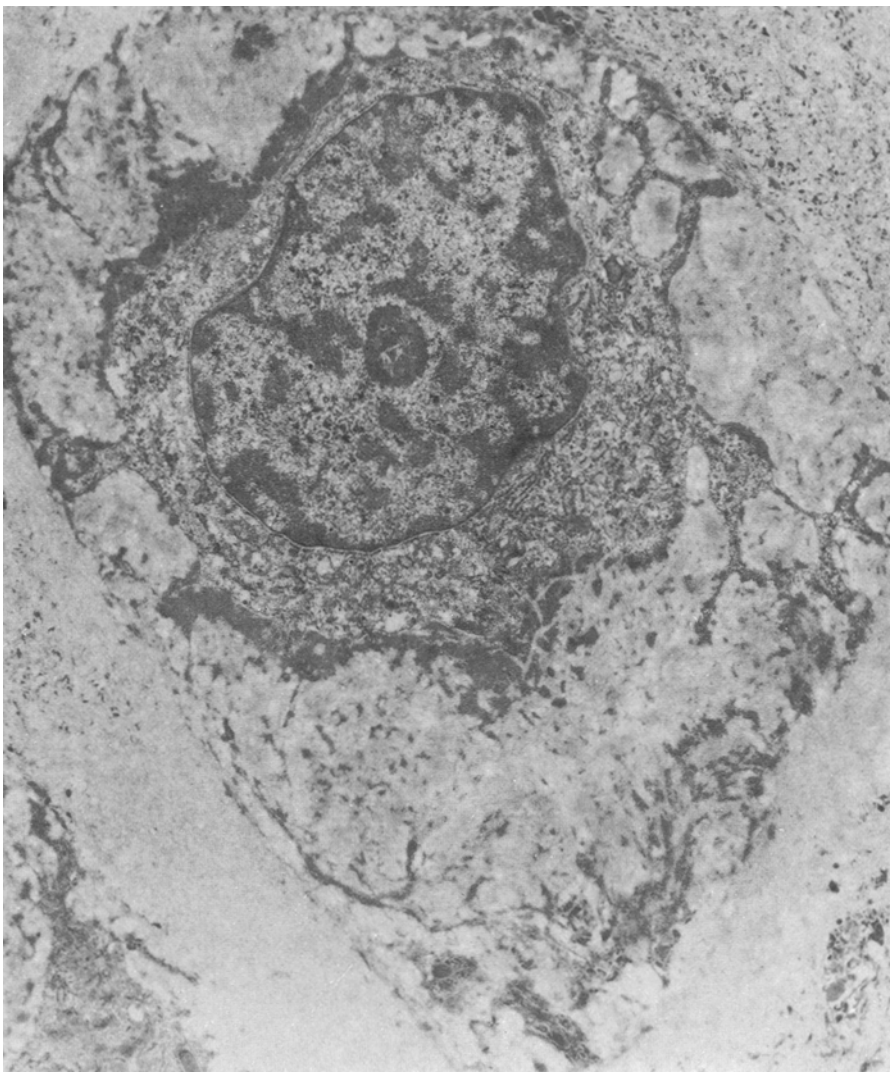

Fig. 11. Electron microscopic appearance of an abnormal chondrocyte with abnormal perilacunar matrix corresponding to the PAS-positive matrix seen in light microscopy. (Uranyl acetate and lead citrate, × 8,000)

Fibrocartilage. Chondrocytes of the fibrocartilage of the intervertebral disk are larger in size and the cellularity is more extensive. The perilacunar matrix of a few chondrocytes also has a PAS-positive rim similar to that seen in the epiglottis.

Electron Microscopic Findings

The abnormal chondrocytes have a moderately abundant cytoplasm with an irregular and long cytoplasmic process (Fig. 11). Mitochondria are moderately

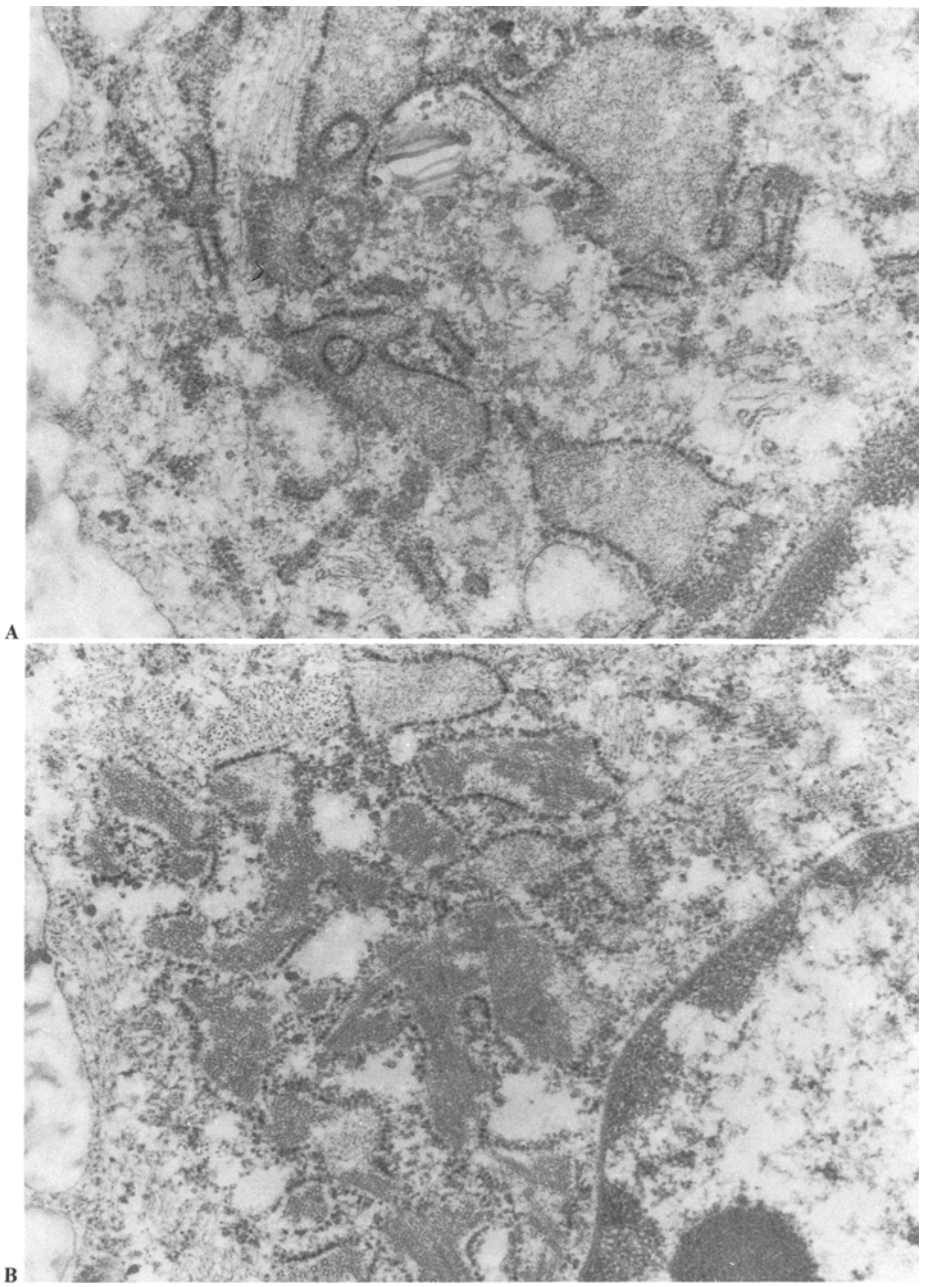

Fig. 12. **A** Detail of a chondrocyte showing intracytoplasmic filaments, small amount of glycogen, and moderately well developed rough endoplasmic reticulum with focal dilatation containing fine granular material. (Uranyl acetate and lead citrate, ×34,000). **B** Another field of a chondrocyte showing rough endoplasmic reticulum containing filamentous and tubular material. (Uranyl acetate and lead citrate, ×34,000)

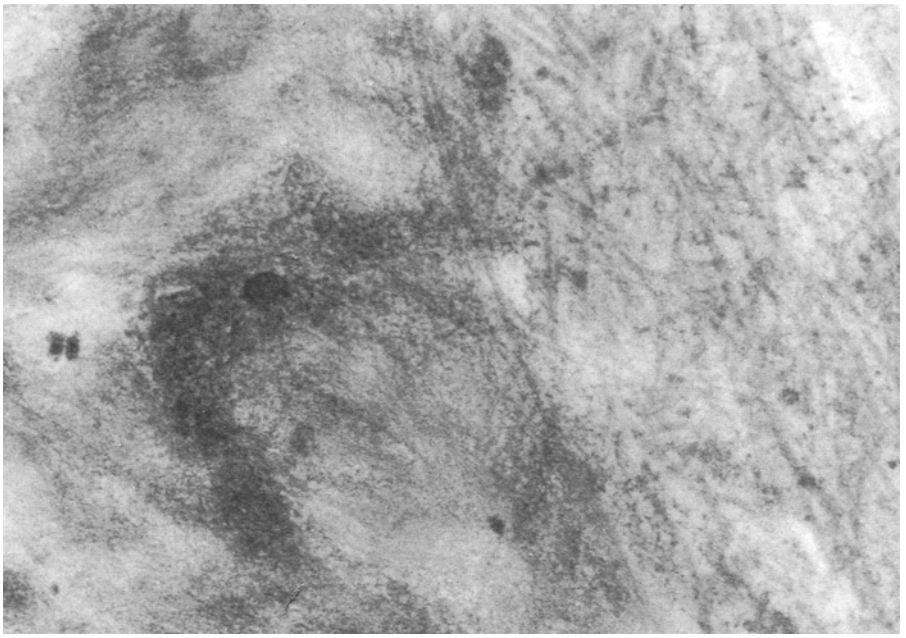

Fig. 13. Detail of the border between perilacunar matrix (left half) and interlacunar matrix (right half). The former contains whorled tightly packed thin collagen fibrils measuring around 100 Å in diameter, while the latter contains thick collagen fibrils measuring around 200 Å in diameter. (Uranyl acetate and lead citrate, × 60,000)

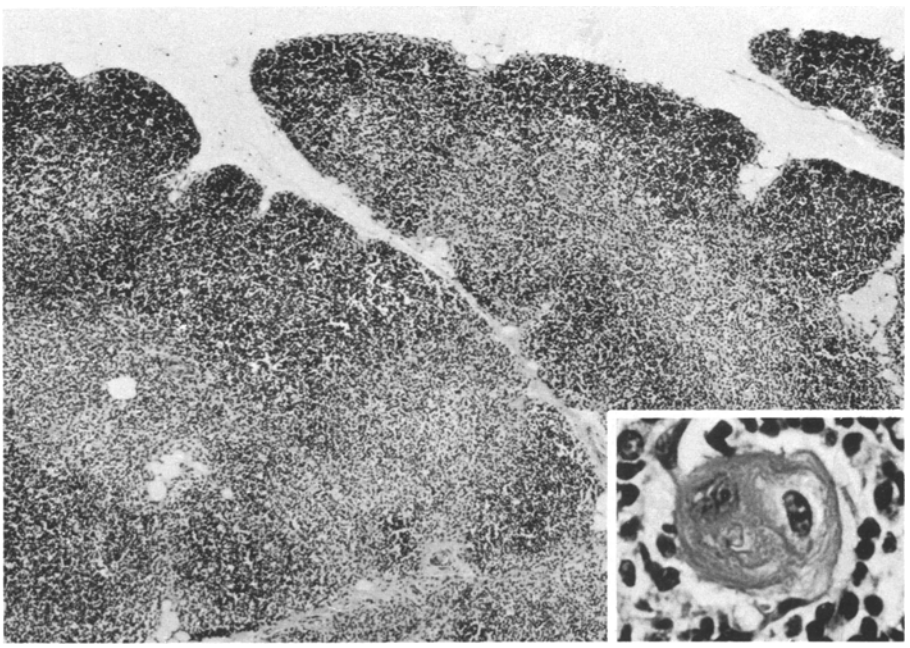

Fig. 14. Histological appearance of the thymus. Note a marked decrease of Hassall's corpuscles. The cortico-medullary differentiation is indistinct. (H-E, × 53). The insert shows a small Hassall's corpuscle. (H-E, × 560)

well developed. The amount of intracytoplasmic filaments and glycogen granules is varied, but is usually small in amount. Rough endoplasmic reticulum is moderately well developed, focally dilated and contains fine granular (Fig. 12A) or filamentous materials (Fig. 12B). Some of the latter have tubular structures. The Golgi apparatus is not prominent. These chondrocytes are surrounded by an abundant perilacunar matrix which can be clearly distinguished from the interlacunar matrix. The collagen fibrils are whorled and packed tightly without obvious periodicity (Fig. 13). Matrix granules are indistinct and appears to be decreased in amount. Collagen fibrils of the perilacunar matrix measure about 100 Å in diameter, while those of interlacunar matrix measure 100 to 200 Å in diameter with an occasional periodicity. Irregular calcification is apparent in areas adjacent to the cell membrane and to the periphery of the perilacunar matrix (Fig. 11).

Other Autopsy Findings

Other autopsy findings include bilateral bronchopneumonia which is the cause of death. The bone marrow shows depressed granulopoiesis with increased erythropoiesis and megakaryopoiesis. The thymus weighed 5.5 g. Microscopically, cortico-medullary differentiation is indistinct in many places with slightly to moderately reduced number of small lymphocytes. The number of Hassall's corpuscles is markedly reduced (14/cm^2 histologic preparation) (Fig. 11). They are small in size (40 micron in mean diameter) and consisted mainly of solid forms with a few cystic ones. Nuclear debris are not conspicuous and stromal connective tissue is not increased. In the other lymphoid organs such as the lymph nodes, spleen or intestine, marked depletion of lymphocytes is seen especially in T-cell dependent areas. Other organs, especially the pancreas, kidneys, parathyroids, and heart are unremarkable.

Discussion

The radiological and clinical findings in the skeletal system of this patient were consistent with findings in cases of metaphyseal chondrodysplasia (metaphyseal dysostosis).

The major pathological abnormality of the chondro-osseous tissues was widespread evidence of abnormal chondrocytes with an abnormal perilacunar matrix in the cartilaginous tissues, including the hyaline and elastic cartilages, and fibrocartilage. There was a decrease in number and an almost total absence of columnar arrangement of chondrocytes in the growth plates with only an incomplete maturation in the scattered chondrocyte nests. Absence of a columnar arrangement of the chondrocytes in the growth plates also occurs in other osteochondrodysplasias, such as achondrogenesis, thanatophoric dysplasia, short rib-polydactyly syndrome, homozygous achondroplasia, adenosine deaminase deficiency, etc. Most are characterized by severe growth failure with stillbirth or early neonatal death. Hwang et al. (1979) distinguished two types of chondrocytes, namely, chief cell and dark cell and suggested that the former is responsible for orderly development of the growth plate. Occasional nests of chondrocytes occur in conditions when there is failure of chondrocyte mitosis and of early cell orientation (Siffert 1966). This evidence is seen in metaphyseal chondrodysplasia (Jansen 1934; Cameron et al. 1954; Rimoin et al. 1976; Sillence et al. 1979), thanatophoric dysplasia (Sillence et al. 1979), Morquio's disease (Ander-

son et al. 1962), or multiple epiphyseal dysplasia (Anderson et al. 1962). However, the characteristic abnormal perilacunar matrix seen in our patient was not reported.

These peculiar and characteristic findings of perilacunar matrix do not seem to be artefacts because we have never seen similar structures in a number of specimens processed the same way. The matrix seems to be composed of glycoprotein with a small amount of acid mucopolysaccharide. Prominent lacunae may be seen in diastrophic dysplasia, however, and are attributed to the accumulation of a large amount of mucopolysaccharide, predominantly chondroitin sulphate, with cellular debris surrounded by collagen fibrils (Rimoin et al. 1976; Horton and Rimoin 1978). Rasmussen (1975) also described a similar lacunar PAS-positive substance in the subarticular zone in Beagle puppies, and here too this substance was composed mainly of chondroitin sulphate and glycoprotein. Though it is not clear whether the difference in these substances is quantitative or qualitative, marked deviation from normal constituents of cartilage matrix is evident in our specimen.

Focal dilatation of rough endoplasmic reticulum observed by electron microscopy may represent elevated synthetic activity or retention of synthesized products due to disturbed transport to the Golgi apparatus. The granular, filamentous and tubular structures in rough endoplasmic reticulum may represent synthesized abnormal substances. The perilacunar matrix consisted of thin collagen fibrils with a tightly packed whorled pattern with matrix granules and ground substance. Chondrocytes control polymerization of collagen fibrils by regulating chemical environments of the extracellular matrix (Revel and Hay 1963). Our findings suggest a disturbance in the environmental control as well as synthesis and secretion of the abnormal matrix.

Thus, the fundamental pathological process in our case appears to be a disturbance in the chondrocyte function and maturation. The chondrocytes synthesize and secrete an abnormal matrix and do not multiply and arrange themselves in the growth plates for subsequent orderly maturation, thereby resulting in a defective calcification and ossification. The disorder is probably not an aquired one due to the direct effect of nutritional or hormonal influences. Though it appears to be an inborn error of chondrogenesis, true nature is unknown. Further investigations including enzymatic, metabolic and biochemical studies are required.

There are reports of skeletal dysplasia associated with agranulocytosis. Some were also associated with pancreatic insufficiency (Shwachman et al. 1964; Burke et al. 1967; Taybi et al. 1969), or hypoplasia of hair (Mckusick 1967; Beals 1968). In our case, the pancreas and hair were unremarkable, and the pathological changes of chondro-osseous tissues differed from these descriptions.

Seemayer and Bolande (1980) demonstrated that the markedly involuted thymus is indistinguishable from the dysplastic thymus showing reduction of thymic size and lymphoid cell mass, loss of definable cortex and medulla, and loss of Hassall's corpuscles. The dysplastic thymus may be the result of an intrauterine failure of embryonic maturation or precocious involution. Thus, it is reasonable that differentiation between thymic dysplasia and marked involution of the thymus is sometimes difficult or even impossible from the morphologi-

cal point of view. In the early life in our patient, a thymic shadow was not evident on the chest roentgenogram. At autopsy, the thymus was small in size and showed a marked decrease of Hassall's corpuscles (less than 5% of the normal number). The corpuscles were composed mainly of the solid type. The interstitial fibrosis was minimal, the small lymphocytes were not markedly decreased and there was minimal cell debris. These findings do not indicate a markedly involuted thymus. They are similar to those of the dysplastic thymus (Berry and Thompson 1968) though not typical. The changes may be called hypoplasia.

Association of abnormalities of the growth plate and the thymus has been demonstrated in experimental animals (Mándi et al. 1971; Teixeira et al. 1978). Coexistence of skeletal dysplasia and thymic dysplasia or immune deficiency in man is known (Mckusick and Cross 1966; Alexander and Dunbar 1967; Gatti et al. 1969; Say et al. 1972; Cederbaum et al. 1976). Many of these investigators suggested a common genetic basis. Moreover, there are reports demonstrating the coexistence of achondroplasia, aplastic anemia, and Swiss-type agammaglobulinemia (Clinicopathological conference at the Royal Postgraduate Medical School, 1966); and of cartilage-hair hypoplasia, chronic neutropenia, and abnormal cellular immunity (Lux et al. 1970). A combination of these abnormalities resembles to that of our case. However, again, the pathological description of chondro-osseous tissues in these cases differs from our case. In summary, there is no description in the literature of the changes of the chondro-osseous tissues identified in our patient suggesting a new disorder associated with agranulocytosis and hypoplasia of the thymus.

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