X-RAY FINDINGS AND PATHOLOGICAL BASIS OF BONE FLUOROSIS

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146 patients with bone fluorosis were collected from endemic areas (100 from Yangyuan county of Hebei province and 46 from Beijing suburbs). X-rays of the chest, spinal column, pelvis, elbow, forearm, knee joint and leg bones were taken in every case. The drinking water fluorine content was also determined. All patients were followed up once a year for 3 years. Our investigation revealed that in different areas with similar drinking water fluorine content, X-ray findings of bone fluorosis were significantly different. Some cases presented mainly rarefaction whereas others had mainly malacia. For further research into this problem, we observed the principal X-ray changes of bone fluorosis and its pathologic basis.

Bone fluorosis caused by endemic fluorine poisoning was once thought to result merely in bone sclerosis, presenting marble-like changes. Later, animal experiments demonstrated that excess fluorine intake could lead to osteoporosis. In recent years, many authors have observed that patients with bone fluorosis show varying pathological changes and X-ray findings. Our investigation revealed that in different areas with the same drinking water fluorine concentration bone fluorosis X-ray findings differed significantly. Even in the same endemic area where the source of drinking water was the same, the incidence of the disease and extent of bone changes differed. Some cases presented mainly bone rarefaction, whereas others had mainly malacia. To help further research into this problem, we have observed the principal X-ray changes of bone fluorosis and its pathologic basis.

MATERIAL

100 cases of bone fluorosis from the severely endemic area, Yangyuan county of Hebei province, where fluorine content of drinking water was 5-17 ppm, all had distinct clinical symptoms and signs. X-ray films of the chest, spinal column, pelvis, elbow, forearm, knee joint and leg were taken in every case. All the patients were followed up once a year for 3 years.

46 cases of bone fluorosis were from the Beijing suburbs, where fluorine content in drinking water was 5-7 ppm, and had X-ray films taken of the chest, spinal column, pelvis, and upper and lower limbs.

One dog, 11 years old, from the heavily endemic area of Yangyuan had X-ray findings in the ribs, spinal column and joints of the limbs similar to those of human sclerotic bone fluorosis. Angiography was performed under general anesthesia for visualization of the microvessels in the whole body, and roentgenography for visualization of all joints, the spinal column, ribs and mandible. Pathologic sections were made for comparison with the X-ray findings.

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ANALYSIS

The 146 cases from Yangyuan County and the Beijing suburbs were analysed for bone striation, bone density and changes of the joints, particularly where ligaments and tendons are attached. The X-ray findings could be classified into 6 categories: osteosclerosis (53 cases, 36%), osteoporosis (44 cases, 30%), osteomalacia (25 cases, 17%), progressive articular degeneration (107 cases, 73%), ligament ossification (98 cases, 67%) and intermittent growth arrest line (105 cases, 72%). The dog X-rays showing bone fluorosis were compared with human gross pathological sections of osteosclerosis, ligament ossification, and degenerative articular change, the changes are quite similar.

RESULTS

Bone sclerosis. Bone sclerosis due to endemic fluorine poisoning is a general term denoting bone increment. Comparison of the X-ray findings with those of gross pathologic sections show the following changes.

a. The mildest change was bone increment and thickening at the junctions of the trabeculae, presenting a noded reticular appearance (Fig 1).

b. There was new bone attached to the surface of the cancellous bone trabeculae, and X-rays showed thickening and condensation of the trabeculae, with course reticular or woven bone striations. The proliferated bones were fused into one, and X-rays showed bone speckles of various sizes (Fig 2).

c. In severe cases the trabeculae were fused together, becoming compact in structure and even forming Haversian systems. X-rays showed eburneous bone (Fig 3).

d. The periosteum slowly proliferated and ossified, forming compact bone which then fused with the original cortical bone. X-rays showed cortex thickening. After the periosteal new bone thickened, compact bone formed in its superficial layer, and the deeper layer turned into cancellous bone. The original cortex remained clearly visible. At this stage the X-ray biframe sign appeared.

It is worth mentioning that in the gross pathologic sections large amounts of calcospherites and minute calcium salt particles were seen precipitated in the bones, including cancellous and cortical bones, and remained there even after decalcification. In some areas the calcospherites were precipitated only in the central part of the bone trabeculae and in the superficial osteoid tissue of the trabecula no precipitation was seen.
These calcospherites and minute calcium salt particles could also be seen in the calcification zone of the articular cartilage deep layer.

Of the 146 cases, 53 (36.5%) had bone proliferation of varying degrees. Some had mainly one kind of pathologic change while others had several kinds of changes equally predominating in the same bone. Therefore, although all cases were sclerotic type, the X-ray findings were different, including sand-like and course reticular bone striations, and even and uneven osteosclerosis.

Osteoporosis. This is reduction of bone density due to decrease in bone quantity. It was observed in the gross pathological sections of dog bones with fluorosis. Some trabeculae were atrophied and finer, and some thicker or uneven in thickness, presenting a picture of disturbance in osteogenesis and osteoclastosis. In our series, as many as 44 (30%) cases were shown to have osteoporosis by X-ray. The X-ray findings were quite complicated and manifold.

1. Even osteoporosis. The bone trabeculae were generally atrophied and thinner, showing even and homogenous reduction of bone density.

2. Thick and sparse striation. The trabeculae were sparse but thick, clustering in the cancellous bone. In the weight bearing parts the clustered trabeculae were arranged along the force direction. Trabeculae of the flat bone appeared sparse and disarranged, showing thick reticular striations (Fig 4). In some patients, the bones of the whole body were thickened and deformed, the thick, sparse trabeculae in the cancellous bone intersected each other and were disarranged, simulating the X-ray appearance of periostitis deformans. Osteogenesis and osteoclastosis disorder was extremely marked.

Fig 4. Ilium. The trabeculae were discorded, showing thick reticular striations.
3. Partial absorption of bone cortex. This was often found in the lower ribs. In severe cases a great proportion of the bone cortex had disappeared, or the ribs looked moth-eaten.

Osteomalacia. Fluorine poisoning can result in osteomalacia, this has been confirmed pathologically. No pathological changes of osteomalacia were found in this series. Of the 146 cases, 25 (19 female and 6 male) including 2 boys showed osteomalacia in X-ray films. The chief X-ray findings were reduced bone density, blurred striations and bone cortex absorption. Verterbral bodies showed biconcave deformity of varying degrees and the spinal column was kyphotic. The acetabular bottom was depressed and the pelvic inlet was triangular. Severe kyphosis can result in pelvic retroversion, pelvic inlet flattening, pubes and ischia upward shifting and obturator foramina enlargement. The malacic vertebral body then becomes dense and sclerotic. Biconcave deformity of the vertebral body caused by bone fluorosis is often associated with ossification of the spinal ligaments. Of the 100 cases from Yangyuan, 15 were clinically found to be associated with genu varum or genu valgum.

Intermittent growth lines of bone. Intermit- tent growth lines are traces left in the process of osteogenesis owing to transient disorders in calcium-phosphorus metabolism and osteogenetic modelling during growth. These lines do not affect bone growth. X-rays showed the following features.

1. Lines of growth arrest in limb long bones. In X-rays, 105 cases (72%) had transverse, dense linear shadows first seen in the osteogenetic area beneath the provisional zone of calcification in the metaphysis. With bone growth, these moved toward the diaphysis. The number of growth arrest lines differed. In some cases there were several, and in others there were 10 or even over 50. The number represents the frequency of intermittent growth arrest, each leaves one line. The distance between the lines represents the time interval between growth arrests.

2. Tiered growth of the metaphysis. This sign was seen in the area beneath the provisional zone of calcification in the metaphysis of limb long bones. It was a thick band like layer of ground glasslike ossification zone beneath which there were rarefied or thick dense striations with clearly defined borders, forming multilayered, dense structures alternating with rare bone structures in the metaphysis.

3. Concentric growth line. The concentric growth line is layered growth of flat or irregular bones, mostly seen in the vertebral body and pelvis. There is an additional smaller vertebral body within a vertebral body of the same or different density. Its size indicates the age of bone growth disturbance. In some sick children the smaller vertebral body contour corresponds to that of a 2-year-old infant. Multilayered concentric growth arrest lines were also observed in the iliac ala (Fig 3). In one case there were as many as 6 layers. The trace of the childhood acetabulum was seen above the acetabulum in some and a smaller ischium in the ischium. In some cases, there are traces of smaller costal cortex contours within the ribs. These changes are generally termed “bone within bone”. 38% of the 146 cases had these signs.

Degenerative joint changes. Extensive degenerative changes may occur in patients with fluorine poisoning, resulting in osteoarthritis. Of the 146 cases, 107 (73%) had articular changes. Of these 107 cases, 12 were below 50 years of age and 2 were children. In the X-rays of dog’s limb big joints, changes resembling those in humans were seen. The following findings were shown in gross pathological sections.

1. Necrosis of articular chondrocytes, degeneration of the matrix and proliferated chondrocyte aggregation in the periphery of the necrotic region. Superficial cartilage necrosis was not seen in X-rays. In extensive necrosis, narrowness of the joint space was visible.

2. Formation of articular cartilage ulcer. The entire articular cartilage layer was necrotized
and sloughed, resulting in local defects (Fig 5). The deep calcified zone and subarticular bone plate were absorbed. Newly formed blood vessels and connective tissue from the bone marrow were proliferated, and the necrotized cartilage was absorbed and organized. In X-rays small cystoid destruction was seen beneath the articular cartilage, and the bony articular surface was blurred, damaged and interrupted.

3. Multilayered linear calcification in the articular cartilage. In the normal articular cartilage there was a clear calcification line in the deep layer, called “tide mark”. In the deep layer of the articular cartilage of the dog with bone fluorosis there could be seen multilayered tide marks overlapping each other, forming a very thick calcification zone. This change was one of the causes for necrosis of the articular cartilage visualized in X-rays.

4. Calcification of the articular cartilage. The articular cartilage was hyperplastic and thickened. The calcification zones were broadened and thickened, some even had more than 10 layers of cells (Fig 6). They were above the tide...
mark and fused with the calcnosis line. Patients with such calcified articular cartilage were found roentgenologically to have local eminences in their bony joint surfaces which increased in density, sclerotic and rough.

5. Calcosphere deposition in the deep layer of the articular cartilage. There was deposition of evenly distributed calcospheres and finer calcium salt particles. This also was one of the contributors to sclerosis of the bony articular cartilage surface seen in X-rays.

6. Ossification of articular cartilage. This was most often seen in the margins of the joint surface. The proliferated chondrocytes fused with the cartilaginous tissue formed from the metaphysic synovial tissue and invaded by the blood vessels from the synovial vessels and the bone marrow producing intracartilaginous osteogenesis. This finally ends in articular hyperostosis and mushroom-like deformity of the bone end.

In addition, in places were these pathologic changes were marked, thickened subcartilaginous plate and coarsened trabecular bone fusion and even formation of Haversian systems were seen, forming compact bone. X-ray showed the bony articular surface was thickened and sclerosed.

These X-ray shown pathologic changes of dog articular cartilage matched the degenerative changes seen in human joints.

Of the 146 cases of bone fluorosis, 107 (73%) had degenerative changes in the limbs. The main roentgenological presentations were:

a. Subcartilaginous cystoid bone destruction was generally several mm in diameter, adjacent to the articular surface. In individual cases the cystoid destruction of the femoral epicondyle was 1-2 cm long and often had peripheral bone proliferation and sclerosis.

b. Bone absorption occurring on the bony articular surface looked blurred, interrupted or dissolved. c. The joint space was narrowed or irregular, sometimes even widened.

d. The articular surface was sclerotic, the bone ends flattened and enlarged, and the bone spurs in the joint margins multiplied. The X-ray findings conformed to the cited X-ray pathologic changes.

Hip joint acetabular circumferential cartilage was ossified, the acetabulum was deepened and the femoral head was enlarged with mushroom-like deformation (Fig 5). The elbow joint showed localized bone absorption and cystoid change of the surface of the lateral epicondyle of the humerus, the humeral capitulum was enlarged and hyperostosis was seen in the inner margin of the ulnar notch. Similar changes were observed in the knee and ankle joints. The joint surfaces of the distal end of the radius and carpal bone were sclerosed and the carpal bone striations were thickened. Patients with these articular changes had thickened articular capsule or intraarticular free bodies. These were the overall findings showing degenerative changes and were the main cause of joint pain and functional disturbance in patients with bone fluorosis.

Calcification and ossification of the sites to which the interosseous membranes, ligaments and tendons are attached. This is an important pathologic change of bone fluorosis. Of the 126 adult cases, 98 (78%) had this change.

For comparison, the pathologic process of calcification and ossification of the ribs, elbow extensor tendon, patellar ligament and perivertebral ligament were observed in fluorotic dog bone.

Normally ligaments are attached to the bone by fibrocartilage. Near the bone surface, the matrix of only 1-2 layers of chondrocytes is in a static state and calcified but not ossified. In the fluorotic dog bone, active proliferative hypertrophy and calcification of fibrocartilaginous cells were seen at the ossified site where the ligament attached. Subsequently the fibrocartilage was invaded by capillaries from the bone tissue, with intracartilaginous osteogenesis ensuing. Ligament calcification is the prelude of fibrocartilage ossification (Fig 7), not simply precipitation of calcium fluoride in the ligament. In gross pathological sections this calcification zone of the fibro-
cartilage appeared to be very thin, and in X-rays, ligament calcification was actually an indication or commencement of ossification and its main component was bone. In X-rays a thin layer of curved calcification zone of high density was seen on the surface of the bone, beneath which was cancellous bone. The more prominent the ligament ossification, the more distinct the bone structure. At the sites as the patellar ligament, extensor tendon of the forearm, and paravertebral ligament (Fig 8), where the big tendons were attached, proliferated periosteum took part in the ligament ossification also. Spurs on the margins of vertebral bodies and bone bridges were formed by fusion of fibrocartilage proliferation and ossification of the intervertebral ligament with periosteal new bone formation of vertebral bodies. Vertebral body spur formation was, in fact, ligament ossification.

**DISCUSSION**

**Roentgenological diagnosis of bone fluorosis.** Not all of the 6 X-ray features described necessarily appear in one patient. Of them systemic osteosclerosis and extensive ligament ossification are most valuable for diagnosing bone fluorosis. Osteoporosis, osteomalacia and ligament ossification are also diagnostically helpful. Osteoporosis, osteomalacia, bone growth arrest line and degenerative changes are significant in the diagnosis of the disease in endemic areas. However, a correct diagnosis of bone fluorosis should not be based solely on the X-ray changes in nonendemic areas. So it is unwise to put undue emphasis on certain X-ray changes. A comprehensive investigation including epidemiology, water-air pollution, clinical and X-ray examinations is indispensable.
Relationship between the 6 basic X-ray changes of bone fluorosis and its classification. Osteoporosis, osteosclerosis and osteomalacia are all changes of bone structure and density (osteosclerosis and osteoporosis are difficult to find clinically), but their X-ray presentations are extremely different. We suggest that bone fluorosis be classified roentgenologically on the basis of these 3 features into 3 types: the osteosclerosis type (53 cases, 36.3%), osteoporosis type (18 cases, 12.3%), and mixed type (51 cases, 34.9%). The articular degenerative changes and ligament ossification are important causes of clinical symptoms. Roentgenology is incapable of visualizing lesions of the nervous system and enhancement of muscular tension. So it is impractical to mix the X-ray and clinical types as they are based on different evidence and characteristics.

Recognition of X-ray appearance of various types of bone fluorosis. The different manifestations of osteosclerosis in bone fluorosis reflect the degrees of bone proliferation and its process of development. a. In the early stage, proliferation at the trabecular intersection is manifested as sand-like or particle-like bone structure. b. In the mid-stage, the trabeculae are generally thickened, i.e., in X-rays the bone striation is roughened and increased in density. If the trabeculae are fused together, bone speckles occur in the cancellous bone. c. In the late stage, as more bony substance is formed, bone X-rays show eburneous sclerosis. Although it is not quite clear under what circumstances osteosclerosis occurs, it is realized that the development of osteosclerosis is a result of the activity of osteogenetic cells, not merely the consequence of precipitation of calcium fluoride in the bone. According to the cited 3 developmental stages, sclerotic type bone fluorosis may be divided into 3 degrees: mild, moderate and severe.

The different X-ray appearances of osteoporosis in fluorosis are the related stages of development. Even and homogenous osteoporosis reflect the early, active and severe stages of the disease. Rough and sparse striations are signs of the late stage. This indicates that the bone, after osteoporosis, undergoes osteogenesis and reconstruction and finally turns into rough and big trabeculae.

In mixed type fluorosis, osteosclerosis, osteoporosis and osteomalacia coexist in one patient. In the most heavily endemic areas the incidence of this type is very high, accounting for 34.9%. Pathologically it is difficult to distinguish which changes are primary and which secondary, but chronic fluorine poisoning can lead to disturbances of osteogenesis and bone destruction. In pathologic sections of the sclerotic type, the trabeculae are atrophied and diminished, and there are dilated Haversian canals and formation of large amounts of osteoid tissue in the cortex. This indicates that changes in the bone structure caused by fluorine poisoning are not absolute sclerosis, absolute osteoporosis, or osteomalacia. During bone development, when osteogenesis predominates, it manifests as osteosclerosis; when osteoclastosis predominates, it manifests as osteoporosis and when excessive osteoid tissue is present it manifests as osteomalacia. This law of pathogenesis should be considered as a pathologic basis for X-ray typing.

Early X-ray diagnosis of bone fluorosis. The lesions of bone fluorosis are manifold. These pathologic changes are a long-term but rather slow process. Once fluorotic bone structure changes occur, they may be discovered radiologically. From radiopathological observations of the 146 cases in this series we consider that slight changes in the structure of bone striations in X-rays taken with small focus are very important to early X-ray diagnosis. Particularly in the sclerotic type microscopic changes in striations of cancellous bones including the ribs, lower angle of the scapula, spinal column, pelvis and limbs are important, reliable radiological clues for early diagnosis. Ossification of interosseous membranes of the forearms, legs and muscular tendon-attaching sites also serves as an important diagnostic basis. The appearance of sand and particle-like striations, unevenly thickened striations (some being course and streak-like), speckles and
"bone within bone" in children and adults in endemic areas are valuable references for diagnosis too.

Problems in X-ray diagnosis of bone fluorosis. The pathologic mechanism of bone fluorosis is controversial. The following points are the generally acknowledged views: a. Excessive fluoride intake causes increased osteogenesis, the main feature being osteosclerosis. b. Hyperparathyroidism resulting from fluoride poisoning may cause increase of osteoclastic activity, leading to osteoporosis or osteomalacia. c. Excessive calcium consumption during pregnancy and lactation may induce exaggeration and worsening of fluorosis. d. Fluorine is detrimental to the kidney and affects calcium and phosphorus resorption, resulting in osteoporosis and osteomalacia. e. Disordered calcium metabolism may cause disordered phosphorus metabolism and may affect metabolism of carbohydrates, lipids and proteins. Excessive fluoride in the body influences the enzyme system, endocrine system, and central nervous system, giving rise to very complicated pathologic changes and metabolic disorders, further affecting bone growth. These theories can roughly explain the X-ray findings of bone fluorosis. Nevertheless, many problems still remain unclear. For instance, the disease in many people in highly endemic areas may be very severe whereas approximately half of the local population have no obvious fluorotic symptoms or signs. Patients live in the same village and drink the same high fluorine content water but their presentations differ. In some, osteoporosis and osteomalacia are predominant while in others osteosclerosis is predominant. Although many patients have consumed high fluoride water continuously for a long time, their growth arrest lines are intermittent. The causes of ligament ossification and articular cartilage necrosis, the pathological basis of the X-ray findings, and the actual disease mechanism require further investigation.