FAMILIAL EXPANSILE OSTEOLYSIS

A NEW DYSPLASIA


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We report 40 cases in one family of an autosomal dominant bone dysplasia, which, though similar in some aspects to Paget’s disease, seems unique in some features and in its natural history. The disease shows both general and focal skeletal changes, the latter being mainly in the limbs with an onset from the second decade. Progressive osteoclastic resorption is accompanied by medullary expansion which leads to pain, severe deformity and a tendency to pathological fracture. The serum alkaline phosphatase and urinary hydroxyproline are variably elevated, while other biochemical indices are normal. Most patients had an associated deafness of early onset and loss of dentition. No previous description of this disease has been found in the literature.

In 1939 a 35-year-old man (II,4 in Figure 1) presented with a one-year history of swelling of the forearm caused by a pathological fracture of the left radius. Radiographs showed cystic expansion of the radius; the histology of the lesion was suggestive, but not typical, of osteitis fibrosa cystica. It was found that the shafts of both tibiae and of the right clavicle were also involved.

Other members of the family, similarly affected, presented in the early 1950s and it then became apparent that this was a familial disease affecting at least five generations of the family, involving a total of 40 of the 90 members of the family so far located. In addition to these, 51 children of unaffected parents have been identified, none of whom have any signs of the disease. All our attempts to control the relentless course of the disease have failed; major limb amputation has been required for patients with intractable pain.

Genetic aspects. The family tree shows affected members in five generations (Fig. 1), all descendants of one progenitor. Of this progenitor, (I,1), clinical details are sparse, having been furnished by surviving members of the family. He was born in 1865 and had an arm amputated for a bony disorder, while apparently his sister (not shown in the tree) had a leg amputated, possibly for the same bony disorder.

The disease has an autosomal dominant pattern of inheritance, with eight examples of affected males having affected sons. The disease has not yet been found in any of the children of unaffected members of the family. We have undertaken routine screening of the children of affected patients in order to achieve early diagnosis and to facilitate recognition of the preclinical features of the disease.

NATURAL HISTORY

Hearing loss occurred in most of those affected by the disease. It was the earliest manifestation, presenting as early as four years of age. Initially there was a pure conductive deafness in which compliance of the middle ear was high, excluding otosclerosis. With time this became a mixed conductive and sensorineural deafness.

The age of onset of bone pain varied from 18 to 44 years. Pain was usually limited to sites of focal radiographic change, but in some instances these lesions were painless. Pain varied greatly with time and from one patient to another. In some cases pain became so severe that it was resistant to opiates and the limb required amputation. Direct trauma to the site of localised disease often produced pain which was out of proportion to the injury sustained.
Generalised radiographic changes were present in the late teens and early twenties, but subsequent focal disease could develop at any time. Almost all focal lesions were in the limb bones, none being found in the skull or pelvis. Pathological fractures in focal lesions tended to heal at normal rates. The lower limb was affected more frequently than the upper; one or other tibia seemed to become involved in every patient. The frequency of involvement of bones by focal disease is shown in Figure 2. Characteristic features were seen on radioisotope scan from the time of skeletal maturity. Ultimately, all sites of focal disease progressed to cause variable deformity, this becoming clinically evident from the third decade (Fig. 3).

RADIOGRAPHY AND SCANS

There were both general and local changes. Generalised bone changes were seen in all affected patients and have been absent in all unaffected members of the family who have been investigated. They presented in the mature skeleton at an early stage, before any localised disease had developed.

The general feature was a slight abnormality of modelling, most common in the humerus, radius, ulna and tibia (Fig. 4). This was slight, but it was seen so frequently in affected patients that it did not appear to be a normal variation. The second general feature was a disordered trabecular pattern. While great variations in pattern are seen in a normal population, the tightly meshed appearance shown in Figure 5 was constant in all affected patients.

The localised bony changes peculiar to this disease were rarely seen in the girdles and axial skeleton (see Fig. 2), in contrast with the distribution in Paget’s disease (Guyer 1981). Local dysplastic changes frequently became multiple, though they were often solitary in the early stages. New foci developed in bone which previously had shown no early changes, again unlike Paget’s disease. Progress was by expansion, leading eventually to an end-stage of gross loss of density of the affected bone. There was great variation in the rate of progress, both between patients and also between different lesions in an individual. All affected bones did not necessarily progress to this end-stage.

Focal changes began with a rounded area of loss of trabeculae; this could be juxta-articular, metaphyseal or diaphyseal. The translucent area gradually increased in size and endosteal scalloping and tunnelling of the cortex occurred. An appearance of buttress formation on the concave cortex of weight-bearing bones was sometimes seen in the early stages, but was not sustained. Eventually there was cortical thinning and expansion of the bone with complete loss of trabecular pattern (Fig. 6).

Fig. 1
The family tree showing five generations. (□ unaffected male, ○ unaffected female, ■/□ affected male/female, deceased, ▲ propositus, ◊ sex unknown.)

Fig. 2
Distribution of focal lesions.
The rate at which the disease front advanced along the shaft of a long bone, where unaffected by surgery or pathological fracture, varied from 10 to 18 mm per year and did not depend on the long bone affected. The rate of advance in Paget's disease varies from 5 to 10 mm per year (Doyle, Banks and Pennock 1980).

In some bones the disease process did not progress beyond a certain stage; however, it frequently continued until the whole bone was involved and had become expanded, leaving a very fine cortical shell with some local loss of continuity. The appearance was multilocular with irregular fine septa and a striking degree of translucency. Ultimately, longitudinal collapse followed bony disintegration. In the forearm and lower leg it was more usual for only one bone to be affected.

The disease process did not seem to cross joints or interposed soft tissues, but where operation had resulted in direct contact between diseased and normal bone, radiographs showed spread of the process into the normal bone. The radiographic features were relatively constant throughout the family and were sufficiently distinct from those of any other recognised disease to support the thesis that this condition was unique.

Isotope scans. Isotope bone scans were carried out on all the affected members of the family and also on several unaffected members. In each case $^{99m}$Tc-labelled methylene diphosphonate was given intravenously.

Before 1981 the standard dose was 10 mCi; since then 370 MBq have been used.

In all affected patients there was a proportionately greater uptake of isotope in the tibia when compared with the femur (Fig. 7). This was always bilateral and was not present in unaffected members of the family. This striking abnormality does not appear to have been described in any other bone disease. Usually, but not always, there was a focal increase in uptake at the sites of local radiographic abnormalities.
BIOCHEMISTRY

Biochemical investigation showed evidence of increased bone turnover. The serum alkaline phosphatase level, reflecting osteoblastic activity, was elevated, ranging from 150 to 7000 u/l, where the upper limit of normal was 120 u/l. Electrophoresis confirmed that this was bone isoenzyme, and there was a tendency for the alkaline phosphatase level to follow the severity of the disease.

Urinary hydroxyproline levels, reflecting osteoclastic activity, varied from normal to more than 10 times the upper limit of normal. Serum calcium and phosphate were invariably normal and parathyroid hormone levels were not elevated. The ESR was usually normal; when it was elevated its level did not reflect the severity of either the disease or the symptoms.

HISTOPATHOLOGY

Since 1948 a total of 16 bone biopsies have been taken from 11 affected members of the family. On the biopsies of early disease pathologists reported active remodelling, but proposed no specific diagnosis. In later reports various diagnoses were put forward for consideration, including fibrous dysplasia, osteitis fibrosa cystica and Paget's disease. Although pathological opinion was diverse, accounted for partly by variation at different stages of the disease, the early stage showed a similarity to Paget's disease (Jaffe 1933). Later stages, however, are less compatible with this diagnosis. Biopsies taken in recent years accord well with the descriptions in the earliest reports, indicating that the pathological appearance has remained essentially unchanged over a 40-year period.

Light microscopy showed a wide range of morphological features, each biopsy representing a static part of an overall dynamic process. Although there was a complex spectrum of changes which varied from one patient to another, the primary feature was one of active remodelling. Bone matrix was abundant and dense in the early stages of the disease, but with increased numbers of osteoblasts lining the trabeculae and focal collections of multinucleated osteoclasts at areas of active resorption.

As the disease progressed, matrix became more scanty, with osteoblastic activity becoming intense but ineffective in advanced cases. This was accompanied by a decrease in the number of osteoclasts. Mosaic cement lines were prominent in all but the earliest stages. Under polarised light there was an apparent reduction in lamellar bone, with a marked but variable increase in woven bone. With progression of the disease there was less bone matrix with an increasingly disorganised arrangement of bone trabeculae and a corresponding increase in fibrous tissue, with more extensive vascularity (Fig. 8). In sections from late-stage radiolucent bone, von Kossa staining showed poor calcification. In the end-stage of the disease there was almost complete fatty replacement of the bone, with few remaining features of the original nature of the tissue.

Fig. 7

Technetium scan of the lower limbs of a patient aged 18 years who has not yet developed focal disease. Note the increased uptake in the tibiae compared with that in the femur.

Fig. 8

Light microscopy. Note the multinucleated osteoclasts, many osteoblasts, disorganised trabeculae and increased fibrous tissue (haematoxylin and eosin, \( \times 55 \)).

From seven patients, sections which had been prelabelled with tetracycline markers revealed that an abnormally high proportion of the surface of the bone was undergoing formation at one time. The rate of matrix apposition was 1.5 to 1.7 \( \mu \)m per day, twice normal, with five times the normal rate of bone formation.

In eight patients, tetracycline-labelled biopsies from radiographically unaffected iliac crest revealed no histological abnormality and showed a normal turnover in six with a raised turnover in two. One of these two had normal osteoclasts, while the other showed abnormal osteoclasts, but neither showed any other features of the
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disease. Biopsies from radiographically normal parts of affected bones revealed no abnormality.

Ultrasound. Sections of both diseased and normal bone from eight affected patients were examined. Numerous large osteoclasts were seen in diseased bone from all patients. All of these cells showed characteristic nuclear microcylindrical inclusion bodies (Fig. 9), within the size range and with similar ultrasound to measles, respiratory syncytial and canine distemper virus (Rebel et al. 1980; Mills et al. 1981). Some nuclei were seen to be completely engulfed. Cytoplasmic inclusions were not found.

In more advanced disease there was increasing vascularity, and perivascular mononuclear cells with numerous lysosomes were seen. At the end-stage of the disease, osteoclasts were not seen and those osteoblasts which were present appeared to be unable to form bone. Some fibroblasts and fibrous tissue were present, but the overwhelming picture was that of replacement of bone by vascularised fatty tissue.

OTHER FEATURES

ENT changes. Deafness was present in most affected members of the family, but not in unaffected members. This started as a middle ear disorder, often before the age of 10 years, and appeared to spread to involve the inner ear. Thus, a purely conductive hearing loss was seen in the younger patients, while their older relatives had a mixed conductive and sensorineural deafness. Tympanograms, which assess stiffness of the middle ear system, characteristically showed a very high compliance in the presence of normal middle ear pressure. This suggests some discontinuity in the ossicular chain, and in those explored surgically the long process of the incus was absent, thin or replaced by fibrous tissue. The stapes footplate was mobile in most cases, but in some it was fixed and associated with an incudo-stapedial joint problem. In all patients, the tympanic was macroscopically normal and fixation of the head of the tympanic was not a feature. Histological examination of the body of the stapes revealed thickened and irregular trabecular bone with very irregular cement line mosaic. There was little osteoblastic or osteoclastic activity, but a large amount of woven bone was present.

Dental abnormalities. Patients affected by the disease tended to show distinctive dental abnormalities, with bizarre and extensive resorption of the roots of the teeth (Fig. 10). This resorption was mainly in the cervical region of the teeth, but the root apex could also be affected. Clinically, root resorption manifested itself as progressive tooth mobility, spontaneous tooth fracture and, in one case, pulpitis affecting several teeth. There was early loss of dentition and the remaining roots often required operative removal.

DIFFERENTIAL DIAGNOSIS

Some individual radiographs showed features of multiple myeloma, haemangioma, neurofibromatosis and melorheostosis, but these were isolated findings and easily excluded from the differential diagnosis. Paget's disease, polyostotic fibrous dysplasia and osteitis fibrosa cystica were all possible diagnoses. Histologically, familial expansile osteolysis showed greatest similarity to Paget's disease but the age of onset, natural history, distribution, radiographic features, and unique scintigraphy, dental and middle ear findings were all against this diagnosis. Furthermore, while the biochemical findings and initial
response to diphosphonate therapy were similar to those found in Paget's disease, the response achieved was of a much shorter duration (Yates et al. 1985). Enderle and von Gumppenberg (1979) described three patients with a dysplastic disease which bears great similarity to the disease we are describing but differs somewhat in distribution. They proposed that their patients suffered from an unusual form of Paget's disease or a tarda-type hyperphosphatasia. We could not accept either of these as an appropriate diagnosis. Familial expansile osteolysis appears to be an inherited bone dysplasia which does not fit into any previously described diagnostic category.

Conclusions. This disease is a generalised skeletal dysplasia with focal areas of increased bone turnover. Histological and biochemical findings indicate increased activity of osteoclasts and osteoblasts. Increased osteoclastic activity causes increasing bone destruction, and the associated increase in osteoblastic activity does not result in a proportionate increase in new bone formation. Whether this is due to a failure to produce an adequate quantity of matrix, a defect in the collagen deposition, a failure of mineralisation or a combination of these, is not known. It is tempting to speculate that there is an inherited defect in one or more of the enzyme systems essential for normal bone formation. Further study is required to test such a theory.

This condition appears to be a new disease; we have termed it familial expansile osteolysis.

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REFERENCES


