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CASE REPORT

Ivo Marik
A. Marikova
E. Hyankova
K. Kozlowski

Familial expansile osteolysis—not exclusively an adult disorder

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I. Marik · A. Marikova · E. Hyankova
Ambulant Centre for Patients
with Locomotor Defects,
Prague, Czech Republic

K. Kozlowski (✉)
The Children's Hospital at Westmead,
Locked Bag 4001,
Westmead, Sydney, 2145, Australia
e-mail: Kazimiek@chw.edu.au
Fax: +612-9845-2948

Abstract Familial expansile osteolysis (FEO, MIM174810) is a rare syndrome which was observed worldwide in only three kinships and in two unrelated American individuals. We report a patient with familial expansile osteolysis from the Czech Republic, not related to the previously reported cases. This patient's extraordinary clinical course does not conform to the ordinary. Her radiographic bone involvement was unusually extensive, involving most of the peripheral skeleton and the skull. This case documents that familial expansile osteolysis is not only a disease of adults but does occur in childhood.

Keywords Familial expansile osteolysis · Skeletal deformity · Alkaline phosphatase · Osteolysis · Fracture · Radiographs

Introduction

Familial expansile osteolysis (FEO) is a well-documented autosomal dominant genetic syndrome which has been reported in a small German family (FEO-G) [1], a large Irish family (FEO-I) [2, 3] with 40 members affected, and a small American family (FEO-A) [4]. Two non-related American cases were reported in 2003 [5].

The disease is characterised clinically by early hearing loss, bone pain preceding skeletal abnormalities and dental involvement. Hearing loss occurred in 95% and dental abnormalities in 94% of affected Irish patients. Onset of bone pain varies between 18–44 years. Diagnostic skeletal changes consist of focal (lytic areas, cortical thinning, progressive bone deformity) and generalised changes (disordered modelling, altered trabecular pattern). The onset of the focal disease varied from 15 to 45 years, with focal changes seen most commonly in the limb bones (90%) and only exceptionally in the girdles, axial skeleton and skull. The lytic lesion shows loss of trabecular pattern and gradual increase in size, causing cortical thinning. These early changes are later followed by bone expansion, deformity and fractures. Generalised changes are the result of the multifocal, progressive nature of the disease. Serum alkaline phosphatases (reflecting osteoblastic activity) and hydroxyproline (reflecting osteoclastic activity) are elevated. Serum P, Ca and parathyroid hormone levels are normal. Scintigraphy should be done before radiography because abnormal findings may be detected earlier.

Case report

The patient was referred to the Ambulant Centre for Defects of Locomotor Apparatus in Prague, for clinical assessment, without any definite diagnosis. This 39-year-old woman was the product of 39-week gestation and normal delivery to young, healthy, unrelated parents. Her younger sister and her son are healthy. There is no history of any bone disorders in the family. The motor development during the first few years of life was normal. At the age of 5 years she fractured her right femur. Conservative treatment was applied. She re-fractured the right femur at the age of 7 years. Kuntscher nailing was applied. Soon

after she started walking again, she fractured her left femur at the age of 8 years. Again, operative treatment was carried out. At that time, the diagnosis of osteogeneis imperfecta was made. Thereafter her walking skills regressed, and from the age of 9 she was walking with crutches. At the age of 20 she got pregnant, and at 21 she had a healthy son. During pregnancy, she experienced femoral pain followed by progressive Shepherd's crook deformity of femora. At the ages of 24 and 28, corrective osteotomies of the femora were performed. At that time she endured increasing pain in the left tibia and both humeri, followed by progressive deformity of the affected bones. Since the age of 32 she has been using a wheelchair. Since the age of 38 she noted that

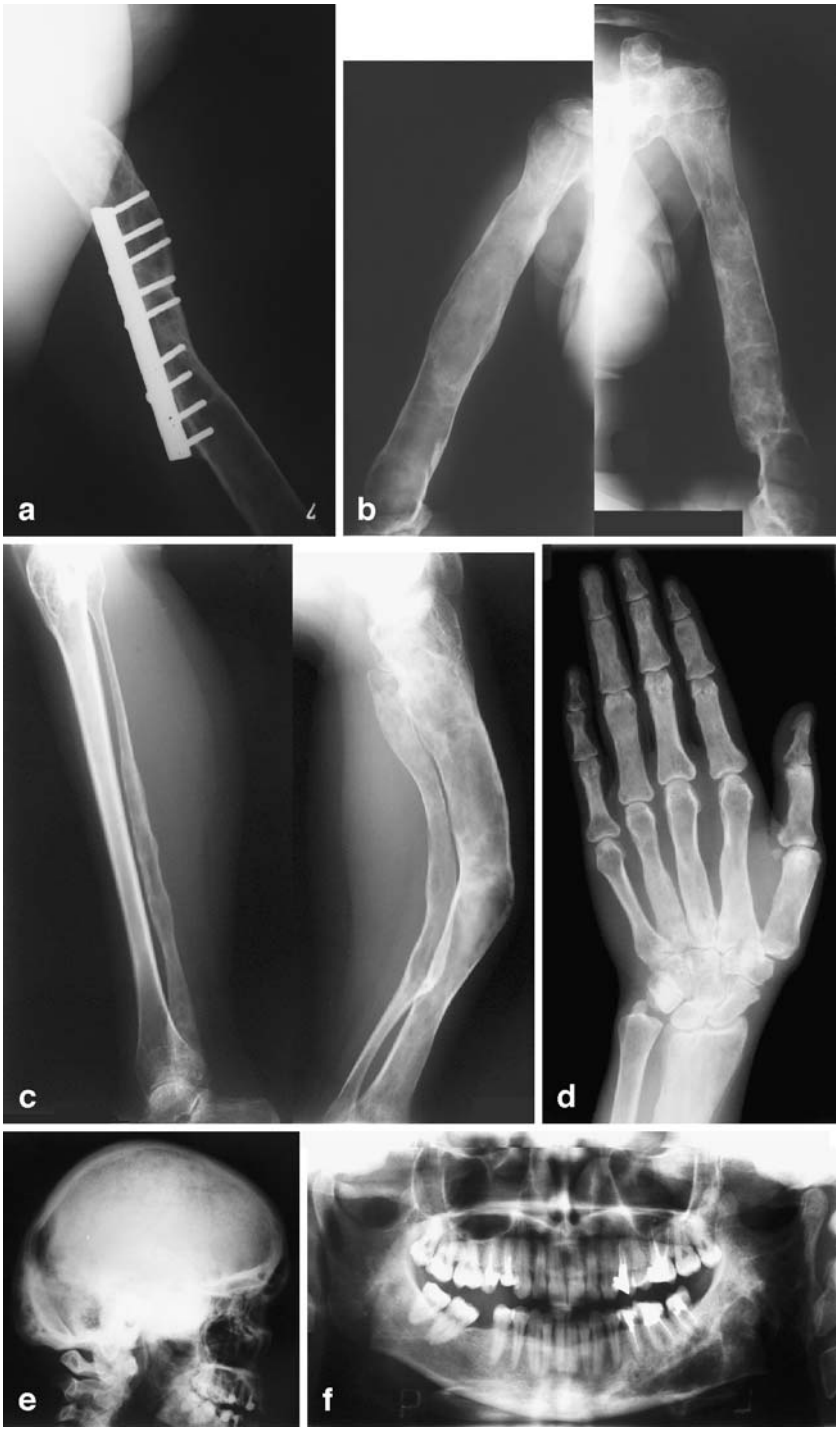

Fig. 1 **a** Left femur. **b** Humeri. **c** Legs. Note abnormal modelling, thinning of the cortex, expansion and loss of the normal trabecular pattern with multiple irregular lytic areas in the affected bones. There is a fracture at the distal end of left humerus. **d** Left hand. Almost all of the short tubular bones are involved—loss of normal trabecular pattern. The most severely affected bones—such as I–IV metacarpals, 2nd and 4th proximal and 2nd middle phalanx—show thinning of the cortex and expansion. **e** Skull. Note thickening of the occipital squama with multiple, small, irregular radiolucencies. **f** Orthopantomogram. Loss of lamina dura and periodontal disease are part of the disease. Short roots of molars are consistent with normal anatomical variants

the circumference of her cranium was increasing—she needed larger hats.

At the time of examination at the age of 39 her height was 150 cm, weight 55 kg, OFC 57 cm. Her face is normal. The sclerae are light blue. The teeth are normal. She has an asymmetric chest due to severe kyphoscoliosis. There is marked antero-medial bowing of the left tibia, and anterior bowing of both humeri. The right thigh is shorter. Her speech, hearing, and mental development are all normal.

The routine blood and urine examinations were normal. The serum markers of bone turnover showed normal calcium 2.25 (norm 2.05–2.90) mmol/l, slightly low phosphorus 0.63 (norm 0.65–1.61) mmol/l and significantly abnormal alkaline phosphatase 6.56 (norm 0.62–2.40) ukat/l, bone alkaline phosphatase 2.15 (norm 0.20–0.5) ukat/l, osteocalcin 72.6 (norm 3.1–13.7) ug/l and tartrate-resistant acid phosphatase 97.0 (norm 0–92.0) nkat/l. Urinary deoxypyridinoline was markedly increased at 51.4 (norm 0–13) nmol/mmol.

The radiographic examination at the age of 39—her childhood clinical notes were destroyed by the hospital—documented generalised osteoporosis, disordered modelling with cortical thinning, expansion and loss of the normal trabecular pattern of femora, humeri , left tibia and fibula and metacarpals. The right tibia and fibula and the forearm bones were little affected. In the skull there was thickening of the occipital squama with multiple small lucent, irregular foci (Fig. 1 a–f). The spine, apart from kyphoscoliosis in the thoraco-lumbar spine and the pelvic deformity secondary to femoral involvement, was normal.

Discussion

Our patient presents with an unusual clinical course of FEO. These include absence of prodromal hearing loss, atypical early onset of bony involvement, and dormant phase between the age of 9 years and her pregnancy at 20 years which exacerbated the disorder, acceleration of the clinical course after surgery, and head involvement at the age of 38. Absence of cervical teeth resorption, leading to premature loss of teeth, is interesting in view of unusually severe bony involvement including the skull. There are indications that trauma may incite FEO [4]. Exacerbation of FEO following pregnancy has been observed. The rare head involvement was noted in two patients of the FEO-G and in one patient of the FEO-I.

Our patient's clinical course attests that FEO is a disorder which may manifest in early childhood without the major, common prodromal symptom of hearing loss. The first fracture, which occurred at the age of 5 years, was certainly a late manifestation of local osteolysis with cortical thinning, as the traumatic episode was minimal—a fall at home. We do not believe that our patient had osteogenesis imperfecta associated with FEO. There were no Wormian bones, no basilar impression, no temporal bulging of cranium, no dentinogenesis imperfecta, no bowing of the long bones and no compression of the vertebrae. At least some of these abnormalities would be present in an adult patient with osteogenesis imperfecta.

Phenotypic variation between the three families with FEO which show identical DNA defects was analysed by White and Mumm [4] The differences in clinical course are probably the result of modifying genes, dietary differences and medical intervention. The clinical course of the FEO—due to decreased penetrance—was less severe in FEO-A than in FEO-I and especially in FEO-G. In the FEO-A the osteolytic changes were localised in one long tubular bone, dental involvement was less severe and no skeletal malignant transformation was observed.

The **differential diagnosis** of FEO is predominantly with the *familial form of early-onset Paget disease of bone* (FDB2) and *expansile skeletal hyperphosphatasia* (ESH)—heritable disorders which share with FEO the same chromosomal location 18q21.1-q22 and a remarkably similar gene defect (TNFRSF11A) leading to constitutive activation of RANK essential in osteoclast formation—and with *idiopathic hyperphosphatasia*, known also as juvenile Paget disease (IHH) due to homozygous deletion of the gene encoding OPG (TNFRSF11B) which suppresses bone turnover [4, 6]. All of them show elevated markers of bone formation and bone destruction.

FDB2 reported in the Japanese family shows a distinctive gene defect. It affects the long bones like FEO but also the axial skeleton like Paget disease of bone (PDB) [7]. The precise pathogenesis of PDB is unknown, and its relationship to RANK/OPG diseases is undetermined [4, 8]. In PDB the first progressive osteolysis phase is similar to FEO. It is progressive and/or stabilising in FEO, without the reactive hyperostotic/osteosclerotic phase characteristic of PDB. Lastly, axial skeleton is spared in FEO. *ESH*, reported only in two patients—mother and daughter—is characterised by early onset of deafness, premature loss of teeth, progressive hyperostosis of long bones and remarkably expanded proximal phalanges. Large osteolytic lesions are not a feature of ESH. Autosomal dominant inheritance and episodic hypercalcaemia are further notable features [9, 10]. The autosomal recessive idiopathic hyperphosphatasia (*IHH*), known also as juvenile Paget disease, is caused by homozygous delation of the gene encoding OPG [4]. Deafness, premature loss of teeth, bone pain, fractures and deformities characterise the severe forms of IHH. Rapid skeletal remodelling affects the whole skeleton. Enlargement and thickening of the skull, platyspondyly, osteomalacic pelvis deformity, symmetrical long-bone involvement with disorganised trabecular pattern, radiolucent expansile lesions and cortical thickening are distinctive radiographic findings. The mild forms of IHH are characterised by osteosclerotic and hyperostotic changes [11].

Polyostotic fibrous dysplasia may be associated with hyperphosphatasia. It can be easily differentiated by

characteristic phenotype, associated endocrine abnormalities if present and different radiographic appearances. *Osteolysis of Gorham* causes a total bony resorption. Analysing the clinical history of our patient, we believe that in the differential diagnosis of the radiolucent defects in the long bones, specifically *uncharacteristic in location for simple bone cysts* with or without fractures, FEO should be considered.We do not know the skeletal turnover biochemical markers in our patient in the early stages of the disease. These tests should be performed in any patient suspected of FEO. If abnormal, they may be the earliest manifestations of the disease, preceding deafness. Although serum calcium and phosphate in FEO are reported as invariably normal, the level of calcium was low normal and that of phosphate was decreased in our case. This may be a mark of severity of the disease in our patient. Radiographic examination documented generalised and focal changes. The former consisted of modelling of femora, humeri, left tibia and short tubular bones. The focal abnormalities consisted of loss of the normal trabecular pattern, confluent lytic areas with irregular septa, cortical thinning and expansion. Fractures of femora and left humerus and deformity of left tibia were associated abnormalities.

Conclusions

FEO has been considered as a syndrome of adults. Our patient demonstrates that the disorder may develop early in childhood. Early appearance of the clinical and radiographic signs is a forewarning of a severe clinical and radiographic course of the disease.

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