Eur Respir J 1999; 14: 478–479
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European Respiratory Journal
ISSN 0903-1936

CASE STUDY

Hip fracture and bone histomorphometry in a young adult with cystic fibrosis

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Hip fracture and bone histomorphometry in a young adult with cystic fibrosis. C.S. Haworth, A.J. Freemont, A.K. Webb, M.E. Dodd, P.L. Selby, E.B. Mawer, J.E. Adams. ©ERS Journals Ltd 1999.

ABSTRACT: A 25-yr-old male with cystic fibrosis sustained a fragility fracture of the left femoral neck, which required surgical correction. He had several risk factors for the development of low bone density and despite treatment with an oral bisphosphonate, his bone mineral density reduced further. The patient died 2 yrs after sustaining the fracture. Bone specimens obtained at *post mortem* demonstrated severe cortical and trabecular osteopenia, but the histological features were not typical of osteoporosis or osteomalacia.

Osteoporosis is thought to be a common complication of cystic fibrosis. The novel histomorphometric appearances reported here suggest that the bone disease of cystic fibrosis may be more complex and possibly unique. Labelled bone biopsies are required to clarify the bone defect leading to low bone density in cystic fibrosis patients so that appropriate therapeutic strategies can be developed.
Eur Respir J 1999; 14: 478–479.

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Keywords: Bone histomorphometry, cystic fibrosis, fracture, low bone density

Received: December 29 1998
Accepted after revision May 15 1999

As cystic fibrosis (CF) patients live longer, new extrathoracic complications of the disease are being recognized and one such example is low bone density. The pathogenesis of low bone density and the optimum therapeutic strategy for its improvement are currently unclear. This study reports a fragility fracture in a patient with CF and the histological features of CF bone.

Case report

A 25-yr-old male with CF was diagnosed as having osteoporosis by dual-energy X-ray absorptiometry (DEXA), having initially complained of back pain. The total hip and lumbar spine bone densities were 0.627 $g \cdot cm^{-2}$ (Z score -2.68) and 0.762 $g \cdot cm^{-2}$ (Z score -2.99), respectively. He was commenced on Didronel PMO (Proctor & Gamble Pharmaceuticals UK Ltd., Staines, Middlesex, UK) and was advised to continue to take his long-term vitamin D supplements (900 $IU \cdot day^{-1}$). After 3 months treatment with Didronel PMO, he tripped over a paving stone and fractured his left femoral neck, which required surgical correction (fig. 1).

The patient had several risk factors for the development of osteoporosis, including advanced CF lung disease (per cent predicted forced expiratory volume in one second 44%) and a high oral corticosteroid requirement (~15 mg $prednisolone \cdot day^{-1}$ in the year prior to his fracture) to control his unstable lung disease. Additional contributory factors to the development of low bone density in this patient included pancreatic insufficiency, malnutrition (body mass index (BMI) 19.7 $kg \cdot m^{-2}$, despite nocturnal percutaneous gastrostomy feeding), insulin-dependent CF-related diabetes (HbA1C 4.2%), hypogonadism (testosterone 10.0

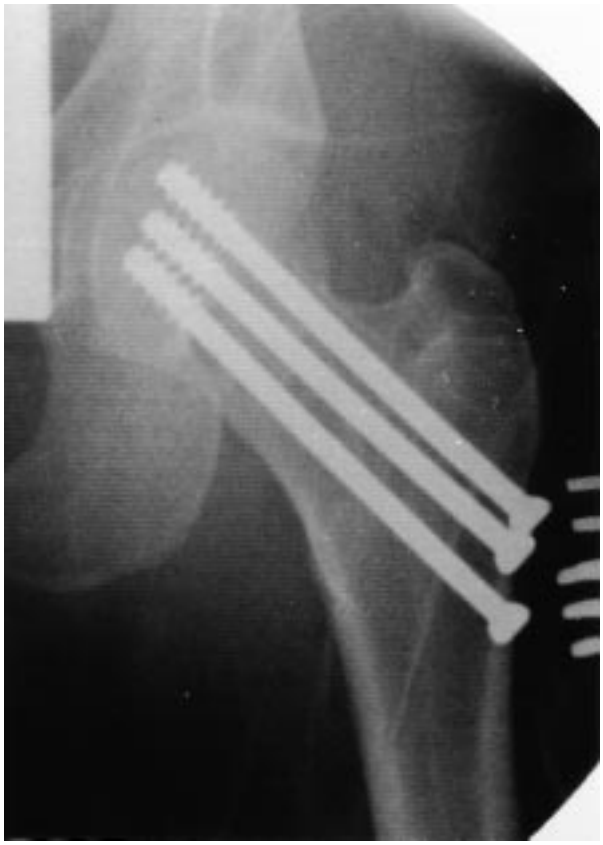

Fig. 1. – Repair of a femoral neck fracture in a patient with cystic fibrosis and low bone density.

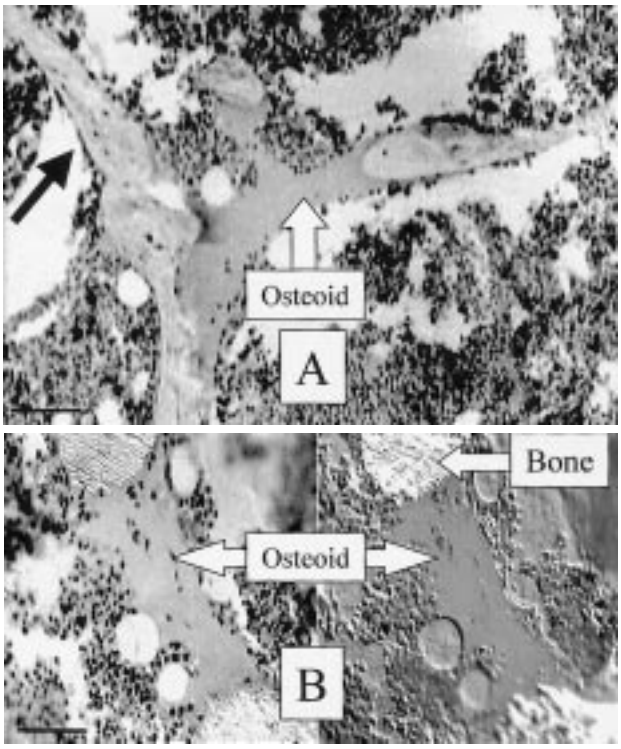

Fig. 2. – Sections of bone stained with Toluidine blue. A) Osteoid linking two of the residual bone islands (open arrow). There is no excess of surface osteoid (black arrow). B) Higher magnification of osteoid viewed in conventional (left) and Nomarski phase (right) optics. Both A and B show the typical pattern of collagen within bone but not osteoid. (Internal scale bar=100 μm (A); 50 μm (B)).

nM), ultrasound-confirmed CF-related liver disease (alkaline phosphatase 275 mM), and reduced levels of physical activity. Serum concentrations of amended calcium (2.32 mM), phosphate (1.28 mM), urea (3.9 mM), creatinine (80 mM) and vitamin D (25-hydroxyvitamin D 31.3 $ng \cdot mL^{-1}$, 1,25-dihydroxyvitamin D 33 $pg \cdot mL^{-1}$) were normal.

After 16 months treatment with Didronel PMO, DEXA demonstrated further bone loss. The total hip and lumbar spine bone densities were 0.593 $g \cdot cm^{-2}$ (Z score -2.89) and 0.719 $g \cdot cm^{-2}$ (Z score -3.39), respectively.

The patient died from respiratory failure 2 yrs after the fracture. Sections of undecalcified, resin embedded *post mortem* bone from the lumbar spine and iliac crest demonstrated severe cortical and trabecular osteopenia, although cortical osteopenia was the predominant feature. In addition, some of the bone ends were linked by an amorphous, nonmineralized matrix (fig. 2) which stained in a similar manner to osteoid but was not birefringent (indicating that it did not contain the ordered collagen arrays typical of osteoid). Bone surfaces did not have an excess of osteoid. Osteoblastic activity was considerably reduced and osteoclastic activity was markedly increased. These histological features are neither typical of osteoporosis (of any cause) or of any of the recognized forms of osteomalacia. Indeed, this precise combination of disturbances in cellular and matrix morphology/morphometry has not been encountered by the authors in >1,000 undecalcified "metabolic bone biopsies" performed in patients with other disease states.

Discussion

Osteoporosis is reported to be a frequent complication of CF, and has been described in both children and adults with the disease [1, 2]. A recent study of 70 patients referred for lung transplant assessment concluded that osteoporosis is universal in adults with late stage disease, its complications including increased fracture rates and severe kyphosis [3]. Cumulative prednisolone dose, BMI and age at puberty were the strongest predictors of bone density. Longitudinal studies of bone density in CF patients indicate that the reductions in bone density result from reduced bone accretion in childhood as well as increased bone resorption in adult life [4].

Although the bone densitometry results and bone biochemical results in these studies are consistent with osteoporosis, to the authors′ knowledge, there are no published reports detailing the analysis of labelled bone biopsies. The novel histomorphometric appearances reported here suggest that the bone disease of cystic fibrosis may be more complex and possibly unique. These findings warrant further detailed investigation with labelled bone biopsies to allow the development of appropriate therapeutic strategies.

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