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Case report

# Novel syndrome of four-limb proximal fragility fractures associated with HIV infection, cholestatic liver failure, and histiocytic infiltration of bone marrow

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**ABSTRACT**

**We report a syndrome of four-limb proximal fragility fractures associated with HIV infection, cholestatic liver failure, and histiocytic infiltration of bone marrow in a 40-year-old African American man. The patient presented with multiple fractures in the proximal humeri and femurs without osteopenia in the vertebrae. His right humerus appeared normal on chest X-ray film 3 years before presentation when he was first diagnosed with HIV infection and abnormal liver functions. At presentation, the patient had vitamin D deficiency, hypogonadism, and low IGF-1 levels, but did not have hyperparathyroidism. Bone biopsy showed diffuse foamy histiocytic infiltration of bone marrow at all fracture sites without evidence of infectious or neoplastic processes. Exhaustive search did not identify any similar cases in the English literature. Our case likely represents a novel syndrome, the etiology of which is probably multifactorial and includes HIV infection, cholestatic liver failure, immobility, and endocrine abnormalities. The case further calls for the need for monitoring of bone health in patients with HIV infection or liver disease.**

**Key words:** Bone marrow, Cholestasis, Fragility fracture, HIV, Histiocytic infiltration

## INTRODUCTION

Osteoporosis is not rare in patients with HIV infections or liver diseases and its cause is multifactorial in those conditions.[1,2] Cholestatic liver diseases are particularly associated with osteoporosis.[3] Axial bones such as the vertebrae are most commonly affected, and to a lesser degree the hips can also be involved. Long bones are usually spared. Osteoporosis progression is slow, clinically significant fractures not common, and long bone fractures rare in patients with HIV infections or liver diseases. Histologically the bones and bone marrow do not exhibit specific changes. Here we report a novel case of four-limb proximal long-bone fragility fractures associated with HIV infection and cholestatic liver failure. Most interestingly, diffuse histiocytic infiltration of bone marrow was found on bone biopsy.

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## CASE REPORT

A 40-year-old African American man with HIV infection and cholestatic liver failure presented with severe bone loss and multiple fractures in the extremities. Three years before, the patient was diagnosed with HIV infection. His liver enzymes were elevated but bilirubin levels were normal. The right humerus cortical thickness was normal as retrospectively assessed on a chest X-ray film intended for lung examination (Figure 1A). Bone scan showed general increased uptake in axial bones and a rib hotspot (Figure 1B). Two years before, he started anti-retroviral treatment with darunavir, emtricitabine-tenofovir, raltegravir, and ritonavir. In the same year, he developed jaundice with elevated bilirubin levels which was attributed to HIV cholangiopathy. The patient's bilirubin levels remained elevated in spite of biliary stenting and ursodiol treatment. One year before, his general condition gradually deteriorated with a weight loss of 40 pounds. Two months before, he suffered a fragility fracture of the left subtrochanteric femur which was surgically fixed. Bone survey revealed normal axial bones but severe bone loss in the humeri and femurs (Figure 1C, E, G), and bone scan did not detect significant changes. Total bilirubin levels were 40 mg/dl (0.1-1.2), alkaline phosphatase 1500 u/l (<125), bone-specific fraction 71 (<55), and coagulation times prolonged. CD4 cell count was 164/μl and HIV viral load undetectable. The patient became bedridden and developed hypercalcemia. His albumin-corrected total calcium levels were 12.6 mg/dl (8.4-10.2), free calcium 1.47 mmol/l (1.12-1.23), vitamin D 6.5 ng/ml (30-150), phosphorus 2.5 mg/dl (2.5-5.0), PTH 6.2 pg/ml (14-72), and PTHrp normal; he was diagnosed with hypercalcemia due to immobility and treated with pamidronate with resolution of hypercalcemia, followed by high-dose vitamin D. Two weeks later, the patient developed bilateral shoulder pain, and bilateral proximal humerus frailty fractures were diagnosed and both humeri and right femur (for impending fracture) were internally fixed (Figure 1D, F, H). Bone biopsy revealed foamy histiocytic infiltration in the bone marrow at all fracture sites (Figure 1I, J). No inclusion bodies or pigments were seen inside the histiocytes. The results of anti-fast stain (to identify tuberculosis bacilli), Gomori methenamine silver stain (to identify Pneumocystis), and Gram stains were all negative, and there was no evidence of neoplastic lesions. Further endocrine workup showed total testosterone 35 ng/dl (250-1100) and IGF-1 45 ng/ml (52-328). The patient developed multiple complications including renal failure and died shortly afterwards.

## DISCUSSION

The patient's multiple fractures are clearly due to osteoporosis by definition.[4] HIV infection and cholestatic liver failure both cause osteoporosis and fractures.[1-3] Inflammatory cytokines and anti-HIV medications may contribute to osteoporosis in HIV infection. The mechanisms for osteoporosis in cholestatic liver failure (hepatic osteodystrophy) are many, including vitamin D deficiency, hypogonadism, and low IGF-1 levels, as exhibited by this patient. In both diseases, the fractures are most commonly in the vertebrae and hip and rarely in the extremities, and the disease progression is slow. The unique features of this case are the distribution of the osteoporotic bones, the fracture sites, the rapid progression of osteoporosis, and the histiocytic infiltration of bone marrow.

We did an exhaustive literature search during the care of this patient to find potentially similar cases to guide management. Unfortunately, we could not find any similar cases and our case appears to be the only one reported to date in which osteoporosis and fracture only inflict the humeri and femurs with relentless progression but spare the axial bones, regardless whether HIV infection or cholestatic liver failure is present. Selective bone loss in the long bones (cortical bones) is seen in primary hyperparathyroidism, type 2 diabetes, and Turner's syndrome and the fractures sites are usually in the forearm.[5-7] Our patient, however, did not have any of those concomitant diseases and the locations of his fractures were in the proximal humeri and subtrochanteric femurs, uncommon sites of osteoporotic fractures. Subtrochanteric fractures can be seen in patients on long-term use of bisphosphonates.[8] Our patient was on bisphosphonate only briefly, after his left femur fracture; thus, bisphosphonate use was unlikely to have affected the site of the fractures. The rapid bone loss in this patient was also remarkable. We did not

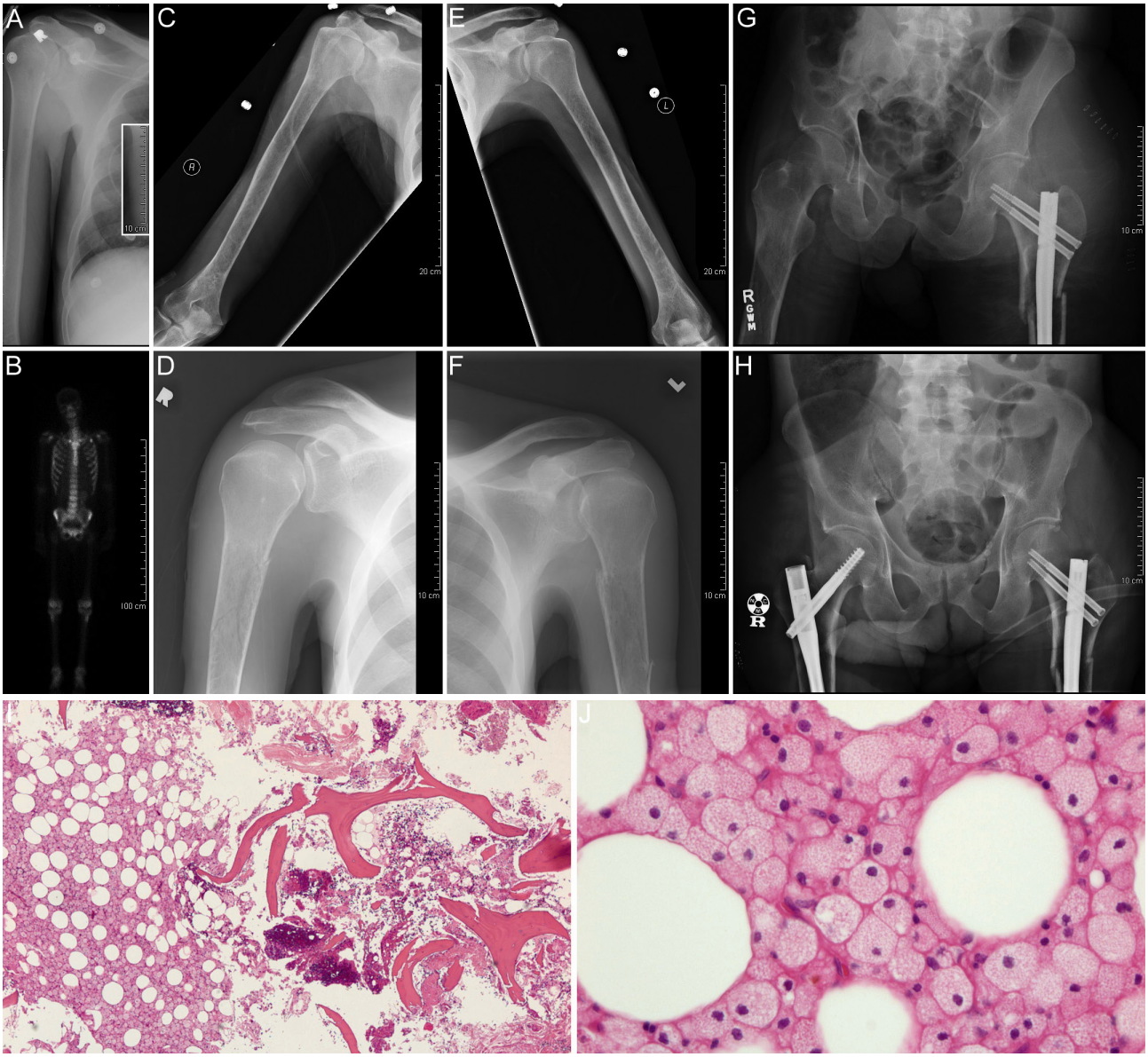


**Figure 1.** Osteoporosis, fractures, and histiocytic infiltration of bone marrow. (A) Right humerus seen on chest X-ray 3 years before presentation. (B) Bone scan 3 years before presentation. (C, E, G) Right humerus (C), left humerus (F), and pelvis (G) 20 days before presentation. (D, F, H) Right humerus (D), left humerus (F), and pelvis (H) at presentation. (I) Micrograph of bone biopsy of a humerus by curetting (5x). Note the histiocytic infiltration of bone marrow on the left and fragmented bone on the right. (J) Micrograph of bone marrow showing details of histiocytes (40x).

have data on his bone health between 3 years before and at presentation but his right humerus initially appeared normal on chest X-ray so that the bone loss must have occurred in the last 3 years. The histiocytic infiltration was likely diffuse as it was found at all fracture sites. The causes and consequences of the histiocytic infiltration of bone marrow are not clear. Diffuse histiocytic infiltration of the bone marrow is very rare and can be seen in Erdheim-Chester disease or Rosai-Dorfman disease.[9-11] Our patient did not have features consistent with the two rare diseases. Histiocytic osteolysis can be associated with hyperbilirubinemia,[12] which was present in our patient; the lack of inclusion bodies or pigments in the

histiocytes, though, suggests a distinct process in our patient. With the multiple unique features, our case could represent a novel syndrome. The underlying etiology of the syndrome is probably a combination of HIV infection, cholestatic liver failure, immobility, and endocrine abnormalities.

Management of this syndrome is challenging. As this patient's HIV infection was controlled well without development of opportunistic infections and his initial left femur fracture limited him to bed rest, we contemplated liver transplant as a definitive, etiological treatment for the cholestatic liver failure; however, it was concluded that his multiple complications made liver transplant impractical. Almost all endocrine interventions considered came up against contra-indications: the renal failure and the risk of hypercalcemia in this immobile patient made bisphosphonate and vitamin D questionable, respectively, while the efficacy of testosterone and growth hormone in a patient undergoing rapid clinical decline was not clear.

In summary, we report a possibly novel syndrome of four-limb proximal fragility fractures associated with HIV infection, cholestatic liver failure, and histiocytic infiltration of bone marrow. Although HIV infection and cholestatic liver failure likely play important roles in the pathogenesis, it is not clear if the diffuse histiocytic infiltration of bone marrow is primary or secondary or contributes to the severe osteoporosis and multiple fractures in the long bones. This case also highlights the importance of monitoring bone health in patients with HIV infection or liver disease.

*The authors have no conflicts of interest to disclose.*

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