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Multiple Looser zones of osteomalacia in Byler disease with associated vitamin D deficiency, phosphaturia, and elevated FGF23

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ABSTRACT

INTRODUCTION: Byler disease (progressive familial intrahepatic cholestasis) is associated metabolic bone disease as a consequence of chronic malabsorption.
CASE PRESENTATION: A 33-year-old man with decompensated liver disease secondary to Byler disease was referred to the orthopaedic department with progressive pain over this right proximal tibia. On examination, he had an antalgic gait. Tenderness was localised to the proximal tibia just distal to the tibial tubercle and bilateral foot swelling. Radiographs showed multiple stress fractures characteristic of Looser zones at various stages of healing in both tibia, metatarsals (third, fourth, and fifth on the right side, and second and fourth on the left) and left femur. Bone mineral density was extremely low. Subsequent investigations were consistent with severe osteomalacia due to a combination of vitamin D deficiency and phosphaturia with elevated fibroblast factor 23 (FGF23). A good clinical response was achieved following supplementation with calcium 1000 mg and vitamin D 20 μg daily.
DISCUSSION: Stress fractures are often associated with delay in diagnosis. Our patient presented to the orthopaedic service with multiple Looser zones that had not been previously detected. As expected, there was biochemical evidence of vitamin D deficiency. An unexpected finding was phosphaturia that was associated with marked elevation in FGF23, which has never been reported previously.
CONCLUSION: Byler disease may result in Looser zones of osteomalacia due to chronic malabsorption. Renal phosphorus wasting as a consequence of unexplained marked elevation in FGF23 is thought to have contributed to the onset of osteomalacia.

1. Introduction

Progressive Familial Intrahepatic Cholestasis (PFIC) is a heterogenous group of disorders characterised by defective secretion of bile acids or other components of bile. The type I variant of PFIC is called Byler disease, which was described originally in the Amish descendants of Jacob Byler [1]. It was subsequently shown to be caused by a mutation in the P-type ATPase gene (ATP8B1), localised to chromosome 18q21 [2]. ATP8B1 encodes FIC1 (familial intrahepatic cholestasis 1), a widely expressed membrane P-type ATPase. F1C1 may function as an aminophospholipid flippase, transferring phosphatidylserine from the outer to the inner leaflet of the plasma membrane [3].

Severe pruritus, diarrhoea, and growth failure are common manifestations. The disease progresses rapidly to liver cirrhosis or hepatic failure in the first or second decade and usually requires liver transplantation as a curative therapy [4]. Although rickets is identified as a complication of Byler disease in childhood [3], we did not find any reports of Looser zones in adults, which is an indicator of severe osteomalacia. We report a case of multiple Looser zones in an adult with Byler disease.

2. Case presentation

This case report is in keeping with the CARE guidelines [5]. A 33-year-old man, who was an inpatient for treatment of decompensated liver disease secondary to Byler disease, was referred to the Orthopedic department for a review because he was complaining of progressive pain over this right proximal tibia for over one month. There was no history of trauma and the pain was present primarily on weight bearing on the right side; it was noted that he was a vigorous walker despite his poor health. He gave a history of similar pain at multiple sites at various times in the past

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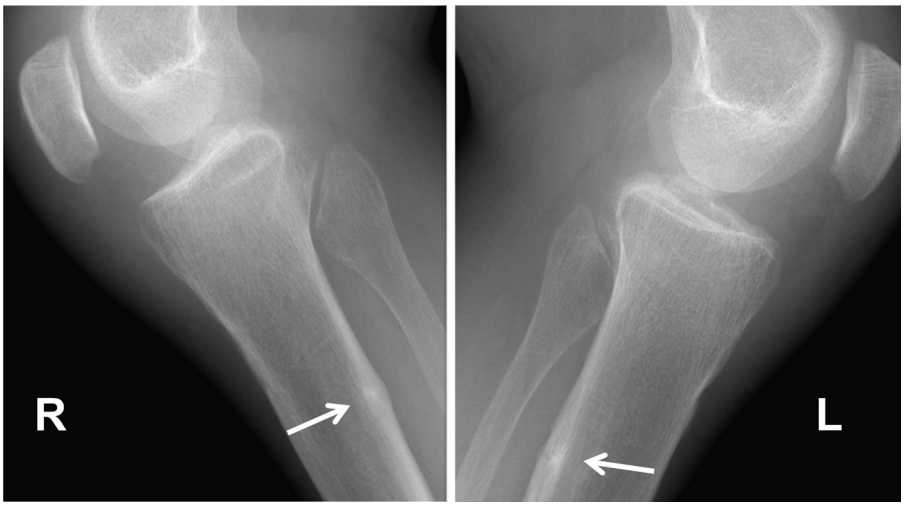

Fig. 1. Lateral radiographs of right and left tibiae and fibulae showing symmetrical Looser zones with evidence of healing on the right.

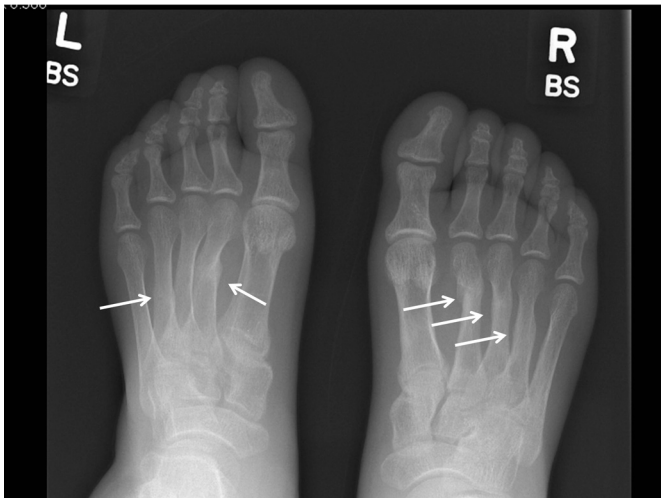

Fig. 2. Radiographs of both feet showing healing right third, fourth, and fifth metatarsal fractures, as well as left second and fourth metatarsal fractures.

that resolved spontaneously within 6–8 weeks of onset. These sites included the contralateral left tibia, both feet and left hip.

On examination he was a man who was of short stature and visibly jaundiced. He had an antalgic gait but was able to ambulate independently. Tenderness was localised to the proximal tibia just distal to the tibial tubercle and he had bilateral foot swelling. Radiographs of his tibiae demonstrated symmetrical bilateral areas of abnormality along the posterior cortex with a lucent line consistent with a stress fracture on the left and cortical thickening consistent with a healed stress fracture of the right (Fig. 1). Radiographs of his feet showed healed stress fractures of third, fourth, and fifth metatarsal shafts on the right side, and fractures of second and fourth metatarsals on the left (Fig. 2).

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) using an Hologic Discovery Model A densitometer, as previously described [6]. BMD was extremely low at all sites measured with Z-scores of −5.5 at lumbar spine, −3.5 at left femur neck, −3.6 at left femur site, and −3.3 at whole body. Coincidentally, the DXA image of the hip suggested an incomplete fracture on the medial aspect of the left femur just below the lesser trochanter (Fig. 3). Subsequently, single-energy imaging was performed using the densitometer in order to obtain an higher definition of the suspected fracture [7]. This confirmed the presence of an incomplete fracture (Fig. 4).

Serum total calcium was low following adjustment for albumin at 2.0 mmol/l (N: 2.2–2.6). Fasting serum phosphorus was low at 0.69 mmol/l (N: 0.84–1.48 mmol/l). Serum creatinine was high at 190 μmol/l with an estimated glomerular filtration rate of 38 ml/min giving a diagnosis of chronic kidney disease (CKD3b). He had a low 25-hydroxyvitamin D at 15.2 mmol/l (N: >30 nmol/l), and elevated parathyroid hormone at 94.1 ng/ml (N: 15–65 ng/ml). Renal phosphorus threshold (TmP/GFR) was low at 0.53 mmol/l (N: 0.84–1.48). Carboxyterminal fibroblast growth factor 23 (FGF23) was very high at 2170 RU/ml (N: <100 RU/ml). The following bone turnover markers in serum were all high: bone specific alkaline phosphatase at 81.3 μg/ml (N: 3.7–20.9 μg/ml); intact osteocalcin at 45.5 μg/ml (N: 14–42 μg/ml); procollagen I aminopropeptide at 110.2 μg/ml (N: 22.1–96.2 μg/ml); and, carboxyterminal telopeptide of type I collagen at 1.41 μg/ml (N: 0.025–0.584 μg/ml).

He was commenced on calcium 1000 mg and vitamin 20 μg daily, at first. Regarding specific management of the multiple Looser zones, he was treated conservatively with analgesia and protected weight bearing as tolerated with crutches. Pain resolved within four weeks and he was allowed to resume full weight bearing, as tolerated. He was advised to return for further assessment if his pain returned or he developed new bone pain.

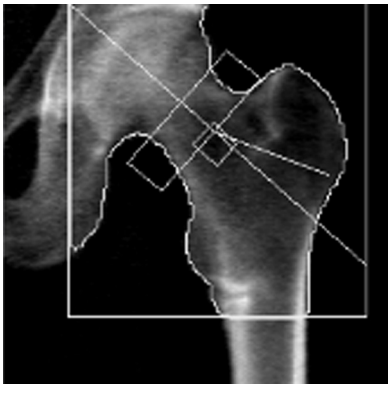

Fig. 3. DXA image of left femur demonstrating incomplete subtrochanteric stress fracture.

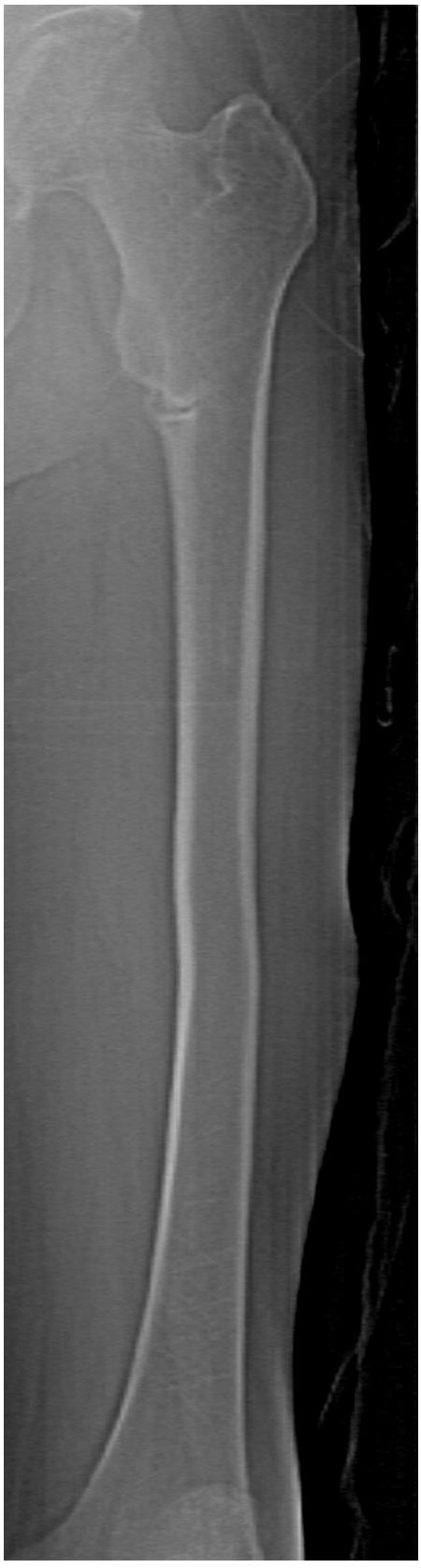

Fig. 4. Single-energy image of left femur using DXA machine demonstrating Looser zone.

3. Discussion

We describe an adult with Byler disease, who presented with multiple Looser zones of osteomalacia. These multiple stress fractures had all the typical radiographic characteristics of Looser zones, as discussed in detail below [7]. Two major causes for his bone disease were identified: vitamin D deficiency and renal phosphorus wasting with elevated FGF23. Chronic vitamin D deficiency in the setting of chronic cholestasis is an expected finding in view of the propensity for malabsorption of fat soluble vitamins that would lead to chronic calcium malabsorption. The phosphaturia and elevated FGF23 was unexpected and is unexplained, as discussed below. Compounding factors that would contribute to bone disease included chronic liver failure and CKD3b. Despite this complexity, his bone disease responded to the simple measure of ensuring adequate calcium and vitamin D intake by supplementation.

Stress fractures are repetitive strain injuries that occur in normal bones and in abnormal bones [7]. Conceptually, a stress fracture is a repetitive strain injury. An individual mechanical load must not be large enough to cause a fracture. The repeated mechanical loads – either tensile, compressive, shear, or commonly mixed – may consist of small number of cycles with a large load, large number of cycles of a small load, or intermediate combination of cycles and loads. The occurrence of a stress fracture in normal bone, as occurs in athletes, is termed a fatigue-type of fracture. Whereas, the occurrence of a stress fracture in the setting of abnormal bone is called and insufficiency-type of stress fracture. For insufficiency-type of fracture to occur, the repetitive activity need not be as pronounced as for fatigue-type fractures. In our patient, the repetitive activity predisposing to repeated Looser zones was vigorous walking. All the stress fractures in our case fitted the characteristics of Looser zones: typical sites such as metatarsals and the medial aspect of femur and tibia, symmetrical occurrences, a broad rather than a narrow band of lucency, parallel margins, minimal marginal sclerosis, and delayed healing [7]. An unusual finding in this report is that the femur Looser zone was suspected at the time of DXA, and the diagnosis of Looser zone was confirmed by single-energy imaging using the DXA machine, which is a novel way for diagnosing stress fractures [6].

We and many others have shown that end stage liver disease is associated with osteoporosis [8]. It is well recognized for many decades that chronic cholestasis in adults is an even higher risk for bone disease [9,10]. Not surprisingly, having cholestasis from birth should be associated with even more severe bone disease. The majority with Byler disease have growth failure as consequence of chronic malabsorption and chronic hepatic failure, but weight for height is often normal [4]. In addition, patients with Byler disease are more likely to manifest extrahepatic disease due to the broad tissue distribution of FIC1 expression, and mark FIC1 deficiency as a multisystem disorder [3].

Renal phosphorus wasting is a much rarer cause of osteomalacia than vitamin D deficiency. Phosphaturia is diagnosed by finding a low TmP/GFR [11]. The principal phosphorus regulation hormones are PTH and FGF23. Our patient had secondary hyperparathyroidism that causes phosphaturia, but FGF23 levels should not be elevated because the level of carboxyterminal FGF23 is directly related to the phosphorus level. A confounding factor in the interpretation of the elevated FGF23 is CKD stage 3b. FGF23 levels rise with progressive in renal function. The estimated mean FGF23 level for CKD stage 3 is 225 RU/ml [12]; but the result in our patient of 2170 RU/ml is nearly 10-fold higher. The explanation for the finding is unknown. It is possible that it is another systemic manifestation of FIC1 deficiency. This is worthy of study in Byler disease.

In conclusion, we report a case of Byler disease who presented with multiple Looser zones of osteomalacia that had been occurring for an unspecified time. He was found to have vitamin D

deficiency, secondary hyperparathyroidism, phosphaturia, and elevated FGF23. His severe bone disease responded in part to simple supplementation with vitamin D and calcium, but he will need ongoing surveillance. We do not have an explanation for the elevated FGF23 level; further research in this area is needed.

Competing interests

The authors declare that they have no competing interests.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Author contribution

All authors contributed in the study design, writing of the paper, and final approval of the case report.

Guarantor

Mr Munir Tarazi, Mr Prasad Ellanti, Dr Malachi J McKenna, Dr Mark Kilbane, Dr P Aidan McCormick, Mr Conor Hurson.

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