CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 19 (2016) 150–153

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

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

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ARTICLE INFO

Article history:
Received 5 November 2015
Received in revised form
16 December 2015
Accepted 19 December 2015
Available online 24 December 2015

Keywords:
Byler disease
Cholestasis
Looser zones
Osteomalacia
FGF23

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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http://dx.doi.org/10.1016/j.ijscr.2015.12.037

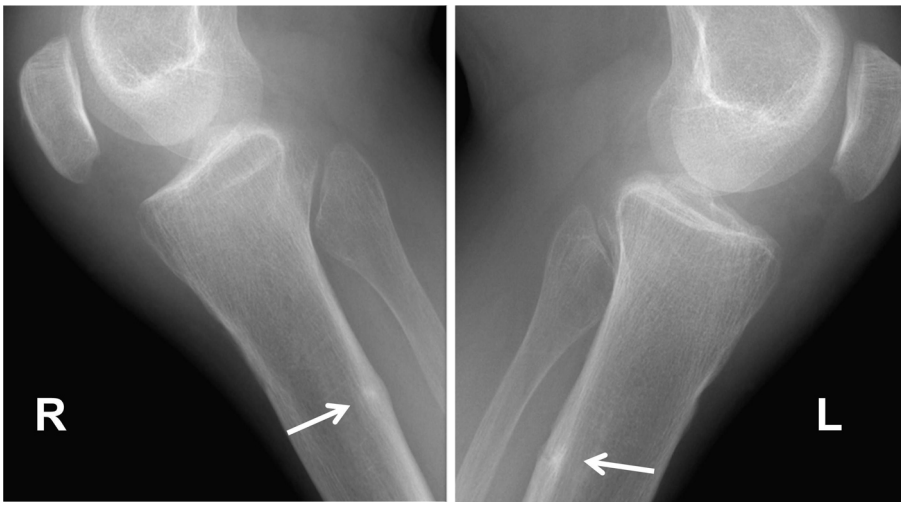

Fig. 1. Lateral radiographs of right and left tibiae and fibulae showing symmetrical Looser zones with evidence of healing on the right.

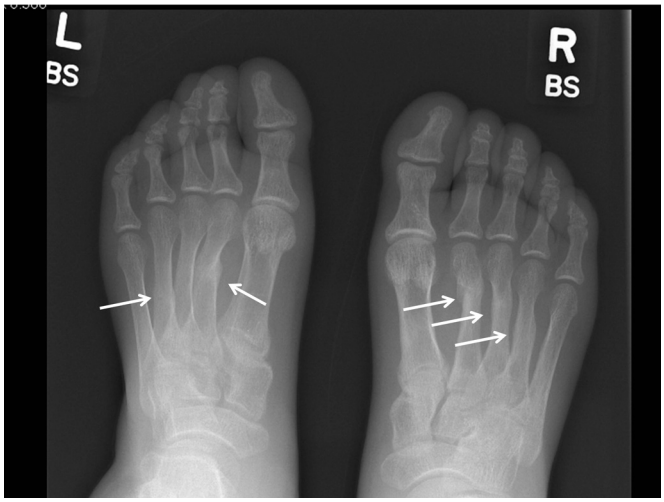

Fig. 2. Radiographs of both feet showing healing right third, fourth, and fifth metatarsal fractures, as well as left second and fourth metatarsal fractures.

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.

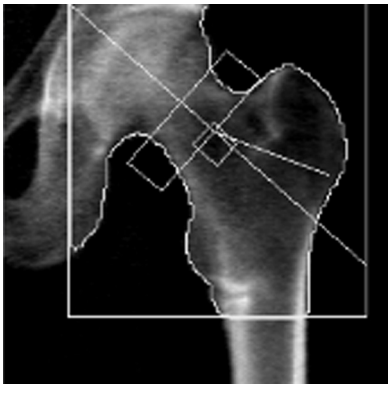

Fig. 3. DXA image of left femur demonstrating incomplete subtrochanteric stress fracture.