Osteomalacia: a case series of patients with atypical clinical orthopaedic presentations

Osteomalacia is uncommon in an affluent subtropical city like Hong Kong, where sunlight exposure is adequate and nutritional support is good. We present three patients who had osteomalacia with different presentations. A 74-year-old male with oncogenic osteomalacia presented with multiple bone pain. His biochemical markers returned to normal 4 days postoperatively after resection of a second toe giant cell tumour of tendon sheath. A 62-year-old woman with a history of liver problem and proximal muscle weakness was admitted with atraumatic fracture of the left distal humerus due to osteomalacia. An 81-year-old vegetarian woman with inadequate sun exposure complained of multiple bone pains. Subsequent investigation revealed dietary- and sunlight-deficient osteomalacia with multiple bony abnormalities including marked femur bowing.

Introduction

Osteomalacia is a metabolic bone disease that leads to softening of bone. In Hong Kong, vitamin D supplements and milk fortification with vitamin D are common. Sunshine is abundant even during winter, and hence excessive body exposure to sunlight is the problem rather than limited exposure. Hence, very often the disease has been overlooked by physicians. Here we present three osteomalacia patients with different clinical manifestations.

Case series

Case 1: Oncogenic osteomalacia

In 2007, a 74-year-old man with a history of gout and hypertension complained of left lower limb pain and bilateral lower limb weakness on-and-off for half a year. He had no constitutional or thyroid symptoms, such as fever, weight loss, history of fracture, steroid use, exposure to heavy metals, or malignancy. Clinical examination showed proximal myopathy, diffuse tenderness at left distal fibula and tibia. He had an X-ray of the left lower limb at the government out-patient clinic, which revealed para-articular osteopenia with lucent areas in proximal phalanges of left big toe, left distal fibula and tibia. The patient was then referred to the specialist clinic for further investigation.

Blood phosphate (PO₄) was low at 0.49 mmol/L (reference range, 0.88-1.45 mmol/L), serum alkaline phosphatase (ALP) was elevated to 173 U/L (51-141 U/L), and tubular reabsorption of PO₄ based on 24-hour urine was decreased, at 0.58 mmol/L (0.82-0.95 mmol/L). Serum 25-hydroxy-vitamin D and 1,25 dihydroxy-vitamin D were reduced, with 15.2 ng/mL (20-100 ng/mL) and 10.3 pg/mL (25.1-66.1 pg/mL), respectively. Serum calcium, parathyroid hormone, and creatinine were normal, and there was no glycosuria or aminoaciduria.

A bone scan was then arranged, and showed multiple hot spots over the rib cage, mainly involving the costochondral and costovertebral junctions, L3-5 vertebrae and the feet (Fig 1). Findings were suggestive of pseudofractures due to osteomalacia.

Oncogenic osteomalacia (OOM) was suspected by the endocrinologist. A positron emission tomography–computed tomographic scan was performed and revealed a hypermetabolic subcutaneous soft tissue mass on the plantar surface of left second metatarsal head. A magnetic resonance imaging of the left foot showed there was a soft tissue mass (2.8 x 2.2 x 0.9 cm) on the plantar aspect adjacent to the second metatarsal head. The soft tissue mass was then excised and histology confirmed it to be giant cell tumour of the tendon sheath. The patient’s PO₄ returned to normal 4 days postoperatively. At latest follow-up (September 2009), all blood parameters were normal.

Case 2: Liver disease–related osteomalacia

A 62-year-old woman was admitted because of atraumatic supracondylar fracture of the

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Department of Orthopaedics and Traumatology, Queen Mary Hospital, Pokfulam, Hong Kong
AWM Fok, FHKCOS, FHKAM (Orthopaedic Surgery)
TP Ng, FHKCOS, FHKAM (Orthopaedic Surgery)

Correspondence to: Dr AWM Fok
Email: augustfok@hotmail.com
left elbow. She had a history of hepatitis B cirrhosis for which she had had a liver transplant in 2006. She also complained of progressive bilateral lower limb weakness and hip pain over the past 1 year; for 1 month she could only walk with assistance. Blood tests showed a reduced \( PO_4 \) level of 0.63 mmol/L, an elevated (bone) ALP of 656 U/L, a reduced level of 25-hydroxy-vitamin D (13.5 ng/mL) and 1,25 dihydroxy-vitamin D (<8 pg/mL). The liver function was deranged.

Other than the supracondylar fracture of the distal humerus, X-ray pelvis showed marked coxa vara (Fig 2). A bone scan revealed multiple hot spots (indicative of metabolic disease) bilaterally over the rib cage and the left elbow. Open reduction and internal fixation was performed and the patient was treated with 1,25 dihydroxy-vitamin D supplement (Rocaltril; Roche, Basel, Switzerland), and her hips were regularly monitored. At latest follow-up in December 2009, the fracture had healed uneventfully and her blood calcium and phosphate levels had normalised.

Case 3: Dietary- and sunlight-deficient osteomalacia
An 81-year-old woman, who was a strict vegetarian and homebound most of the time, was admitted to our unit because of bilateral thigh pain. X-ray revealed marked femoral bowing with cortical thickening, which was characteristic of osteomalacia (Fig 3). Serum \( PO_4 \) was reduced to 0.77 mmol/L and also with reduced serum vitamin D. The patient was treated with vitamin D supplementation in view of dietary deficiency, and her femur was regularly monitored by X-rays.

Discussion
Vitamin D plays a very important role in calcium and phosphate metabolism. Dietary vitamin D is absorbed through the small intestine, and converted by liver to 25-hydroxy-vitamin D and then to 1,25 dihydroxy-vitamin D by the kidney. A slight lack of vitamin D (vitamin D insufficiency) results in osteoporosis (decrease in bone mass), and a major lack of vitamin D (vitamin D deficiency) leads to osteomalacia, a qualitative mineralisation defect of the bone.

Animal-derived food provides significant amount of vitamin D in the form of vitamin D3 (cholecalciferol). Another supply comes from the action of ultra-violet B light on 7-dehydrocholesterol in the skin. Pure vegetarians are at risk of developing osteomalacia without vitamin D supplements and adequate sunlight exposure, as ensued in our third patient. It is also reported that the prevalence of osteomalacia in Europe is high, as vitamin D synthesis in skin is significantly diminished during the long periods of winter with limited daylight.

Clinical manifestations of osteomalacia are usually insidious. Bone pain described by patients is characteristically diffuse and may affect several body

FIG 1. Bone scan of case 1 showing multiple hot spots over rib cages mainly involving the costochondral and costovertebral junctions, L3-5 vertebrae and feet, suggestive of osteomalacia.

骨質軟化症的非典型臨床病徵的病例系列
在香港這個亞熱帶氣候的富裕城市，陽光充沛，營養補充支援充足，骨質軟化症實在少有。本文報告三名分別出現不同病徵的骨質軟化症患者。一名74歳患有瘤源性骨質軟化病的男性，身體多處地方出現骨痛，病人接受於第二只腳趾腱鞘位置的巨細胞瘤切除術，術後第四天，病人的生化指標回復正常水平。另一名62歳一向有肝病及近端肌無力的女性，因骨質軟化症而出現肱骨遠端的非創傷性骨折。最後一名81歳女性有骨痛，病人是一名素食者，加上缺乏日照，檢查顯示她因食物中攝取所需物質不足，以及很少接受陽光的照射而導致骨質軟化症，病人更出現包括股骨彎曲的多處骨性畸形的情況。
parts, for examples, back, knee, and rib cage. These symptoms may mimic fibromyalgia, polymyalgia, early rheumatoid arthritis, or even psychosomatism. Skeletal deformities such as kyphoscoliosis, protrusio acetabuli and limb bowing occur very late in the disease. As in our first two cases, acquired deformity with symmetric limb involvement affects elderly patients and should alert clinician to the possibility of metabolic bone disease including osteomalacia and renal osteodystrophy. Simple renal functional test, blood calcium profiles and ALP can provide important clues to diagnosis.

Although uncommonly seen nowadays in adult patients with chronic liver disease, historically, osteomalacia has been reported in up to 64% of individuals with primary biliary cirrhosis. About two thirds of patients with cirrhosis and 96% of those awaiting liver transplantation have low vitamin D levels, in which abnormality is also associated with decreased bone mineral density, high bone turnover, and increased risk of osteoporotic fracture.
For osteomalacia patients with deficient vitamin D intake, treatment involves 50 000 IU of vitamin D2 once or twice per week, plus 1 g of elemental calcium per day until blood parameters returned to normal. This usually occurs within 6 months. Patients with liver disease and impaired 1,25 dihydroxy-vitamin D synthesis can be treated with daily oral doses of 1,25 dihydroxy-vitamin D supplement (0.25-1 mg/day). The prognosis is good if treatment is appropriately directed at the underlying aetiology.

Oncogenic osteomalacia is a paraneoplastic syndrome in which the presence of a soft tissue or bone tumour causes vitamin D-resistant osteomalacia. Though it is more common in patients older than 30 years, the age can range from 7 to 73 years, and has a male-to-female ratio of 1.2:1. Symptoms of osteomalacia—for examples, muscle weakness, diffuse bone pain, and pathological fractures—usually manifest before the tumour. A variety of benign and malignant bone and soft tissue tumours—including giant cell tumours, pigmented villonodular synovitis, vascular tumours, and non-ossifying fibromas—have been accounted for OOM. Characteristic metabolic derangements in OOM are phosphaturia, hypophosphataemia, and low serum levels of 1,25 dihydroxy-vitamin D. Serum alkaline phosphatase is elevated, with a normal-to-low serum calcium level. Recent studies have identified fibroblast growth factor 23 (FGF-23) to be elevated in these patients’ venous blood, and as this tumour tissue factor may be the possible causative paraneoplastic substance, it could be regarded as a serum marker of this condition. However, FGF-23 serum testing is not available in Hong Kong yet, and blood samples have to be sent to an overseas laboratory if this test is required. Most of the time, the metabolic derangement, including serum FGF-23 level, will return to normal once the causative tumour is removed. Diagnosis of OOM is often more difficult than its treatment, and requires high clinical alertness, especially if the tumour is small and not obvious to the patient or to doctors. Skeletal survey may show features of osteomalacia, eg looser’s zones. Bone and radiolabelled-octreotide scans are reported to be sensitive in identifying such occult tumours.

Establishing the diagnosis of osteomalacia is paramount to proper management of the patient. Careful evaluation of patients with respect to clinical, biochemical, and radiological examinations is essential, as severe disability (bone pain, weakness, and pathological fracture) and even mortality can be avoided with simple treatment.

References