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Tumour-induced osteomalacia (TIO)

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A 52-year-old physically disabled miner, professionally inactive for 5 years, was admitted to the endocrinology clinic to diagnose the causes of bone fractures. The man had suffered from bone pain and muscle weakness for over 5 years. The chronic pain he was suffering led to his long-term and sustained use of non-steroidal anti-inflammatory drugs (NSAIDs) and morphine. Three-year pre-hospital diagnostics excluded malignant neoplasm and haematological diseases.

On admission, the patient's general condition was quite good. Physical examination revealed thoracic kyphoscoliosis, leg deformation, spine pain on palpation, and slight muscle weakness. The patient moved with a waddling gait using a walker.

X-ray examinations showed symmetrical fractures of V–VII ribs, fractures of both fibulas with symptoms of abnormal healing, as well as generalised bone loss (Fig. 1). Bone scintigraphy with ^{99m}technetium-methylene diphosphonate (^{99m}TC-MDP) revealed multifocal lesions with increased activity (Fig. 2). Densitometry (DPX) revealed osteoporosis (Supplementary File — Tab. S1). Laboratory tests showed significant hypophosphataemia, a low concentration of 1α,25-dihydroxyvitamin D 1,25(OH)2D, increased alkaline phosphatase (ALP) activity, and low normal serum parathormone, calcium, and 25-hydroxy-vitamin D 25(OH). Renal phosphate reabsorption was significantly reduced (Supplementary File — Tab. S2). This raised the suspicion of hypophosphataemic osteomalacia, which most often results from genetic disorders or fibroblast growth factor 23 (FGF23) overproduction in neoplastic tumours. Examination of pathogenic mutations in the FGF23 gene did not reveal any genetic basis for the disease. Therefore, positron emission tomography-computed tomography with fluorode-

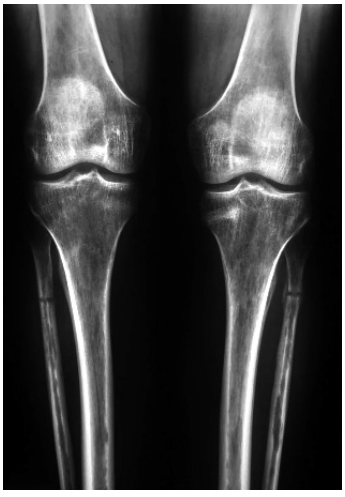

Figure 1. *X-ray of the lower limbs — symmetrical fractures of both fibulas*

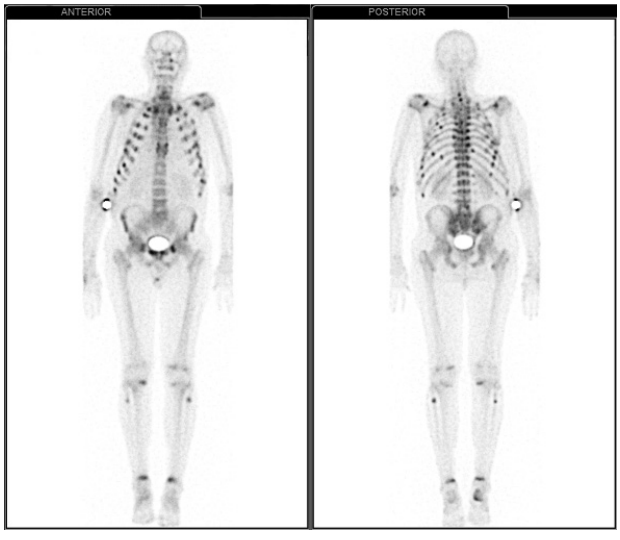

Figure 2. *Anterior (left) and posterior (right) whole-body scintigraphy with (^{99m}Tc-MDP) show multifocal lesions of increased activity*

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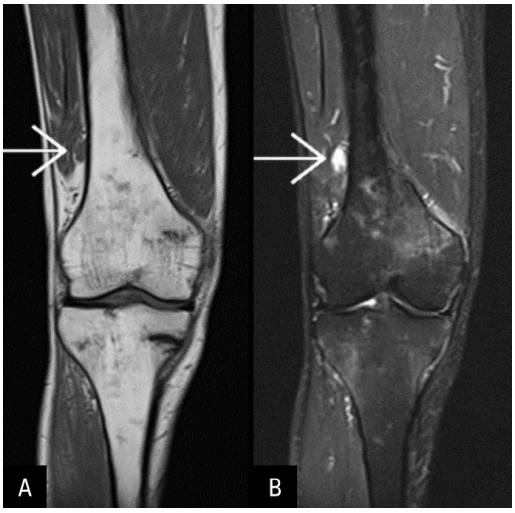

Figure 3. *Magnetic resonance (MR) of the lower limbs. The arrow indicated the focus in the right thigh. There are also numerous speckled, low-density foci in the bone structure.* **A.** *T1-weighted imaging;* **B.** *T2-weighted imaging*

oxyglucose ([^{18}F]FDG-PET/CT) was performed to identify the source of the excessive FGF23 production. A lesion within the soft tissues of the right thigh with a metabolism suggesting its benign nature was identified. Magnetic resonance imaging (MRI) confirmed the existence of a small tumour in the biceps femoris (Fig. 3). The patient was referred for surgery. Preoperative treatment with alfacalcidol, phosphate salts, and calcium carbonate resulted in clinical and biochemical improvement. The tumour was resected, and histopathological examination diagnosed capillary haemangioma. The outcome of surgery was very good. Serum phosphate, 1,25(OH)2D, and ALP normalised, and serum FGF23 concentrations decreased 100-fold (Supplementary File — Tab. S2). Bone mineral density improved significantly (Supplementary File — Tab. S1). Bone scintigraphy revealed regression of previous changes. Three months after surgery, the patient was able to move independently and did not require analgesic therapy.

Hypophosphataemic osteomalacia most often results from an excess of tumour-secreted FGF23 or has a genetic basis. Adults undergo genetic tests for autosomal dominant hypophosphataemic rickets (ADHR), and in the absence of pathogenic mutations in the *FGF-23* gene, as in this case, a FGF23-secreting tumour is sought [1, 2].

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome that results from the production of FGF23 in benign mesenchymal tumours. FGF23 reduces renal reabsorption of phosphates, leading to hypophosphataemia, and it inhibits vitamin D 1-alpha-hydroxylase activity, thereby reducing calcitriol synthesis and intestinal phosphate and calcium absorption [1, 2]. Calcium, phosphate, and calcitriol deficiency impairs bone mineralisation, leading to osteomalacia. Bones become soft and deform easily, which causes distortion, pathological fractures, and pain [1, 2]. Identification of FGF23-producing tumours is difficult because they are usually small and can be found anywhere in the body, although most often in the head and legs. MRI is recommended for locating tumours, but due to its low specificity, many authors suggest [^{18}F]FDG-PET/CT or the more specific PET/CT with gallium-68 or scintigraphy of somatostatin receptors [1, 2]. The treatment of choice is tumour removal [1–3]. The prognosis after complete tumour resection is good; however, some tumours may be malignant. Until the tumour is resected, pharmacological treatment with phosphates and active vitamin D is recommended. Metabolic disorders quickly normalise after surgery. Bone fractures heal within a few months, restoring the patient's physical fitness [1–3]. Unfortunately, low awareness of this rare disease and difficulty in locating the source of excess FGF23 often delay diagnosis and treatment.

In the case of the presented patient, his ailments were perceived for a long time as being a consequence of physical exertion during his years as a miner. However, bone X-rays revealed osteolytic lesions and pseudo-fractures, suggesting myeloma, neoplastic metastases, or primary hyperparathyroidism. Extensive diagnostics excluded these pathologies and led to the diagnosis of tumour-induced osteomalacia. Histopathological examination of the removed tumour revealed a capillary haemangioma. The phosphaturic tumour pattern consists of small mesenchymal cells lying in a richly vascularised stroma with a disrupted microvascular network; therefore, they can be described as haemangioma, as in this case [4]. Serum FGF-23 decreased by more than 100-fold post-surgery, and although there are no strict laboratory standards for serum FGF-23 levels, we believe that such a significant drop confirmed the diagnosis of a FGF-23-producing tumour. Gradual normalisation of metabolic disorders, improvement of bone quality, and relief of pain and myopathy confirmed the effectiveness of the treatment. There was no relapse on 2-year follow-up.

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