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Oncogenic osteomalacia — detection of the tumour site upon physical examination

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A 50-year-old Caucasian woman was referred to our Department of Endocrinology in February 2018 for exacerbating bone pain, general fatigue, muscle weakness, and walking difficulties.

The symptoms appeared in 2015 for the first time, and during the primary diagnosis the laboratory results showed a low level of 25-hydroxyvitamin D3: 17 ng/mL (reference range: 30–100 ng/mL) with normocalcaemia (phosphates were not estimated hitherto). Several imaging studies showed multiple fractures including distal fibula and tibia (Fig. 1A), fifth metatarsal shaft in the left foot, both sides of the ribs, and sacral bone (Fig. 1B). There was no history of trauma or any familial inherited bone disorders. She was diagnosed with osteoporosis (T-score L1–L4: –2.9), and bisphosphonates treatment and vitamin D supplementation in standard doses were recommended.

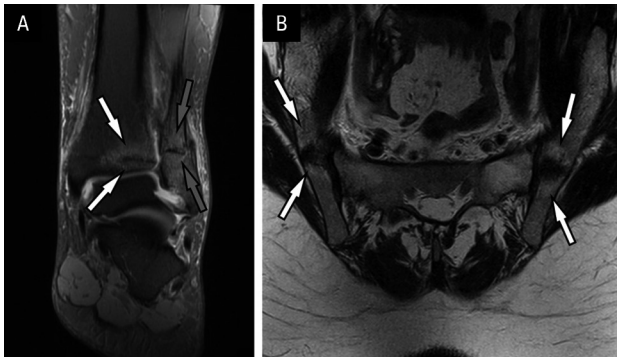

Figure 1. *Coronal T1-weighted magnetic resonance (MR) image of the left ankle joint (***A***) shows left distal fibula fracture (grey arrows) and left distal tibia fracture (white arrows). Coronal T2-weighted MR image of the sacroiliac joints (***B***) shows sacral bone fracture (arrows)*

Due to the worsening of symptoms despite the treatment, the patient was hospitalized in October 2017 in the physiotherapy department. Psoriatic arthritis, ankylosing spondylitis (negative HLA-B27), and rheumatoid arthritis [rheumatoid factor (RF) < 10 IU/mL] were all ruled out. During the differential diagnosis, a full laboratory evaluation of calcium-phosphate balance was finally carried out revealing mild hypophosphataemia: 1.6 mg/dL (reference range: 2.3–4.7 mg/mL) and increased activity of alkaline phosphatase: 197 U/L (reference range: 41.0–108.0 U/L). Following an endocrinological consultation, the patient was referred to our clinic to complement the diagnosis and treatment.

On the day of the admission to our clinic, a waddling gait was noticeable, she required walking assistance, and had difficulty getting up from a sitting position. On physical examination, upon palpation, the patient was found to have a firm, flat subcutaneous mass located inferior and lateral to the right scapula, measuring approximately 3 cm in its longest diameter (Fig. 2). The patient had noticed the lesion for the first time about 5 months earlier, and it was then of a similar size.

A biochemical evaluation was significant for hypophosphataemia (1.5 mg/dL), phosphaturia (transport maximum of phosphate per glomerular filtration rate was 0.3 mmol/L [normal range: 0.80–1.35 mmol/L]), mildly increased activity of alkaline phosphatase, reduced 1,25-dihydroxyvitamin-D: 5.49 pg/mL (refer-

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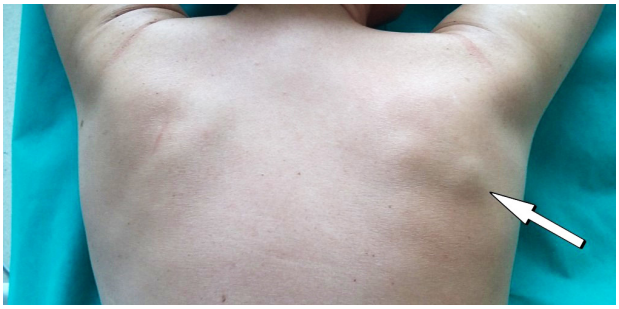

Figure 2. *The flat, cohesive lesion in the subcutaneous tissue (arrow) in the region of the patient's right scapula. The mass was slightly movable, and no lymphadenopathy was found in the surrounding areas*

ral ranges: 25.0–86.5), with normocalcaemia, and increased fibroblast growth factor 23 (FGF23): 412 kRU/L (26.0–100.0).

On ultrasound, the lesion in the soft tissues of the right scapular region measured 27 × 21 × 6 mm and presented with heterogeneous, decreased echogenicity, smooth contours, and increased vascularity features. Due to easily accessible location, the tumour was resected (Supplementary File — Fig. S1), regardless of an apparent lack of time correlation between the commencement of musculoskeletal symptom manifestations and the first report of the lesion. On histopathology, the diagnosis of phosphaturic mesenchymal tumour (PMT) was rendered (Supplementary File — Fig. S2).

On post-surgery day 1 her serum phosphorus improved to 2 mg/dL. Three weeks after surgery it normalized to 3.5 mg/dL, the serum concentration of FGF23 decreased to 36.0 kRU/L, and 1,25-dihydroxyvitamin-D increased to 77.8 pg/mL.

The symptoms of the disease subsided very slowly: the patient began to walk on her own after approximately a month, and after 2 months her swaying and waddling gait disappeared. Muscle pain and general fatigue lasted up to 4 months. At almost 4 years (45 months) of follow-up the patient claims to feel healthy with a good quality of life.

Oncogenic osteomalacia (OO) is a rare paraneoplastic syndrome, resulting from hypersecretion of phosphatonins, most commonly FGF23. The FGF23 overproduction causes phosphaturia due to a reduction of tubular phosphate reabsorption. Moreover, it may reduce the activity of 25-hydroxyvitamin D 1a-hydroxylase. The consequence of chronic hypophosphataemia is inadequate bone mineralization, presenting as osteomalacia. The PMT is the main culprit of OO [1].

Detecting a primary tumour may be extremely challenging, due to its usually small size, slow growth, and benign nature. Finding the PMT may require advanced imaging modalities, including functional nuclear imaging and selective venous FGF-23 sampling [1–3].

However, based on our own experience and a review of the available literature, performing sophisticated imaging modalities for the effective treatment of OO is not obligatory in all cases [1, 4]. The role of physical examination in locating superficial PMT should not be underestimated. In these cases, ultrasound may be a sufficient imaging technique before tumour resection [1, 4]. However, we would like to highlight that in cases of no biochemical or clinical improvement after resection of PMT, the multifocality of the tumour and malignant dissemination should be considered [1–3]. Therefore, thorough postoperative follow-up for all patients with OO is obligatory.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Author contributions

E.Z., M.N., and S.K.J. wrote the manuscript and reviewed the literature. A.O.P., M.Ś., M.P., W.B., and K.S. carried out critical interpretations. E.Z. secured ethical approval for the study. All authors treated the patient, collected the data, contributed to the article, and approved the submitted version.

Ethical approval

This study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/333/2021). The patient gave written informed consent for the publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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