Submitted: 30.12.2021
Accepted: 05.01.2023
Early publication date: 27.04.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0022
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 2/2023

Multiple bone fractures caused by severe hypophosphatemia in the course of the mandible tumour

Monika Ogrodowczyk-Bobik[1], Tomasz Miś[1], Klaudyna Borucka[1], Dariusz Kajdaniuk[1, 2], Agata Urbanek[1], Szymon Janyga[1], Franciszek Mazur[1], Halina Borgiel-Marek[3], Anatol Wodołażski[4], Bogdan Marek[1, 2]

[1]Department of Endocrinology and Metabolic Diseases, Regional Specialist Hospital No. 3, Rybnik, Poland
[2]Department of Pathophysiology, Chair of Pathophysiology and Endocrinology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[3]Department of Craniomaxillofacial Surgery, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[4]Department of Pathomorphology, University Clinical Centre n. prof. K. Gibinski, Medical University of Silesia, Katowice, Poland

Key words: *TIO; tumour-induced osteomalacia; FGF-23; phosphatonin-1; hypophosphataemia*

A 37-year-old woman was admitted to the Endocrinology Department for the diagnosis of multiple fractures of the bones of the upper and lower limbs, pelvis, and thorax. The patient reported 2 years of musculoskeletal pain, muscle weakness, and chronic fatigue. She was treated for arterial hypertension, autoimmune thyroid disease, and psoriatic arthritis (she was waiting to start biological therapy). On admission to the endocrinology department, the following deviations from the normal state were noted in a physical examination: musculoskeletal pain, sallow complexion, dull hair, and forced body position. Technetium 99m methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy performed one month before hospitalization described increased accumulation of radioactive tracer in the bones of the pelvis, midfoot, ribs, and upper and lower limbs, corresponding to the coexistence of inflammatory changes and past fractures, with ambiguous image of the left femoral neck. Basic laboratory tests showed severe hypophosphataemia — phosphorus (P): 0.61 mmol/L (n. 0.74–1.52), hyperphosphaturia 41 mmol/24 h (n. 11–32), slightly elevated parathyroid hormone level — 82.7 pg/mL (n. 10–68.2) accompanied by a significantly reduced concentration of 1,25 $(OH)_2$ D3: 6.3 pg/mL (25–86.5). There were no abnormalities in calcium level: 2.2 mmol/L (n. 2.1–2.55), ionized calcium level (Ca2+): 1.18 mmol/L (n. 0.98–1.3), or 25OHD_3 level: 56.6 ng/mL (n. 30–60). Also, the values of basic tumour markers such as carcinoembryonic antigen (CEA), cancer antigen 19-9 (Ca 19-9), cancer antigen 125 (Ca-125), and chromogranin A were normal.

Chest, abdominal, and pelvic computed tomography (CT) showed multiple bone fractures including ribs, pelvic bones, upper limb bones, and leg bones with atypical subtrochanteric femoral fracture. No symptoms of malignancies were found. Patient was admitted to the Orthopaedic Department where she was operated on (closed repositioning and internal stabilization with an intramedullary nail — MEDIN). Histopathological characteristics of postoperative material showed microarchitecture disorders of bone barrels. Replacement therapy was recommended: phosphate-rich diet, active forms of vitamin D_3 (alfacalcidol 2 ug per day), and mixtures of phosphate salts (*Natrii phosphorici monobasici* 9.0 g, *Natrii fosforici bibasici* 72.5 g, *aqua destillata* ad 500 g, 3 × 10 mL orally). Clinical improvement occurred rapidly, with a significant reduction of bone pain, fatigue, and muscular weakness. Laboratory tests showed compensation for 1.25$(OH)_2$ D3 deficiencies; however, the serum phosphate concentration was still reduced as a result of incorporation into bone.

Gallium-68 dotatate positron emission tomography/computed tomography (68Ga-DOTATATE PET/CT) performed after the recovery period showed multiple foci of pathological accumulation of radiolabel corresponding to the previously described fractures and inflammatory changes within the bone (including at the level of the left femoral neck); standardized uptake values (SUV max: 5.03) and its highest accumulation at the level of the mandibular body on the left side (SUV max: 14.39).

Monika Ogrodowczyk-Bobik, Department of Endocrinology and Metabolic Diseases, Regional Specialist Hospital No. 3, Rybnik, Poland; e-mail: monikaobobik@gmail.com

Ultrasound examination showed a hypoechoic structure 14 × 24 mm in size with rich mixed vascularization, located along the left lower mandibular gall. Computed tomography confirmed the presence of a well-demarcated soft-tissue lesion closely adjacent to the inner surface of the mandibular body, measuring 22 × 9 × 17 mm, enhancing after contrast administration, with visible small defects in the cortical layer of bone and a small periosteal reaction. The result of a fine-needle aspiration biopsy was inconclusive, with smears containing blood and cells with oxyphilic cytoplasm and granular nucleus. For technical reasons, it was not possible to determine phosphatonin-1 in the blood. The patient was referred for surgical treatment. Histopathological examination of the removed structure revealed a benign neoplasm, the microscopic picture of which may speak for myoepithelioma.

Myoepithelioma (myoepithelial adenoma) is a very rare neoplasm of the salivary glands, made up of myoepithelial cells. They are mostly benign lesions, locating mainly in the parotid gland or palate, and are treated by surgical removal.

A gradual increase in phosphate concentrations was achieved after surgery (up to 0.69 mmol/L), but oral supplementation was still used, due to the process of its incorporation into bone structures.

The overall clinical picture is in favour of hypophosphataemic osteomalacia in a tumour of the mandibular region. It is a rare disease entity with severe hypophosphataemia resulting from ectopic production of fibroblast growth factor 23 (FGF-23 — phosphatonin-1) by tumours [1]. Benign tumours of predominantly mesenchymal origin [phosphaturic mesenchymal tumour mixed connective tissue variant (PMTMCT)] have been described most frequently (epitheliomas, mesotheliomas) [2], usually located in the limbs or head.

Due to the small size of the lesion, isotopic studies [68Ga-DOTATATE PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT)] are important in addition to classical diagnostic imaging [3]. FGF-23 reduces blood phosphorus concentrations by increasing phosphaturia and it inhibits 1-alpha hydroxylase catalysing the conversion of $25OHD_3$ to 1.25 $(OH)_2D_3$, resulting in a reduction in 1.25(OH)2 D3 concentrations and an increase in parathyroid hormone concentrations [4]. In the differential diagnosis, genetically determined hypophosphataemic rickets should be considered, but this has a different clinical picture (onset of symptoms in childhood, characteristic phenotype — short stature, sabre-like lower extremities, familial occurrence). The treatment of choice for TIO is surgery, but this is not always possible due to the difficulty of localising the lesion and active vitamin D and phosphate substitution [5]. In recent years, attempts to treat the syndrome with burosumab (KRN23), i.e. a human anti-FGF-23 antibody, have also been described [6].

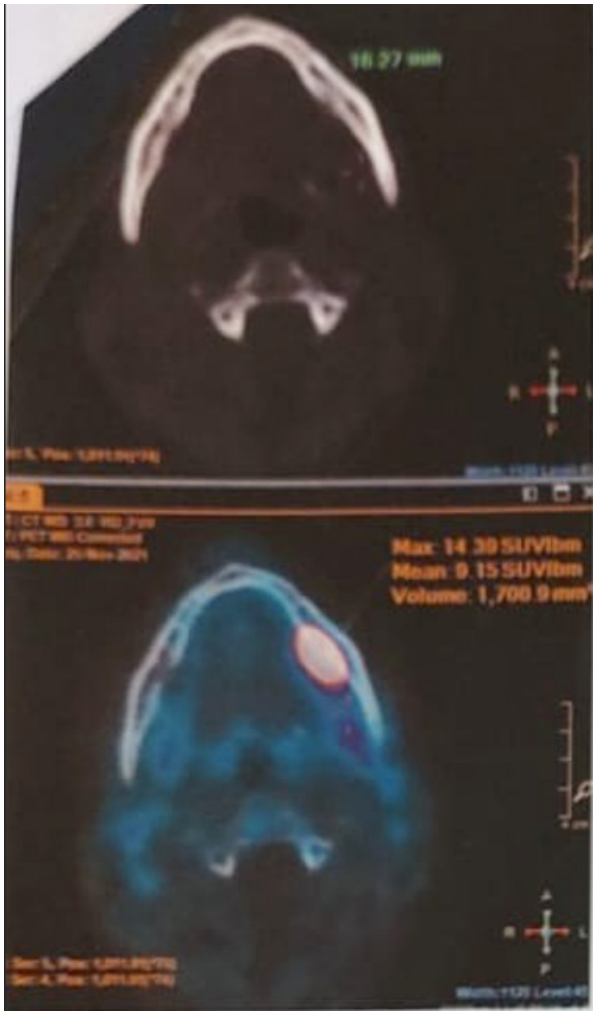

Figure 1. *68Ga-DOTATATE PET/CT scans; pathological tracer accumulation in the mandibular body on the left side*

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