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Oncogenic osteomalacia should be considered in hypophosphatemia, bone pain and pathological fractures

Hipofosfatemia, bóle kostne, złamania patologiczne — pomyśl o onkogenicznej osteomalacji

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Abstract

The clinical manifestation of oncogenic osteomalacia includes bone pain, pathological fractures, general fatigue and muscle weakness. Such unspecific symptoms hinder the establishment of a proper diagnosis which very often requires long-lasting investigations with many diagnostic imaging methods. Here, we discuss difficulties in the diagnosis of oncogenic osteomalacia using the example of our own clinical case: a 56 year-old woman with a history of pain in the left hip and two years of walking difficulties. A plain radiograph and CT scan revealed pathological fractures. Multiple myeloma, primary hyperparathyroidism and bone metastatic disease were excluded. Routine laboratory tests showed elevated alkaline phosphatase and a mild degree of hypophosphatemia. CT and MR imaging confirmed the presence of a pathological mass in the thorax. Tumour excision and histopathological test results revealed the diagnosis of a phosphaturic mesenchymal tumour. Our case, showing the clinical course of the disease from the symptoms manifested at the beginning to the establishment of the diagnosis, can serve as a model illustration of the diagnostic struggle involved with oncogenic osteomalacia. **(Pol J Endocrinol 2012; 63 (3): 234–238)**

Key words: *oncogenic osteomalacia, tumour-induced osteomalacia, hypophosphatemia, bone pain, pathological fractures*

Streszczenie

Osteomalacja onkogeniczna jest rzadkim zespołem paranowotworowym klinicznie charakteryzującym się bólami kostnymi, złamaniami patologicznymi, uogólnionym zmęczeniem i osłabieniem mięśniowym. Niecharakterystyczne i mało specyficzne objawy powodują, że postawienie właściwej diagnozy jest często bardzo trudne, czasochłonne i wymaga wielu badań dodatkowych. Autorzy omówili problemy i trudności diagnostyczne tej jednostki chorobowej na podstawie własnego przypadku klinicznego — 56-letniej chorej z objawami bólu lewego stawu biodrowego i trudnościami w poruszaniu się od około 2 lat. W RTG i tomografii komputerowej miednicy zobrazowano złamania patologiczne. Przeprowadzono diagnostykę różnicową w kierunku szpiczaka mnogiego, nadczynności przytarczyc i rozsiewu choroby nowotworowej. Podstawowe badania laboratoryjne wykazały podwyższenie aktywności fosfatazy alkalicznej i umiarkowanego stopnia hipofosfatemię. Badania tomografii komputerowej i rezonansu magnetycznego klatki piersiowej potwierdziły obecność masy patologicznej wewnątrz klatki piersiowej. Usunięcie guza i badanie histopatologiczne tkanki przyniosło rozpoznanie fosfaturycznego guza mezenchymalnego. Prezentowany przypadek kliniczny — od pojawiania się pierwszych objawów, poprzez proces diagnostyczny, do wyleczenia — może stanowić lekcje pokazową zmagań diagnostycznych w onkogenicznej osteomalacji. **(Endokrynol Pol 2012; 63 (3): 234–238)**

Słowa kluczowe: *onkogeniczna osteomalacja, hipofosfatemia, bóle kostne, złamania patologiczne*

Case report

A 56 year-old woman was referred to our Department of Endocrinology and Internal Medicine at the Medical University of Gdansk for evaluation of multiple fractures.

She had had pain in her left hip for two years. The pain was the reason why she visited her general practitioner, a neurologist and an orthopaedic consultant. Plain radiograph and magnetic resonance imaging (MRI) of the vertebrae and radiographs of the hip joints had been carried out, yet these imaging tests had not revealed the cause of her complaints. Rehabilitation and sanatorium treatment did not improve the patient's condition. Gradually, the discomfort intensified and additionally pain of the lower right extremity occurred. A radiograph of her hip joints, taken 18 months after the first examination, revealed fractures of the ileum and superior pubic ramus on the right (Figure 1).

A CT scan of the abdominal region detected pathological fractures in the 10th rib, ischiadic, pubic and iliac bones on the right, as well as osteolytic lesions in the

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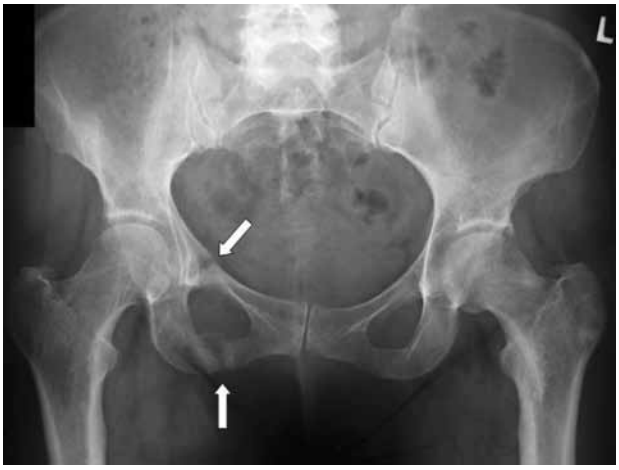

sacral and iliac bones, second lumbar vertebral body, and in the neck of the right femur; the largest being 32 mm (Figures 2A, 2C, 2E, 2G).

The patient was hospitalised. Existing fractures were initially mistaken for secondary bone lesions. Differential diagnoses between multiple

Figure 1. *Frontal radiograph of the pelvis. White arrows point to fractures of the right ileum and superior pubic ramus*

Rycina 1. *Badanie RTG stawów biodrowych. Białymi strzałkami zaznaczono miejsca złamania górnego ramienia kości łonowej oraz kości kulszowej po prawej stronie*

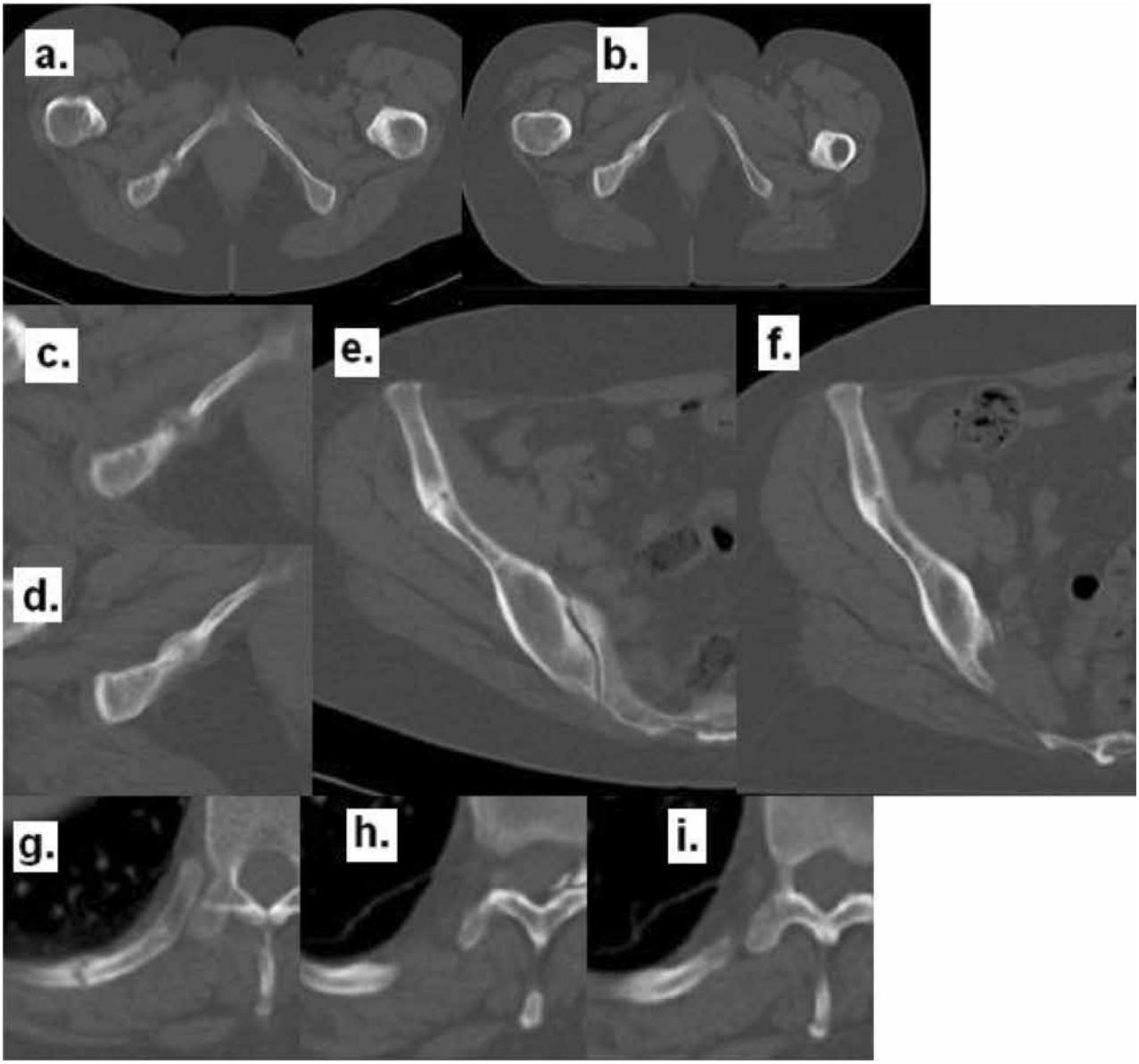

Figure 2. *Abdominal CT: pathological fractures of pelvic bones and 10th rib — images A, C, E and G taken before diagnosis; images B, D, F, H, and I taken six months after surgical removal of the tumour in the healing phase*

Rycina 2. *Badanie TK: złamania patologiczne kości miednicy i X żebra; obrazy A, C, E, G wykonane przy rozpoznaniu; obrazy B, D, F, H, I wykonane 6 miesięcy po zabiegu, w fazie gojenia*

Table I. *Laboratory findings before, ten days after, and six months after neurosurgical resectioning*

Tabela I. *Ocena gospodarki wapniowo-fosforanowej pacjentki przed, 10 dni po oraz 6 miesięcy po zabiegu neurochirurgicznym*

	Normal ranges	Before surgery	10 days after surgery	6 months after surgery
Serum				
Calcium [mg/dL]	8.9–10	9.07	9.2	9.9
Phosphate [mg/dL]	2.3–4.7	1.9	4.2	3.3
Parathyroid hormone [pg/mL]	15–65	47	119	31.4
Alkaline phosphatase [U/L]	40–150	217	124	–
25-hydroxyvitamin D3 [ng/mL]	19.8–60	66	4.43	–
Urine				
Urine calcium [mg/dL]		2.9	0.4	9.7
Urine phosphorus [mg/dL]		15	12	40.8
Urine 24-hour calcium [mg/24h]	100–300	64	8	291
Urine 24-hour phosphorus [mg/24h]	400–1,300	330	246	1,224

myeloma and bone metastatic disease were both excluded. The imaging tests taken during the diagnostic process, such as thoracic and cranial radiographs, thyroid, parathyroid, breast and transvaginal ultrasound, double contrast barium enema and upper endoscopy, revealed no abnormalities, and neither did gynaecological or neurosurgical consultations. The biopsy did not reveal any bone marrow infiltration, either. The trephine biopsy showed cancellous bone with wide trabecular spaces and hypocellular bone marrow with 8% of plasmocytes, without infiltration by non-haemopoietic neoplasms or other non-haemopoietic cells.

Routine laboratory tests, including complete blood count, coagulation tests, liver and kidney function tests and tumour markers — all except elevated alkaline phosphatase — were within reference values. The calcium and phosphorus balance checks for primary hyperparathyroidism revealed normal PTH and calcium levels and mild hypophosphatemia (Table I).

A technetium (99 mTc) sestamibi scan revealed an increased uptake in the second and third thoracic vertebrae, both shoulders, all ribs, ischial and iliac bones, the right pubic and radial bones, and both necks of the femur. The patient was admitted to the Department of Endocrinology and Internal Medicine at the Medical University of Gdansk.

The patient was generally in a good state. Upon physical examination, due to severe pain in the hip joints, she had difficulty walking and required crutches.

For the purposes of a suspected neuroendocrine tumour, a chest CT scan was taken. At the level of the fifth vertebra, the scan disclosed a pathological mass, and this was confirmed in the MR imaging. The tumour, which was located on the level of Th4-Th6, resembled a neuroma (Figure 3).

The neurosurgical resection was performed. In the neurosurgeons' opinion, the operated tissue showed the macroscopic character of a neuroma.

In anticipation of the histopathological results, and determined to continue diagnosing, we scheduled a CT-guided biopsy of bone lesions. Ten days after the neurosurgical treatment, unexpectedly the CT scan revealed hardly any osteomalatic changes, seen before. The only exception was the fracture of the ischial bone in its healing phase, poorly accessible to biopsy, meaning that the biopsy was finally cancelled. Laboratory investigations revealed mild anaemia, a decrease in the calcium level, and an increase in the previously low or normal phosphate level (Table I).

During postoperative observation, the patient reported a gradual decrease in pain and a reduction in walking difficulties. Moreover, she started to walk unaided, and the clinical picture suggested a healing in the previously observed bone fractures.

The last piece in the jigsaw was the histopathological test result which provided the correct solution to this mysterious disease and helped us establish the final diagnosis. In postoperative tissues, PMT deriving from nerve roots was found.

Laboratory tests conducted six months after surgery showed calcium and phosphate compensation (Table I), a resolution of clinical signs with relief of pain symptoms, and healing in the bone fractures shown in the CT scan (Figures 2B, 2D, 2F, 2H, 2I).

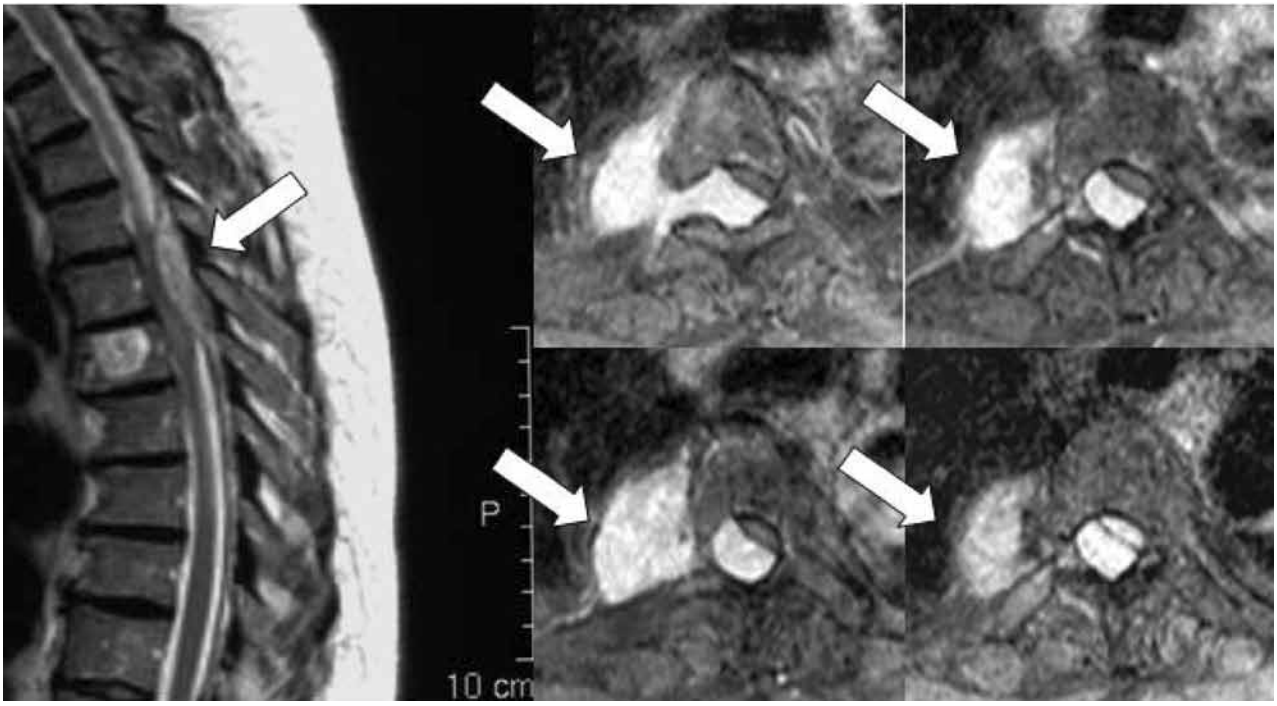

Figure 3. *MRI revealed pathological mass (white arrows), most probably of a neuromal nature, penetrating through the intervertebral foramen into the spinal canal and the epidural space*

Rycina 3. *Badanie MRI: masa patologiczna (białe strzałki), najpewniej o charakterze nerwiaka, penetrująca przez otwór międzykręgowy do światła kanału kręgowego i przestrzeni zewnątrzoponowej*

Discussion

The first description of a patient with oncogenic osteomalacia (OO) appeared in 1947, but at that time McCance [1] did not suspect any connection between a tumour located in the thigh and the osteomalatic lesions. Prader et al. [2] in 1959 first suggested the causal role of a tumour in osteomalacia.

The disease is clinically manifested by intense muscular and bone pain, very often related to pathological fractures, increasing fatigue and general weakness, and proximal muscle myopathy. Gradually increasing difficulty in walking is observed, so in the final stage of the disease, patients require wheelchair assistance. The clinical signs and symptoms are so unspecific, and the disease itself so rare, that establishing a proper diagnosis takes approximately 2.5 years [3–4]. It took us two years from the moment our patient showed the first symptoms described as a pain in the left hip, right up until the time when the final diagnosis was established.

According to the most frequent causes of bone destruction, the patient was initially diagnosed with multiple myeloma, primary hyperparathyroidism, and finally with metastatic bone disease. The mild level of hypophosphatemia was overlooked during the diagnosis of primary hyperparathyroidism when normal calcium and PTH levels were shown in the calcium and phosphate balance. Similarly, the concept of the action of parathyroid hormone related peptide (PTHrP) as a causative factor of symptoms, without hypercalcaemia, with normal PTH level and no features of solid tumour mass which could eventually produce PTHrP in imaging tests, was rebutted in spite of existing hypophosphatemia.

When mild hypophosphatemia is the only abnormality in estimating the calcium and phosphate balance, it should not be surprising that it can easily go unnoticed.

However, isolated hypophosphatemia caused by renal phosphate loss with deficiency of the active form of vitamin D, and both clinical and histological features of osteomalacia, is a main symptom of OO.

The main sign of OO in laboratory findings is hypophosphatemia. The plasma phosphate level is usually very low [5–7]. A decrease in $1.25(OH)_2D_3$ level and hyperphosphaturia are also characteristic features of OO. 24-hour urine phosphorus excretion can be normal [8], because phosphaturia is represented by a decrease in the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmP/GFR) or tubular reabsorption of phosphate (TRP) [9]. It can hardly be expected that such an unusual disease as OO could have been diagnosed solely on the basis of mild hypophosphatemia (through the

lack of $1.25(OH)_2D_3$ an estimation with normal $25(OH)D_3$ level and decreased phosphorus excretion in 24-hour urine collection).

Neurosurgeons intraoperatively assessed the tumours as neuroma-like tissue. While final histopathological examination was being processed, not suspecting that the tumour deriving from the nerve tissue could be the reason for the patient's complaints, it came as a surprise to us that the CT scan revealed regression of the bone lesions. The second assessment after surgery, an assessment of the calcium and phosphate balance, showed the results normally observed in hungry bone syndrome (an increase of PTH and a decrease in the vitamin D_3 precursor). We observed a rapid bone demineralisation with compensation of biochemical disturbances, a few days or months after a tumour resection. These are both characteristic features of OO [10]. Usually, a clinical improvement is noticeable in the first week after the tumour resection [11]. Before we received the histopathological result, our patient reported a decrease in pain and could walk unaided.

Confirmation of the diagnosis of OO comes with the detection of an increased activity of phosphaturic factors (phosphatonins) such as fibroblast growth factor 23 (FGF-23), matrix extracellular phosphoglycoprotein (MEPE), stanniocalcin, and frizzled-related protein 4 (FRP4) [12]. The cause of an increased activity of FGF23 in OO is its excessive production in tumour cells. Similar symptoms with an excessive renal tubular phosphate loss are observed in rare genetic disorders such as autosomal dominant hypophosphatemic rickets (ADHR) and X-linked hypophosphatemic rickets (XLH), both caused by mutations preventing FGF23 from degeneration.

Nowadays, the diagnosis of OO may be confirmed through the estimation of FGF23 with commercially available laboratory kits. Phosphates and FGF23 levels become normalised just a day after tumour resection. That is why normalisation of phosphates level at the time of diagnosis proved the recognition of OO. Unfortunately, the estimation of FGF23 at that moment, without its basic assessment, was worthless from this diagnostic point of view.

Establishing an accurate diagnosis may be difficult. The first step in recognising OO is to be aware of the occurrence of this type of ailment. Unspecific clinical symptoms, and not very spectacular abnormalities in the laboratory findings, do not suggest a rare disease. Usually, imaging pathological fractures begins the diagnostic process which is long, laborious, and extensive. In basic laboratory tests, we can only expect an increased level in alkaline phosphatase and hypophosphatemia. In analysis of the calcium and phosphate balance in the presence of normal calcium and PTH levels, a mild decrease in phosphorus levels is often asymptomatic, and therefore unnoticeable.

We are convinced that, next time, awareness alone of such a rare disease will be enough to combine hypophosphatemia, bone pain, fractures and long-term complaints into a diagnosis of OO.

We wish all readers who have studied our case report excellent diagnoses and rapid diagnostic processes.

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