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Abstract

Hypophosphatemic osteomalacia is a rare condition caused by different causes, all resulting in disturbances of calcium-phosphate management. One of the most common causes among adults is tumor-induced osteomalacia, which is characterized by increased secretion of fibroblast growth factor-23. Its symptoms are vague, tests necessary for diagnosis are not commonly used by clinicians and some of them are only available in highly specialized
centers. Due to these reasons, patients often are misdiagnosed for more common conditions and are left without proper treatment for many years. We present a case of a patient suffering from multiple fractures, diffuse bone pain, and muscle weakness, who was previously misdiagnosed for osteoporosis, primary and secondary hyperparathyroidism. We discuss the pathophysiology of tumor-induced osteomalacia, diagnostic path, differential diagnosis, available forms of treatment and possible complications.

Keywords: osteomalacia, tumor-induced osteomalacia, hypophosphatemia, fibroblast growth factor-23, vitamin D, calcium-phosphate management

Introduction
Calcium and phosphate (Pi) metabolism is a complex physiological process. Its maintenance within the normal range is crucial for sustaining essential processes in human body, as phosphate is a component of bone, teeth, nucleic acids, enzymes, adenosine triphosphate (ATP) being the main carrier of energy and many others. Because of that the disturbance in its metabolism can cause symptoms from various organs, mainly the skeletal and muscular system. The principal factors which are responsible for and optimal maintenance of serum phosphate levels are 1,25-dihydroxyvitamin D3, parathyroid hormone and fibroblast growth factor-23 (FGF-23). We present a case where FGF-23 was significantly high, what led to search for its source. Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome and one of the causes of hipophosphatemic osteomalacia. The first case of tumor-induced osteomalacia was described by McCance in 1947. Until 2018 there have been reported about 500 cases of TIO worldwide and the number has risen significantly after that study, as in 2022 there have been conducted a systematic review indicating about 1700 cases. Its prevalence varies by country. TIO is characterized by hypophosphatemia due to high FGF-23 levels what leads to decreased renal phosphate reabsorption and low or normal vitamin D level. Tumors producing FGF-23 can be located anywhere in the body in both bones and soft tissue what makes them hard to locate. The symptoms of this condition are generalized weakness, diffused bone pain, frequent bone fractures, bone deformities, what causes functional impairment. Tests that should be run to the confirmation of diagnosis are not commonly used, some of them are very expensive and the disease itself is rare, therefore patients remain many years without treatment.

Case presentation
55-year old female was admitted to the Department of Endocrinology and Metabolic Diseases for an unexplained hypophosphatemia to carry out diagnostics. The patient reported severe
generalized bone pain for several years and increasing difficulty walking. Attention was
drawn to gait disturbances in the form of a duck-like gait. She had a history of multiple bone
fractures: double fracture of the pelvic bones, fracture of both femoral necks, fracture of the
6th right rib, fracture of the left foot bone. Osteoporosis was found in densitometry and the
treatment with calcium preparations, vitamin D and alendronate was implemented. Previous
studies showed slightly elevated parathyroid hormone (PTH) levels, normal calcemia,
hypophosphatemia, hypocalciuria and normophosphaturia. Due to an abnormal level of PTH,
the patient was prior hospitalized in various endocrinology departments with suspicion of
once primary and then secondary hyperparathyroidism. During these stays, parathyroid
scintigraphy was performed, which ruled out the presence of parathyroid adenoma. The
thyroid and neck ultrasound was normal as well. Also, vitamin D deficiency was found
despite its supplementation.

On admission to the Clinic the patient had significantly reduced level of phosphate (0,51
mmol/l; normal 0,87-1,45 mmol/l), slightly increased level of PTH (92,45 pg/ml; normal 15-
65 pg/ml), normocalcemia (2,33 mmol/l; normal 2,2-2,55 mmol/l), hypokalciuria (0,16
mmol/24h; normal 2,5-8,0 mmol/24h) and normophosphaturia (21,96 mmol/24h; normal
19,9-42,0 mmol/24h). Apart from these abnormalities, the patient had hypertension and was
overweight. Based on the overall clinical picture the suspicion of hypophosphatemic
osteomalacia was raised. Alendronate was discontinued and treatment with high doses of
active vitamin D and phosphates was initiated. This treatment resulted in both laboratory and
slight clinical improvement over the next few months. Patient’s blood samples were taken to
measure concentration of FGF-23, which ended up being significantly increased (406 RU/ml;
normal <40 RU/ml). This raised the suspicion of tumor-induced osteomalacia. Computed
tomography (CT) of abdomen and chest was normal. 68Ga-DOTA-TATE PET scan identified
a nodule with increased expression of somatostatin receptors (13 mm in diameter) deep in the
adipose tissue in the area of the pubic joint. CT scan showed this nodule with calcification. Its
surgical removal was conducted, but postoperative histopathological examination showed
only adipose tissue. The next FGF-23 concentration levels were 137,4 RU/ml and 23331
RU/ml. After 6 months another 68Ga-DOTA-TATE PET scan again showed an increased
expression of somatostatin receptors in the same area as earlier. It was not clear weather it
was due to postoperative scar or tumor’s recurrence. The second surgery was planned, during
which the source of FGF-23 secretion was not identified and was complicated with long-term
postoperative wound infection. The next 68Ga-DOTA-TATE PET scan showed slightly
increased expression of somatostatin receptors in pelvic lymph nodes (probably inflammatory), liver and thyroid (like in previous exams). 68Ga-DOTA-NOC PET scan identified slightly increased expression of somatostatin receptors in the pubic joint area. After both surgeries and PET scans, laboratory levels of phosphate, calcium and PTH were normal, concentration of vitamin D was decreased (17 ng/ml) and the patient reported a slight bone pain. Due to the tendency of hypercalcemia during increasing the dosage of active form of vitamin D, this form of treatment was not continued. Oral phosphates were also retreated. The patient was forwarded to ambulatory care, where oral cholecalciferol treatment in dosage of 6000 IU daily was induced. Over the next few years normalization of 25(OH)D was reached and the patient did not report bone pain, difficulty walking or new bone fractures. Blood levels of phosphate, calcium and PTH remained normal. One episode of subdepression was notified. During cholecalciferol reduction attempt, the patient reported muscle fatigue, thus supplementation at high level was maintained. Total observation time from the second surgery to the last ambulatory visit was 10 years.

![Graph showing serum phosphorus levels over the course of treatment.](image)

**Figure 1.** Patient’s phosphate levels over the course of treatment.

**Discussion**

We present a rare, complex case of hypophosphatemic osteomalacia, the cause of which is TIO complicated by vitamin D deficiency. Chronic hypophosphatemia led to weakening of the bone structure, thus the patient had multiple fractures. Another complications were muscle
weakness and diffuse bone pain, what led to duck-like gait and functional impairment. Although there was not a histopathological confirmation of characteristic TIO tissue (PMT), characteristic functional and anatomical imaging localizing the tumor, the reduction in drugs need and eventually their discontinuation speaks in favor of this diagnosis. Symptoms of this condition are not very specific and tests that should be run to set the diagnosis are not commonly used by clinicians, therefore patients are often left undiagnosed and untreated for years or are diagnosed with other diseases as in this case. Attention should be drawn to the fact that the use of bisphosphonates can aggravate the condition and deepen hypophosphatemia, cause hypocalcemia, increase the PTH and ALP concentration.  

Physiology
In the human body 90% of phosphate resides in the skeleton, where it forms hydroxyapatite crystals with calcium. The rest 10% is a part of nucleotides, phospholipids, ATP and different enzymes. 

Phosphate is retrieved from diet in the small intestine. The main factor mediating intestinal phosphate uptake is 1,25(OH)2D. It induces membrane calcium and phosphate transporters what leads to elevating their serum levels. Other paths of maintaining the normal phosphate levels are its releasing from bones and regulation in kidneys in the proximal tubule. The renal regulation of Pi is mediated by PTH and FGF-23. If the serum Pi rises, secretion of there hormones is stimulated which reduces the expression of Npt2a and Npt2c in proximal tubules – transporters that are responsible for renal Pi reabsorption. This leads to increased urinary Pi excretion and lowers its serum concentration. FGF-23 is secreted by osteoblasts and osteocytes what is stimulated by 1,25(OH)2D and high Pi levels. Another crucial organ in maintenance of phosphate management is parathyroid gland that not only responds to calcium and Pi serum levels but also is regulated by 1,25(OH)2D. Parathyroid glands are the source of PTH that influences both FGF-23 and 1,25(OH)2D management. PTH can also stimulate phosphate release from bones.
**Figure 2.** Direct action of FGF-23, PTH and 1,25(OH)₂D in regulation phosphate homeostasis. 1,25(OH)₂D - 1,25-dihydroxyvitamin D; FGF-23 - fibroblast growth factor 23; PTH – parathyroid hormone. Source: adapted from Figure 2. Aljuraibah F, Bacchetta J, Brandi ML, et al.\(^{18}\)

Figure 3 shows the complexity of PTH, FGF-23 and 1,25(OH)₂D correlation. These hormones regulate phosphate serum level and each other, thus the pathological disturbance of one of them often leads to an abnormal level of the others.
Figure 3. Overview of physiologic interactions between phosphate and its key regulators. 1,25(OH)₂D - 1,25-dihydroxyvitamin D; FGF-23 - fibroblast growth factor 23; PTH – parathyroid hormone. Source: adapted from Figure 2 Aljuraibah F, Bacchetta J, Brandi ML, et al.¹⁸

In cases of TIO the tumor’s abnormally high FGF-23 production reduces the expression levels of NPT2A and NPT2C in kidneys by binding to Klotho-FGF receptor complex in proximal tubules, thus the phosphate reabsorption is decreased. It also decreases the expression of 1α-hydroxylase (enzyme that takes the principal role in producing the active form of vitamin D, 1,25(OH)₂D) and increases the 24-hydroكسيلاز (enzyme involved in degradation of 1,25(OH)₂D) expression, what leads to lower intestinal phosphate absorption.¹⁹ ²⁰ By those mechanisms FGF-23 lowers phosphate serum levels, what leads to characteristic bone and muscle symptoms (Figure 4).

Figure 4. Patophysiology of TIO. 1,25(OH)₂D - 1,25-dihydroxyvitamin D; FGF-23 - fibroblast growth factor 23; NPT2 - type II sodium phosphate contrnsporter; PMT - phosphaturic mesenchymal tumor. Source: adapted from figure 1 from Jan de Beur SM, Minisola S, Xia Wbo, et al. ²¹

Diagnosis

Example causes of hypophosphatemia

1. Hypophosphatemia mainly caused by excessive renal excretion
   1.1 FGF-23 mediated²²
1.1.1 Genetic
- XLH\textsuperscript{23}
- NF1\textsuperscript{24,25}
- Osteoglophonic dysplasia
- ADHR

1.1.2 Acquired
- chronic alcohol consumption and withdrawal\textsuperscript{18}
- chronic intravenous iron supplementation therapy\textsuperscript{26,27,28}
- TIO

1.2 Non-FGF-23-mediated
- Renal Fanconi syndrome\textsuperscript{29,30}
- Primary and secondary hyperparathyroidism

2. Impaired actions of vitamin D metabolites
- Vitamin D deficiency\textsuperscript{31}
- Vitamin D metabolism defects

3. Malabsorption, malnutrition\textsuperscript{32}

4. Transcellular shifts
- Diabetic ketoacidosis
- Hyperventilation
- Refeeding syndrome
- Respiratory alkalosis

5. Drugs
- Aminoglycosides
- Antiretrovirals\textsuperscript{29,30}
- Bisphosphonates
- Catecholamines
- Diuretics
- Glucose or insulin infusion
- Mannitol
- Tetracyclines

**Table 1. Differential diagnosis of hypophosphatemia\textsuperscript{31}**
Definition of chronic hypophosphatemia was set as “at least three consecutive, morning fasting serum phosphate reading below the lower limit of normal (LLN) for healthy age and sex-matched reference ranges, taken at least 3 months apart.”

There is a variety of causes of hypophosphatemia, from genetic to drug-induced.

Table 1 shows the plurality and difficulty in setting the right diagnosis. Each patient with hypophosphatemia needs individual approach, running different test and management. It is utterly important to carry out a thorough interview directed to these differential diagnoses, as even commonly used drugs such as tetracyclines or diuretics can cause low phosphate levels.

As there are many causes of hypophosphatemia with high FGF-23 prevalence, a thorough interview should be carried out. Patient should be asked about his medical history to rule out acquired causes of high FGF-23 concentration such as intravenous iron treatment or alcohol withdrawal. Attention should be also drawn to the patients family history, especially to frequent fractures, unexplained muscle weakness or diffuse bone pain among relatives. This can lead toward the genetic background of patients complaints, among which the most common is X-linked Hypophosphatemia (XLH).

Other factors that can suggest genetic disease are lower than expected height, limb deformities, skull structure deviations, impaired hearing or dental abnormalities such as numerous fillings, teeth loss and implants. Characteristic biochemical tests that should be conducted are calcium, phosphate, vitamin D, FGF-23 concentration, total or bone-specific alkaline phosphate (ALP) and tubular maxim transport of phosphate per glomerular filtration rate (TmP/GFR). Another step is setting the tumor’s localization. For that functional imaging is used including somatostatin receptor imaging (\(^{68}\)Ga/\(^{64}\)Cu-DOTATATE, -DOTANOC, or DOTATOC, or octreotide scan) and fluorodeoxyglucose positron emission tomography. Usually whole-body imaging is needed.

To prepare for surgery and confirm the tumor’s localization and its surroundings magnetic resonance imaging or computed tomography should be performed. Venous sampling of FGF-23 levels can be used to differentiate, localize or confirm a suspected tumor in functional imaging. A typical finding in postoperative histopathological material is phosphaturic mesenchymal tumor (PMT) or mixed connective tissue tumors (MCT).

**Treatment**

The primary and most recommended form of TIO therapy is its surgical removal with tumor-free margins. If the tumor cannot be resected, ablative therapy in the form of using heat, cold, chemical agents or radiofrequency can be performed. In some cases location of the cancer...
cannot be identified or its removal attempts are unsuccessful. In those patients oral phosphate and active vitamin D can be administered to alleviate symptoms. This form of therapy is also recommended in patients with identified tumor before the operation performance. Also cow milk can be used as a source of oral phosphate. However, using oral phosphate salts and active vitamin D can lead to side effects such as abdominal pain, diarrhea, secondary-tertiary hyperparathyroidism, hypercalciuria, nephrocalcinosis. Therefore another form of conservative treatment was sought. Recent studies has proved berosumab, human MAB for FGF-23, effectiveness in FGF-23 related conditions. It has been found that it is more effective than phosphate (a mixture of Na$_2$HPO$_4$ and NaH$_2$PO$_4$) and active vitamin D in increasing serum phosphate, TmP/GFR and 1,25(OH)$_2$D, decreasing alkaline phosphate, improving osteomalacia. Berosumab is approved for patients with TIO in several countries. After inducing oral or berosumab therapy, patients should be put under regular surveillance: every 3-4 months tests for serum and urine calcium, phosphate, creatine, PTH, total or bone-specific ALP and renal ultrasound. If patient underwent a surgical tumor resection, 3-6 months check-ups assessing serum phosphate and calcium should be administered.

**Complications**

Hypophosphatemic osteomalacia is a rare disease manifested by nonspecific symptoms. Because of that patients may remain undiagnosed and untreated for a long period of time, what can lead to various complications. Their condition can also be misdiagnosed for more common conditions, such as stroke, a variety of rheumatological disorders, osteoporosis, multiple sclerosis, polymyalgia rheumatica and many others. The most common misdiagnosis is hyperparathyroidism as has been shown in this case. Tests used to reach the diagnosis are not commonly used and hard to access by many clinicians. Patients with hypophosphatemia have higher risk of glucose intolerance, obesity and other manifestations of the metabolic syndrome. There have also been conducted a study assessing elevated morbidity caused by chronic hypophosphatemia. It showed that these patients have higher risk of cardiovascular outcomes such as heart failure, hypertension and other severe diseases like chronic kidney disease, multi-organ failure and even depression and anxiety. Hypophosphatemia also affects dental health, thus periodontitis occurs with a greater frequency among these patients. Therefore it is utterly important to carry out a thorough interview, run tests assessing the calcium-phosphate management including PTH and vitamin D and conduct proper imaging diagnostics before reaching the diagnosis and inducing a treatment.
Conclusions
We presented a case of hypophosphatemic osteomalacia caused by TIO. The patient was experiencing its symptoms like multiple fractures, muscle weakness and diffuse bone pain for 5 years before reaching the proper diagnosis and receiving the treatment. She also had hypertension, was overweight and later suffered from subdepression, what possibly could be hypophosphatemia complications. At first she was misdiagnosed for osteoporosis and treated with bisphosphonates, what could possibly worsen the symptoms, and then with both primary and secondary hyperthyroidism. The case shows the importance of conducting a comprehensive assessment of calcium-phosphate management if one of its components is out of the norm and the patient is experiencing skeletal and muscular symptoms.

Disclosure

Author's contribution
Conceptualization: Agnieszka Nowak and Alicja Partyka; Methodology: Justyna Dobrzańska; Software: Magdalena Pach; Check: Zuzanna Chmielowiec and Agnieszka Fugas; Formal analysis: Karolina Smykiewicz and Magdalena Pach; Investigation: Aneta Michaleczewska and Natalia Wierzejska; Resources: Mariola Dziedzic; Data curation: Karolina Smykiewicz; Writing - rough preparation: Agnieszka Nowak and Zuzanna Chmielowiec; Writing - review and editing: Alicja Partyka and Justyna Dobrzańska; Visualization: Mariola Dziedzic; Supervision: Natalia Wierzejska; Project administration: Aneta Michalczewska and Agnieszka Fugas; Receiving funding - no specific funding.

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Institutional Review Board Statement
Not applicable. The study was conducted in accordance with the Declaration of Helsinki. In accordance with the law in force in the Republic of Poland, case report retrospective studies do not require the opinion of consent of the Board of Bioethics Committee, as they are not a medical experiment in which human organisms would be interfered with. For this reason, we did not seek the consent of the Commission. What is more, the results of the study did not
affect the management of patients at any stage, so the above-mentioned procedure was followed.

**Informed Consent Statement**

Not applicable.

**Data Availability Statement**

Not applicable.

**Conflict of interest**

The authors deny any conflict of interest.

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